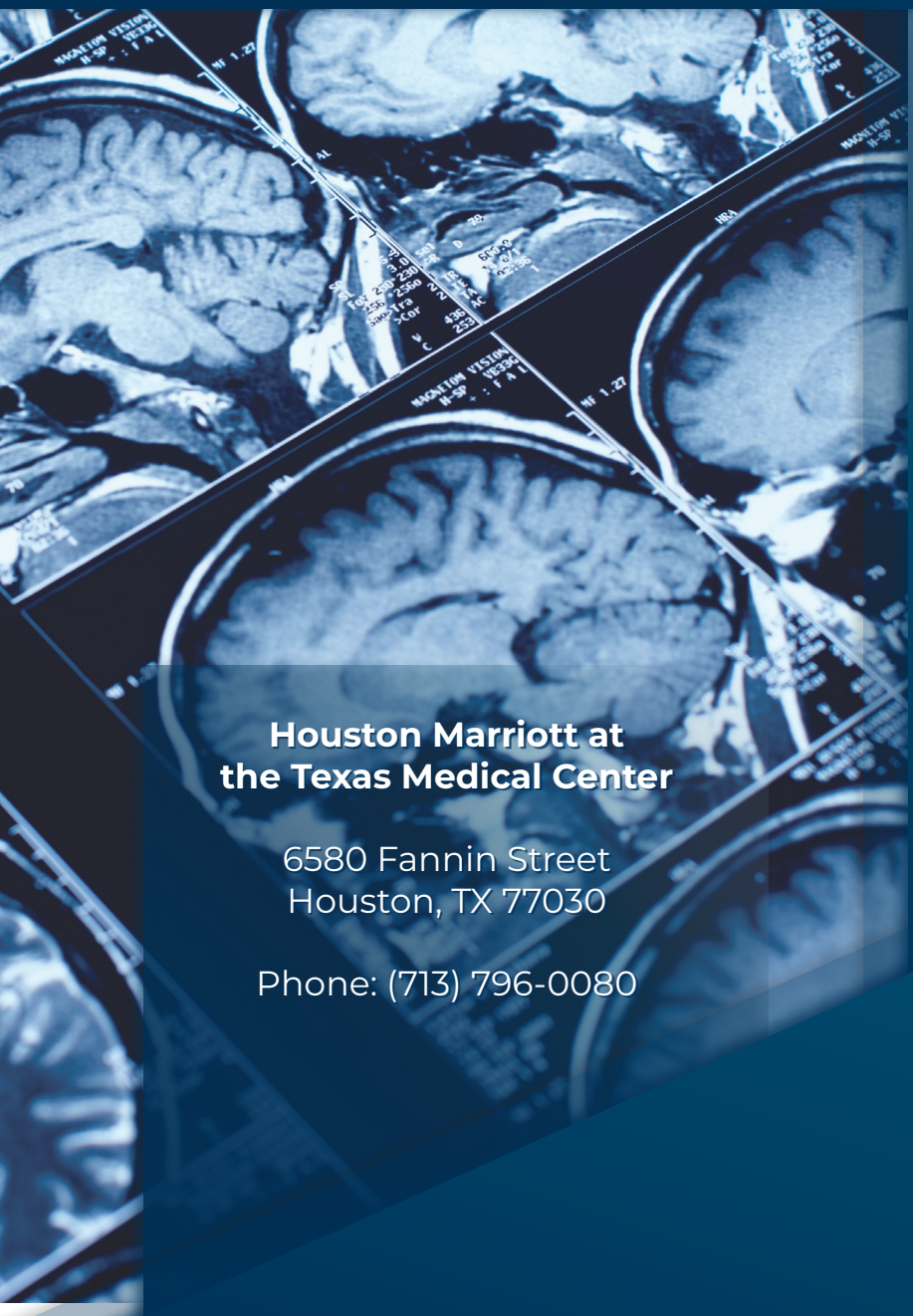
Saturday, October 27, 2018
7:00 AM - 3:45 PM

Changing Treatment Paradigms with Immunotherapy and Targeted Therapy in Advanced Non-Small-Cell Lung Cancer and Head & Neck Cancer



Program Director

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Department of Thoracic/Head & Neck Medical Oncology,
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Statement of Need/Program Overview

This symposium is intended to improve care of patients with non-small cell lung cancer and head & neck cancer by accelerating adoption of new guidelines and evidence-based practice change. The format will include didactic lectures from known opinion leaders, question and answer sessions, and ample opportunity for participant interaction with faculty.

Target Audience

This symposium is directed primarily to hematologists/oncologists, radiation oncologists, researchers, pharmacists, registered nurses, physician assistants, nurse practitioners and fellows in training interested in new development in non-small cell lung cancer and head & neck cancer. No specific skill or knowledge other than a basic training in hematology/oncology is required for successful participation in this activity.

Learning Objectives

- Select NSCLC patients based on new molecular profiling for personalized chemotherapy
- Outline the clinical data on the use of epidermal growth factor receptor (EGFR) and EGFR-T790M–inhibitors in the treatment of NSCLC
- Identify strategies to overcome secondary or acquired resistance to EGFR-positive and EGFR-T790M–positive NSCLC
- Outline the clinical data on the optimal use of anti-PD-1 and PD-L1 antibodies in the treatment of NSCLC
- Outline the clinical data on the optimal use of anti-PD-1, PD-L1 antibodies and combination approaches in the treatment of NSCLC
- Outline the mechanisms of action of PD-1 and PD-L1 blockade in SCCHN with high mutational burden and implication of immune resistance in SCCHN
- Evaluate PD-1/PD-L1 interactions that contribute to better outcomes for patients with SCCHN
- Identify strategies in the treatment of NSCLC patients with ALK inhibitors
- Identify strategies to overcome secondary or acquired ALK TKI resistance in patients with NSCLC

Agenda

SATURDAY – October 27, 2018

7:00 AM	Registration and Continental Breakfast	
7:55 AM	Welcome and Introductions	*John Heymach, MD*
	EGFR-TKI TARGETED THERAPY	
8:00 AM	Pretest – Case Report Vignettes	*John V. Heymach, MD, PhD / Don L. Gibbons, MD, PhD*
8:15 AM	Molecular Profiling in the Treatment of NSCLC: Guidelines from the CAP, IASLC and AMP	*John V. Heymach, MD, PhD*
8:45 AM	EGFR Inhibitors: Perspective on Molecular Markers and Patient Selection	*Don L. Gibbons, MD, PhD*
9:15 AM	Emerging Strategies and Challenges Due to Secondary or Acquired EGFR-TKI Resistance	*Don L. Gibbons, MD, PhD*
9:45 AM	Posttest – Case Report Vignettes	*John V. Heymach, MD, PhD / Don L. Gibbons, MD, PhD*
10:00 AM	BREAK	
	IMMUNOTHERAPY - NSCLC	
10:15 AM	Pretest – Case Report Vignettes	*John V. Heymach, MD, PhD / Jianjun Zhang, MD, PhD*
10:30 AM	Immunotherapy with PD-1/PD-L1 (Nivolumab, Pembrolizumab, Durvalumab) and Anti CTLA-4 (Ipilimumab) Antibodies in NSCLC	*John V. Heymach, MD*
11:00 AM	Immunotherapy with Anti-PD-L1 (Pembrolizumab) and Combination Therapy Approaches in NSCLC	*Jianjun Zhang, MD, PhD*
11:30 AM	Posttest – Case Report Vignettes	*John V. Heymach, MD, PhD / Jianjun Zhang, MD, PhD*
	IMMUNOTHERAPY – HEAD & NECK CANCER	
11:45 AM	Pretest – Case Report Vignettes	*Tanguy Seiwert, MD*
12:00 PM	Overview of Molecular, Histologic Tumor Testing, High Mutational Burden and Implication of Immune Resistance in HPV-associated Head & Heck Cancer	*Tanguy Seiwert, MD*
12:30 PM	LUNCH	
1:15 PM	Immunotherapy Options in the Treatment of Metastatic Head & Heck Cancer	*Tanguy Seiwert, MD*
1:45 PM	Posttest – Case Report Vignettes	*Tanguy Seiwert, MD*
	ALK-REARRANGED –TKI TARGETED THERAPY	
2:00 PM	Pretest – Case Report Vignettes	*Anne Tsao, MD / Vincent Lam, MD*
2:15 PM	Overview of Molecular Targeted Therapy on the Outcome of Early-stage NSCLC Patients with EML4-ALK Fusion Gene and the Application of TKIs	*Anne Tsao, MD*
2:45 PM	BREAK	
3:00 PM	Discuss Emerging Strategies and Challenges Due to Secondary or Acquired Resistance to Small Molecule TKIs in Patients with ALK-rearranged NSCLC	*Vincent Lam, MD*
3:30 PM	Posttest – Case Report Vignettes	*Anne Tsao, MD / Vincent Lam, MD*
3:45 PM	Adjournment	*John V. Heymach, MD, PhD*

Faculty

Don L. Gibbons, MD, PhD
Assistant Professor, Depts. of Thoracic, Head/Neck Medical Oncology & Molecular and Cellular Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

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Name	Conflict of Interest Disclosures
Don L. Gibbons, MD, PhD	**Advisory Board:** Sanofi, Janssen Research and Development **Research Support:** Janssen Research and Development, AstraZeneca
John V. Heymach, MD, PhD	**Advisory Board:** BrightPath Biotherapeutics, Hengrui Therapeutics **Consultant:** AstraZeneca, Genentech, Inc., GlaxoSmithKline, Spectrum Pharmaceuticals, Foundation Medicine
Vincent Lam, MD	No relevant financial disclosures
Tanguy Y. Seiwert, MD	**Consultant:** Arduro, Astra Zeneca, Bayer, BMS, Merck, Nanobiotix **Research Support:** BMS, Jounce Therapeutics, and Merck
Anne Tsao, MD	**Advisory Board:** BMS, Genentech/Roche, Merck, Eli Lilly, Novartis, Ariad, EMD Serono, Boehringer Ingelheim, AstraZeneca, Takeda Oncology
Jianjun Zhang, MD, PhD	**Advisory Board:** AstraZeneca **Consultant:** Geneplus **Speakers' Bureau:** OrigiMed, Geneplus, Innovent
Kamatham A. Naidu, PhD	No relevant financial relationships

All other individuals in a position to control content have no relevant financial relationships to disclose.

Physicians/Nurses/Pharmacists

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First Name _____ Middle Initial _____ Last Name _____

❑ Physician ❑ Pa-C ❑ NP ❑ PhD ❑ Pharmacist ❑ Industry ❑ Nurse ❑ Other

Mailing Address _____

_____

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E-Mail _____

Speciality _____

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Fax registration to:
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860 Hebron Pkwy, Suite 1104
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Registration fee partially covers breakfast buffet, lunch and syllabus book

	Early Registration Fee (Up to 10/5/18)	Discounted Registration Fee (10/6/18 - 10/20/18)	Regular Registration Fee (10/21/18 - 10/27/18)
❑ Physicians	$100.00	$130.00	$160.00
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Molecular Profiling in the Treatment of NSCLC: Guidelines from the CAP, IASLC and AMP

John V. Heymach, MD, PhD

Molecular Profiling in the Treatment of NSCLC: Guidelines from the CAP, IASLC and AMP

John Heymach, MD, PhD.
Chair, Dept. of Thoracic/Head and Neck Medical Oncology
David Bruton, Jr. Chair in Cancer Research

Changing Treatment Paradigms with Immunotherapy and Targeted Therapy in Advanced Non-Small-Cell Lung Cancer and Head & Neck Cancer

Houston
Oct 27, 2018

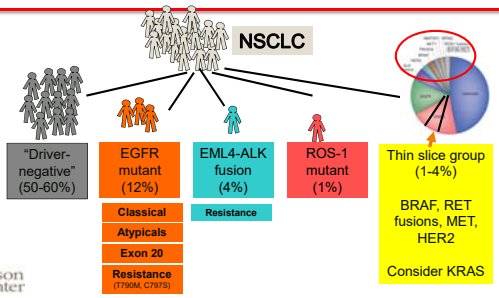
Conflict of Interest Disclosure

- **Advisory Committees** – AstraZeneca, Boehringer Ingelheim, Exelixis, Genentech, GSK, Guardant Health, Hengrui, Lilly, Novartis, Spectrum, EMD Serono, and Synta
- **Research Support** – AstraZeneca, Bayer, GlaxoSmithKline, Spectrum
- **Royalties and Licensing fees** – Spectrum

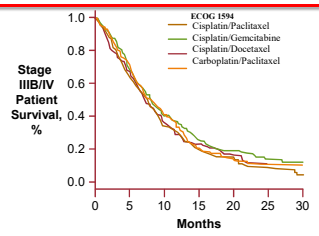
Key points regarding molecular profiling for NSCLC

- We now have a lot of new drugs that are effective for mutation-defined subgroups
  - 2015: EGFR (classical), ALK
  - 2018: EGFR (classical, atypicals), ALK, ROS1, BRAF
  - Active drugs with potential approvals in near future: MET exon 14 splice, RET fusion, NTRK fusion, EGFR exon 20, HER2 mutant
- Survival can be improved by years using appropriate TKIs
- Making sure targetable oncogenic drivers are detected may be the most important thing medical oncology team does
- Oh yeah: now we have immunotherapy markers (but everyone should now get immunotherapy anyway)
- **Proper profiling is critical for optimum management**

NSCLC landscape 2018: Major Mutation Subgroups



Comparison of Top Four Chemotherapy Doublets for NSCLC Patients (2002)

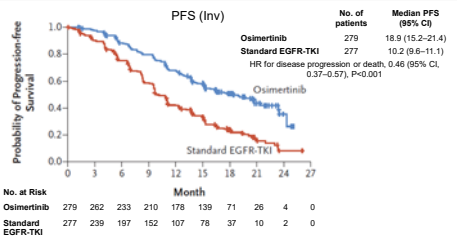


- No significant differences
- **Median overall survival 7.9 m**
- Objective response rate 19%
- Triplets not better than doublets

Schiller JH et al. *N Engl J Med*. 2002;346:92-98.

Advances in Mutation-defined Subgroups

FLAURA Phase III Study: Osimertinib Prolongs PFS Compared with Gefitinib/Erlotinib



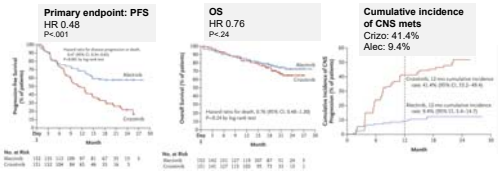
EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
Soria JC et al. *N Engl J Med*. 2018;378(2):113–125.

Osimertinib Approved as First-line Therapy for EGFR M+ NSCLC

- April 18,2018: FDA approved osimertinib for 1L EGFR M+ (exon 19, L858R) NSCLC based on FLAURA
- NCCN guidelines updated to include osimertinib for first-line therapy
- FDA label includes safety info:
  - Cardiomyopathy: 1.9% with LVEF drop ≥10% in 4% of patients. Baseline and periodic LVEF assessment recommended
  - QT prolongation: 2.9% had increase >60ms; no arrhythmias. Periodic monitoring if congenital QT, CHF, electrolyte abnormalities, meds that prolong QT.

EGFR, epidermal growth factor receptor; FDA, Federal Drug Administration; LVEF, left ventricular ejection fraction; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

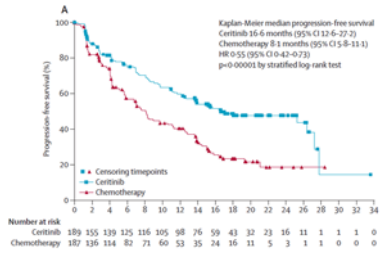
ALEX: Alectinib Vs Crizotinib for 1L ALK+ NSCLC



Bottom line: Alectinib with superior PFS, tolerability, activity vs CNS mets

1L, first-line; Alec, alectinib; ALK, anaplastic lymphoma kinase; CI, confidence interval; CNS, central nervous system; Crizo, crizotinib; HR, hazard ratio; mo, month; OS, overall survival; PFS, progression-free survival.
Peters S et al. *N Engl J Med* 2017;377:829-838.

ASCEND-4: Ceritinib vs Crizotinib for 1L ALK+



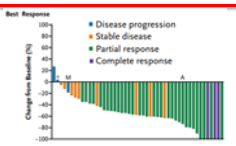
1L, first-line; ALK, anaplastic lymphoma kinase; CI, confidence interval; HR, hazard ratio.
Soria JC et al. *Lancet*. 2017; 4;389(10072):917–929.

Summary of ALK+ Space

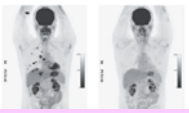
1. 1L: Alectinib superior to crizotinib in ALEX and J-ALEX, better tolerated, better CNS activity. New standard
   - FDA appoved for 1L NSCLC November 6, 2017
2. Ceritinib (ASCEND-4) also improves PFS vs Crizo, but PFS shorter (~16m), tolerability not as good as alectinib
   - FDA approved May 26, 2017
3. Brigatinib (ALTA-1L) improved PFS vs crizotinib
4. 2L space:
   a) Brigatinib and ceritinib likely to be most used
   b) Lorlatinib with promising data, could move into this space

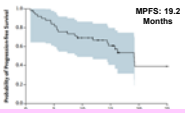
1L, first-line; 2L, second-line; ALK, anaplastic lymphoma kinase; Atezo, atezolizumab; Bev, bevacizumab; CNS, central nervous system; Crizo, crizotinib; PD1, programmed death receptor-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; VEGFi, vascular endothelial growth factor inhibitor.

Crizotinib has Marked Antitumor Activity in Advanced ROS1-rearranged NSCLC



Complete response	6%
Partial response	66%
Stable Disease	18%
Progressive Disease	6%
ORR	72%
Med Duration of response	17.6 months

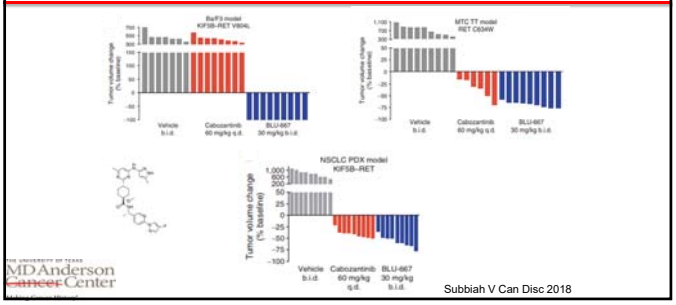




March 11, 2016: **Crizotinib FDA-approved for ROS-1 NSCLC**

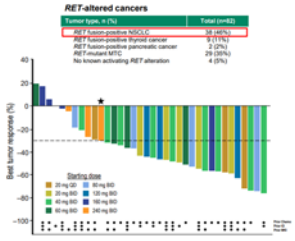
Shaw A NEJM 2018

Antitumor Activity of BLU-667 Across Ret-driven Solid Tumor Models In Vivo



Subbiah V Can Disc 2018

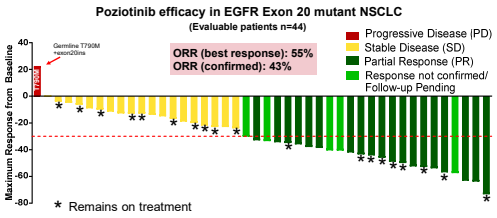
Clinical Activity of LOXO-292 RET Inhibitor in Patients with RET Fusion+ NSCLC



ORR (95% CI)	68% (n=26/38) (51–83%)
Confirmed ORR* (95% CI)	68% (n=25/37) (50–82%)
CR	–
PR**	26
SD	8
PD	2
NE	2

Oxnard G WCLC Toronto Sept 2018

Poziotinib is Active in EGFR Exon 20 Mutant NSCLC

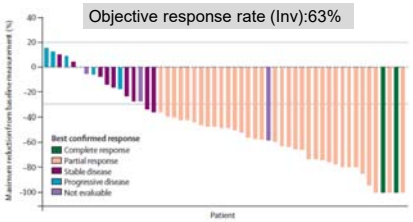


Heymach et al, WCLC 2018

Dabrafenib plus trametinib in patients with previously treated $BRAF^{V600E}$-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial

David Planchard, Benjamin Besse, Harry J M Groen, Pierre-Jean Souquet, Elisabeth Quoix, Christina S Baik, Fabrice Barlesi, Tae Min Kim, Julien Mazieres, Silvia Novello, James R Rigas, Allison Upalawanna, Anthony M D'Amelio Jr, Pingkuan Zhang, Bijoyesh Mookerjee, Bruce E Johnson

Objective response rate (Inv):63%



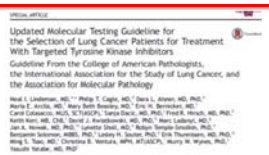
Plancard et al, Lancet Oncology 2016

Other Advances in Subgroups

- Dabrafenib and trametinib approved for BRAF-mutant (V600E) NSCLC
  - FDA approval June 22, 2017
  - Oncomine NGS test approved as diagnostic
  - BRF113928 study (N=97): ORR 63%, mDOR 12.6m
- Crizotinib, tepotinib highly active for MET exon14 mutant NSCLC

Recommendations for Profiling

2018 CAP/IASLC/AMP Recommendations for Profiling


Updated Molecular Testing Guideline for the Selection of Lung Cancer Patients for Treatment With Targeted Tyrosine Kinase Inhibitors

Guideline From the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology

- Who? Why?

"The College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology convened an expert panel to develop an evidence-based guideline to help define the key questions and literature search terms, review abstracts and full articles, and draft recommendations"

Lindeman et al, JTO 2018

Major Changes in Guidelines

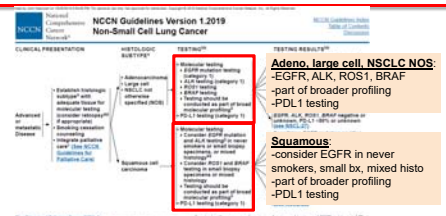
18 new recommendations

1. Profiling should include:
   - Absolute minimum: EGFR, ALK, ROS1 for all adenocarcinoma patients
   - HER2, MET, BRAF, KRAS, and RET should be included for laboratories that perform NGS
   - Multigene profiling preferred over single tests
2. IHC ok for ALK or IHC. Not for EGFR.
3. cfDNA assays to "rule in" targetable mutations when tissue limited or hard to obtain

Recommendations for Profiling Patients with Targetable Mutations Who Progress

- EGFR mutant NSCLC patients should have T790M testing (5% allele sensitivity)
- No recommendation made for profiling AKL mutant patients with PD

NCCN Guidelines October 2018


NCCN Guidelines Version 1.2019
Non-Small Cell Lung Cancer

Adeno, large cell, NSCLC NOS:
-EGFR, ALK, ROS1, BRAF
-part of broader profiling
-PDL1 testing

Squamous:
-consider EGFR in never smokers, small bx, mixed histo
-part of broader profiling
-PDL1 testing

"The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC"

What About Plasma Assays?

- On June 1, 2016, the FDA approved cobas plasma EGFR mutation test v2 (Roche) for the detection of EGFR exon 19 del and L858R
- First "liquid biopsy" approved
- Multiplexed targeted gene assays in plasma available (Guardant, FoundationOne, etc)

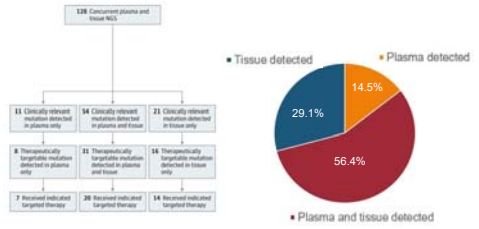
CAP/IASLC/AMP Recommendations for cfDNA

- cfDNA may be used to determine EGFR status when tissue limited or insufficient
- No recommendation for using cfDNA for primary diagnosis
- Sensitivity <80% but false positives low: can "rule in" but if not detected should try to get tissue

Looking Ahead: Potential Applications of Blood-based Profiling in the Future

(not currently recommended)

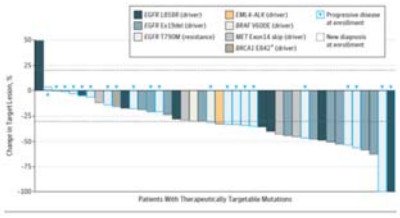
Plasma-based Genotyping vs Tumor in Metastatic NSCLC



JAMA Oncol Aggarwall et al 2018

Response of Patients to Plasma-directed Targeted Therapy

86% of patients had PR/CR or SD as best response



JAMA Oncol Aggarwall et al 2018

Analysis of cfDNA Profiling from >1000 Patients with Advanced NSCLC: The MDA cohort

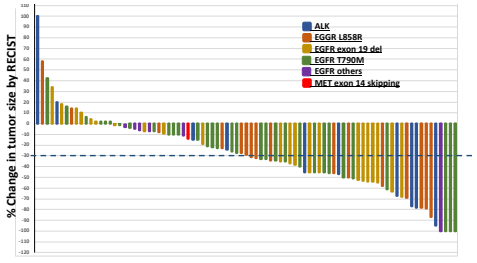
- N=1078, with Guardant360;
- outcomes captured in MDA Gemini database **
- Targetable alterations in **22.4% of tests** that directly led to treatments based on FDA labeling, NCCN guidelines or clinical trials eligibility

cfDNA reports identified any molecular alterations	927/1078 (86%) tests
cfDNA reports with at least 1 targetable molecular alteration	242/1078 (22.4%) tests 195/1011(19.3%) patients
EGFR exon 19 DEL	74
EGFR exon 19 DEL + T790M	22
EGFR L858R	44
EGFR L858R + T790M	19
EGFR/ERBB2 exon insertions	33*
EGFR others	15
EGFR T790M	4
ALK fusions	12*
MET exon 14 skipping	10*
BRAF V600E/G466E	4*
RET fusions	4*
ROS1 fusion	1*
	* potential eligibility for clinical research trials for some patients
Long-term follow-up (LTFU) for standard of care patients	109/242 (45%) tests 102/195 (52%) patients
LTFU with imaging of measurable disease for RECIST	87/109 (80%) tests 81/102 (79%) patients

**MDA protocol PA16-00061

Tran et al, WCLC 2018

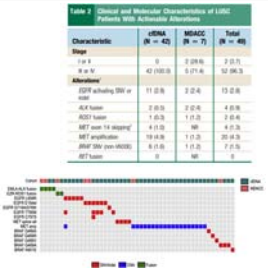
Best Response in 81 Patients with ctDNA-identified Alterations Treated with Targeted Agents



Tran et al, WCLC 2018

Should Profiling be Limited to Non-squamous? or Should we Profile LUSC as Well?

- Analysis of 492 squamous lung pts with Guardant 360
- **10.5%** had targetable alterations
  - EGFR (2.8%),
  - ALK/ROS1 (1.3%),
  - BRAF (1.5%)
  - MET amp/exon 14 skipping (5.1%)



Lam V et al Clinical Lung Cancer 2018

ctDNA First, Tissue First, or Concurrently?

Tissue first

- Tissue often needed anyway for diagnosis
- May need PD-L1
- More cost effective

But:

- If no actionable alterations seen, do you send ctDNA anyway? Or potentially miss some?
- Delays if QNS tissue

ctDNA first

- Easier for patient
- Typically quicker- no need to wait for biopsy

But:

- If no actionable seen, need to send tissue
- Might need PD-L1 anyway

concurrent

- Actionable results as quickly as possible (may be important for early stage in future)
- Increases likelihood of catching targetable alteration- probably the most impactful thing an oncologist can do

But:

- Cost

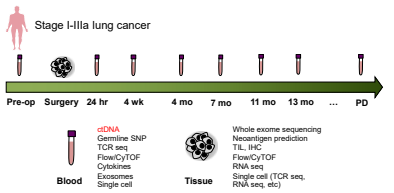
Circulating tumor DNA analysis with a novel variant classifier for recurrence detection in resected, early-stage lung cancer

V.K. Lam[1], H.T. Tran[1], L. Diao[1], C.C. Wu[1], M. Vasquez[1], K. Li[4], K. Yuen[4], F. Vang[4], A. Jaimovich[4], D. Kennedy[4], J.I. Odegaard[4], S. Mortimer[4], S. Olsen[4], V.M. Raymond[4], A. Vaporciyan[2], M.B. Antonoff[2], G. Walsh[2], E. Roarty, L. Lacerda, J. Roth[2], S. Swisher[2], C. Bernatchez[3], J. Wang[1], J.J. Lee[1], B. Sepesi[2], D. Gibbons[1], J. Zhang[1], J.V. Heymach[1]

[1]*The University of Texas MD Anderson Cancer Center, Houston, USA*
[2]*Guardant Health, Medical Affairs, Redwood City, USA*

ICON: Prospective Trial for Comprehensive, Longitudinal Immunogenomic Profiling of Resected, Early-stage Lung Cancers

Goal: Determine MRD prevalence (detected by ctDNA) in resected, early-stage NSCLC and correlate with recurrence free survival



Abbosh et al, Nature 2017 Chabon et al, MA 13.01, WCLC 2017

Project LUNAR: ctDNA Assay for Early-stage Detection

- Multigene panel designed for >90% theoretical sensitivity across major cancer types
- Paired tissue is not required
- Specificity is improved with a variant classifier trained on ~30,000 lung cancer patients to help exclude non-tumor related mutations
- Mutant allele frequency (AF) < 0.01% detectable

SNVs

AKT1	*ALK*	***APC***	*ATM*	*BRAF*
CTNNB1	*EGFR*	*ERBB2*	*ESR1*	*GATA3*
KIT	***KRAS***	*MET*	***MYC***	*NRAS*
PIK3CA	*PTEN*	***STK11***	*TERT*	***TP53***

Bolded genes indicate genes with complete exon coverage.

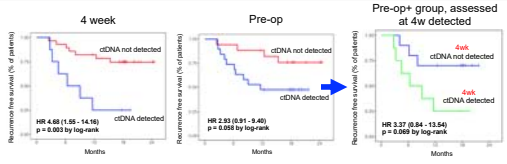
Indels

APC	*ATM*	*EGFR*	*ERBB2*
MET	*PTEN*	*STK11*	*TP53*

Fusions

ALK

ctDNA Detection at 4 Weeks Identifies High-risk Pts

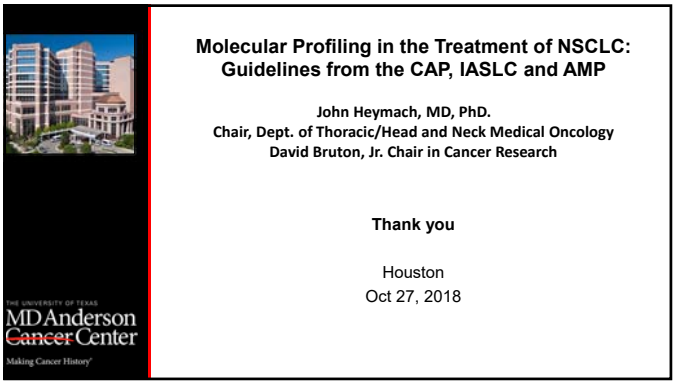


75% PPV / 75% NPV 53% PPV / 77% NPV

- **4 week ctDNA detection has high accuracy for recurrence**
- **4 week ctDNA detection associated with worse RFS in multivariate model** accounting for stage, histology, neoadjuvant/adjuvant treatment (p = 0.01)

The Bottom Line: Recommendations for Molecular Profiling

- The landscape is quickly evolving with a growing number of new targeted agents for genomically defined subgroups, and methods for profiling.
  - **Absolute minimum: EGFR, ALK, ROS1 for all adenocarcinoma patients**
  - HER2, MET, BRAF, KRAS, and RET should be included for laboratories that perform NGS
  - Multigene profiling preferred over single tests
  - IHC ok for ALK, not for EGFR
- **cfDNA assays** to "rule in" targetable mutations when tissue limited/hard to obtain. In future, may be used for TMB or risk
- **Proper profiling is critical for optimum management**



Molecular Profiling in the Treatment of NSCLC: Guidelines from the CAP, IASLC and AMP

John Heymach, MD, PhD.
Chair, Dept. of Thoracic/Head and Neck Medical Oncology
David Bruton, Jr. Chair in Cancer Research

Thank you

Houston
Oct 27, 2018

EGFR Inhibitors: Perspective on Molecular Markers and Patient Selection

Don L. Gibbons, MD, PhD

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

EGFR Inhibitors: Perspective on Molecular Markers and Patient Selection

October 27, 2018

Don L. Gibbons, MD, PhD

Director, Translational Genetic Models Laboratory,
Dept. of Thoracic/Head & Neck Medical Oncology,
Dept. of Molecular and Cellular Oncology,
MD Anderson Cancer Center, Houston, TX

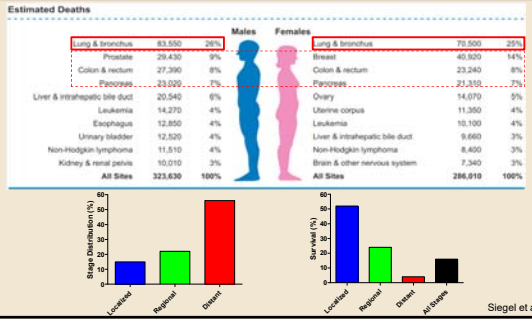
Conflict of Interest Disclosure

Advisory Board: Janssen R&D and Sanofi.
Research Funding: Janssen R&D and AstraZeneca.

Agenda

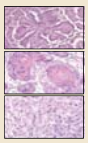
- Evolution of thinking about lung cancer heterogeneity & targetable drivers, e.g. mEGFR
- Current first-line drugs and the evolving usage based on common resistance mechanisms
- The potential for & cautions of TKI combinations
- New advances in TKI unresponsive EGFR mutations

Lung Cancer has High Disease Burden and Mortality



Siegel et al, 2018

Traditional View of Lung Cancer Circa 2000



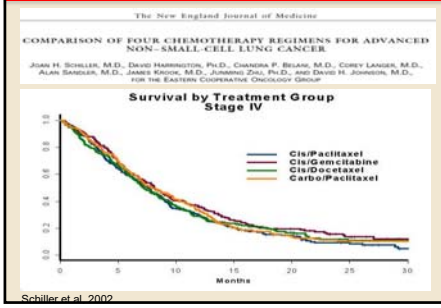
Adenocarcinoma
Squamous cell carcinoma
Large cell carcinoma

→ Non-small cell lung cancer → Platinum doublet (carbo/taxol/taxotere/ gemcitabine)

Small cell carcinoma

→ Small cell lung cancer → Platinum doublet (cis/etoposide)

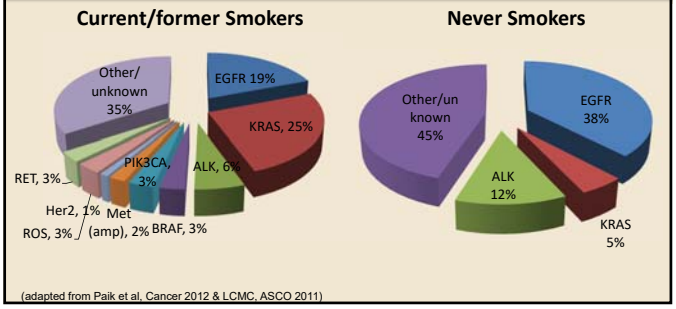
Similar Response Rates Among Frontline Chemotherapy – *No breakout winner*



Schiller et al, 2002

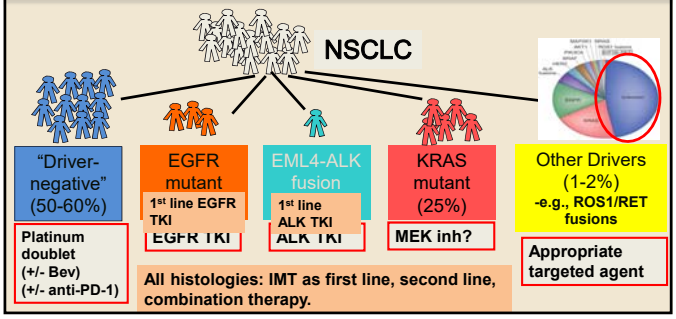
- All randomized studies had similar results
- Treatment selected based on side effect profile

An Epidemic with Many Faces: The Heterogeneity of Driver Mutations in NSCLC



(adapted from Paik et al, Cancer 2012 & LCMC, ASCO 2011)

Rapidly Evolving View of NSCLC Treatment, Based on Molecularly-defined Subsets



Targeting Mutant Oncoproteins: EGFR Signaling & Therapeutic Inhibition

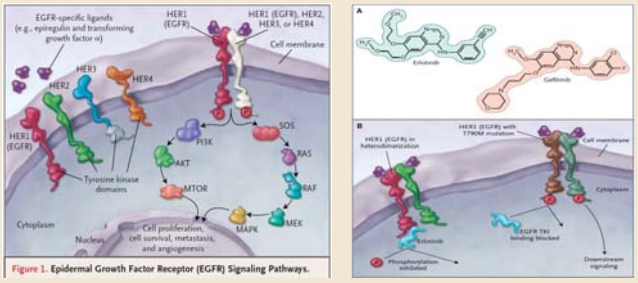
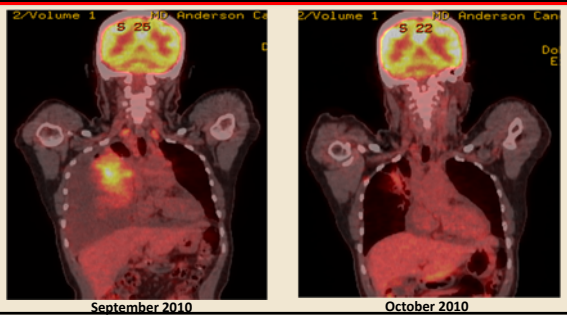


Figure 1. Epidermal Growth Factor Receptor (EGFR) Signaling Pathways.

Cataldo, Gibbons, Perez-Soler, Quintas, *NEJM*, 2010.

EGFR Inhibitors Demonstrate that Mutations Confer Profound Sensitivity



September 2010 October 2010

EGFR Mutations are Not All Equal

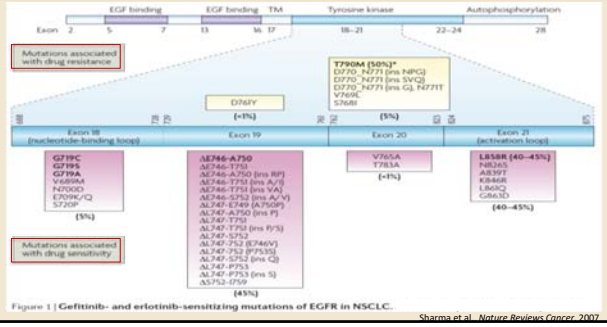


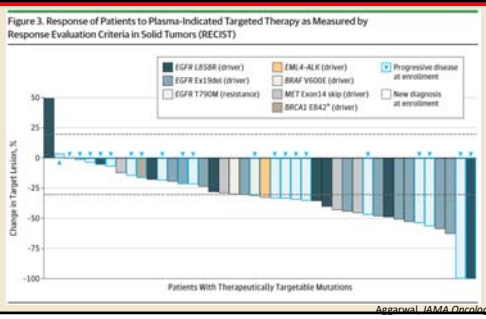
Figure 1 | Gefitinib- and erlotinib-sensitizing mutations of EGFR in NSCLC.

Sharma et al., *Nature Reviews Cancer*, 2007

Blood & Tissue Mutation Testing

- When possible, obtain a tissue biopsy for testing (or re-biopsy at progression)
- Cobas EGFR mutation test v2, FDA approved 6/1/16
- First approved blood-based genetic test for EGFR mutations
- Assays for 42 mutations in exons 18-21
- Blood-based testing with multiple assays is being increasingly used
  - NGS for multigene panels with Guardant 360 and Foundation One Liquid
  - Other tests use ddPCR or BEAMing techniques

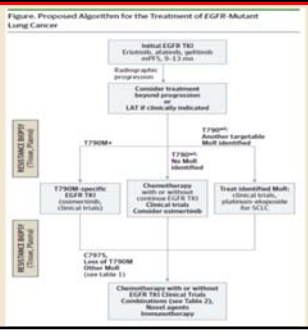
Prospective Clinical Use of Serum ctDNA Testing



show stats and outcomes

Aggarwal, *JAMA Oncology*, 2018

Sequential Treatment Strategy for EGFR Mutant NSCLC

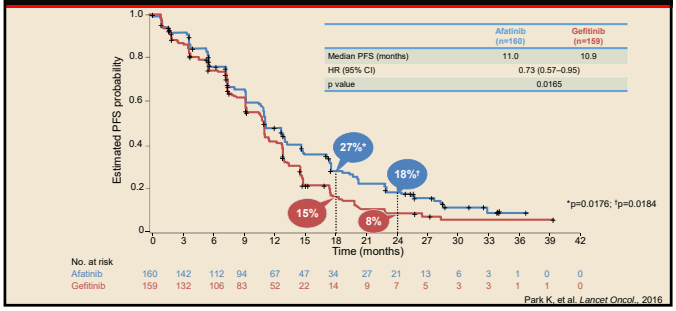


Piotrowska & Sequist, *JAMA Oncology*, 2016

Choice of First-line Therapy

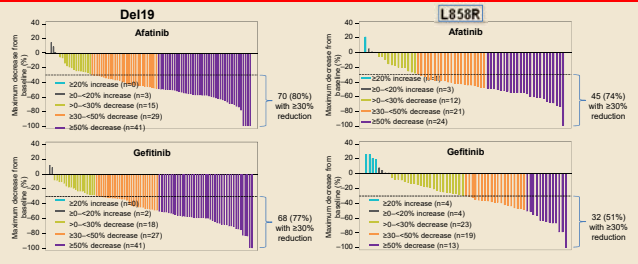
- Erlotinib, gefitinib and afatinib all approved
- Use had been somewhat interchangeable, or dependent upon toxicity profiles, until data from head-to-head comparisons
- And now dacomitinib and **osimertinib** approved in 2018
- Resistance patterns between the 1st, 2nd & 3rd generation TKI's now critical to selection

LUX-Lung 7: PFS by Independent Review



Park K, et al. *Lancet Oncol.*, 2016

LUX-Lung 7: Tumor Shrinkage by Independent Review



*Based on maximum percentage decrease from baseline in the sum of target lesion diameters

Park K, et al. *Lancet Oncol.*, 2016

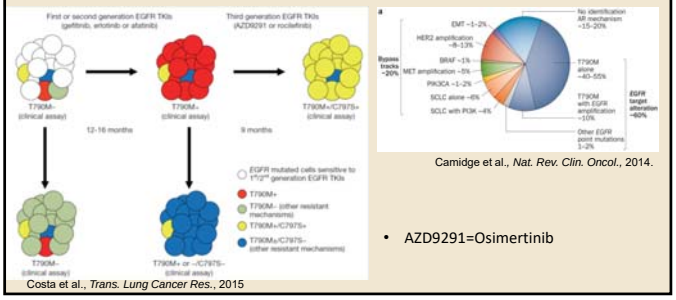
LUX-Lung 7: Drug-related AEs (>10%)

	Afatinib (n=160)			Gefitinib (n=159)		
AE category, n (%)	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Diarrhea	144 (90.0)	19 (11.9)	1 (0.6)	97 (61.0)	2 (1.3)	
Rash/acne*	142 (88.8)	15 (9.4)		129 (81.1)	5 (3.1)	
Stomatitis*	103 (64.4)	7 (4.4)		38 (23.9)		
Paronychia*	89 (55.6)	3 (1.9)		27 (17.0)	1 (0.6)	
Dry skin	52 (32.5)			59 (37.1)		
Pruritus	37 (23.1)			36 (22.6)		
Fatigue*	33 (20.6)	9 (5.6)		23 (14.5)		
Decreased appetite	26 (16.3)	1 (0.6)		19 (11.9)		
Nausea	26 (16.3)	2 (1.3)		22 (13.8)		
Alopecia	17 (10.6)			24 (15.1)		
Vomiting	17 (10.6)			6 (3.8)	1 (0.6)	
ALT increased	15 (9.4)			38 (23.9)	12 (7.5)	1 (0.6)
AST increased	10 (6.3)			33 (20.8)	4 (2.5)	

- There were four cases of ILD with gefitinib (three were grade ≥3) and no cases of ILD with afatinib

*Grouped terms of Aes. Park K, et al. *Lancet Oncol.*, 2016

Mechanisms of Resistance to 1st & 2nd-generation EGFR Tyrosine Kinase Inhibitors

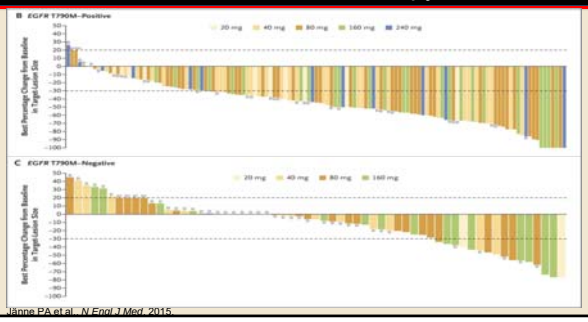


Costa et al., *Trans. Lung Cancer Res.*, 2015

Camidge et al., *Nat. Rev. Clin. Oncol.*, 2014.

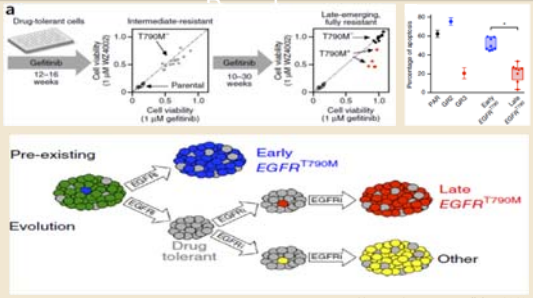
- AZD9291=Osimertinib

Osimertinib (AZD9291) Treatment After Resistance to Front-line TKI Therapy



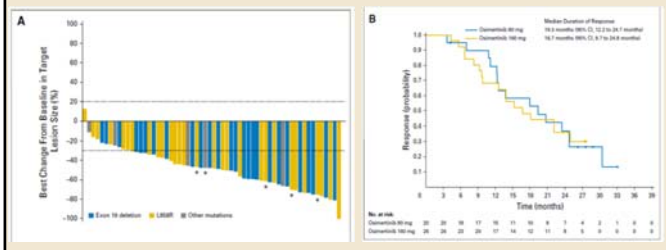
Jänne PA et al., *N Engl J Med*, 2015.

Observed Patterns & Mechanisms of Resistance have Shifted Choice of Front-line TKI Therapy



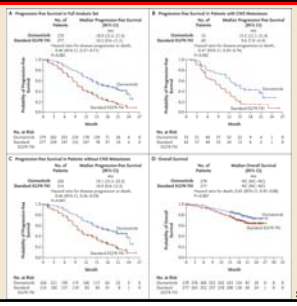
Hata et al., *Nature Medicine*, 2016.

Front-line Use of Osimertinib from Phase I/II AURA Trial



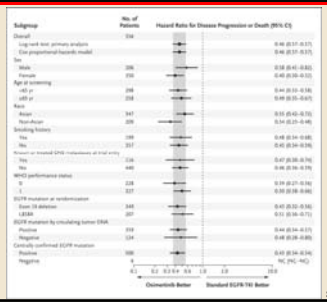
Ramalingan et al., *JCO*, 2017.

PFS and OS for Front-line Use of Osimertinib from Phase III Randomized FLAURA Trial



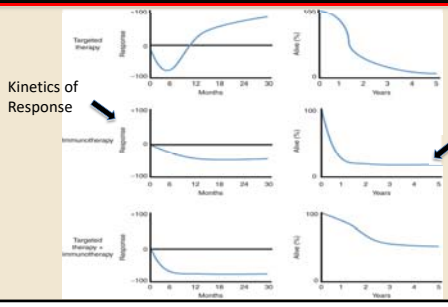
Soria J-C et al., *N Engl J Med*, 2018.

Subgroup and PFS for Front-line Use of Osimertinib from Phase III FLAURA Trial



Soria J-C et al., *N Engl J Med*, 2018.

Using Immunotherapy to Combat TKI Resistance & Bend the Survival Curve

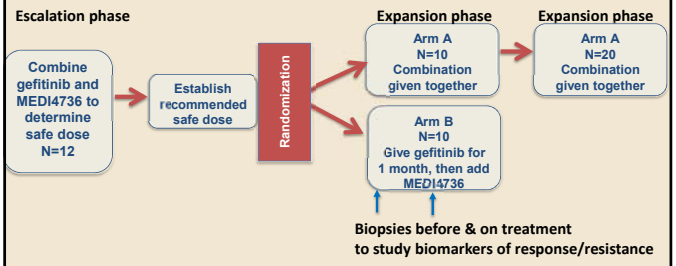


Wargo et al., *Cancer Discovery*, 2014.

Trials with EGFR TKI-IMT Combination

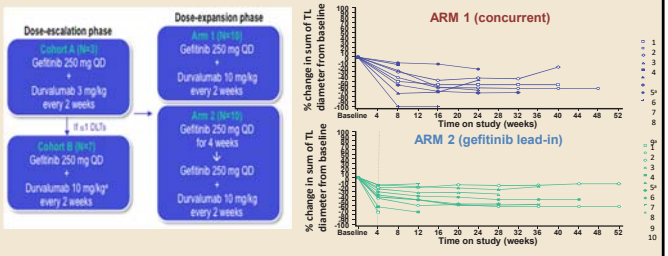
- **Keynote 021: cohort E, F (+erlotinib, gefitinib), first line**
- **Pembrolizumab + afatinib (UC Davis), erlotinib failure**
- **Nivolumab + erlotinib or Crizotinib (U Utah), 1st line**
- **Atezolizumab + erlotinib or Alectinib, 2nd line, phase I/2**
- **TATTON: Osimertinib+Durvalumab, 1st, 2nd line: Halted**
- **CAURAL : phase III, (Osi+Durva vs Osi) : Halted**
- **Rociletinib + atezolizumab (UCLA), 2nd line : discontinued**
- **Gefitinib + durvalumab (MDACC & multisite) : finished accrual, data maturing**

Combination Therapy Strategies: Gefitinib & Durvalumab (Anti-PD-L1)



NCT02088112: 3 US sites (MDACC, Moffitt CC, Univ. of Wash.), 2 in Korea, and Japan.

Phase 1 Dose-expansion of Gefitinib and Durvalumab (MEDI4736): Design and Changes in Tumor Lesions



Gibbons, ELCC, 2016

Dose-expansion Phase: Overall Tolerability (Safety Analysis Set)

Patients experiencing an event[a]	Arm 1 N=10 (%)	Arm 2 N=10 (%)	Total N=20 (%)
Treatment-related AE	10 (100)	10 (100)	20 (100)
All-cause CTC Grade 3–4 AE	5 (50)	7 (70)	12 (60)
ALT increased	3 (30)	5 (50)	8 (40)
Aplastic anemia	0	1 (10)	1 (5)
AST increased	0	3 (30)	3 (15)
Bone pain	1 (10)	0	1 (5)
Diarrhoea	0	1 (10)	1 (5)
Dry skin	1 (10)	0	1 (5)
Hyperglycaemia	1 (10)	0	1 (5)
Hyponatraemia	1 (10)	0	1 (5)
Pneumonitis	0	1 (10)	1 (5)
Urinary tract infection	1 (10)	0	1 (5)
Treatment-related CTC Grade 3–4 AE	4 (40)	7 (70)	11 (55)
All-cause serious AE	2 (20)	2 (20)	4 (20)
Treatment-related AE → discontinuation	0	4 (40)	4 (20)

ALT, alanine aminotransferase; AST, aspartate aminotransferase
[a]Patients may have experienced >1 AE. [b]occurring in over half (>5) of patients in each Arm
Arm 1: gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks
Arm 2: gefitinib 250 mg QD monotherapy for 4 weeks followed by gefitinib 250 mg QD plus durvalumab 10 mg/kg every 2 weeks

[b]Most common treatment-related AEs:

–Arm 1
- Diarrhoea (n=8), ALT increased (n=7), rash (n=6)

–Arm 2
- Diarrhoea (n=6), ALT increased (n=6), pruritis (n=6)

–Treatment-related AEs leading to discontinuation:

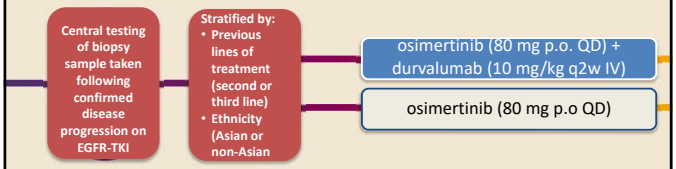
•Arm 2 only
- Increased ALT and / or AST (n=3), pneumonitis (n=1)

Data as of 15 Sept 2015

Gibbons, ELCC, 2016

CAURAL Study Design

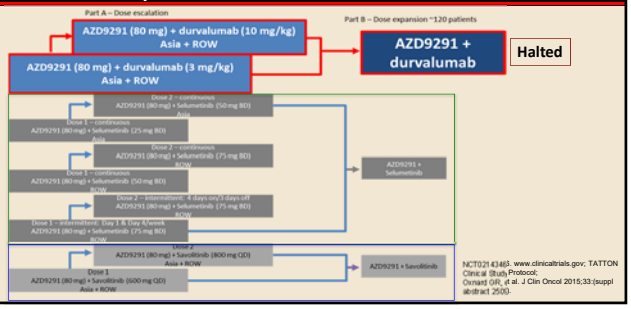
Phase III trial: Sample size of ~350 patients (≥ second line) with advanced *EGFR*m T790M NSCLC who have received a prior EGFR-TKI



- **Approximately 350 patients, consisting of 2 populations will be evaluated:**
1. **Second line: Patients who have progressed following an approved first-line EGFR-TKI who have not received further treatment**
2. **Third line or higher: Patients who have progressed following prior therapy with an approved EGFR-TKI and an additional anti-cancer treatment. Patients may also have received additional lines of treatment**

NCT02454933 www.clinicaltrials.gov.

TATTON: Multi-arm Phase IB Trial in Patients with Acquired Resistance to EGFR TKI



NCT02143613. www.clinicaltrials.gov; TATTON Clinical Study Protocol; Oxnard GR, et al. J Clin Oncol 2015;33:(suppl abstract 2500.

Increased ILD with Osimertinib and Durvalumab Combination

Part A	6/23 (26%)
Dose 1: Osimertinib 80 mg QD / durvalumab 3 mg/kg Q2W	2/10 (20%)
Dose 2: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	4/13 (31%)
Part B: Osimertinib 80 mg QD / durvalumab 10 mg/kg Q2W	7*/11 (64%)
Part A and Part B	13/34 (38%; 95% CI 18, 52)[1]

[1]5 events were Grade 3/4 and there were no fatalities; most cases were managed using steroids

Osimertinib monotherapy (entire clinical programme, Phase I and II)	35/1207 (2.9%)
Durvalumab monotherapy	23/1149 (2.0%)

*One patient reported ILD following 13 Nov 2015 data cut-off
TATTON Population: safety analysis set; data cut-off: 13 Nov 2015

Ahn, ELCC, 2016

EGFR Mutations are Not All Equal

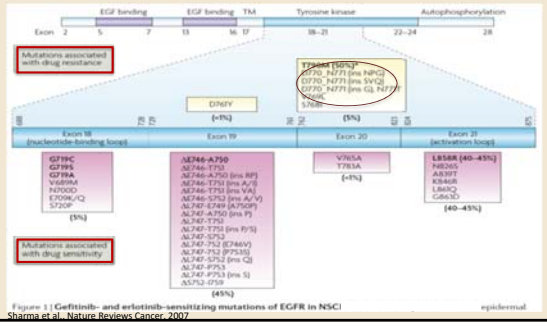
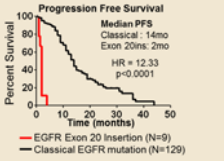


Figure 1 | Gefitinib- and erlotinib-sensitizing mutations of EGFR in NSCI

Sharma et al., Nature Reviews Cancer, 2007

Patients with EGFR or HER2 exon 20 NSCLC have poor response rates to approved TKIs

	N	PR	ORR
EGFR exon 20			
Gefitinib/erlotinib	26	0	0%
Gefitinib/erlo* (with 763FQEA)	28	2*	7%
Afatinib	9	1	11%
Total for EGFR TKIs	**37**	**3**	**8% (w/ 763insFQEA)**
Luminespib (AUY922)	29	5	17%
HER2 exon 20			
Neratinib	11	0	0%
Afatinib	11	2	18%
Afatinib	6	2	33%
Dacomitinib	26	3	11.5%
Lapatinib	5	0	0%
Total for HER2 TKIs	**59**	**7**	**11.9%**
TDM-1	12	6	50%

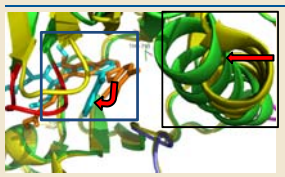


Non-targeted standard 2L therapies	ORR%
Docetaxel	9-13%
PD-1/PD-L1 inhibitors	3.6-19%

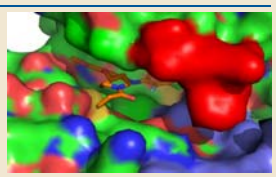
*both responders were known 763insFQEA. Robichaux et al 2018 Nat Med; Piotrowska JTOsupp 12:1152, 2017; Kris et al, Ann Oncol 2015; Li et al, JCO 2018; Mazieres et al, Ann Oncol 2015; Peters et al, JTO 2018; Hyman et al, Nature 2018; Gainor CCR 2016; Borghaei NEJM 2015; Hanna JCO 2004; Herbst Lancet 2016; Rittmeyer Lancet 2017

JV Heymach, WCLC, 2018.

Ex20 Insertions have a Sterically Hindered Binding Pocket



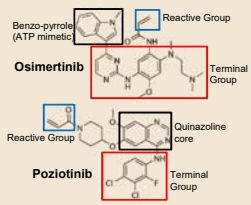
Yellow: EGFR T790M
Green: EGFR D770insSVD
Red: p-loop shift

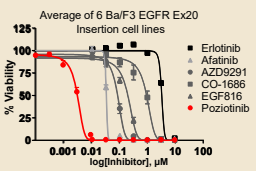


Green: EGFR D770insSVD
Red: Steric hindrance induced by insertion

Robichaux et al, *Nature Medicine*, 2018

Steric Hindrance of Ex20 Insertions can be Overcome by Poziotinib





Poziotinib average IC_{50}: 1.09nM
100X more potent than osimertinib

Robichaux et al, *Nature Medicine*, 2018

Patient characteristics from the Phase II trial of Poziotinib

	EGFR cohort	HER2 cohort
Characteristic	**Total (n=50)**	**Total (n=13)**
Female/Male n(%)	30 (60%) / 20 (40%)	11 (85%) / 2 (15%)
Median age (range)	62 (29-77)	60 (54-64)
Brain metastases	14 (28%)	4 (31%)
Mutation type		
Exon 20 insertion n (%)	46 (92%)	13 (100%)
Exon 20 point mutation	4 (8%)	0 (0%)
Prior systemic therapy		
Naïve	3 (6%)	2 (15%)
1 prior	13 (26%)	6 (46%)
2 prior	17 (34%)	2 (15%)
3 prior	11 (22%)	1 (8%)
≥4 prior	6 (12%)	2 (15%)
Prior platinum n (%)	43 (86%)	10 (77%)
Prior TKI n (%)	17 (34%)	2 (15%)
Prior PD1/PDL1 inhibitor n (%)	27 (54%)	8 (62%)

JV Heymach, WCLC, 2018

Safety Summary from the Phase II trial of Poziotinib

	(N=63)
All Cause AE N(%)	**N (%)**
Grade 3-4	50 (79%)
Grade 5	12 (19%)
Treatment related AEs N (%)	
Grade 3-4	35 (56%)
Grade 5*	1 (1.5%)
AE leading to treatment dose reduction N (%)	38 (60%)
AE leading to treatment discontinuation N (%)	**2 (3%)**

Afatinib (Lux-Lung 3): 52% dose reduction, 8% discontinuation

Dacomitinib (Archer1050): 67% dose reduction, 10% discontinuation

* 59 YOF with 3 prior lines of treatment presented with dyspnea and PD; ddx included lymphangitic spread, infection, vs pneumonitis. It was refractory to steroids and antibiotics. Outside treating physician attributed it as "possibly related" to drug vs PD. Sequist et al, JCO 2013; Wu et al, Lancet Oncol 2017

JV Heymach, WCLC, 2018

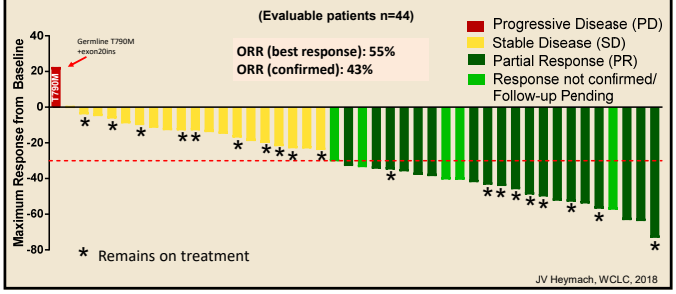
Patient characteristics from the Phase II trial of Poziotinib

Treatment related AEs in >10% of patients (N=63)

AE	All Grade N (%)	Grade 3-4 N(%)	Grade 5 N(%)
Diarrhea	44 (69.8%)	11 (17.5%)	-
Oral mucositis	44 (69.8%)	1 (1.6%)	-
Paronychia	38 (60.3%)	6 (9.5%)	-
Dry skin	37 (58.7%)	-	-
Skin rash	35 (55.6%)	22 (34.9%)	-
Alopecia	22 (34.9%)	-	-
Anorexia	19 (30.2%)	-	-
Nausea	15 (23.8%)	5 (7.9%)	-
Vomiting	13 (20.6%)	3 (4.8%)	-
Pruritus	9 (14.3%)	-	-
Weight loss	8 (12.7%)	3 (4.8%)	-
Weight loss	8 (12.7%)	3 (4.8%)	-
Fatigue	7 (11.1%)	3 (4.8%)	-
Hypokalemia	5 (7.9%)	2 (3.2%)	-

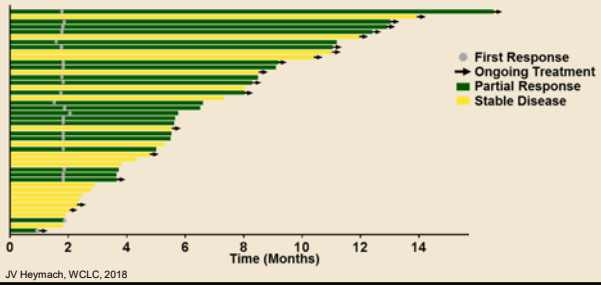
JV Heymach, WCLC, 2018

Poziotinib efficacy in EGFR Exon 20 mutant NSCLC



JV Heymach, WCLC, 2018

Duration of treatment on the Phase II trial of Poziotinib



JV Heymach, WCLC, 2018

Take Home Points…

- **Even after 15 years this is a continuously changing space diagnostically & therapeutically**
- **Resistance is still the biggest problem, but sequential testing & therapies make this more manageable**
- **EGFR TKI-based combinations may be a better option in some cases, but can have unexpected side effects.**
- **New treatment options are emerging for mutational types not sensitive to prior TKIs**

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MD Anderson Cancer Center
Making Cancer History®

Thank you

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Director, Translational Genetic Models Laboratory, Department of Thoracic/Head & Neck Medical Oncology, Department of Molecular and Cellular Oncology,
MD Anderson Cancer Center, Houston, TX

Emerging Strategies and Challenges Due to Secondary or Acquired EGFR-TKI Resistance

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October 27, 2018

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MD Anderson Cancer Center, Houston, TX

Conflict of Interest Disclosure

Advisory Board: Janssen R&D and AstraZeneca.
Research Funding: Janssen R&D and AstraZeneca.

Agenda

- Treating the common resistance mechanisms
  - First-line: T790M +/-, etc.
  - T790M: C797S
- How the face of resistance is changing due to changing first-line drugs
- Development of new combinations

EGFR Displays a Range of Activating Mutations

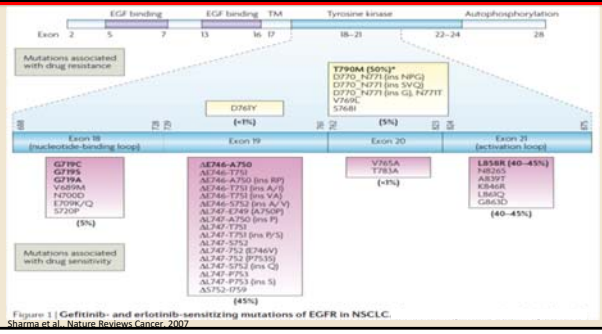


Figure 1 | **Gefitinib- and erlotinib-sensitizing mutations of EGFR in NSCLC.**
Sharma et al., Nature Reviews Cancer, 2007

Targeting Mutant Oncoproteins: EGFR Signaling & Therapeutic Inhibition

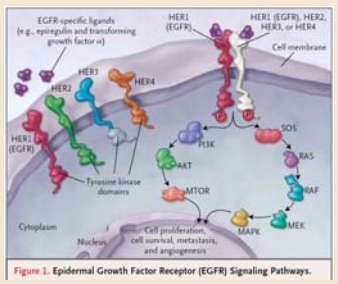
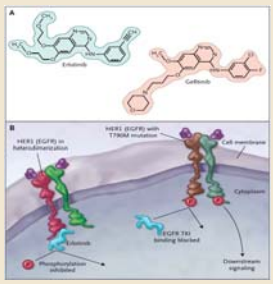
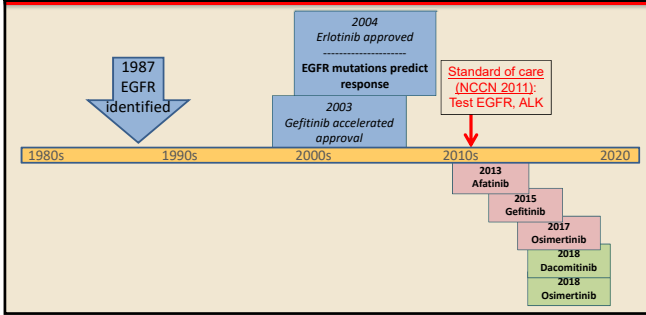


Figure 1. **Epidermal Growth Factor Receptor (EGFR) Signaling Pathways.**

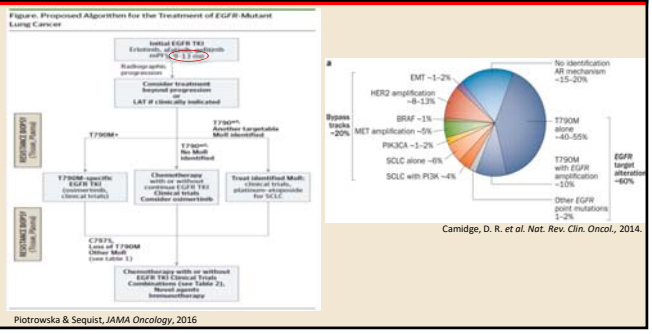


Cataldo, Gibbons, Perez-Soler, Quintas, NEJM, 2010.

EGFR Targeted Therapy for NSCLC: 1987-2018



Sequential Treatment Strategy for EGFR Mutant NSCLC



Camidge, D. R. *et al. Nat. Rev. Clin. Oncol.*, 2014.

Piotrowska & Sequist, *JAMA Oncology*, 2016

Mechanisms of Resistance to EGFR Tyrosine Kinase Inhibitors

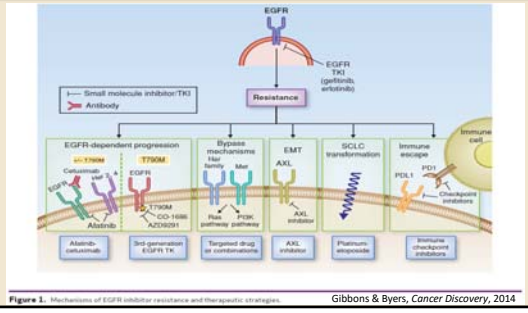
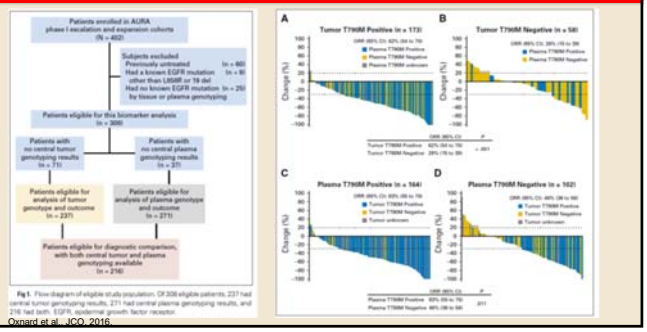


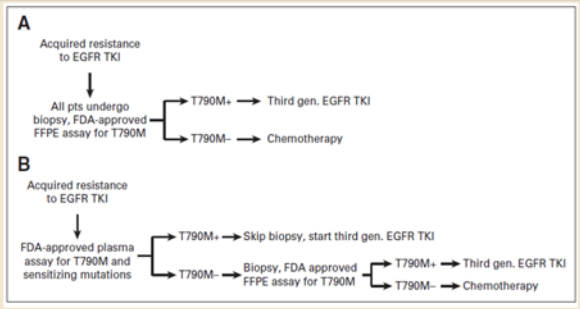
Figure 1. Mechanisms of EGFR inhibitor resistance and therapeutic strategies. Gibbons & Byers, *Cancer Discovery*, 2014

cfDNA vs. Tumor Mutation Analyses from AURA trial



Oxnard et al., JCO, 2016

Proposed Testing Schema Based on cfDNA Analyses from AURA Trial



Oxnard et al., JCO, 2016

Mechanisms of Resistance to EGFR Tyrosine Kinase Inhibitors

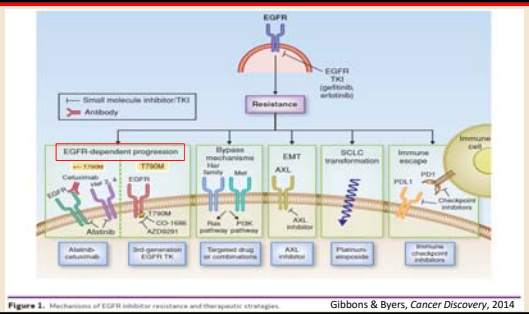
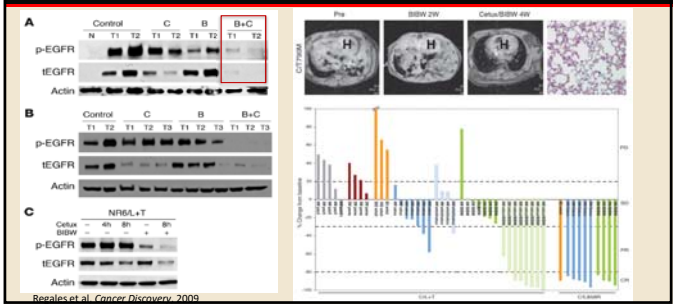


Figure 1. Mechanisms of EGFR inhibitor resistance and therapeutic strategies. Gibbons & Byers, *Cancer Discovery*, 2014

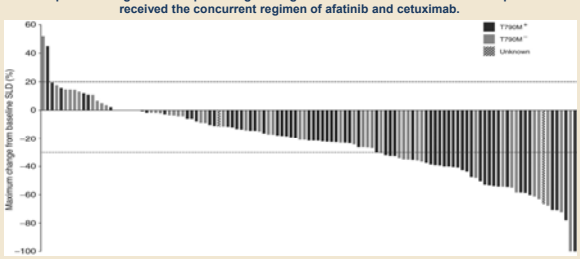
Efficacy of Afatinib (BIBW2992) and Cetuximab in Pre-Clinical Models



Regales et al. *Cancer Discovery*, 2009

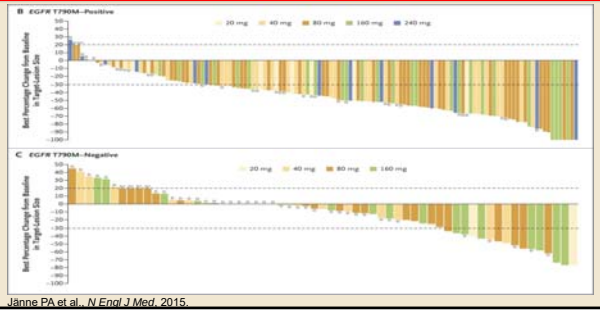
Clinical Efficacy: Combination Treatment After Resistance to 1st Generation TKI

Waterfall plot showing maximum percentage change from baseline in size of tumors in patients who received the concurrent regimen of afatinib and cetuximab.



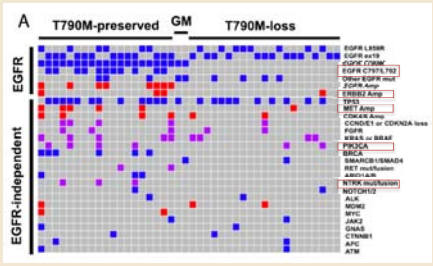
Janjigian et al., *Cancer Discovery*, 2014.

Osimertinib (AZD9291) Treatment after Resistance to 1st Generation TKI Therapy



Jänne PA et al., *N Engl J Med*, 2015.

Mechanisms of 2nd-line Osimertinib Treatment Resistance



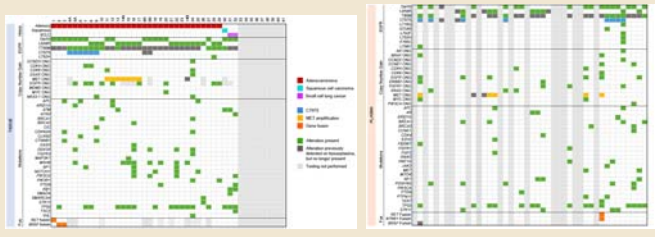
Le et al., *CCR*, 2018

Mechanisms of Early Treatment Resistance to 2nd-line Osimertinib, with T790M Loss

New targetable gene fusions identified

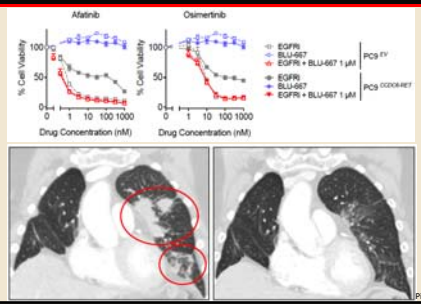
Oxnard et al., *JAMA Oncology*, 2018

Mechanisms of 2nd-line Osimertinib Treatment Resistance: Tissue vs. Plasma Findings



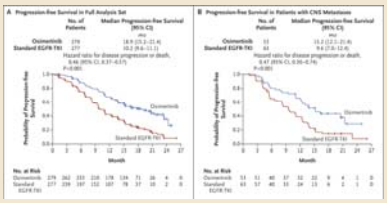
Piotrowska et al., *Cancer Discovery*, 2018

Combination Osimertinib and BLU-667 Treatment Overcomes Resistance Due to RET Fusion



Piotrowska et al., *Cancer Disc.*, 2018

Resistance to Front-line Use of Osimertinib in Phase III FLAURA Trial: Paired plasma analyses

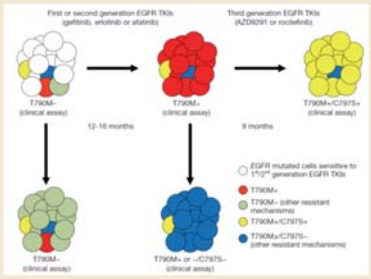


Osimertinib	Standard TKI
MET amp (15%)	MET amp (4%)
C797S (7%)	--
HER2 amp (2%)	HER2 amp (2%)
PIK3CA mtn (7%)	PIK3CA mtn (3%)
KRAS mtn (3%)	KRAS mtn (1%)
T790M (0%)	T790M (47%)

Soria et al., *N Engl J Med*, 2018.

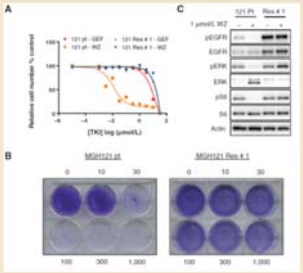
Ramalingam, ESMO, 2018.

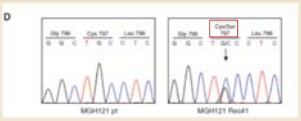
Mechanisms of Resistance to Third Generation EGFR Inhibitors



Costa et al., *Trans. Lung Cancer Res.*, 2015.

Acquired Resistance in T790M Tumor Due to Secondary C797S Mutation

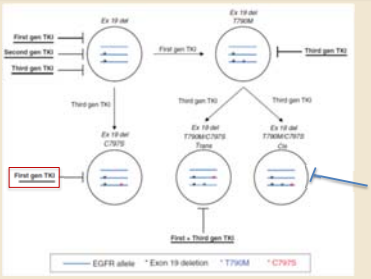




- C797 forms a covalent bond with all third-generation EGFR TKIs
- Acquisition of C797S can be on the same EGFR allele as T790M (cis) or on the other allele of EGFR (trans)

Niederst et al., *CCR*, 2015.

Sensitivity of C797S Mutations to Other TKIs Depends on T790M Context

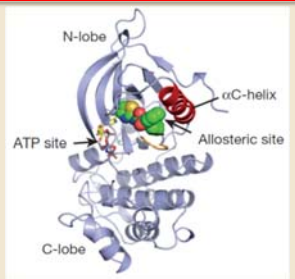


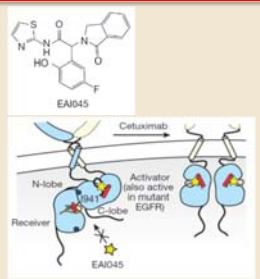
Treatment options:

1. **Allosteric inhibitors, e.g. EAI045, combined with cetuximab**
2. **Brigatinib alone or with combinations**

Niederst et al., *CCR*, 2015.

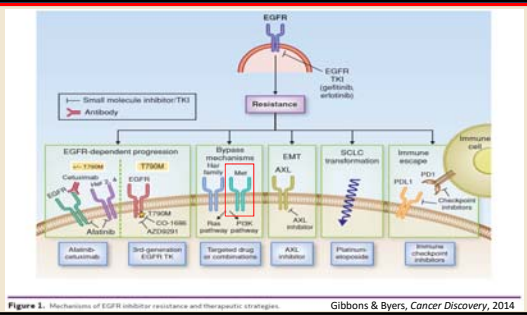
Unique Mechanism of Allosteric Inhibitor Against T790M/C797S Mutant EGFR





Jia et al., *Nature*, 2016.

Mechanisms of Resistance to EGFR Tyrosine Kinase Inhibitors

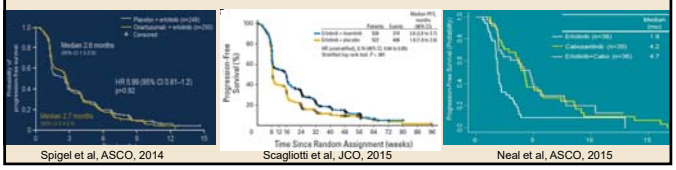


Gibbons & Byers, *Cancer Discovery*, 2014

Targeting MET Bypass as a Mechanism of EGFR inhibitor resistance

Co-targeting EGFR & MET has been disappointing

- **Erlotinib +/- METmab**
- **Erlotinib +/- tivantinib**
- **Cabozantinib +/- erlotinib**



Spigel et al, ASCO, 2014 | Scagliotti et al, JCO, 2015 | Neal et al, ASCO, 2015

Ongoing Trials to Target Bypass Pathways

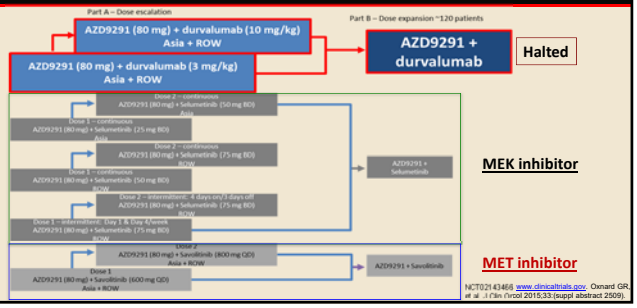
- **9 combination trials of MET & EGFR kinase inhibitors underway**
- **Most in EGFR-mutant disease with acquired resistance**

	Gefitinib	Erlotinib	Dacomitinib	Osimertinib	EGF816
Crizotinib		Phase 1 NCT00965731	Phase 1 NCT01121575		
Cabozantinib		Phase 2 NCT01866410			
Savolitinib	Phase 1b NCT02374645			Phase 1b/2 NCT02143466	
INC280	Phase 1b/2 NCT01610336	Phase 1b/2R NCT0268661			Phase 1b/2 NCT02335944
MSC2156119J	Phase 1b/2R NCT01982955				

2R = randomized phase II

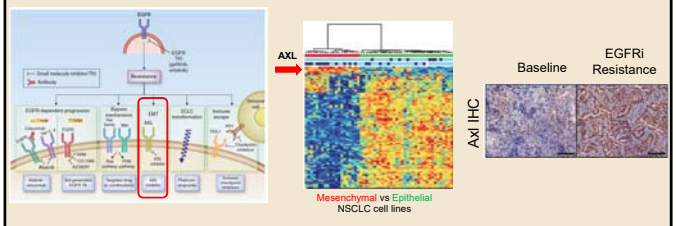
Clinicaltrials.gov

TATTON: Multi-arm Phase IB Trial in Patients with Acquired Resistance to EGFR TKI



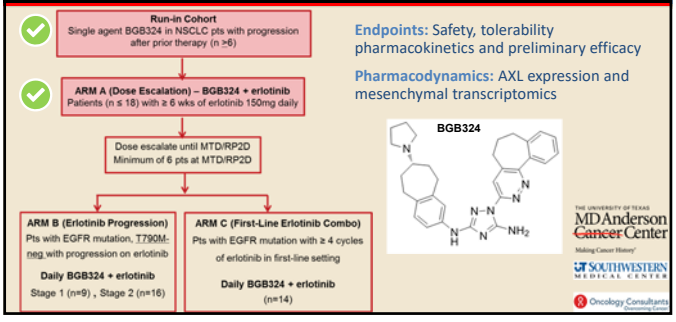
NCT02143466 www.clinicaltrials.gov. Oxnard GR, et al. J Clin Oncol 2015;33:(suppl abstract 2509).

Mechanisms of Resistance to EGFR Tyrosine Kinase Inhibitors



Gibbons and Byers, Cancer Discovery 2014
Byers et al, CCR 2013
Bivona et al., Nature Genetics 2012

A Phase I/II Study of BGB324 in Combination with Erlotinib in Stage IIIb/IV NSCLC



Phase Ib: BGB324 monotherapy & erlotinib combination benefit

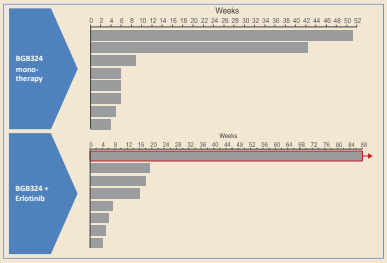
Overview

Monotherapy: 1 year PFS in 25% patients

- Two patients treated for approximately 12 months
  - 1 minor response
  - 1 stable disease
- Very well tolerated, patients discontinued due to disease progression
- Recommended Phase II Dose

Combination therapy: 50% CBR

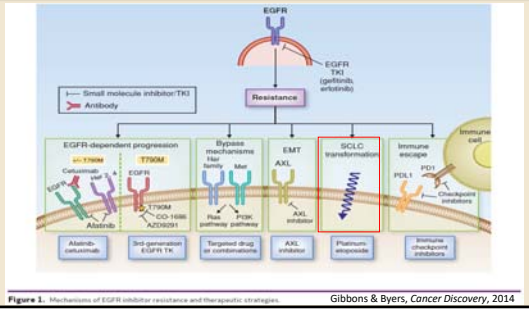
- 3 SD > 4 months
- 1 stable disease
- One patient ongoing > 18 months
- Very well tolerated
- Recommended Phase II Dose



SD= Stable Disease according to RECIST1-1

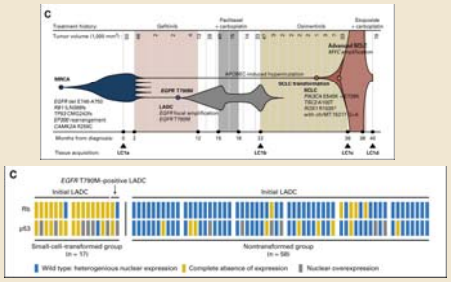
Gibbons & Byers et al, WCLC, 2017.

Mechanisms of Resistance to EGFR Tyrosine Kinase Inhibitors



Gibbons & Byers, *Cancer Discovery*, 2014

Rb and p53 Inactivation Predispose EGFR Mutant NSCLC to Small Cell Transformation



Lee et al, *JCO*, 2017.

Take Home Points…

- With 2nd and 3rd generation EGFR TKIs, patterns of resistance are evolving & new targetable alterations have been identified
- Serial monitoring/mutation testing is SOC to determine the basis for resistance in each patient
- Testing increasingly incorporates blood-based testing
- Additional new combination and sequential strategies to combat resistance mechanisms are in clinical trials

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Making Cancer History®

Thank you

Don L. Gibbons, MD, PhD
Director, Translational Genetic Models Laboratory, Department of Thoracic/Head & Neck Medical Oncology, Department of Molecular and Cellular Oncology, MD Anderson Cancer Center, Houston, TX

Immunotherapy with PD-1/PD-L1 (Nivolumab, Pembrolizumab, Durvalumab) and Anti CTLA-4 (Ipilimumab) Antibodies in NSCLC

John V. Heymach, MD

MD Anderson Cancer Center
Making Cancer History®

Immunotherapy with PD-1/PD-L1 (Nivolumab, Pembrolizumab, Durvalumab) and Anti-CTLA-4 (Ipilimumab) Antibodies in NSCLC

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Houston, TX

Changing Treatment Paradigms with Immunotherapy and Targeted Therapy in Advanced Non-Small-Cell Lung Cancer and Head & Neck Cancer
Houston
Oct 27, 2018

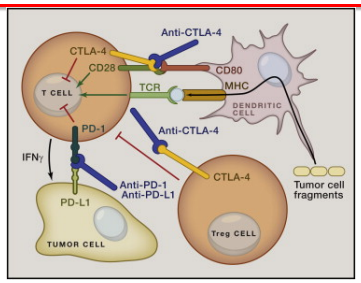
Conflict of Interest Disclosure

Advisory Committees – AstraZeneca, Boehringer Ingelheim, Exelixis, Genentech, GSK, Guardant Health, Hengrui, Lilly, Novartis, Spectrum, EMD Serono, and Synta

Research Support – AstraZeneca, Bayer, GlaxoSmithKline, Spectrum

Royalties and Licensing fees – Spectrum

PD-1 and CTLA-4 Immune Checkpoints



Miller and Sadelain, *Cancer Cell*, 2015

PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors

Michael A. Curran[a], Welby Montalvo[a], Hideo Yagita[b], and James P. Allison[a,1]

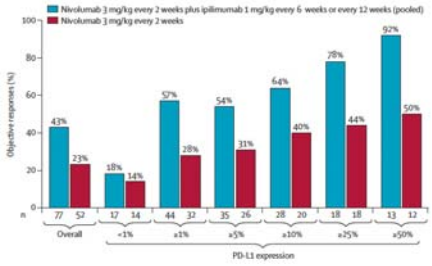
[a]Howard Hughes Medical Institute, Department of Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY 10065; and [b]Department of Immunology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan

Contributed by James P. Allison, January 19, 2010 (sent for review December 17, 2009)

Jim Allison
Nobel Laureate, 2018

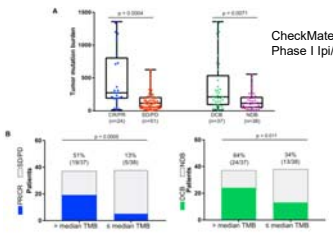
- **Blockade of CTLA-4 promoted rejection of B16 melanoma cells**
- **PD-1 interaction with PD-L1 or PD-L2 blunted T-cell proliferation and cytokine release**
- **The combination of PD-1 and CTLA-4 was more than twice as effective as either alone**
  - **Increased Teff infiltration, increased Teff to Treg ratio in tumor and Teff to MDSC ratios**
  - **Enhanced IFN-gamma/TNF-alpha Tcekss**
  - **Shifted tumor from suppressive to inflammatory**

Objective Response Rates for Nivo and Nivo+Ipi in Untreated NSCLC: Checkmate 12



Hellman et al, Lancet Oncol 2017

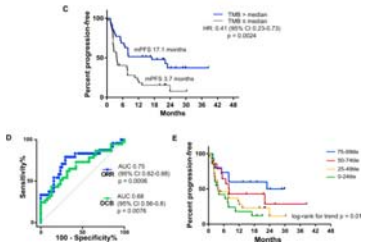
TMB Correlates with Efficacy in ipi/nivo Treated NSCLC



CheckMate-012 study:
Phase I Ipi/nivo in first-line

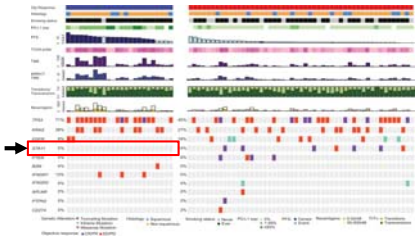
Hellman et al, Cancer Cell, 2018

TMB Correlates with Efficacy in Ipi/Nivo Treated NSCLC



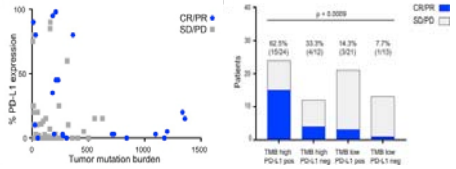
Hellman et al, Cancer Cell, 2018

Clinical and Molecular Features Associated with Response to Ipi/Nivo



Hellman et al, Cancer Cell, 2018

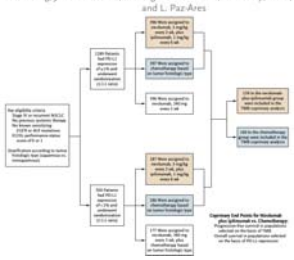
PD-L1 and TMB do not correlate, but TMB-high, PD-L1pos patients do better



Hellman et al, Cancer Cell, 2018

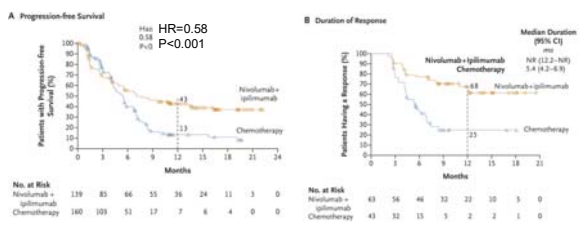
Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden

M.D. Hellmann, T.-E. Ciuleanu, A. Pluzanski, J.S. Lee, G.A. Otterson, C. Audigier-Valette, E. Minenza, H. Linardou, S. Burgers, P. Salman, H. Borghaei, S.S. Ramalingam, J. Brahmer, M. Reck, K.J. O'Byrne, W.J. Geese, G. Green, H. Chang, J. Szustakowski, P. Bhagavatheeswaran, D. Healey, Y. Fu, F. Nathan, and L. Paz-Ares



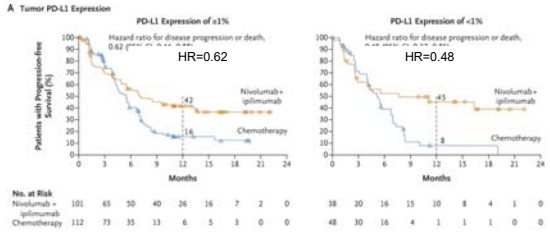
Hellman et al, NEJM 2018

Ipi/nivo Prolongs PFS Compared with Chemo in TMB-high NSCLC



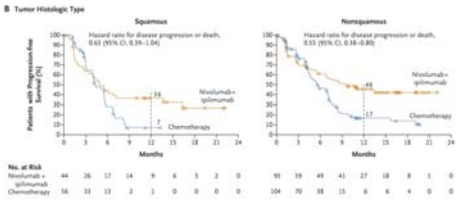
Hellman et al, NEJM, 2018

Ipi/nivo Prolongs PFS Compared with Chemo in TMB-high NSCLC, Regardless of PD-L1 Level



Hellman et al, NEJM, 2018

Ipi/nivo Prolongs PFS Compared with Chemo in TMB-high NSCLC, Regardless of Histology



Bottom Line: Early results indicate TMB-high NSCLC patients do better on ipi/nivo versus chemo

Hellman et al, NEJM, 2018

Checkmate 227: Treatment-related AE in >10%

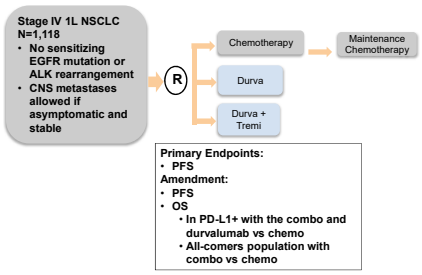
Table 3. Treatment-Related Adverse Events Reported in at Least 10% of Patients Treated with Nivolumab plus Ipilimumab, Nivolumab, or Chemotherapy.*

Event	Nivolumab plus Ipilimumab (N = 574)		Nivolumab (N = 391)		Chemotherapy (N = 570)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)					
Any event	433 (75.2)	180 (31.2)	251 (64.2)	74 (18.9)	460 (80.7)	206 (36.1)
Any serious event	234 (40.6)	180 (31.2)	92 (23.5)	74 (18.9)	73 (12.8)	61 (10.7)
Any event leading to discontinuation†	100 (17.4)	69 (12.0)	45 (11.5)	27 (6.9)	51 (8.9)	28 (4.9)
Rash	96 (16.7)	9 (1.6)	43 (11.0)	3 (0.8)	29 (5.1)	0
Diarrhea	94 (16.3)	9 (1.6)	44 (11.3)	3 (0.8)	55 (9.6)	4 (0.7)
Pruritus	81 (14.1)	3 (0.5)	30 (7.7)	0	5 (0.9)	0
Fatigue	76 (13.2)	8 (1.4)	43 (11.0)	2 (0.5)	105 (18.4)	8 (1.4)
Decreased appetite	71 (12.7)	2 (0.5)	25 (6.4)	0	110 (19.3)	6 (1.1)
Hypothyroidism	67 (11.6)	2 (0.3)	25 (6.4)	1 (0.3)	0	0
Asthenia	56 (9.7)	7 (1.2)	29 (7.4)	2 (0.5)	72 (12.6)	5 (0.9)
Nausea	56 (9.7)	3 (0.5)	21 (5.4)	1 (0.3)	205 (36.0)	12 (2.1)
Vomiting	27 (4.7)	2 (0.3)	10 (2.6)	1 (0.3)	76 (13.3)	13 (2.3)
Constipation	23 (4.0)	0	6 (1.5)	0	86 (15.1)	2 (0.4)
Anemia	23 (4.0)	9 (1.6)	11 (2.8)	2 (0.5)	183 (32.1)	64 (11.2)
Neutrophil count decreased	4 (0.7)	0	0	0	64 (11.2)	36 (6.3)
Neutropenia	1 (0.2)	0	1 (0.3)	0	97 (17.0)	54 (9.5)

Hellman et al, NEJM, 2018

Other Combinations Targeting the PD-1 + CTLA-4 Pathways

MYSTIC: RP3 of Chemo vs Durva vs Durva/tremi



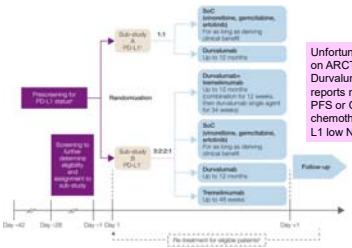
Primary Endpoints:
- PFS

Amendment:
- PFS
- OS
  - In PD-L1+ with the combo and durvalumab vs chemo
  - All-comers population with combo vs chemo

Mystic: Durva/Tremi Fails to Prolong PFS in the >25% PD-L1 Group vs Chemo

- July 27,2017 press release
- Durvalumab plus tremelimumab combination did not meet a primary endpoint of PFS vs chemotherapy
- Secondary endpoint: Durvva monotherapy would not have met a pre-specified threshold of PFS benefit vs chemo
- The MYSTIC trial continues as planned to assess the additional primary endpoints of OS for durvalumab durvalumab plus tremelimumab arms

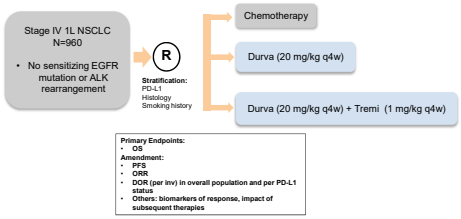
ARCTIC: A Phase III Study of Durvalumab with or without Tremelimumab for Previously Treated NSCLC



Unfortunately press release on ARCTIC trial of Durvalumab-Tremilumumab reports no improvement in PFS or OS over chemotherapy in 3rd line PD-L1 low NSCLC. 2018.

Planchar D Clin Lung Cancer 2016

NEPTUNE: RP3 (open-label) of Durva/tremi vs Chemotherapy



Incorporating PD-1 + CTLA-4 Blockade into Multidisciplinary Care

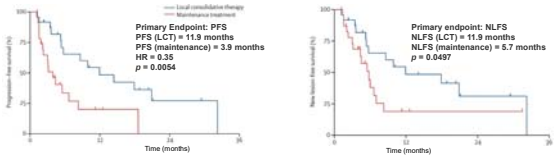
LONESTAR Protocol

Randomized Phase II Trial of Local Consolidation Therapy After Nivolumab and Ipilumumab for immunotherapy-naive Patients with Metastatic Non-small Cell Lung Cancer

PIs: J. Heymach, S. Swisher and D. Gomez
PDOL: 2017-0311

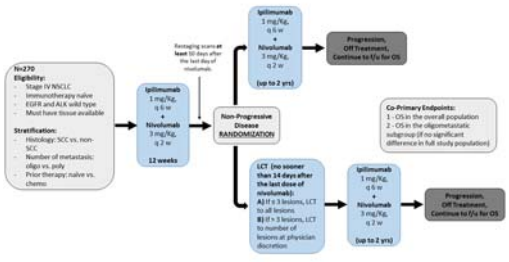
Local Consolidative Therapy (LCT) in Patients with Oligometastatic NSCLC

Local consolidative therapy (LCT) increased the time for tumors to progress and delayed emergence of new metastatic sites



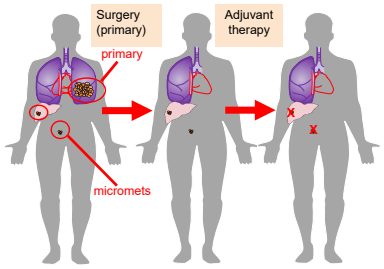
Gomez et al, Lancet Oncology, 2016

LONESTAR: Trial Design

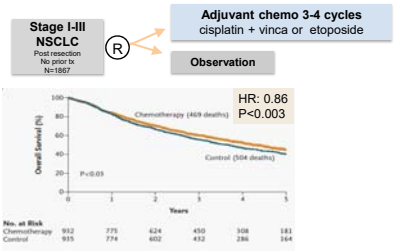


Can PD-1 + CTLA-4 Blockade Increase Cures in Early Stage NSCLC?

The Primary Goal of Adjuvant Treatment is to Eliminate Micrometastatic Disease

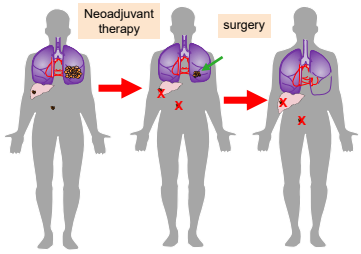


Adjuvant Chemo Prolongs OS and Reduces Likelihood of Recurrence at 5y by ~5%: The IALT Study



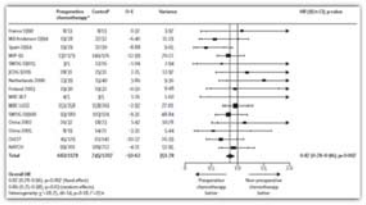
The International Lung Cancer Trial Collaborative (IALT) Group; N Engl J Med, 2004

Neoadjuvant Treatment can "downstage" the Primary Tumor, Potentially Making Surgery Less Morbid, and Enables Analysis of Treated Tumor



How well does neoadjuvant (induction) chemo work? About the same as adjuvant

Meta-analysis- Efficacy



For stage IB-IIIA:

Neoadjuvant: Chemo : HR 0.87 (0.78-0.96)

Adjuv Chemo : HR 0.89 (0.82-0.96)

Burdett et al., Lancet, 383:1561, 2014, Pignon et al., JCO, 26:3552, 2008

Why might PD-1i Impact metastases? Role of PD-L1 in Facilitating Metastatic Spread

nature COMMUNICATIONS

ARTICLE

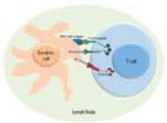
Metastasis is regulated via microRNA-200/ZEB1 axis control of tumour cell PD-L1 expression and intratumoral immunosuppression

Limo Chen[1,2,*], Don L. Gibbons[1,3,*], Sangeeta Goswami[1], Maria Angelica Cortez[1], Young-Ho Ahn[1,4], Lauren A. Byers[1], Xuejun Zhang[5], Xiaohui Yi[5], David Dwyer[6], Wei Lin[1], Livia Diao[7], Jing Wang[8], Jonathon Roybal[1], Mayuri Patel[1], Christin Ungewiss[1], David Peng[1], Scott Antonia[9], Melanie Mediavilla-Varela[9], Gordon Robertson[7], Milind Surakar[1,8], James W. Welsh[8], Baruch Erez[7], Ignacio I. Wistuba[1,8], Lanping Chen[10], Di Peng[11], Shanshan Wang[11], Stephen E. Ullrich[7], John V. Heymach[1], Jonathan M. Kurie[1] & F. Xiao-Feng Qin[1,2,8]

Why neoadjuvant instead of adjuvant?

Take it from Henry V at Agincourt: it is easier to inspire the troops when the enemy is in sight.

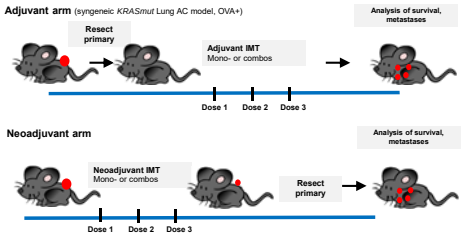
Photo: http://derekwinnert.com/wp-content/uploads/2013/08/2.jpg



-Antitumor immune response to IMT depends at least in part on presence of tumor antigens

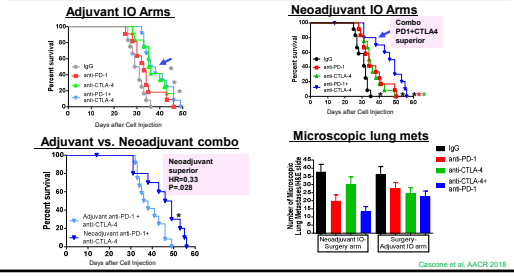
-Tumor and antigen burden highest pre-operatively

Adjuvant Vs Neoadjuvant Immunotherapy in Murine Models of Lung Adenocarcinoma



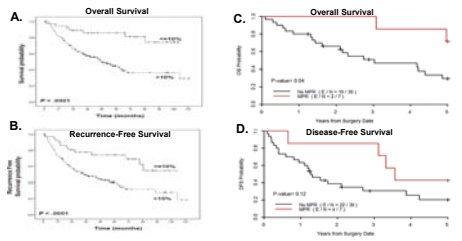
Cascone et al, AACR 2018

Neoadjuvant PD1/CTLA4 Blockade Prolongs Survival and Reduces Mets Compared with Adjuvant Combination Treatment or Monotherapy



Cascone et al, AACR 2018

Is Pathological Response a Suitable Surrogate for Survival After Neoadjuvant Tx?



Pataer et al., *J Thorac Oncol*, 2012; Cascone et al. *Ann Thorac Surg*, 2018

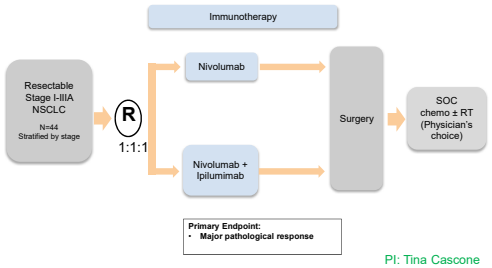
NEOSTAR: NEOADJUVANT NIVOLUMAB (N) OR NIVOLUMAB PLUS IPILIMUMAB (NI) FOR RESECTABLE NON-SMALL CELL LUNG CANCER (NSCLC)

T. Cascone[1], W.N. William Jr.[1], A. Weissferdt[2], C.H. Leung[3], L. Federico[4], C. Haymaker[4], C. Bernatchez[4], F.V. Fossella[1], F.E. Mott[1], V.A. Papadimitrakopoulou[1], L.A. Byers[1], V.K. Lam[1], M.C. Godoy[5], B. Carter[5], J.J. Lee[3], A. Vaporciyan[6], D.L. Gibbons[1], S.G. Swisher[6], J.V. Heymach[1], B. Sepesi[6] and the NEOSTAR investigators

[1]Thoracic/Head & Neck Medical Oncology, [2]Pathology, [3]Biostatisctics, [4]Melanoma Medical Oncology, [5]Diagnostic Radiology, [6]Thoracic & Cardiovascular Surgery, [7]Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX

Other contributors: A. Tsao[1], G. Blumenschein[1], F. Skoulidis[1], A. Reuben[1], J. Zhang[1], A. F. Cruz[7], E. Parra[7], I.I. Wistuba[1,7] and the ICON investigators

Randomized Phase II NEOSTAR: Neoadjuvant Nivolumab or Nivolumab plus Ipilimumab for Resectable NSCLC (MDACC)



PI: Tina Cascone
Co-PI: Boris Sepesi

Major Pathologic Response ≤10% Viable Cells

Evaluable* (Resected)	n=26	N n=14	NI n=12
MPR + pCR	8 (31%)	4 (28%)	4 (33%)
0% viable tumor cells (pCR)	5 (19%)	2 (14%)	3 (25%)
1-10% viable tumor cells	3 (11%)	2 (14%)	1 (8%)

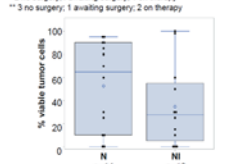
*5 no surgery (2 N, 3 NI)

Overall** Resected + unresectable	n=31	N n=16	NI n=15
MPR + pCR	8 (26%)	4 (25%)	4 (27%)
0% viable tumor cells (pCR)	5 (16%)	2 (13%)	3 (20%)
1-10% viable tumor cells	3 (10%)	2 (13%)	1 (7%)
Path response pending	5**	2	3

**5 pending (2 N, 3 NI)

Evaluable (resected)	N n=14*	NI n=12**	p-value
	Median (min, max)	Median (min, max)	
% viable tumor cells	65 (0, 95)	27.5 (0, 100)	0.364

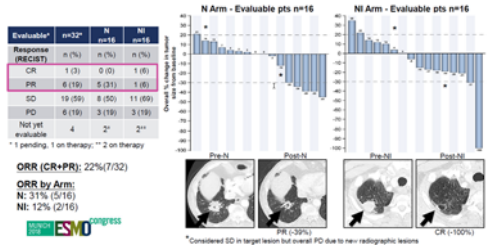
* 2 no surgery; 1 awaiting surgery; 1 on therapy
** 3 no surgery; 1 awaiting surgery; 2 on therapy



MPR calculated as described in Pataer A. et al., J Thorac Oncol 2012

Tina Cascone ESMO Oct 2018

Radiographic Responses



Evaluable*	n=32*	N n=16	NI n=16
Response (RECIST)	n (%)	n (%)	n (%)
CR	1 (3)	0 (0)	1 (6)
PR	6 (19)	5 (31)	1 (6)
SD	19 (59)	8 (50)	11 (69)
PD	6 (19)	3 (19)	3 (19)
Not yet evaluable	4	2*	2**

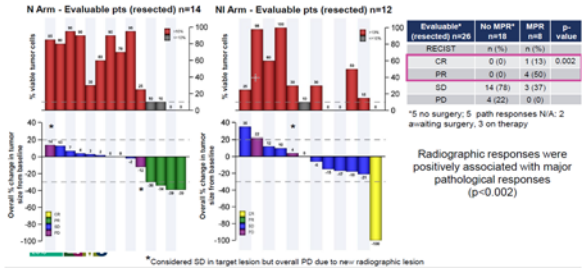
* 1 pending, 1 on therapy; ** 2 on therapy

ORR (CR+PR): 22%(7/32)

ORR by Arm:
N: 31% (5/16)
NI: 12% (2/16)

Tina Cascone ESMO Oct 2018

Radiographic Responses and Association with MPR



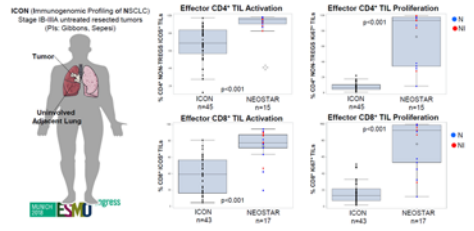
Evaluable* (resected) n=26	No MPR* n=18	MPR n=8	p-value
RECIST	n (%)	n (%)	
CR	0 (0)	1 (13)	0.002
PR	0 (0)	4 (50)	
SD	14 (78)	3 (37)	
PD	4 (22)	0 (0)	

*5 no surgery; 5 path responses N/A; 2 awaiting surgery, 3 on therapy

Radiographic responses were positively associated with major pathological responses (p<0.002)

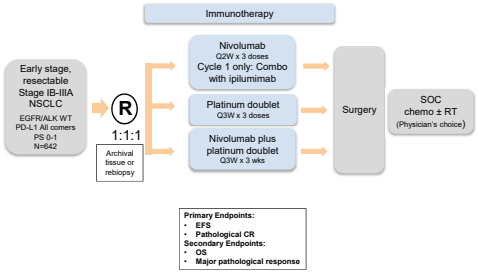
Tina Cascone ESMO Oct 2018

Neoadjuvant N and NI increase proliferative and activated effector TILs vs. untreated lung tumors (ICON set)



Tina Cascone ESMO Oct 2018

Randomized phase III Checkmate 816: Neoadjuvant Nivo/ipi or Nivo Plus Chemotherapy vs Chemotherapy in Early Stage NSCLC



The Bottom Line

- **Preclinical data suggests PD-1 + CTLA-4 blockade is superior to either alone**
- **Clinical trials indicate:**
  - **Ipi/Nivo has higher response rates than Nivo alone and higher but manageable toxicities than Nivo alone**
  - **Ipi/Nivo improves PFS compared to chemo in 1L high-TMB NSCLC (Checkmate 227)**
  - **Awaiting results of Durva/Tremi phase III studies although initial results negative**
- **Our group and others are exploring the use of combination immunotherapy in combination with RT and in neoadjuvant setting in an effort to increase cures.**

MD Anderson Cancer Center
Making Cancer History®

Immunotherapy with PD-1/PD-L1 (Nivolumab, Pembrolizumab, Durvalumab) and Anti-CTLA-4 (Ipilimumab) Antibodies in NSCLC

John Heymach, MD, PhD
Chair, Dept. of Thoracic/Head and Neck Medical Oncology
David Bruton, Jr. Chair in Cancer Research
MD Anderson Cancer Center
Houston, TX

Thank you

Immunotherapy with Anti-PD-L1 (Pembrolizumab) and Combination Therapy Approaches in NSCLC

Jianjun Zhang, MD, PhD

Immunotherapy with Anti-PDL1 and Combination Therapy Approaches in NSCLC

Jianjun Zhang, MD, PhD
Department of Thoracic Medical Oncology
Department of Genomic Medicine
UT MD Anderson Cancer Center

October 27, 2018
Houston

Conflict of Interest Disclosure

Advisory Board: AstraZeneca

Consultant: Geneplus

Speakers' Bureau: OrigiMed, Geneplus, Innovent

Outline

- Combination of anti-PD1/PDL1 and anti-CTLA4 in NSCLC
- Combination of anti-PD1/PDL1 and chemotherapy in NSCLC
- Combination of anti-PD1/PDL1 and chemotherapy in SCLC
- Combination of immune checkpoint blockade with **X** in NSCLC

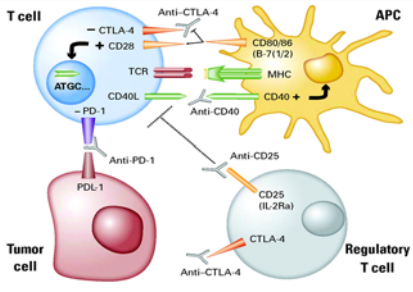
Why combination?

- Tackle the inter-tumor heterogeneity
- Tackle the intra-tumor heterogeneity
- Achieve deeper response: longer duration of response and less risk of resistance
- Produce synergistic effects

Outline

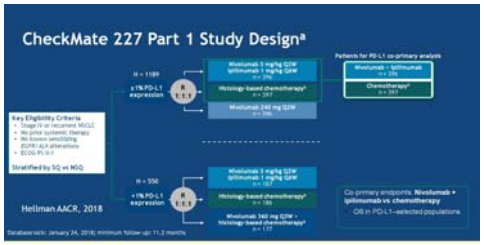
- **Combination of anti-PD1/PDL1 and anti-CTLA4 in NSCLC**
- Combination of anti-PD1/PDL1 and chemotherapy in NSCLC
- Combination of anti-PD1/PDL1 and chemotherapy in SCLC
- Combination of immune checkpoint blockade with **X** in NSCLC

Scientific Rationale: IO+IO



Lana E. Kandalaft, JCO, 2011

Nivolumab (PD1) + Ipilimumab (CTLA4) in NSCLC



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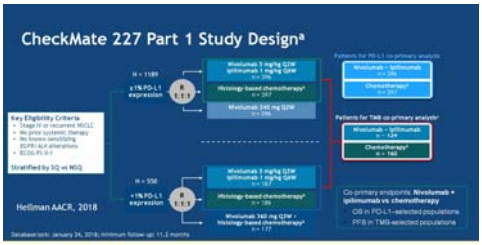
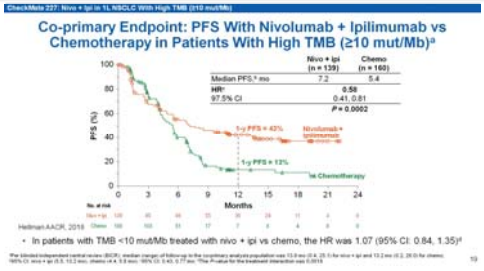


Nivolumab + Ipilimumab vs chemotherapy in NSCLC patients with high TMB: PFS



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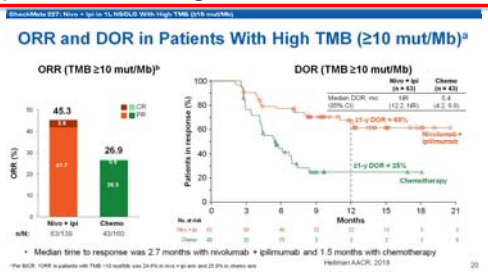
Nivolumab + Ipilimumab vs chemotherapy in NSCLC patients with high TMB: ORR and DOR



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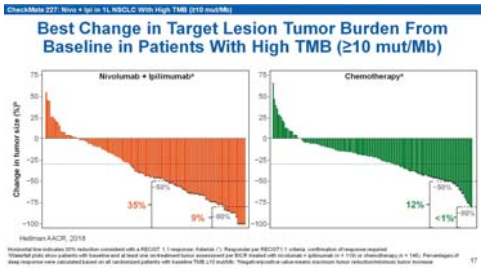
Nivolumab + Ipilimumab vs chemotherapy in NSCLC patients with high TMB: depth of response



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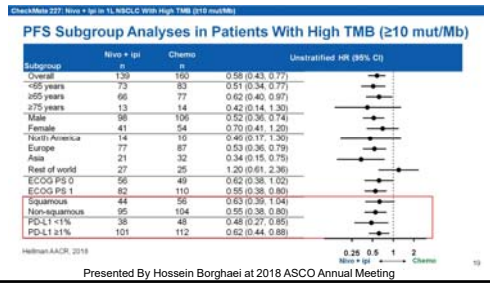
Nivolumab + Ipilimumab vs chemotherapy in NSCLC patients with high TMB: independent of PDL1



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Nivolumab + Ipilimumab vs chemotherapy in NSCLC patients with high TMB: adverse effects

TRAE,* %	Nivolumab + Ipilimumab (n = 576)		Chemotherapy (n = 570)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Any TRAE	75	31	81	36
TRAE leading to discontinuation†	17	12	9	5
Most frequent TRAEs (≥15%)				
Rash	17	2	5	0
Diarrhea	16	2	10	1
Fatigue	13	1	18	1
Decreased appetite	13	<1	19	1
Nausea	10	<1	36	2
Constipation	4	0	15	<1
Anemia	4	2	32	11
Neutropenia	<1	0	17	9
Treatment-related deaths‡	1		1	

Median duration (range) of therapy was 4.2 mo (0.03-24.0+) with nivolumab + ipilimumab and 2.6 mo (0.03-23.1+) with chemotherapy
Median number of doses of nivolumab (Q3W) and ipilimumab (Q6W) received were 9 and 3, respectively

2018 ASCO ANNUAL MEETING

24

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Outline

- Combination of anti-PD1/PDL1 and anti-CTLA4 in NSCLC
- **Combination of anti-PD1/PDL1 and chemotherapy in NSCLC**
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- Combination of immune checkpoint blockade with **X** in NSCLC

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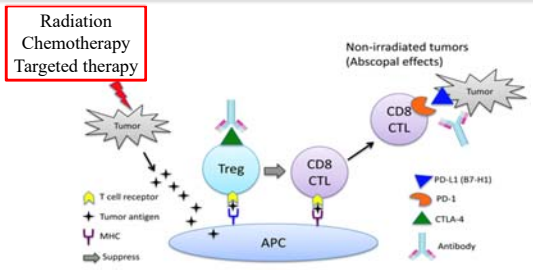
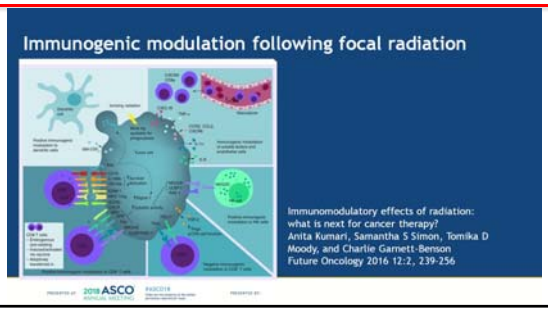
Scientific Rationale: IO + chemotherapy, XRT or TKI

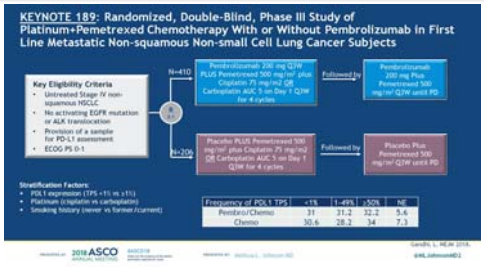


Aaron S. Mansfield, Aging, 2015

Scientific Rationale: IO + chemotherapy, XRT or TKI



Pembrolizumab + chemotherapy for treatment of non-squamous NSCLC



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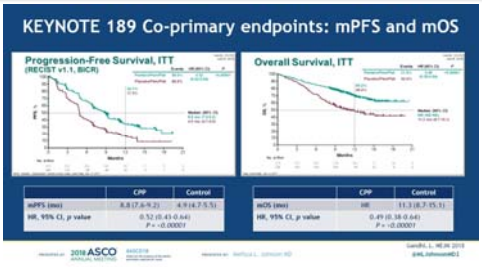

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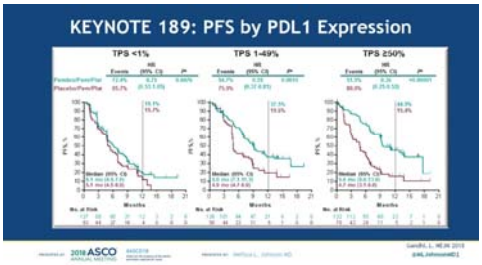
Pembrolizumab + chemotherapy for treatment of non-squamous NSCLC: PFS and PDL1 status



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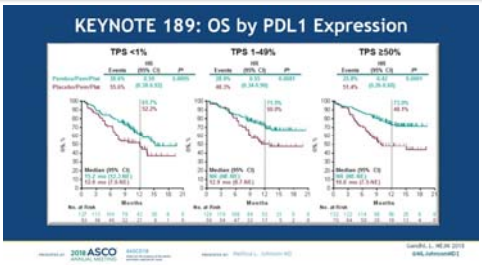
Pembrolizumab + chemotherapy for treatment of non-squamous NSCLC: OS and PDL1 status



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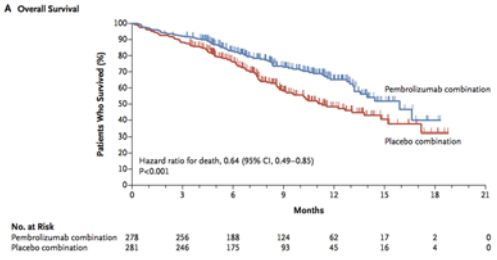
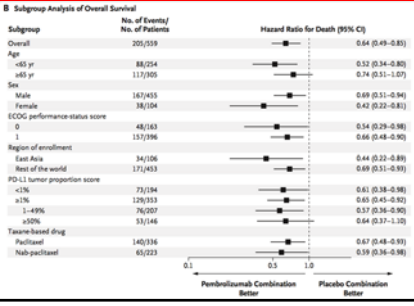
Pembrolizumab + chemotherapy for treatment of squamous NSCLC (Keynote 407): OS



Paz-Ares, NEJM, 2018

Pembrolizumab + chemotherapy for treatment of squamous NSCLC (Keynote 407): OS



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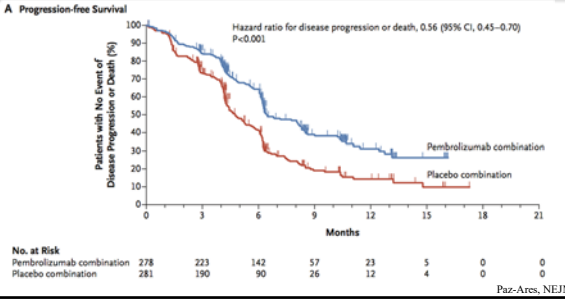

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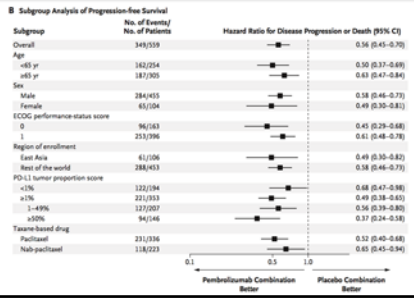
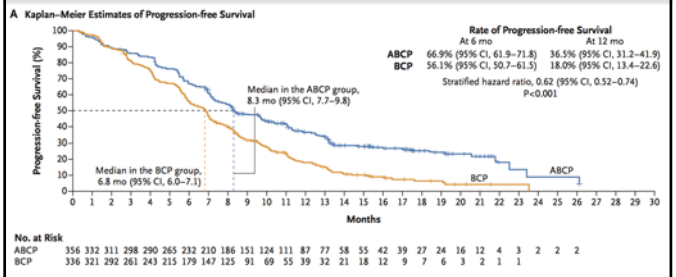


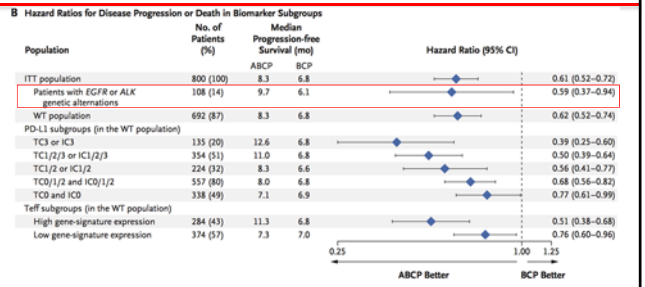
Paz-Ares, NEJM, 2018

Atezolizumab + chemotherapy + bevacizumab for treatment of non-squamous NSCLC: PFS



Socinski, NEJM, 2018

Atezolizumab + chemotherapy + bevacizumab for treatment of non-squamous NSCLC: PFS



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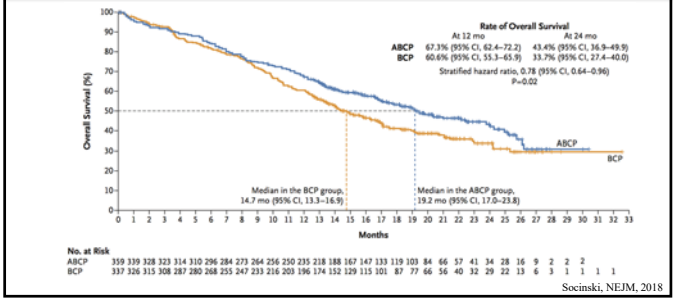
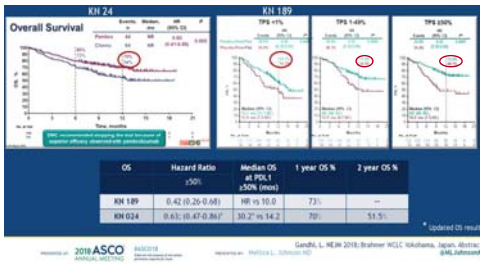


Socinski, NEJM, 2018

IO + chemo versus IO single agent for NSCLC patients with PDL1≥ 50%: OS



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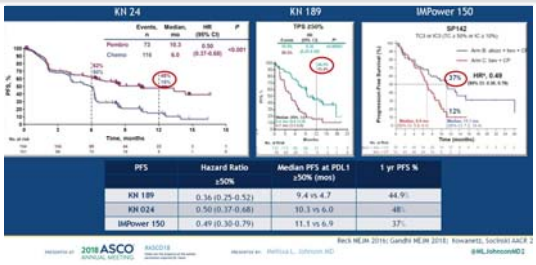

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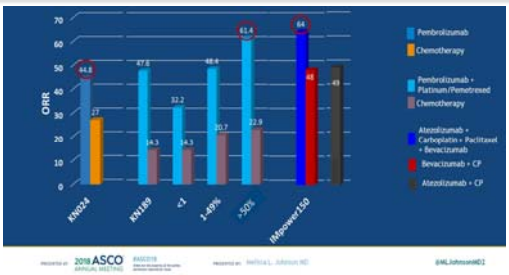

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IO + chemo versus IO single agent for NSCLC patients with PDL1≥ 50%: toxicity

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Outline

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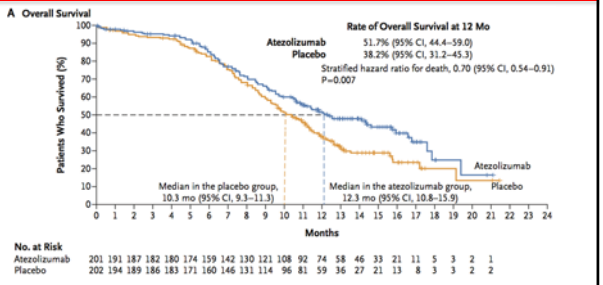
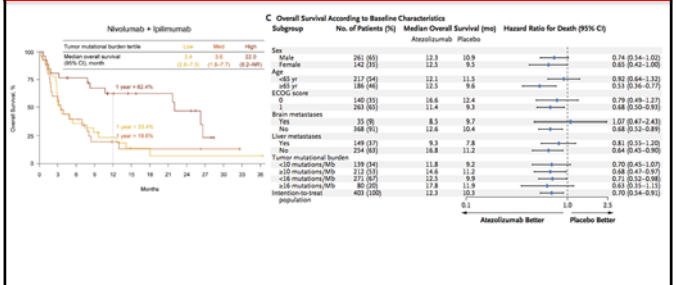
- Combination of immune checkpoint blockade with X in NSCLC

Atezolizumab + chemotherapy for the treatment of SCLC (IMpower 133): OS



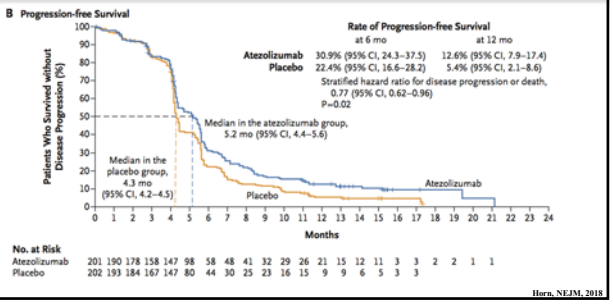
Horn, NEJM, 2018

Atezolizumab + chemotherapy for the treatment of SCLC (IMpower 133): OS



Hellman, Cancer Cell, 2018; Horn, NEJM, 2018

Atezolizumab + chemotherapy for the treatment of SCLC (IMpower 133): PFS

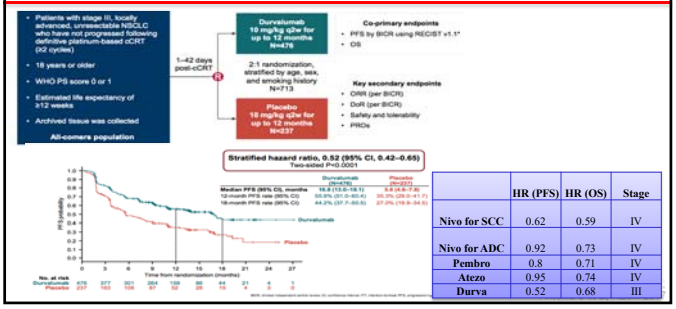


Horn, NEJM, 2018

Outline

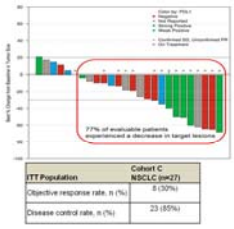
- Combination of anti-PD1/PDL1 and anti-CTLA4 in NSCLC
- Combination of anti-PD1/PDL1 and chemotherapy in NSCLC
- Combination of immune checkpoint blockade in SCLC
- **Combination of immune checkpoint blockade with X in NSCLC**

IO + radiation in Stage III NSCLC (PACIFIC)



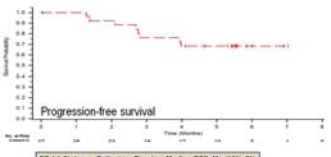
	HR (PFS)	HR (OS)	Stage
Nivo for SCC	0.62	0.59	IV
Nivo for ADC	0.92	0.73	IV
Pembro	0.8	0.71	IV
Atezo	0.95	0.74	IV
Durva	0.52	0.68	III

IO+ VEGF inhibitor: Ramucirumab + pembrolizumab



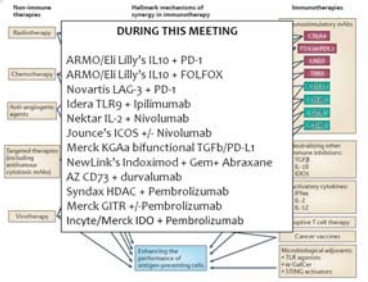
ITT Population	Cohort C NSCLC (n=27)
Objective response rate, n (%)	8 (30%)
Disease control rate, n (%)	23 (85%)

Herbst et al, 2016 ESMO



PD-L1 Status	Patients	Events	Median PFS, Mo (95% CI)
All Patients	27	8	NR (3.98, –)
Negative	10	2	NR
Weak positive	4	2	3.98 (2.76, –)
Strong positive	7	2	NR
Not reported	6	2	NR

IO + X



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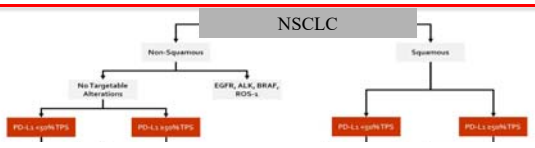
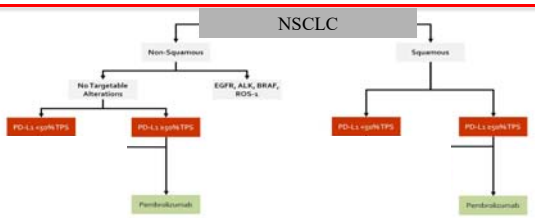
Take home message

- Combination of nivolumab + ipilimumab is superior to chemotherapy for treating NSCLC patients with TMB>10 independent of PDL1 status.
- Immune checkpoint inhibitor + chemotherapy is superior to chemotherapy for treating NSCLC as well as SCLC patients overall with regards to response and survival.
- Single agent pembrolizumab is non-inferior to IO/chemotherapy combination in NSCLC patients with PDL1 ≥ 50%.

Take home message



Take home message



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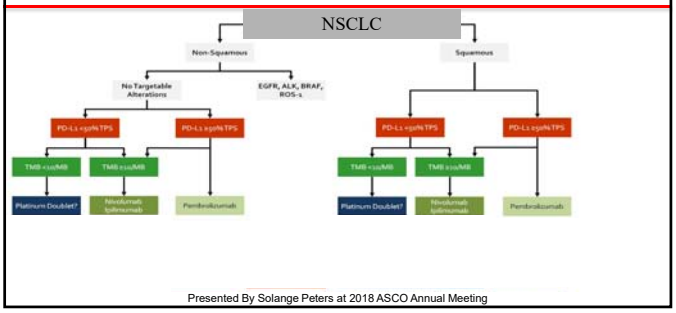
Take home message



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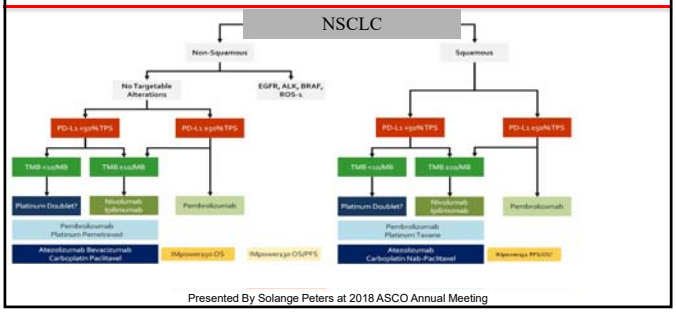
Take home message



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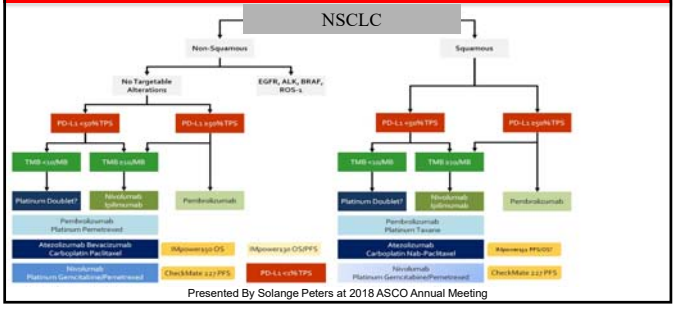

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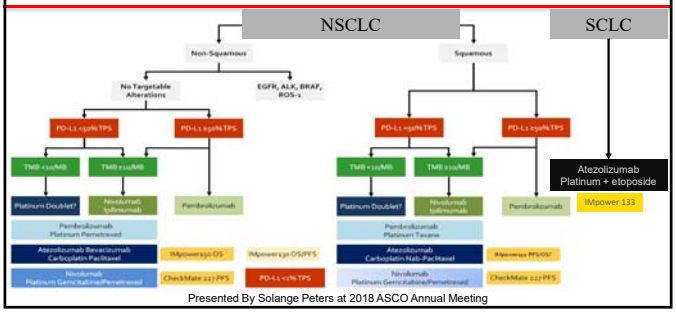


Presented By Solange Peters at 2018 ASCO Annual Meeting

Overview of Molecular, Histologic Tumor Testing, High Mutational Burden and Implication of Immune Resistance in HPV-associated Head & Heck Cancer

Tanguy Seiwert, MD

Overview of Molecular, Histologic Tumor Testing, High Mutational Burden in SCCHN and IO Resistance

10.27.2018

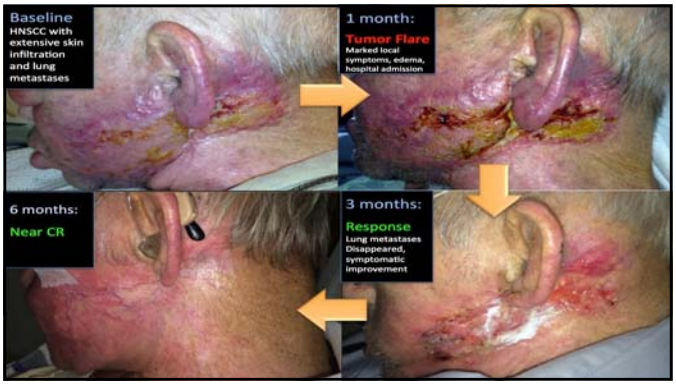
Overview:

1. HNC Background – Genetic Backgrounds
2. HNC Immune Microenvironment - Inflammation
3. Biomarkers
   - *PD-L1 (TPS / CPS → KN048 ESMO 2018)*
   - *Inflammation Signature*
   - *Mutational Burden (TMB)*
4. Resistance to Immune Checkpoint inhibitors
5. Research outlook – new biomarkers

2

OVERVIEW

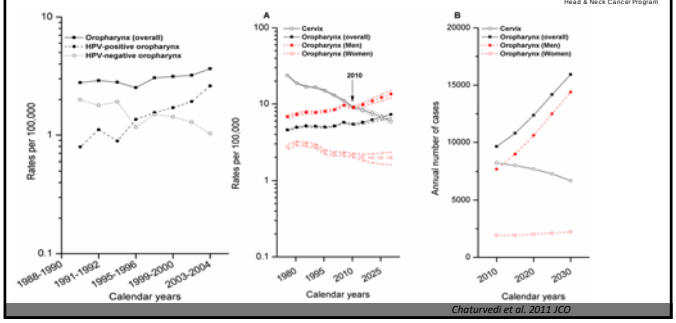
I. HNC Disease Background
II. Mutational Burden / Viral Antigens
III. Tumor Microenvironment
   - PD-L1
   - T-cell inflammation
   - IDO
   - Macrophages /MDSCs



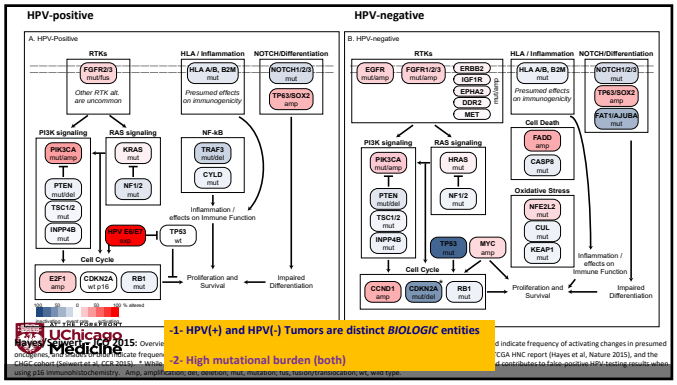
I. HNC Disease Background

- Head and neck cancer (HNC) is 6th most common cancer worldwide; 60,000 new cases per year in the United States
- Human Papilloma Virus (HPV) is involved in the etiology of ~60-80% of Oropharyngeal HNC in the US
- HPV(-)/Tobacco-related HNC AND HPV(+) HNC are distinct clinical entities.

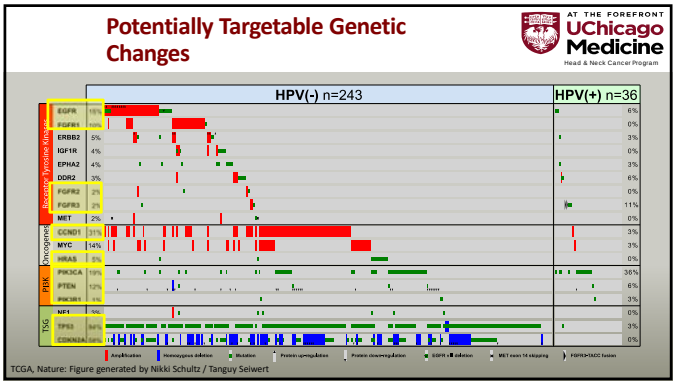
The HPV "Epidemic"



Chaturvedi et al. 2011 JCO



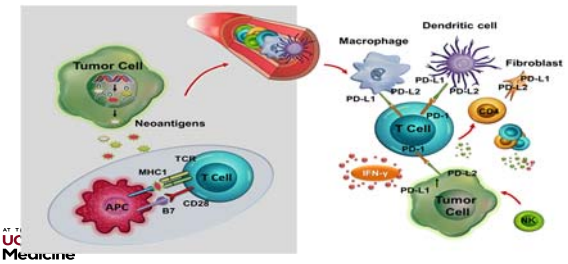
Potentially Targetable Genetic Changes



ANTIGENS ~ INFLAMMATION

TMB / Viral Ag reflects tumor antigenicity

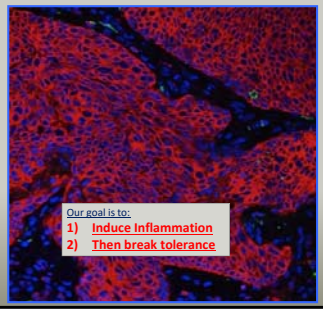
T-cell inflammation reflects activated T-cells in tumor microenvironment

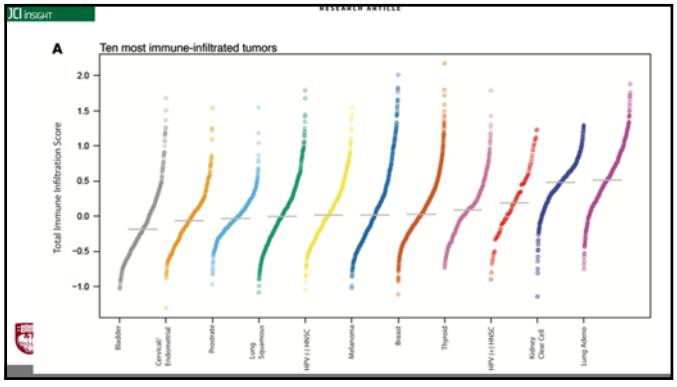


Hayes, Semin. Rad. 2015: Overvie

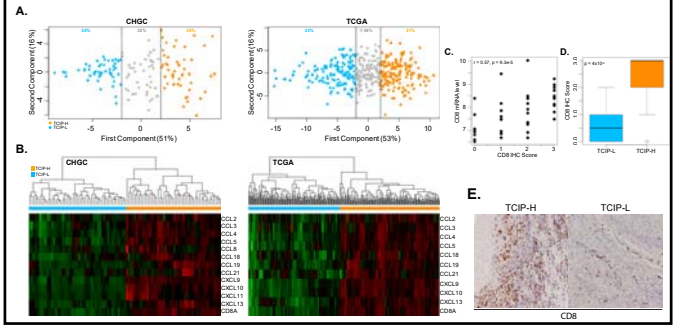
Inflamed Phenotype in HNC

Tumor infiltrating Lymphocytes (TILs)





HNSCC Tumor (Immune) Microenvironment (TME)



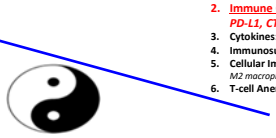
The Yin and Yang of Immune Escape

***Immune Surveillance*:**

- Immune system recognizes malignant cells

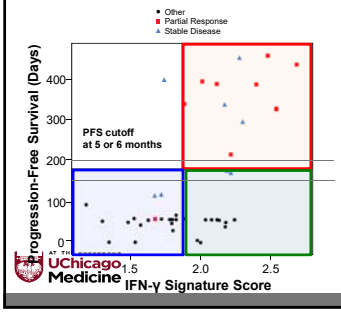
***Immune Escape*:**

1. **Antigen Presentation:** *Loss of Antigen (Immune-editing), HLA↓*
2. **Immune Checkpoints:** ***PD1-PD-L1, CTLA4, TIM3***
3. **Cytokines:** *TGF-ß, IL-4, IL-6*
4. **Immunosuppressive ME:** *IDO*
5. **Cellular Immune Escape:** *T-regs, M2 macrophages, MDSCs*
6. **T-cell Anergy**



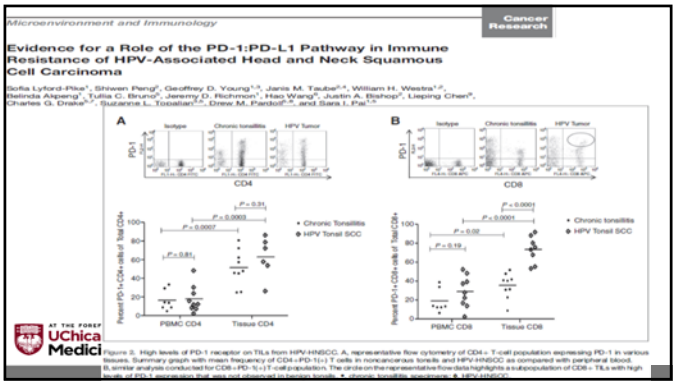
IMMUNE MICROENVIRONMENT (IME)

Association of IFNγ Signature and Progression-Free Survival in Patients with Head and Neck Cancer



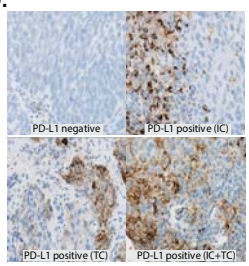
1. ***IB-group*: Inflamed – Benefitting**
   - Gamma-IFN Inflamed
   - Benefitting from anti-PD1 therapy
2. ***INB-group*: Inflamed – NonBenefitting**
   - Gamma-IFN Inflamed
   - Not Benefitting from anti-PD1 therapy
   - Given biologic signal - Can these patients be converted into responders e.g. via combinations, vaccine etc.
3. ***NI-group*: Non-Inflamed**
   - Very high negative predictive value
   - Not benefitting from anti-PD1 therapy
   - Clinically potentially useful: Identify patients who shout NOT receive PD-1 therapy
   - Unclear whether non-inflamed phenotype can be converted into inflamed phenotype

Presented by: Tanguy Seiwert, ASCO 2015



HNSCC Tumor (Immune) Microenvironment (TME)

D.



E.

TCIP status / *IHC Score*	TCIP-L (n=37)	TCIP-H (n=37)
PD-L1 negative (IC+TC)	26 (70%)	14 (38%)
PD-L1 positive (IC+TC)	11* (30%)	23* (62%)

FREQUENCY OF PTS WITH TPS ≥ 50 OR CPS ≥ 20

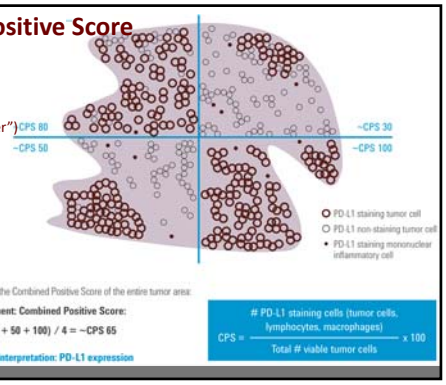
	CPS ≥ 20	TPS ≥ 50
SCCHN	39-44%	22-25%
NSCLC		25-30%

Paz-Ares et al. N. Engl. J. Med 2018, Reck et al. N. Engl. J. Med 2016, Cohen et al. ESMO 2017

CPS – Combined Positive Score

- Gastric,
- HNC,
- likely Bladder

(lung Cancer and TPS is the "outlier")



Calculate the Combined Positive Score of the entire tumor area:

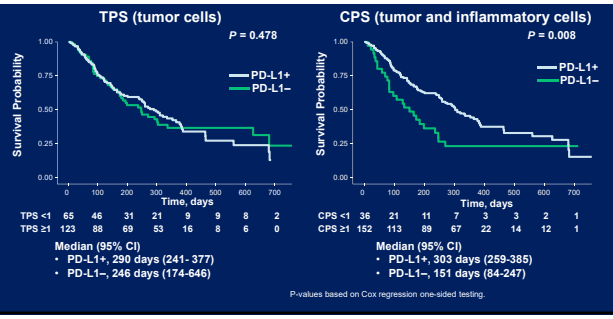
Assessment: Combined Positive Score:

(80 + 30 + 50 + 100) / 4 = ~CPS 65

Clinical Interpretation: PD-L1 expression

$$CPS = \frac{\text{\# PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total \# viable tumor cells}} \times 100$$

Overall Survival by PD-L1 Status



Median (95% CI)

- PD-L1+, 290 days (241- 377)
- PD-L1–, 246 days (174-646)

Median (95% CI)

- PD-L1+, 303 days (259-385)
- PD-L1–, 151 days (84-247)

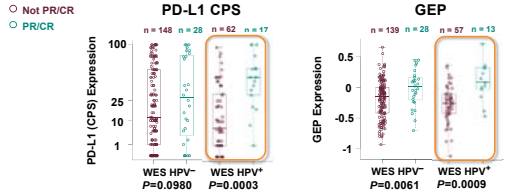
P-values based on Cox regression one-sided testing.

Biomarkers predictive of response to pembrolizumab in head and neck cancer (HNSCC)

Tanguy Y. Seiwert, MD[1]; Robert Haddad, MD[2]; Joshua Bauml, MD[3]; Jared Weiss, MD[4]; David G. Pfister MD[5]; Shilpa Gupta, MD[6]; Ranee Mehra, MD[7,8]; Iris Gluck, MD[9]; Hyunseok Kang, MD[10]; Francis Worden, MD[11]; J. Paul Eder, MD[12]; Makoto Tahara, MD[13]; Barbara Burtness, MD[12]; Stephen V. Liu, MD[14]; Andrea Webber, PhD[15]; Lingkang Huang, PhD[15]; Robin Mogg, PhD[15]; Razvan Cristescu, PhD[15]; Jonathan Cheng, MD[15]; Laura Q. M. Chow, MD[16]

[1]University of Chicago, Chicago, IL, USA; [2]Dana Farber Cancer Institute, Boston, MA; [3]University of Pennsylvania, Philadelphia, PA, USA; [4]Lineberger Comprehensive Cancer Center at the University of North Carolina, Chapel Hill, NC, USA; [5]Memorial Sloane Kettering Cancer Center, New York, NY, USA; [6]Lee Moffitt Cancer center and Research Institute, Tampa FL, USA; [7]Fox Chase Cancer Center, Philadelphia, PA, USA (study conduct); [8]Johns Hopkins University, Baltimore, MD, USA; [9]Sheba Medical Center, Tel Hashomer, Israel; [10]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD, USA; [11]University of Michigan, Ann Arbor MI, USA; [12]Yale University Cancer Center, New Haven, CT, USA; [13]National Cancer Center Hospital East, Kashiwa, Japan; [14]Georgetown University Hospital, Washington, DC, USA; [15]Merck & Co., Inc. Kenilworth, NJ, USA; [16]University of Washington, Seattle, WA, USA

Inflammation (PD-L1/GEP) vs Response

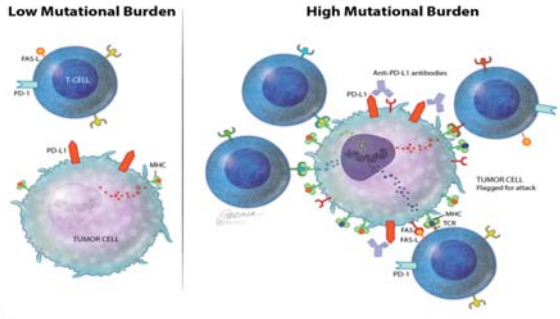


- PD-L1 CPS and GEP were significantly associated with BOR in all patients (P<0.0001 and P=0.0012, respectively) and in HPV⁺ patients
- The association in HPV⁻ patients was less robust

CPS=combined positive score, IMmune=tumor cells, PR=partial response, CR=complete response

25

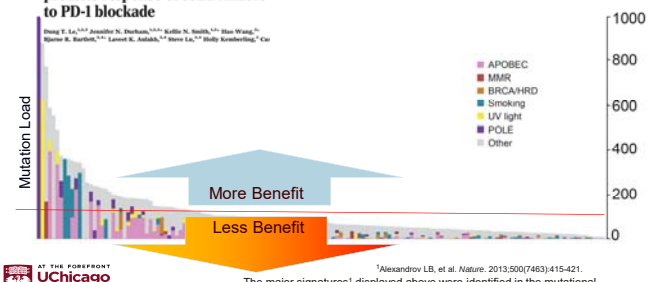
TUMOR MUTATIONAL BURDEN (TMB)



CANCER BIOMARKERS

Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade

Mutational Signatures and ML Across Samples

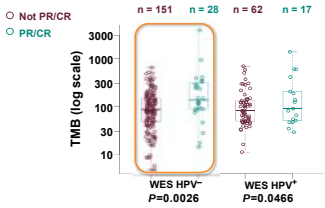


AT THE FOREFRONT UChicago Medicine

[1]Alexandrov LB, et al. *Nature*. 2013;500(7463):415-421.

The major signatures[1] displayed above were identified in the mutational landscape of the patients in this dataset and are illustrated as proportions of ML.

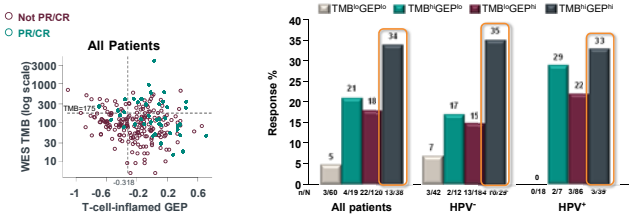
Tumor Mutational Burden (TMB) vs Response



- TMB was significantly associated with BOR in all patients (P=0.0006) and appears stronger in HPV⁻ patients

PR=partial response, CR=complete response.

GEP and TMB Response Rates (BOR)

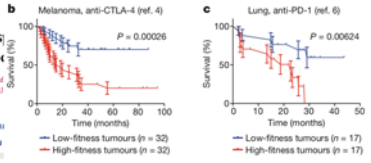


- Responses were also higher in those who had both high GEP and TMB across all patients and in both HPV subgroups than those with low levels of both

Dashed horizontal line is clinically applicable TMB threshold (TMB ≥175 mutations per exome) derived using pan-tumor GEP and TMB data (Panda A et al. *JCO Precis Oncol*. 2017). Dashed vertical line represents discovery cutoff for the T-cell-inflamed GEP (≥-0.318) selected via analysis of pan-cancer data. GEP high (hi) and low (lo): ≥ and ≤ -0.318. TMB hi and lo: ≥ and ≤ 175.

QUALITY OF MUTATIONS MAY MATTER

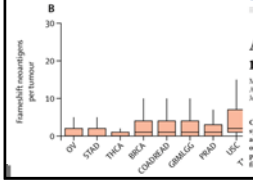
Insertion-and-deletion-derived tumour-s
and the immunogenic phenotype: a pan-c



Summary

Background The focus of tumour-specific antigen analyses has be
contribution of small insertions and deletions (indels) less well cha

LE

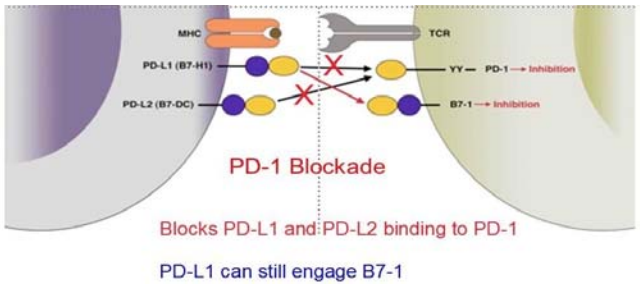


A neoantigen fitness model predicts tumour response to checkpoint blockade immunotherapy

Checkpoint blockade immunotherapies enable the host immune system to recognize and destroy tumour cells[1]. Their clinical activity has been correlated with activated T-cell recognition of neoantigens, which are tumour-specific, mutated peptides presented on the surface of cancer cells[2,3]. Here we present a fitness model for tumours based on immune interactions of neoantigens that are present only in certain subclones. Therapie targeting a fraction of the tumour could disrupt clonal competitive balance and inadvertently stimulate the growth of untargeted clones[4]. Worldwide efforts are being undertaken to model neoantigens an quantify their features from genomic data. A predictive neoantigen based model for immunotherapy response, complementing mut

PD-1 *binds to* PD-L1 + PD-L2
PD-L1 *binds to* PD-1 + B7-1

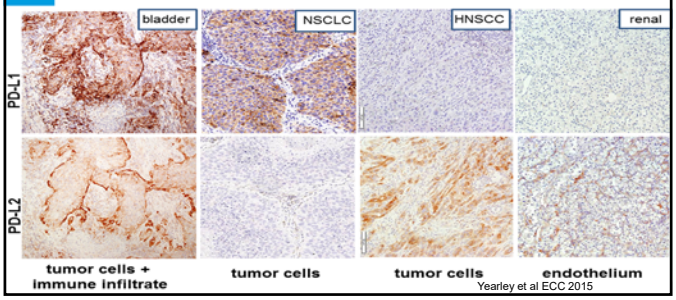
THE UNIVERSITY OF CHICAGO MEDICINE
Head & Neck Cancer Program



J. Yearley, September 27, 2015

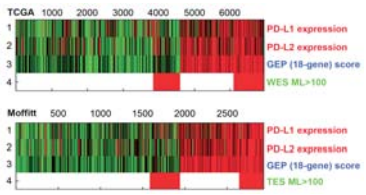
ecco

PD-L2 and PD-L1 in Tumors: Concordance & Discordance



Yearley et al ECC 2015

Association of PD-L1, PD-L2, TCIP/GEP With TMB

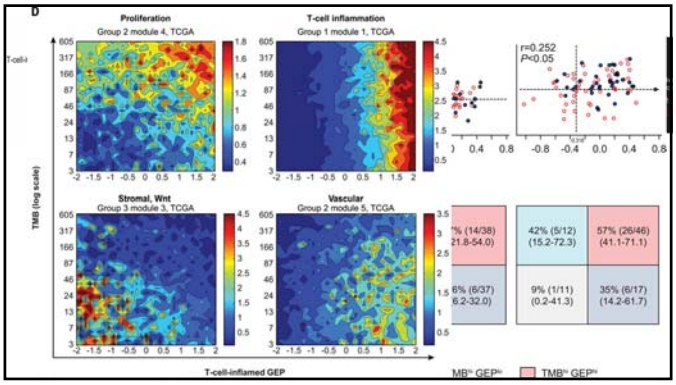


TCGA:
- ML and GEP, r = 0.30
- ML and PD-L1, r = 0.16
- ML and PD-L2, r = 0.22

Moffitt:
- ML and GEP, r = 0.11
- ML and PD-L1, r = 0.18
- ML and PD-L2, r = 0.11

- ML was also significantly but modestly correlated with GEP, PD-L1, and PD-L2 in TCGA and Moffitt databases; all *P* <0.0001

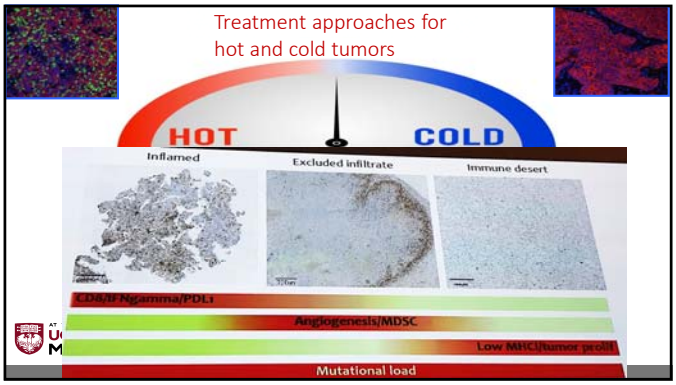
Cristescu et al SITC-ASCO 2017



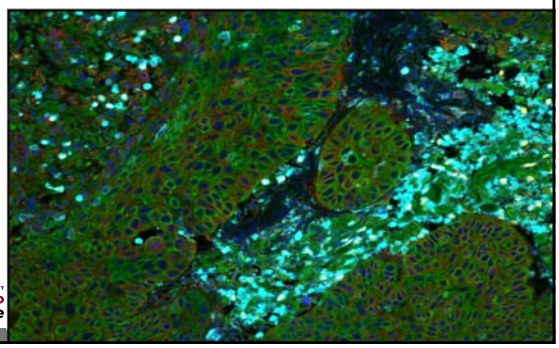
OTHER FACTORS IMPACTING THE IMMUNE MICRO- ENVIRONMENT (MIE)

IDO, Macrophages/MDSCs, etc

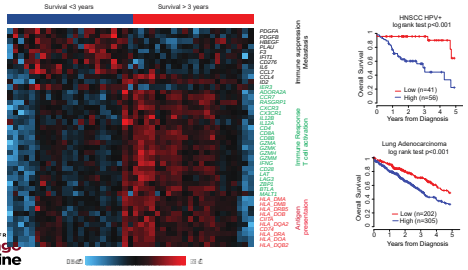
Treatment approaches for hot and cold tumors



Macrophages and MDSCs



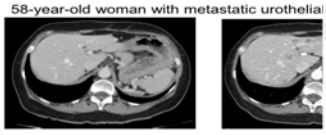
M2-regulated immune response signature is associated with outcome in human tumors



Megan Kaneda, Hongying Li, Karen Messer & Judith Varner

Hyperprogression / Rapid

58-year-old woman with metastatic urothelial



Before

Base

ESMO

ORIGINAL ARTICLE

Hyperprogression during anti-PD-1/PD-L1 therapy in patients with recurrent and/or metastatic head and neck squamous cell carcinoma

E. Saâda-Bouzid[1], C. Defaucheux[2], A. Karabajakian[3], V. P. Coloma[4], V. Servois[5], X. Paoletti[6], C. Even[4], J. Fayette[7], J. Guigay[1], D. Loirat[2], F. Peyrade[1], M. Ali[8], J. Gal[9] & C. Le Tourneau[2,10]

JAMA Oncology | Original Investigation

Hyperprogressive Disease in Patients With Advanced Non–Small Cell Lung Cancer Treated With PD-1/PD-L1 Inhibitors or With Single-Agent Chemotherapy

Roberto Ferrara, MD; Laura Mezquita, MD, PhD; Matthieu Texier, MSc; Jihane Lahmar, MD; Clarisse Audigier-Valette, MD; Laurent Tessonnier, MD; Julien Mezquita, MD, PhD; Gerard Zalcman, MD, PhD; Solène Brosseau, MD; Sylvestre Le Moulec, MD; Laura Leroy, MD; Boris Duchemann, MD; Corentin Lefebvre, MD; Pierre Veillon, MD; Virginie Westeel, MD, PhD; Serge Koscielny, MSc; Stephane Champiat, MD; Charles Ferté, MD, PhD; David Planchard, MD, PhD; Jordi Remon, MD; Marie-Eve Boucher, MD; Anas Gazzah, MD; Julien Adam, MD, PhD; Emilie Bria, MD; Gumpanats Tortora, MD, PhD; Jean-Charles Soria, MD, PhD; Benjamin Besse, MD, PhD; Caroline Caramella, MD

Author Audio Interview
Supplemental content

IMPORTANCE Hyperprogressive disease (HPD) is a new pattern of progression recently described in patients with cancer treated with programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors. The rate and outcome of HPD in advanced non–small cell lung cancer (NSCLC) are unknown.

OBJECTIVES To investigate whether HPD is observed in patients with advanced NSCLC treated with PD-1/PD-L1 inhibitors compared with single-agent chemotherapy and whether there is an association between treatment and HPD.

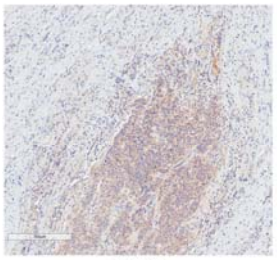
DESIGN, SETTING, AND PARTICIPANTS In this multicenter retrospective study that included patients treated between August 4, 2011, and April 5, 2017, the setting was pretreated patients with advanced NSCLC who received PD-1/PD-L1 inhibitors (8 institutions) or single-agent chemotherapy (4 institutions) in France. Measurable disease defined by Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) on at least 2 computed tomographic scans before treatment and 1 computed tomographic scan during treatment was required.

INTERVENTIONS The tumor growth rate (TGR) before and during treatment and variation per month (ΔTGR) were calculated. Hyperprogressive disease was defined as disease progression at the first evaluation with ΔTGR exceeding 50%.

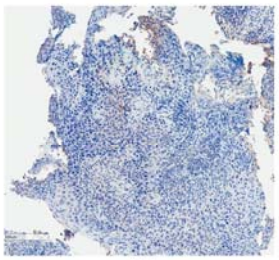
MAIN OUTCOMES AND MEASURES The primary end point was assessment of the HPD rate in patients treated with PD-1/PD-L1 inhibitors vs chemotherapy.

RESULTS Among 406 eligible patients treated with PD-1/PD-L1 inhibitors (63.8% male), 46.3% (n = 188) were 65 years or older, 72.4% (n = 294) had nonsquamous histology, and 52.9% (n = 177) received a PD-1 inhibitor as monotherapy in second-line therapy or later. The median follow-up was 12.1 months (95% CI, 10.1-13.8 months), and the median overall survival (OS) was 13.4 months (95% CI, 10.2-17.0 months). Fifty-six patients (13.8%) were classified as having HPD. Pseudoprogression was observed in 4.7% (n = 19) of the population. Hyperprogressive disease was significantly associated with more than 2 metastatic sites before PD-1/PD-L1 inhibitors compared with non-HPD (82.1% [35 of 56] vs 42.6% [149 of 350]; $P < .0001$). Patients experiencing HPD within the first 6 weeks of PD-1/PD-L1 inhibitor

B2M loss is a mechanism of acquired PD-1 resistance in HNSCC Tumor

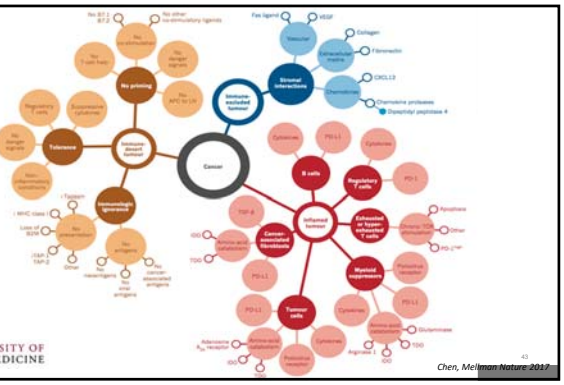


Baseline
B2M positive



AR
B2M negative

42



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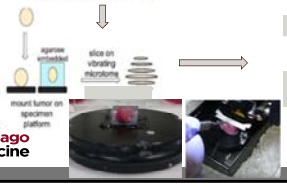
43

Chen, Mellman Nature 2017

Bioreactor / Histoculture

Fresh tumor from surgery



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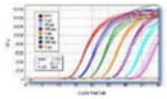
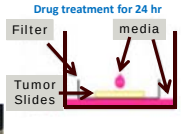
Digital QPCR from Fluidigm



RNA extraction and IFNγ signature gene expression

Drug treatment for 24 hr



scRNAseq and AbSeq

BD Rhapsody system

Antibody-Oligo Construct

BD Developed Applications
- Sample Multiplexing
- Simultaneous RNA + Protein
  - High parameter proteomics
  - Combined with mRNA profiling
  - Simple workflow

CONCLUSIONS

1. Both HPV(+) and HPV(-) HNSCC show:
   - High levels of immune cell infiltration
   - High Mutational burden (TMB) *(but viral antigens may matter more for HPV/EBV+)*
   - An inflamed phenotype (INF-G, PD-L1/2, IDO)
2. Checkpoint blockade with PD-(L)1 agents alone is unlikely to be sufficient for optimal benefit
   - Tregs, NK-cells, Macrophages/MDSC all may contribute to additional therapeutic opportunities *(e.g. PD-1/IDO ASCO 2017)*.
3. HNSCC is an excellent disease to develop Immunotherapeutic agents (Tob & Viral tumor, high levels of TMB/Inflammation, IDO/Macrophages / STILL only modest response rate to PD-1, injectable / accessible for biopsies)

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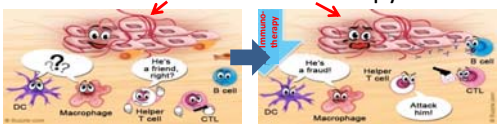
Thanks!

Cancer Immunotherapy



Slide Modified from Jason Luke, MD
http://goldenprague.us/strategies-for-cancer-vaccine-development/

Immunotherapy Options in the Treatment of Metastatic Head & Heck Cancer

Tanguy Seiwert, MD

AT THE FOREFRONT UChicago Medicine

Immunotherapy Options for the Treatment of R/M Head and Neck Cancers

Tanguy Seiwert, MD
Director, Head and Neck Cancer Program
The University of Chicago

10.27.2018

Overview:

1. Background and HNC Immune Biology
2. Approved Use - Platinum refractory
   - *Approval trials to date (KN12, CM141, CN40)*
3. The Future:
   - *First line -- Platinum naïve*
   - *Curative intent*
   - *Combinations*
4. A quick word on biomarkers

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HNC -- I-O exceptional responder

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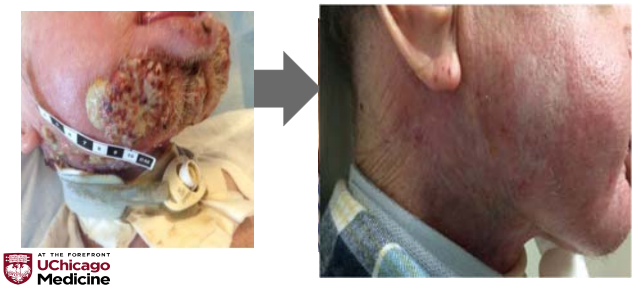

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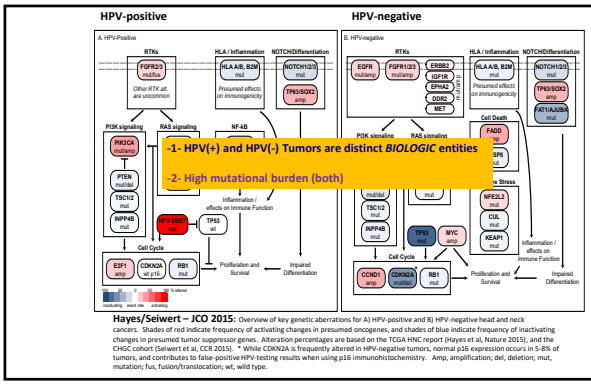
Slide courtesy of Tanguy Seiwert, University of Chicago

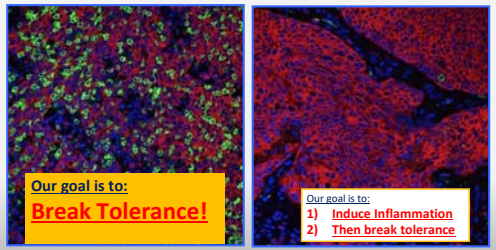


Hayes/Seiwert – JCO 2015: Overview of key genetic aberrations for A) HPV-positive and B) HPV-negative head and neck cancers. Shades of red indicate frequency of activating changes in presumed oncogenes, and shades of blue indicate frequency of inactivating changes in presumed tumor suppressor genes. Alteration percentages are based on the TCGA HNC report (Hayes et al, Nature 2015), and the CHGC cohort (Seiwert et al, CCR 2015). * While CDKN2A is frequently altered in HPV-negative tumors, normal p16 expression occurs in 5-8% of tumors, and contributes to false-positive HPV-testing results when using p16 immunohistochemistry. Amp, amplification; del, deletion; mut, mutation; fus, fusion/translocation; wt, wild type.

I. Inflamed Phenotype in HNC

Tumor infiltrating Lymphocytes (TILs)

THE UNIVERSITY OF CHICAGO MEDICINE Head & Neck Cancer Program



Keck/Seiwert, CCR 2015

Two US FDA Approvals in 2016 for HNSCC

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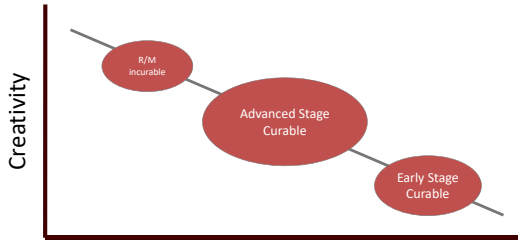
Grand Prize: is curative setting….



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Slide modified from E Cohen

Immunotherapy Trials for HNSCC with Approval Potential

	Treatment Setting				
Company	R/M: first-line Plat. naive	R/M: post-Platinum	Locally Advanced	Neo-adjuvant	Adjuvant/ Consolidation
MSD/Merck	KN048, KN669	KN012 KN055 KN040 KN37	KN412 (w / CRT)	KN689	
BMS	CM651 (ipi-nivo) CM714	CM141 (nivo) CM351, P1 combo expansions	RTOG3504/ BMS fu Study (w / CRT)		
Astra-Zeneca	KESTREL	HAWK CONDOR EAGLE			
Pfizer/EMD			Javelin 100 REACH		
Roche/ Genentech					IMVoke HN

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Slide modified from JPMachiels, 2017

II. Approved Use:

→ Platinum Refractory

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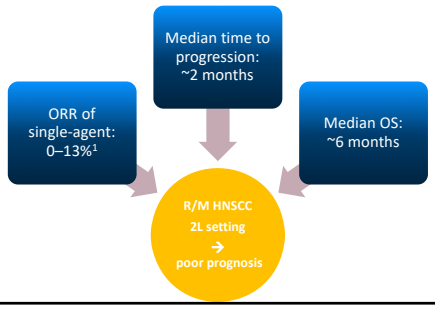
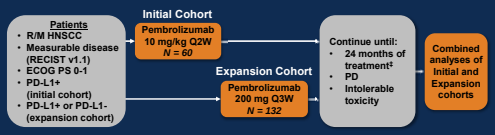
9

2nd line/platinum-refractory:
→ Unmet need in R/M HNSCC



HNSCC Cohorts of Nonrandomized, Phase 1b, Multi-cohort KEYNOTE-012 Trial†



Response assessment: Every 8 weeks

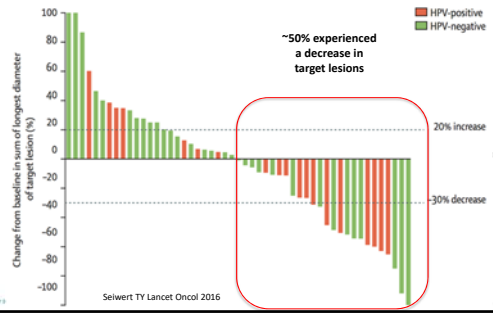
Primary end points: ORR (RECIST v1.1, central imaging vendor), safety

Secondary end points: ORR (investigator), PFS, OS, response duration, ORR in HPV+ patients§

†Additional cohorts included bladder cancer, TN breast cancer, and gastric cancer.
‡Treatment beyond progression was allowed.
§Initial cohort only.

PRESENTED AT: ASCO ANNUAL MEETING '16

Tumor Shrinkage (KeyNote 12)



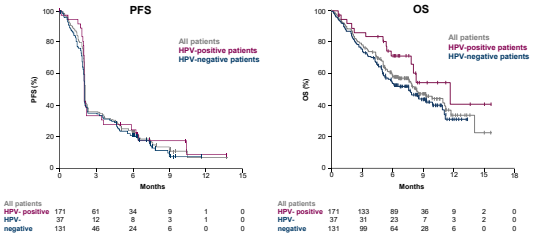
Seiwert TY Lancet Oncol 2016

ASCO Annual '15 Meeting

Pembrolizumab (anti-PD-1): accelerated approval for HNSCC – further supported by 2nd trial

Approval further supported by KEYNOTE-055 (Phase II, n=171)[2,3]

- pre-treated with
  - Platinum
  - cetuximab
- ORR 16%; no effect of HPV status on ORR
- Median OS: 8 months



Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy

Randomized, global, phase 3 trial of the efficacy and safety of nivolumab vs investigator's choice in patients with R/M SCCHN

Key Eligibility Criteria
- R/M SCCHN of the oral cavity, pharynx, or larynx
- Progression on or within 6 months of last dose of platinum-based therapy
- Irrespective of no. of prior lines of therapy
- Documentation of p16 to determine HPV status (oropharyngeal)
- Regardless of PD-L1 status*

Stratification factor
- Prior cetuximab treatment

R 2:1

Nivolumab 3 mg/kg IV Q2W

Investigator's Choice
- Methotrexate 40 mg/m² IV weekly
- Docetaxel 30 mg/m² IV weekly
- Cetuximab 400 mg/m² IV once, then 250 mg/m² weekly

Primary endpoint
- OS

Other endpoints
- PFS
- ORR
- Safety
- DOR
- Biomarkers
- Quality of life

*Tissue required for testing

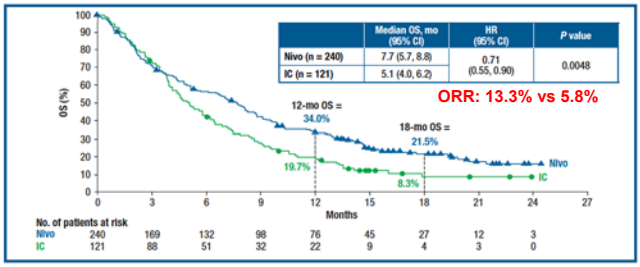
DOR = duration of response; IV = intravenous; ORR = objective response rate; PFS = progression-free survival; Q2W = once every 2 weeks; R = randomized. Clinicaltrials.gov NCT02105636.

Ferris/Gillison NEJM 2016

CheckMate 141: updated OS data

Figure 3. OS, CheckMate 141 all-randomized population

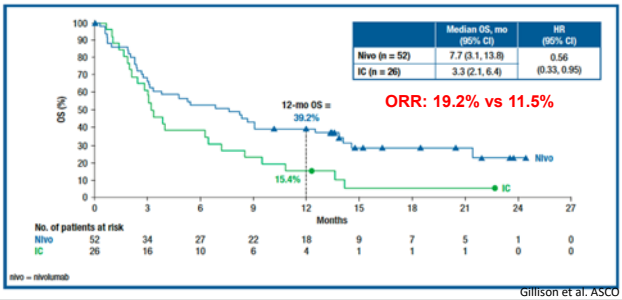
Median follow-up: 11.4 months



Gillison et al. ASCO 2017

CheckMate 141: outcomes in the first-line R/M

Figure 2. OS among patients receiving 1L R/M nivolumab or IC after platinum-based therapy in the primary/adjuvant setting



Gillison et al. ASCO 2017

Phase 3 KEYNOTE-040 Study (NCT02252042)

E Cohen_ESMO 2017

Key Eligibility Criteria
- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 mo of multimodal therapy using platinum[a]
- ECOG PS 0 or 1
- Known p16 status (oropharynx)[b]
- Tissue sample[c] for PD-L1 assessment[d]

Stratification Factors
- ECOG PS (0 vs 1)
- p16 status[b] (positive vs negative)
- PD-L1 TPS[d] (≥50% vs <50%)

R 1:1

Pembrolizumab 200 mg IV Q3W for 2 y

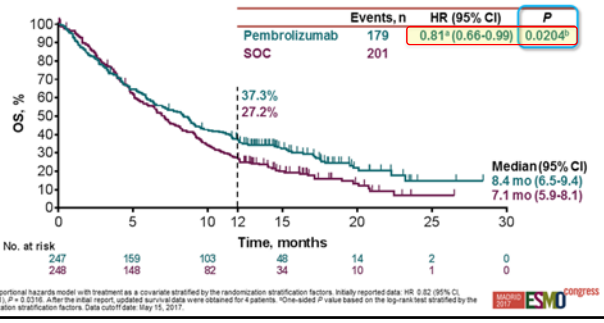
Methotrexate 40 mg/m² QW[e] OR Docetaxel 75 mg/m² Q3W OR Cetuximab 250 mg/m² QW[e]

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

[a]≤4 of 12 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (1+/tentative) cutpoint for positivity = 70%. [c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies); TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression. [e]Could be increased to 60 mg/m² QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

Overall Survival in ITT Population

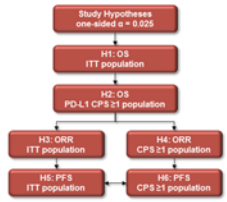
E Cohen_ESMO 2017



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI 0.67-1.01), P = 0.0316. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided P value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

E Cohen_ESMO 2017

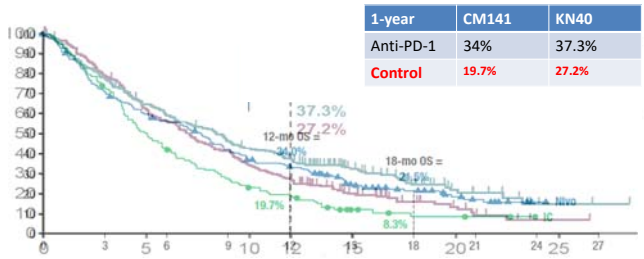
Statistical Considerations



- Multiplicity strategy
  - Family-wise alpha strictly controlled at 0.025 (one sided)
  - Alpha allocated in stepwise fashion
- Final analysis
  - Performed after **380 OS** events in 495 patients
  - Data cutoff date: May 15, 2017
  - **Efficacy boundary**
    - OS, ITT: one-sided α = 0.0175, HR ~0.80
    - OS, CPS ≥1: one-sided α = 0.0178, HR ~0.78
      - Tested only if efficacy boundary in ITT population reached

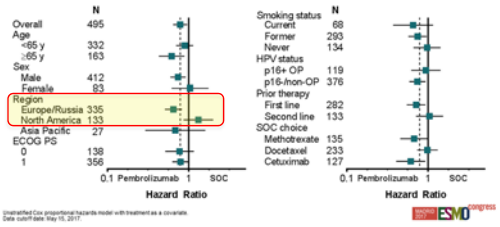
Data cutoff date: May 15, 2017.

1-year	CM141	KN40
Anti-PD-1	34%	37.3%
Control	19.7%	27.2%



E Cohen_ESMO 2017

Overall Survival in Subgroups, ITT Population

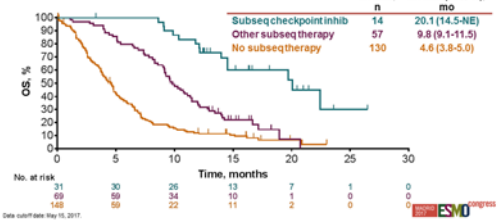


Unstratified Cox proportional hazards model with treatment as a covariate.
Data cutoff date: May 15, 2017.

E Cohen_ESMO 2017

Overall Survival: Effect of Subsequent Immune Checkpoint Inhibitors in the SOC Arm

	Events, n	Median (95% CI), mo
Subseq checkpoint inhib	14	20.1 (14.5-NE)
Other subseq therapy	57	9.8 (9.1-11.5)
No subseq therapy	130	4.6 (3.8-5.0)



Data cutoff date: May 15, 2017.

III. Platinum Naïve – First Line

→ *1 week ago ESMO 2018*

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23

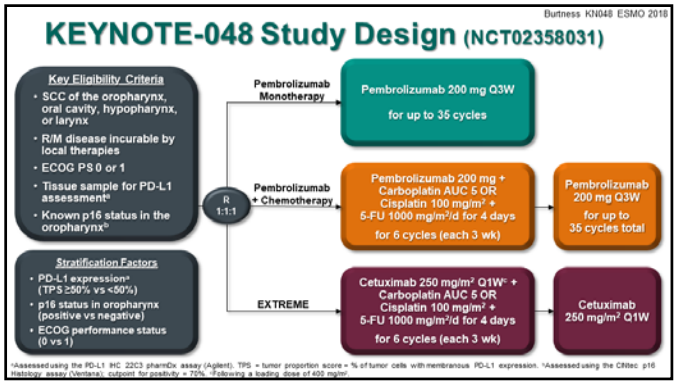
MUNICH 2018 ESMO congress

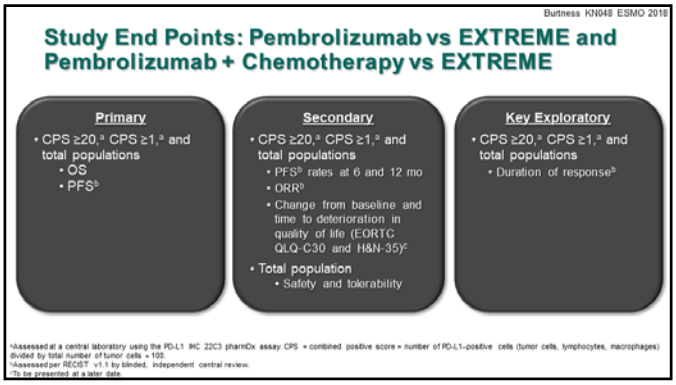
Burtness KN048 ESMO 2018

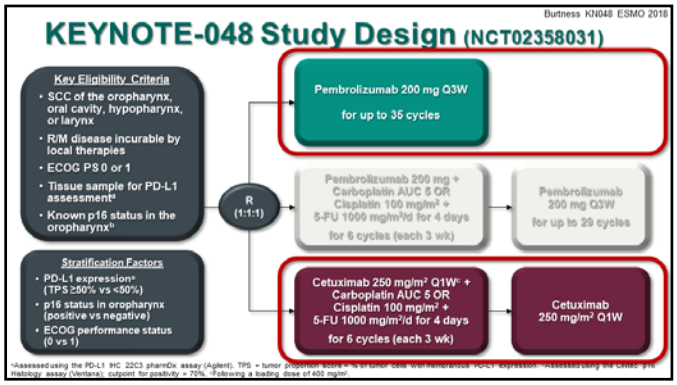
KEYNOTE-048: Phase 3 Study of First-Line Pembrolizumab for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Barbara Burtness,[1] Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté Rotllan,[8] Prakash Neupane,[9] Åse Bratland,[10] Thorsten Fuereder,[11] Brett GM Hughes,[12] Ricard Mesia,[13] Nuttapong Ngamphaiboon,[14] Tamara Rordorf,[15] Wan Zamaniah Wan Ishak,[16] Ananya Roy,[17] Jonathan Cheng,[17] Fan Jin,[17] Danny Rischin[18]

[1]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK; [3]Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; [4]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Barcelona, Spain (currently at Institut Gustave Roussy, Paris, France); [9]University of Kansas Medical Center, Kansas City, KS, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna, Vienna, Austria; [12]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, QLD, Australia; [13]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Malaysia; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia


Burtness KN048 ESMO 2018
KEYNOTE-048 Study Design (NCT02358031)
Key Eligibility Criteria
• SCC of the oropharynx, oral cavity, hypopharynx, or larynx
• R/M disease incurable by local therapies
• ECOG PS 0 or 1
• Tissue sample for PD-L1 assessment[b]
• Known p16 status in the oropharynx[b]
Stratification Factors
• PD-L1 expression[a] (TPS ≥50% vs <50%)
• p16 status in oropharynx (positive vs negative)
• ECOG performance status (0 vs 1)
R 1:1:1
Pembrolizumab Monotherapy
Pembrolizumab 200 mg Q3W for up to 35 cycles
Pembrolizumab + Chemotherapy
Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)
Pembrolizumab 200 mg Q3W for up to 35 cycles total
EXTREME
Cetuximab 250 mg/m² Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)
Cetuximab 250 mg/m² Q1W


Burtness KN048 ESMO 2018
Study End Points: Pembrolizumab vs EXTREME and Pembrolizumab + Chemotherapy vs EXTREME
Primary
• CPS ≥20,[a] CPS ≥1,[a] and total populations
• OS
• PFS[b]
Secondary
• CPS ≥20,[a] CPS ≥1,[a] and total populations
• PFS[b] rates at 6 and 12 mo
• ORR[b]
• Change from baseline and time to deterioration in quality of life (EORTC QLQ-C30 and H&N-35)[c]
• Total population
• Safety and tolerability
Key Exploratory
• CPS ≥20,[a] CPS ≥1,[a] and total populations
• Duration of response[b]


Burtness KN048 ESMO 2018
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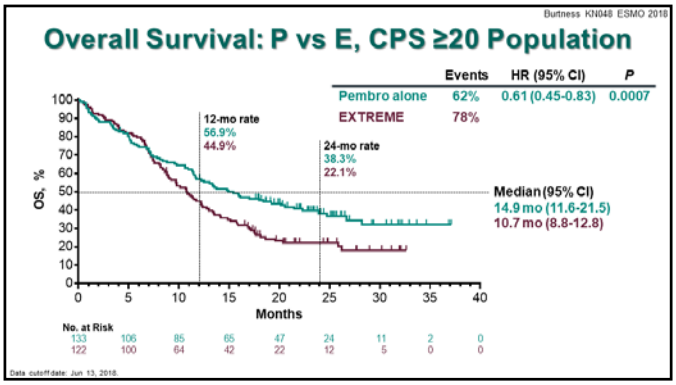
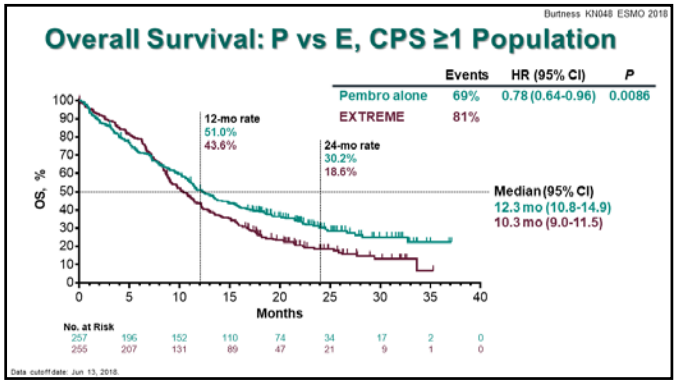
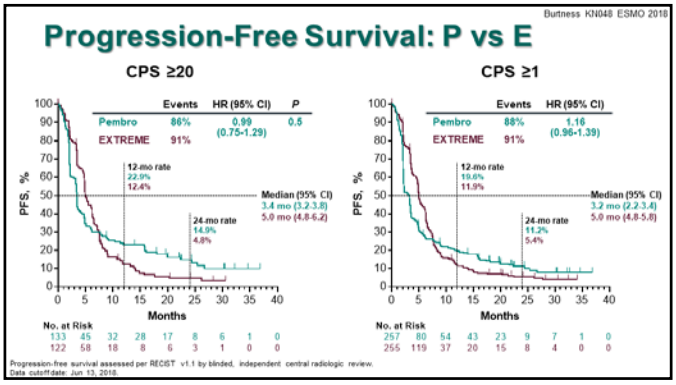
• ECOG PS 0 or 1
• Tissue sample for PD-L1 assessment[b]
• Known p16 status in the oropharynx[b]
Stratification Factors
• PD-L1 expression[a] (TPS ≥50% vs <50%)
• p16 status in oropharynx (positive vs negative)
• ECOG performance status (0 vs 1)
R (1:1:1)
Pembrolizumab 200 mg Q3W for up to 35 cycles
Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)
Pembrolizumab 200 mg Q3W for up to 20 cycles
Cetuximab 250 mg/m² Q1W[c] + Carboplatin AUC 5 OR Cisplatin 100 mg/m² + 5-FU 1000 mg/m²/d for 4 days for 6 cycles (each 3 wk)
Cetuximab 250 mg/m² Q1W


Burtness KN048 ESMO 2018
Overall Survival: P vs E, CPS ≥20 Population
Events HR (95% CI) P
Pembro alone 62% 0.61 (0.45-0.83) 0.0007
EXTREME 78%
12-mo rate 56.9% 44.9%
24-mo rate 38.3% 22.1%
Median (95% CI) 14.9 mo (11.6-21.5) 10.7 mo (8.8-12.8)
OS, %
Months
No. at Risk
133 106 85 65 47 24 11 2 0
122 100 64 42 22 12 5 0 0
Data cutoff date: Jun 13, 2018.


Burtness KN048 ESMO 2018
Overall Survival: P vs E, CPS ≥1 Population
Events HR (95% CI) P
Pembro alone 69% 0.78 (0.64-0.96) 0.0086
EXTREME 81%
12-mo rate 51.0% 43.6%
24-mo rate 30.2% 18.6%
Median (95% CI) 12.3 mo (10.8-14.9) 10.3 mo (9.0-11.5)
OS, %
Months
No. at Risk
257 196 152 110 74 34 17 2 0
255 207 131 89 47 21 9 1 0
Data cutoff date: Jun 13, 2018.

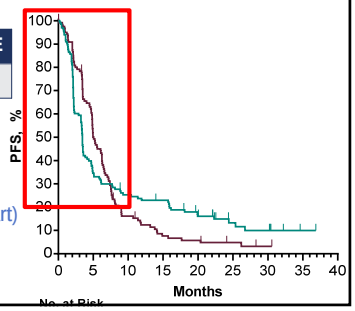

Burtness KN048 ESMO 2018
Progression-Free Survival: P vs E
CPS ≥20
Events HR (95% CI) P
Pembro 86% 0.99 (0.75-1.29) 0.5
EXTREME 91%
12-mo rate 22.9% 12.4%
24-mo rate 14.9% 4.8%
Median (95% CI) 3.4 mo (3.2-3.8) 5.9 mo (4.8-6.2)
CPS ≥1
Events HR (95% CI)
Pembro 88% 1.16 (0.96-1.39)
EXTREME 91%
12-mo rate 19.8% 11.9%
24-mo rate 11.2% 5.4%
Median (95% CI) 3.2 mo (2.2-3.4) 5.9 mo (4.8-5.8)
PFS, %
Months
No. at Risk
133 45 32 28 17 8 6 1 0
122 58 18 8 6 3 1 0 0
257 80 54 43 23 9 7 1 0
255 119 37 20 15 8 4 0 0
Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review.
Data cutoff date: Jun 13, 2018.

ARE WE TAKING RISKS IN CPS ≥ 20 ?

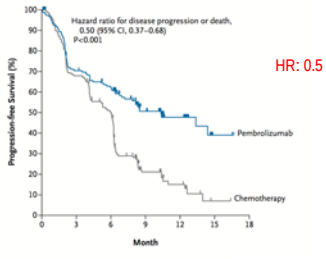
	Pembro	EXTREME
ORR	23%	36%

ORR: +13 % in favor of EXTREME

PFS in favor of EXTREME (at the start)



PEMBROLIZUMAB VS CT IN NSCLC WITH TPS ≥ 50



HR: 0.5

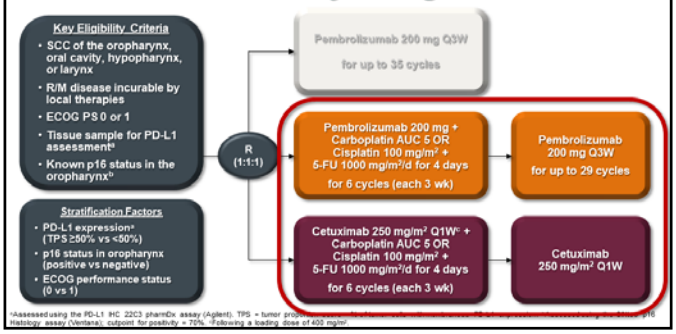
Reck et al. N. Engl. J. Med 2016

FREQUENCY OF PTS WITH TPS ≥ 50 OR CPS ≥ 20

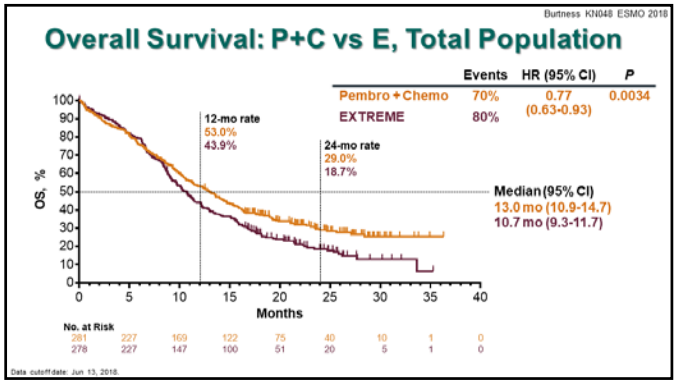
	CPS ≥ 20	TPS ≥ 50
SCCHN	39-44%	22-25%
NSCLC		25-30%

Paz-Ares et al. N. Engl. J. Med 2018, Reck et al. N. Engl. J. Med 2016, Cohen et al. ESMO 2017

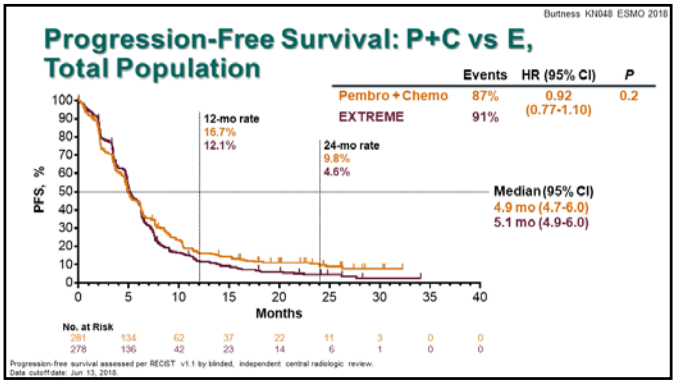
KEYNOTE-048 Study Design (NCT02358031)



Overall Survival: P+C vs E, Total Population



Progression-Free Survival: P+C vs E, Total Population

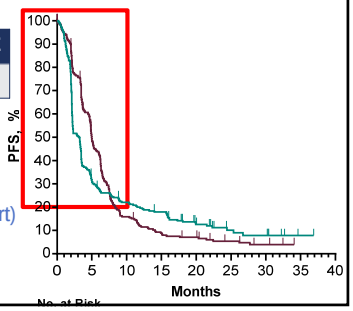


ARE WE TAKING RISKS IN CPS ≥ 1 ?

	Pembro	EXTREME
ORR	19%	35%

ORR: +16 % in favor of EXTREME

PFS in favor of EXTREME (at the start)



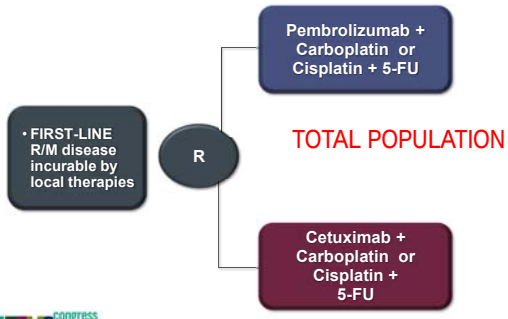
WHAT ABOUT 1 ≤ CPS < 20 ?

NO DATA

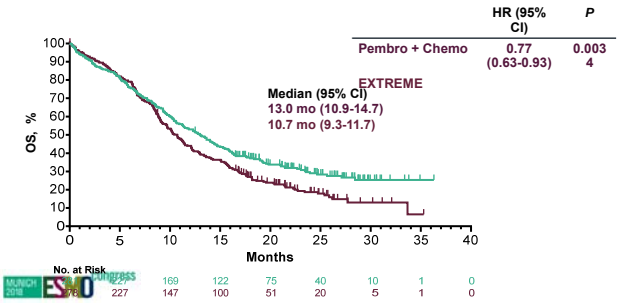
Let's do some mathematics !

1 ≤ CPS < 20 ? (USE WITH CAUTION, NOT VALIDATED)

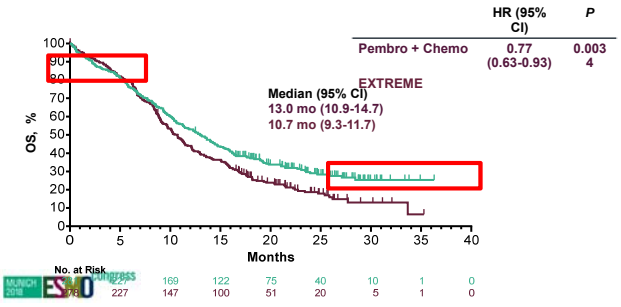
	Pembro N = 124	EXTREME N = 133
ORR	15%	34%
CR	3 %	2 %
PR	11%	32 %
SD	26 %	31 %
PD	47 %	16 %



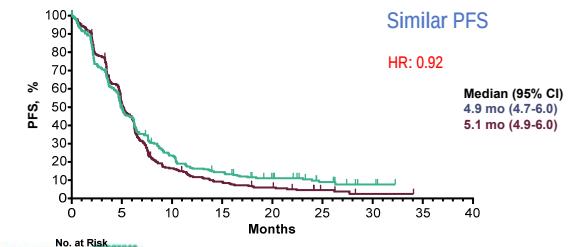
TOTAL POPULATION: SURVIVAL



TOTAL POPULATION: SURVIVAL



TOTAL POPULATION: PFS

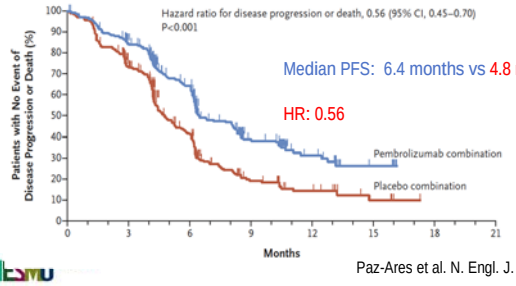


Similar PFS

HR: 0.92

Median (95% CI)
4.9 mo (4.7-6.0)
5.1 mo (4.9-6.0)

PFS IN SQUAMOUS NON-SMALL-CELL LUNG CANCER

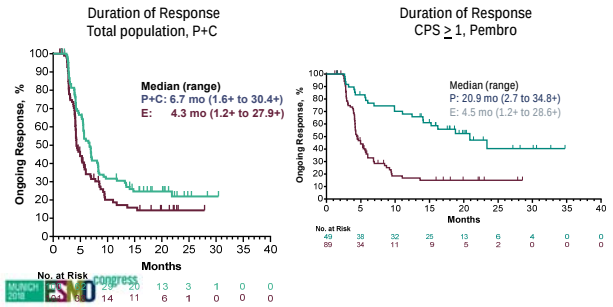


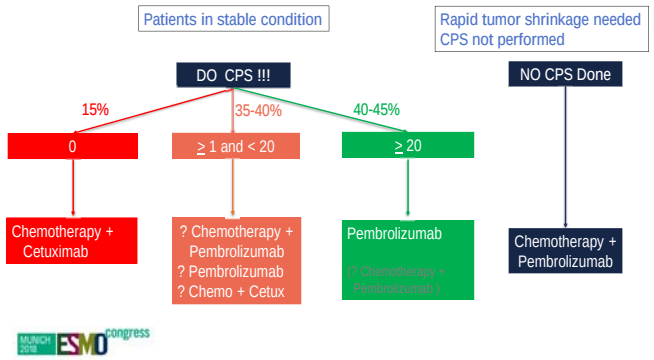
Median PFS: 6.4 months vs 4.8 months

HR: 0.56

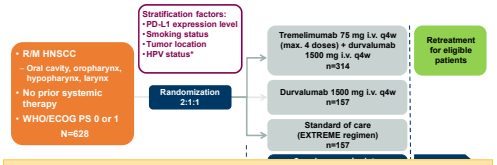
Paz-Ares et al. N. Engl. J. Med 2018

DURATION OF RESPONSE: INTRIGUING





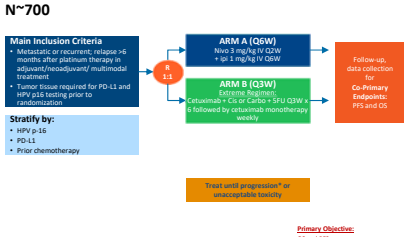
Anti-CTLA4 + anti- PD-(L)1



First line studies:

→ KeyNote 048: Pembro+chemo vs. Pembro vs. Extreme
→ KESTREL: Durva/**Treme** vs. Durva vs. Extreme
→ CheckMate 651: **Ipilimumab**/Nivo vs. Extreme
→ CheckMate 714: **Ipilimumab**/Nivo vs. Nivo

BMS: 1st Line (>6 months) - PIII CheckMate 651



III. The Future

→ **Curative Intent**

→ *years away (~2019/2020)*

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62

I-O CRT/RT combination trial for LA HNSCC:

			Primary Endpoints
RTOG 3504[1], Phase 1/3	Newly diagnosed	Nivolumab + cisplatin + IMRT Nivolumab + cetuximab + IMRT Nivolumab + IMRT	DLT, PFS
KEYNOTE-412[2], Phase 3	I-O naïve	Pembrolizumab + cisplatin + CRT Cisplatin + CRT	EFS
JAVELIN H&N 100[3], Phase 3	Newly diagnosed	Avelumab + CRT CRT	PFS
REACH[4], Phase 3	Newly diagnosed	Cisplatin + IMRT Avelumab + cetuximab + IMRT* Avelumab + cetuximab + IMRT† Cetuximab + IMRT	PFS

Eligibility criteria
•SCCHN
•HPV+ AND HPV
•HPV- STAGE III
•HPV+ T4/N2C/N
•N = 640

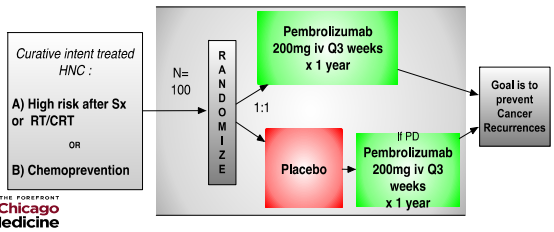
FOLLOW -UP → F/U†

Adjuvant for High Risk

THE UNIVERSITY OF CHICAGO MEDICINE Head & Neck Cancer Program

Patients at High-risk for recurrence:

1. After definitive treatment (surgery or RT/CRT) due to advanced Stage/ (+)Margins etc
2. High-risk – due Leukoplakia/recurrent early stage tumors



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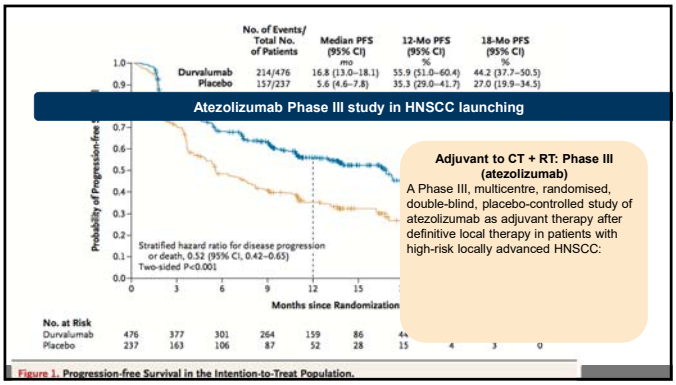

Atezolizumab Phase III study in HNSCC launching

Adjuvant to CT + RT: Phase III (atezolizumab)
A Phase III, multicentre, randomised, double-blind, placebo-controlled study of atezolizumab as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced HNSCC:

Figure 1. Progression-free Survival in the Intention-to-Treat Population.

Take Home messages:

- HNSCC is a good target for immune checkpoint inhibitors — The Present!
  - Highly immunogenic, both HPV(-) and HPV(+)
  - **Pembrolizumab and Nivolumab both approved by the FDA**
- **The field of HNSCC is likely going to change dramatically in 2018** — The Future!
  - **First line trials** are coming – KN48, CM651, with IDO (KN669, first line)
  - **Curative intent** trials are coming – KN412, Javelin, BMS/RTOG3504, as well as neoadjuvant (KN689) and PACIFIC-like Pembro/Atezo trials.
  - **Immunotherapy combination** are coming (CTLA-4, STAT3, TLR…)

Biomarkers **may improve upon PD-L1 IHC – and may find clinical utility (not SOC currently)**

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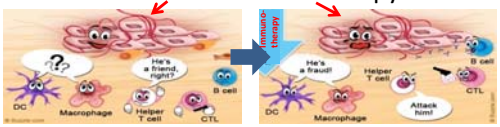
Thanks!

Cancer Immunotherapy



Slide Modified from Jason Luke, MD
http://goldenpraguе.us/strategies-for-cancer-vaccine-development/

Overview of Molecular Targeted Therapy on the Outcome of Early-stage NSCLC Patients with EML4-ALK Fusion Gene and the Application of TKIs

Anne Tsao, MD

ALK – Frontline Option 2018

Anne S. Tsao, M.D.

Professor
Director, Mesothelioma Program
Director, Thoracic Chemo-XRT Program

October 27, 2018

The University of Texas
MD ANDERSON
CANCER CENTER

Department of Thoracic/Head & Neck Medical Oncology

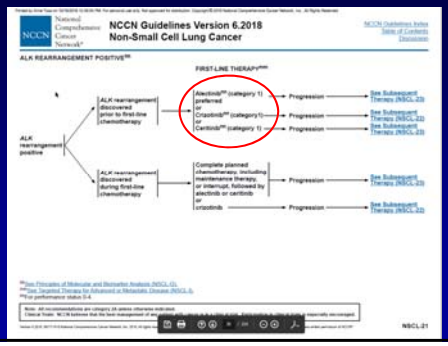
Conflict of Interest Disclosure

Advisory Board: BMS, Genentech/Roche, Merck, Eli Lilly, Novartis, Ariad, EMD Serono, Boehringer Ingelheim, AstraZeneca, Takeda Oncology

Outline: ALK Frontline

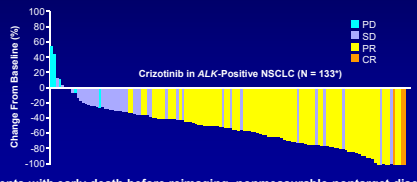
Background	Crizotinib (PROFILE) Ceritinib (ASCEND) Alectinib (ALEX)
IASLC update	ALTA-1L Brigatinib
Upcoming agents	Lorlatinib Ensartinib
ALK and I/O	Current Data

NCCN Guidelines



Targeting *ALK* Gene Translocations

- *ALK/EML4 fusions*
  - Younger patients with light/never smoking history; males > females
  - Found in 2% to 5% of adenocarcinomas
  - Adenocarcinoma ± signet ring morphology
  - Generally mutually exclusive with *EGFR*, *KRAS*, and other driver mutations



*Excluded patients with early death before reimaging, nonmeasurable nontarget disease, or indeterminate responses.

Camidge DR, et al. Lancet Oncol. 2012;13:1011-1019.

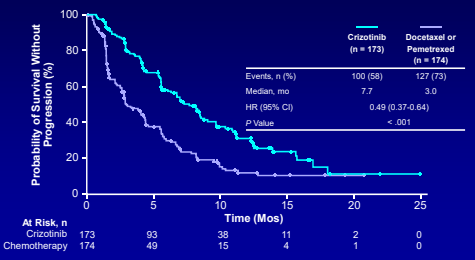
Crizotinib PROFILE Trials

	PROFILE 1001[1] (N=143)	PROFILE 1005[2] (N=259)	PROFILE 1007[3] (N=172)	PROFILE 1014[4] (N=172)
Phase	1	2	3	3
Line of therapy	Any line	2nd line and beyond	2nd line	1st line
ORR	61%	60%	65%	74%
PFS, median (mos)	9.7	8.1	7.7	10.9
Survival probability at 12 mos	75%	NA	70%	NA

[1]Camidge et al., Lancet Onc 13(10): 1011-9, 2012
[2]Kim et al., ASCO 2012
[3]Shaw et al., NEJM 368(25): 2385-94 , 2013
[4]Mok et al., ASCO Abstract #8002, 2014

PROFILE 1007: Crizotinib vs Standard Chemotherapy in *ALK*+ NSCLC: PFS

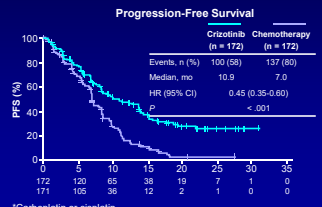
- Phase III trial (N = 347): ALK-positive patients with advanced or metastatic NSCLC and **1 prior platinum regimen**



Shaw AT, et al. N Engl J Med. 2013;368:2385-2394.

PROFILE 1014: Crizotinib vs Pemetrexed/ Platinum* in Advanced NSCLC

- Phase III trial (N = 343) *ALK*-positive patients with nonsquamous NSCLC and no prior systemic treatment for advanced disease



*Carboplatin or cisplatin.

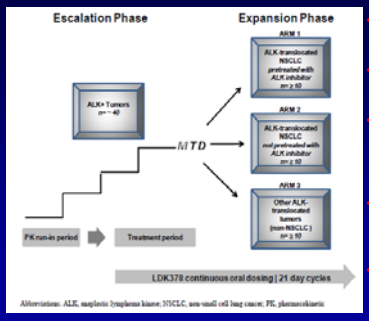
- PFS benefit seen across all subgroups
  - Eg, age, sex, smoker, time since Dx
- ORR: 74% with crizotinib vs 45% with chemo ($P < .001$)

Solomon BJ, et al. N Engl J Med. 2014;371:2167-2177.

Crizotinib

- **Crizotinib had superior RR, PFS, OS compared to frontline chemo in ALK+ NSCLC.**
- **Crizotinib is well-tolerated with twice daily dosing.**
- **Crizotinib was FDA approved August 26, 2011**
- **Crizotinib was also FDA approved March 11, 2016 for ROS-1+ NSCLC.**
- **However, limited CNS penetrance.**

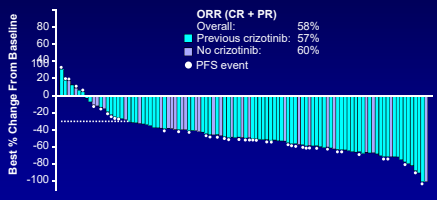
Ceritinib Phase I Trial



- **130 ALK rearranged solid tumor patients**
- **Dose-escalation n=59 Dose expansion n=71**
- **NSCLC patients (n=122) had to have ALK positivity by break apart FISH testing in over 15% of tumor cells.**
- **Ceritinib was started at 50 mg daily for a 21-day cycle with restaging every 6 weeks**
- **Of 122 NSCLC patients, 83 (68%) had prior crizotinib.**

Shaw et al. NEJM Vol 370 (13):1189-1197, March 2014

Ceritinib in *ALK*+ NSCLC: Best % Change From Baseline in Target Lesions



- **Other second-generation ALK inhibitors in development: alectinib; brigatinib; X-396; ASP3026; GSK1838705; CEP-28122**

Shaw AT, et al. N Engl J Med. 2014;370:1189-1197.

Phase III ASCEND-4

KEY ELIGIBILITY
- ***ALK*+ by central IHC testing**
- **Advanced or metastatic *ALK*+ NSCLC**
- **Treatment-naïve for metastatic/recurrent disease**
- **WHO PS 0–2**
- **RECIST Measurable disease**
- **Asymptomatic brain metastases allowed**
- **No GI disease that could impact absorption**
- **h/o ILD**

RANDOMIZE

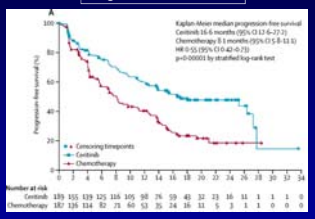
- **Ceritinib 750 mg/day** N=189
- **Cisplatin or Carboplatin plus pemetrexed for 4** → **Pemetrexed maintenance**

*cisplatin 75 mg/m2 or carboplatin (AUC 5 or 6) plus pemetrexed 500 gm/2 IV every 3 weeks for 4 cycles

Soria et al. Lancet Oncology 389: 917-929, 2017

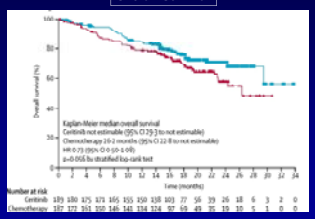
ASCEND-4 Survival

Progression-free Survival



HR 0.55, p<0.00001
Ceritinib 16.6 vs 8.1 months chemo

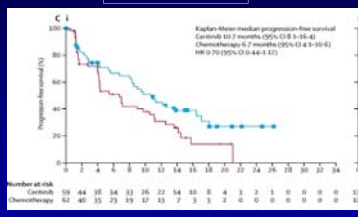
Overall Survival



HR 0.56, p=0.056
Ceritinib NR vs 26.2 months chemo

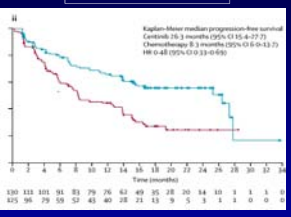
ASCEND-4 PFS by Brain Mets

Brain mets at baseline



HR 0.7
Ceritinib 10.7 vs 6.7 months chemo

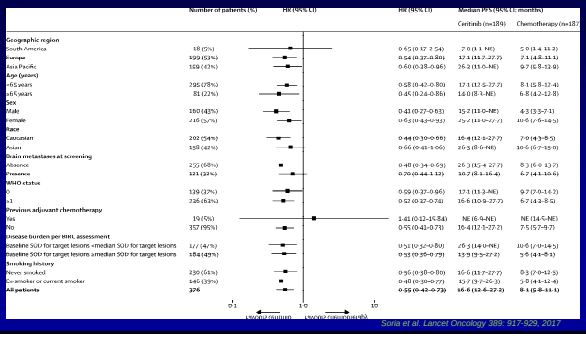
No Brain mets at baseline



HR 0.48
Ceritinib 26.3 vs 8.3 months chemo

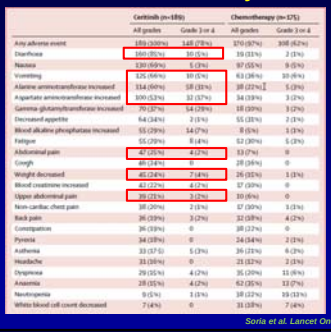
Soria et al. Lancet Oncology 389: 917-929, 2017

ASCEND-4 PFS



Soria et al. Lancet Oncology 389: 917-929, 2017

ASCEND-4 Toxicity



Soria et al. Lancet Oncology 389: 917-929, 2017

Ceritinib Practical GI Toxicity Management

- **Standard practice:**
  - Patient education
  - Symptomatic treatment with antiemetics and/or antidiarrheal medication
  - Take at night
  - Consider taking with food.
    - Prior food effect study in healthy volunteers showed high-fat meals increased ceritinib systemic exposure by 43%
- **Preventative measures**
  - Empiric use of anti-emetics, anti-diarrheals, and anti-cholinergics
- **Dose interruption**
- **Dose modification (600 mg, 450 mg)**

Proposed Prophylactic GI Management Strategies for Ceritinib

Regimen A: ondansetron 8 mg, along with either diphenoxylate and atropine 2.5 mg or loperamide 2 mg, to be taken orally 30 minutes prior to the ceritinib dose.

Regimen B: dicyclomine 20 mg twice daily (to be taken orally starting with the first ceritinib dose), ondansetron 8 mg (to be taken orally 30 minutes prior to ceritinib dose for the first seven doses), and loperamide 2 mg (to be taken orally as needed with the onset of diarrhea; two tablets at onset and one tablet with every loose stool).

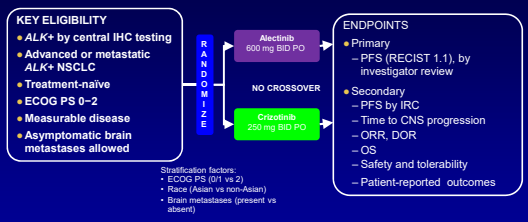
All agents were stopped at week 3 unless symptoms persisted.

Schaefer et al. Cancer Management Research 8: 33-38, 2016

Ceritinib

- Ceritinib has improved RR, PFS and OS compared to chemotherapy in ALK+ NSCLC.
- GI toxicity management is necessary and possibly dose-reductions as well.
- FDA approved ceritinib for ALK+ salvage therapy in April 2014.
- Ceritinib was FDA approved for frontline use in ALK+ NSCLC on May 26, 2017.

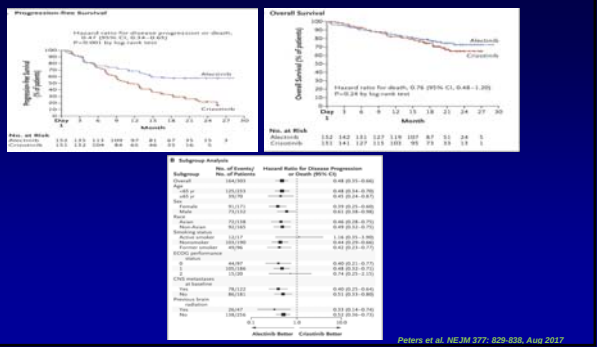
ALEX Study Design



ALK, anaplastic lymphoma kinase; IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PO, by mouth; PFS, progression-free survival; IRC, independent review committee; CNS, central nervous system; ORR, objective response rate; DOR, duration of response; OS, overall survival

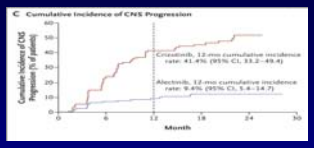
Peters et al. NEJM 377: 829-838, Aug 2017

ALEX Survival



Peters et al. NEJM 377: 829-838, Aug 2017

ALEX CNS Activity



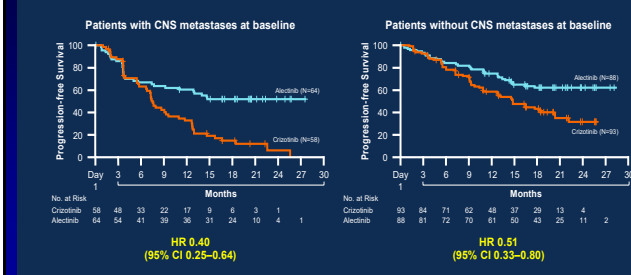
CNS objective response rate*

Measurable CNS lesions at baseline	Crizotinib (N=22)	Alectinib (N=21)
CNS responders, n (%)	11 (50)	17 (81)
(95% CI)	(28–72)	(58–95)
CNS complete response, n (%)	1 (5)	8 (38)
Median DOR in the CNS, months	5.5	17.3
(95% CI)	(2.1–17.3)	(14.8-NE)

Measurable and non-measurable CNS lesions at baseline	Crizotinib (N=58)	Alectinib (N=64)
CNS responders, n (%)	15 (26)	38 (59)
(95% CI)	(15–39)	(46–72)
CNS complete response, n (%)	5 (9)	29 (45)
Median DOR in the CNS, months	3.7	NE
(95% CI)	(3.2–6.9)	(17.3-NE)

Peters et al. NEJM 377: 829-838, Aug 2017

ALEX PFS by Baseline CNS Metastases



*investigator assessment

Peters et al. NEJM 377: 829-838, Aug 2017

ALEX Toxicity

Peters et al. NEJM 377: 829-838, Aug 2017

Alectinib

- Alectinib has improved RR, PFS and OS compared to chemotherapy in ALK+ NSCLC.
- Alectinib is well-tolerated.
- FDA approved alectinib for ALK+ salvage therapy in December 2015.
- Alectinib (600 mg BID) was FDA approved for frontline use in ALK+ NSCLC on November 6, 2017 after the ALEX trial.
- Note – J-ALEX (Japan) uses 300 mg BID.

Comparison First Line ALK Inhibitors

FL Trial Agent	ORR	Median PFS (months)	Intracranial median PFS (months)	OS
PROFILE 1014 (crizotinib)	74%	10.9	-	56.6% (4 Yrs)
ASCEND-4 (ceritinib)	73%	16.6	10.7 (BM+) 26.3 (BM-)	NR
ALEX (alectinib)	83%	NR	NR	NR

Solomon B.J, et al. N Engl J Med. 2014;371:2167-2177
Soria et al. Lancet Oncology 389: 917-929, 2017
Peters et al. NEJM 377: 829-838, Aug 2017

Toxicity Comparison of Selected ALK inhibitors

Agent	Toxicities
Crizotinib	Vision Transaminitis Nausea, diarrhea Peripheral edema
Ceritinib	Abdominal pain Nausea Diarrhea Transaminitis
Alectinib	Myalgia LFT elevation
Brigatinib	Pulmonary toxicity
Lorlatinib	Hypercholesterolemia CNS (delirium, MS changes)

Indirect Comparison* of ALK Inhibitors: Safety

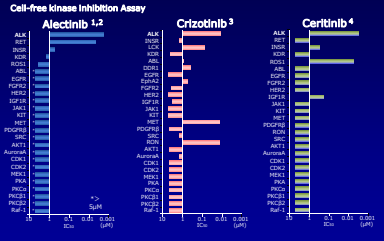
ALK inhibitors	Ceritinib		Alectinib	Brigatinib[a]
Common AEs All grades (≥20%)	Diarrhea 85% Nausea 69% Vomiting 67% Fatigue 45% Abdominal pain 40% ↓Appetite 34% Weight loss 24% Cough 25%	Rash 21% Non-cardiac chest pain 21% Constipation 20%	Fatigue 41% Constipation 34% Edema 30% Myalgia 29%	Nausea 40% Diarrhea 38% Fatigue 36% Cough 34% Headache 27% Vomiting 23% Dyspnea 21% Hypertension 21%
Grade 3-4 AEs / Laboratory abnormalities (≥3%)	Fatigue 7% Vomiting 5% Diarrhea 4.8% Abdominal pain 3.7% Weight loss 3.7%	↑GGT 49% ↑ALT 34% ↑AST 21% ↑Alkaine phosphatase 12% ↑Amylase 8% ↑Lipase 6% Anemia 4.2% ↑Creatinine 4.2% ↓Phosphate 3.7%	Dyspnea 3.6% ↑ALT 4.8% ↑CPK 4.6% Lymphopenia 4.6% Hypokalemia 4% ↑AST 3.6%	Hypertension 6.4% Pneumonia 5.5% Rash 3.6% ↑CPK 12% ↑Lipase 5.5% Lymphopenia 4.5% Hyperglycemia 3.6% ↓Phosphorous 3.6%

[a]AEs are for the 90→180 mg dose of brigatinib
*Cross-trial comparisons are confounded by differences in trial design and study populations
Zykadia (ceritinib) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp;2015.
Alecensa (alectinib) [package insert]. South San Francisco, CA: Genentech USA, Inc;2015.
Alunbrig (brigatinib) [package insert]. Cambridge, MA: Takeda Pharmaceutical Company Limited. USA 2017.

Camidge, R WCLC 2017 Satelite symposium

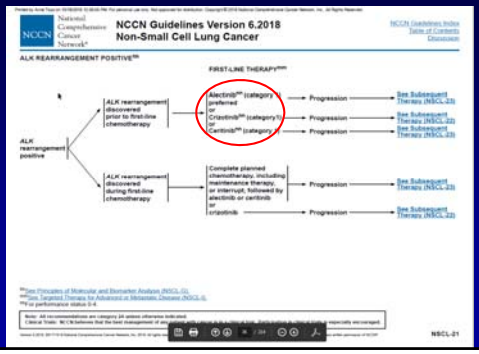
Safety overview based on US prescribing information

First Line ALK Inhibitors



1. Sakamoto H et al. Cancer Cell 2011, 2. Kodama T et al. Mol Cancer Ther 2014, 3. Gadgeel SM et al. WCLC 2013, 4. Adjei AA ASCO 2015

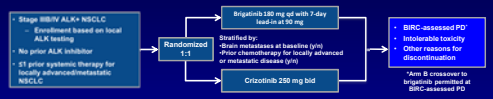
NCCN Guidelines



Outline: ALK Frontline

Background	Crizotinib (PROFILE) Ceritinib (ASCEND) Alectinib (ALEX)
IASLC update	ALTA-1L Brigatinib
Upcoming agents	Lorlatinib Ensartinib
ALK and I/O	Current Data

ALTA-1L: Phase 3, Open-label, Randomized, Multicenter, Study (NCT02737501)



Disease assessment every 8 weeks, including brain MRI for all patients

- Primary endpoint: Blinded independent review committee (BIRC)-assessed PFS per RECIST v1.1
- Key secondary endpoints: Confirmed ORR, confirmed intracranial ORR, intracranial PFS, OS, safety, and tolerability
- Statistical considerations: ~270 total patients (198 events); 135 in each arm to detect a 6-month improvement in PFS (HR=0.625), assuming:
  - 10-month PFS in crizotinib arm
  - 2 planned interim analyses at 99 (50%) and 149 (75%) total expected events

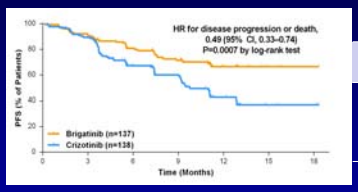
Trial fully accrued in August 2017 (N=275)

First Interim Analysis:
- A total of 99 PFS events are included
- According to the pre-specified O'Brien Flemming Lan-DeMets alpha spending function, a 2-sided P-value of 0.0031 will be used to define the threshold for significance

Camidge et al. IASLC abstract 2018

Primary Endpoint: BIRC-Assessed PFS

- Brigatinib met the prespecified threshold for statistical superiority vs crizotinib



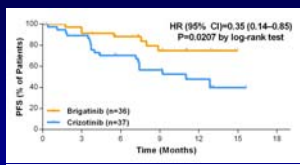
Treatment	No. (%) of Patients With Events	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=137)	36 (26)	NR (NR–NR)	67 (56–75)
Crizotinib (n=138)	63 (46)	9.8 months (9.0–12.9)	43 (32–53)

- Investigator-assessed median PFS was NR (95% CI, NR–NR) in the brigatinib arm and 9.2 months (95% CI, 7.4–12.9 months) in the crizotinib arm (HR, 0.45 [95% CI, 0.30–0.68]; log-rank P=0.0001)
- 1-year OS probability: brigatinib, 85% (95% CI, 76%–91%); crizotinib, 86% (77%–91%)

Camidge et al. IASLC abstract 2018

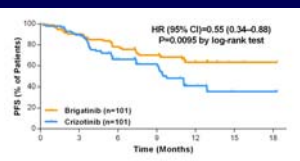
PFS Based on Prior Chemotherapy in the Locally Advanced or Metastatic Setting

Patients With Prior Chemotherapy



Treatment	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=36)	NR (NR–NR)	75 (54–87)
Crizotinib (n=37)	11.0 months (7.2–NR)	48 (29–64)

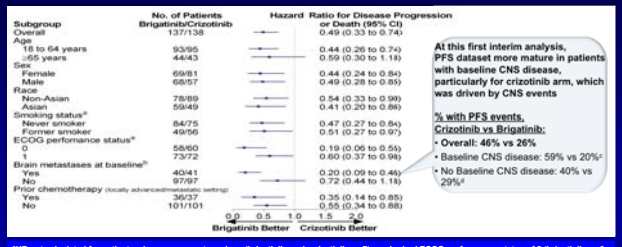
Patients Without Prior Chemotherapy



Treatment	Median PFS (95% CI)	1-Year PFS, % (95% CI)
Brigatinib (n=101)	NR (NR–NR)	63 (50–74)
Crizotinib (n=101)	9.8 months (9.0–12.9)	41 (28–53)

Camidge et al. IASLC abstract 2018

BIRC-Assessed PFS by Subgroup



At this first interim analysis, PFS dataset more mature in patients with baseline CNS disease, particularly for crizotinib arm, which was driven by CNS events

% with PFS events, Crizotinib vs Brigatinib:
- Overall: 46% vs 26%
- Baseline CNS disease: 59% vs 20%[c]
- No Baseline CNS disease: 40% vs 29%[d]

[a]HR not calculated for patients who were current smokers (brigatinib, n=4; crizotinib, n=7) or who had ECOG performance status of 2 (brigatinib, n=6; crizotinib, n=6) due to insufficient patient numbers, as dictated by the Statistical Analysis Plan. [b]Baseline brain metastases as assessed by investigator. [c]Cumulative incidence by competing risk analysis (crizotinib vs. brigatinib), 45% vs 26% with CNS progression (without prior systemic progression or death); [d]5% vs 1% with CNS progression (without prior systemic progression or death).

Camidge et al. IASLC abstract 2018

ORR

Systemic Objective Response[a] (ITT Population)

	Brigatinib n=137	Crizotinib n=138	OR (95% CI)
Confirmed ORR, % (95% CI)	71 (62–78)	60 (51–68)	1.59 (0.96–2.62) P=0.0678
Confirmed CR, %	4	5	
Confirmed PR, %	67	55	
ORR at ≥1 assessment, % (95% CI)	76 (68–83)	73 (65–80)	1.13 (0.66–1.97) P=0.6512
CR, %	7	8	
PR, %	69	65	
Median DoR in confirmed responders, mo (95% CI)	NR (NR–NR)	11.1 (9.2–NR)	
12-month probability of maintaining response, % (95% CI)	75 (63–83)	41 (26–54)	

[a]Assessed by the BIRC.

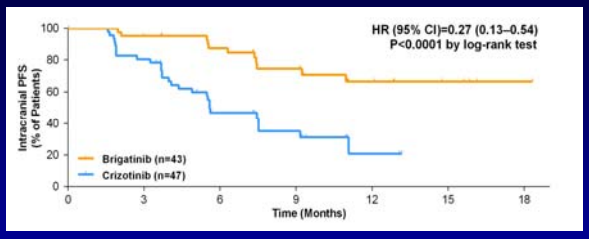
Intracranial Objective Response[a] in Patients with Brain Metastases at Baseline

Measurable[b] brain metastases at baseline	Brigatinib n=18	Crizotinib n=21	OR (95% CI)
Confirmed intracranial ORR, % (95% CI)	78 (52–94)	29 (11–52)	10.42 (1.90–57.05) P=0.0028
CR, %	11	0	
PR, %	67	29	
Intracranial ORR at ≥1 assessment, % (95% CI)	83 (59–96)	33 (15–57)	9.29 (1.88–45.85) P=0.0023
Any brain metastases at baseline	n=43	n=47	
Confirmed intracranial ORR, % (95% CI)	67 (51–81)	17 (8–31)	13.00 (4.38–38.61) P<0.0001
CR, %	37	4	
PR, %	30	13	
Intracranial ORR at ≥1 assessment, % (95% CI)	79 (64–90)	23 (12–38)	16.30 (5.32–49.92) P<0.0001

[a]Assessed by the BIRC.
[b]≥10 mm in diameter.

Camidge et al. IASLC abstract 2018

Intracranial PFS in Patients With Any Brain Metastases at Baseline



Treatment	Median Intracranial PFS (95% CI)	1-Year PFS Probability, % (95% CI)
Brigatinib (n=43)	NR (11.0–NR)	67 (47–80)
Crizotinib (n=47)	5.6 months (4.1–9.2)	21 (6–42)

Camidge et al. IASLC abstract 2018

TEAEs Reported in >20% of All Patients or That Differed by >5 Percentage Points Between Arms

	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	49	1	55	2
Increased blood CPK	39	16	15	1
Nausea	26	1	56	3
Cough	25	0	16	0
Increased AST	23	1	25	6
Hypertension	23	10	7	3
Increased ALT	19	1	32	9
Increased lipase	19	13	12	5
Vomiting	18	1	39	2
Constipation	15	0	42	1
Increased amylase	14	5	7	1
Pruritus	13	1	4	1
Rash	10	0	2	0
Decreased appetite	7	1	20	3
Dermatitis acneiform	7	0	1	0

	Brigatinib (n=136), %		Crizotinib (n=137), %	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Dyspepsia	6	0	13	0
Epistaxis	6	0	0	0
Bradycardia	5	1	12	0
Peripheral edema	4	1	39	1
Dysgeusia	4	0	19	0
Upper abdominal pain	4	1	13	1
Pain in extremity	4	0	12	1
Increased blood creatinine	2	0	14	1
Neutropenia	1	0	9	4
Pleural effusion	1	1	7	1
Photopsia	1	0	20	1
GERD	1	0	9	0
Hypoalbuminemia	1	0	6	1
Visual impairment	0	0	16	0
Deep vein thrombosis	0	0	6	0

- Interstitial lung disease (ILD)/pneumonitis at any time: brigatinib 4% (5/136); crizotinib 2% (3/137)
  - Early-onset ILD/pneumonitis (within 14 days of treatment initiation): brigatinib, 3% (onset: Days 3–8); crizotinib, none reported
- Dose reduction due to AEs (brigatinib/crizotinib): 29%/21%; discontinuation due to AEs: 12%/8%
  - For brigatinib, reductions due to increased CPK (10.3%), increased lipase (5.1%); increased amylase (2.9%) and increased AST, hypertension, pneumonitis, pruritic rash (1.5% each)
- No clinical cases of pancreatitis in either arm; no difference in incidence of any grade myalgia or musculoskeletal pain between arms (brigatinib/crizotinib: 6%/4% and 4%/6%, respectively); no grade ≥3 myalgia or musculoskeletal pain reported

Brigatinib excess AEs dominated by CPK, lipase, and amylase increases

Camidge et al. IASLC abstract 2018

Brigatinib

- ALTA-1L was conducted in ALK+ patients defined using multiple ALK diagnostics and allowed for prior chemotherapy exposure
- Brigatinib has a superior PFS versus crizotinib by BIRC (HR, 0.49; P=0.0007)
- Brigatinib was well tolerated.
- Early-onset pneumonitis may be unique to brigatinib among ALK TKIs, but is rare (3%) and the event rate appears lower in ALTA-1L than in later line trials.
- Brigatinib was granted FDA accelerated approval for crizotinib-refractory ALK+ NSCLC on April 28, 2017.
- Brigatinib is a new first-line treatment option for ALK+ NSCLC

Camidge et al. IASLC abstract 2018

Outline: ALK Frontline

Background	Crizotinib (PROFILE) Ceritinib (ASCEND) Alectinib (ALEX)
IASLC update	ALTA-1L Brigatinib
Upcoming agents	Lorlatinib Ensartinib
ALK and I/O	Current Data

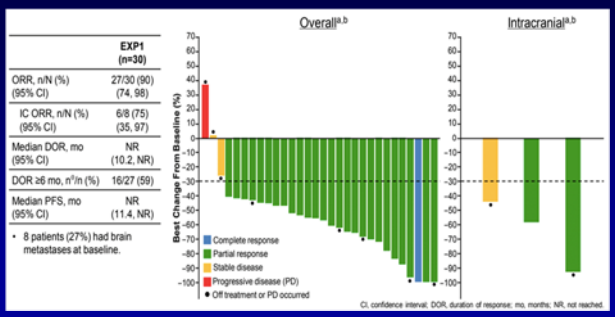
Frist Line ALK-TKI - Phase III Trials

Sponsor	Trial	Agent	Comparison	N	Anticipated dates	NCT
Pfizer	CROWN	Lorlatinib	Crizotinib	280	Dec 2019	NCT03052608
XCovery	eXalt3	Ensartinib	Crizotinib	402	April 2020	NCT02767804

Lorlatinib in Treatment-Naïve ALK+ Patients

	EXP1 (n=30)
ORR, n/N (%) (95% CI)	27/30 (90) (74, 98)
IC ORR, n/N (%) (95% CI)	6/8 (75) (35, 97)
Median DOR, mo (95% CI)	NR (10.2, NR)
DOR ≥6 mo, n[c]/n (%)	16/27 (59)
Median PFS, mo (95% CI)	NR (11.4, NR)

- 8 patients (27%) had brain metastases at baseline.



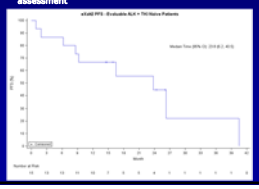
Solomon BJ, et al. WCLC 2017 abstr#8573

Ensartinib in Treatment-Naïve ALK+ Patients

- Ensartinib targets EML4-ALK and point mutations T1151M, G1269A, L1196M, G1202R, and V1149M.
- Ensartinib also targets MET, ABL, Axl, EPHA2, LTK, ROS1, and SLK.
- In crizotinib refractory ALK patients, ORR 72%
- In pretreated patients with at least one 2nd gen TKI, ORR 23% and DCR 50%
- Ensartinib 225 mg po daily

Best Response, n (%)	ALK+ TKI Naïve Evaluable Pts at ≥ 200 mg (n=15)
PR	12 (80%)
SD	1 (7%)
PD	2 (13%)
Overall Response Rate	12 (80%)

* Evaluable ALK+ patients at ≥ 200 mg who completed 1 cycle and had post baseline response assessment



Wakelee et al, WCLC 2017, MA07.02

Outline: ALK Frontline

Background	Crizotinib (PROFILE) Ceritinib (ASCEND) Alectinib (ALEX)
IASLC update	ALTA-1L Brigatinib
Upcoming agents	Lorlatinib Ensartinib
ALK and I/O	Current Data

PD-1 Immunotherapy Is No Longer Recommended by the NCCN as a Treatment Alternative for *ALK*+ NSCLC

NCCN Guidelines previously recommended PD-1 immunotherapy as a treatment alternative after progression on a second-line ALK inhibitor in PD-L1 expression positive (≥50%) patients.[1] This recommendation has been removed.[2]

- Never-smokers may have decreased responses to a PD-1/PD-L1 antibody in comparison with current/former smokers[3-6]
- A retrospective analysis of 58 patients treated with PD-1/PD-L1 inhibitors suggested that patients with ALK rearrangements may have shorter PFS and lower response rates to PD-1/PD-L1 immunotherapy compared with ALK-negative patients[7]

Reprinted from Gainor JF, et al. Clin Cancer Res. 2016;22(18):4585-4593. with permission from AACR.

ORR=objective response rate; WT=wild-type.

NCCN Guidelines Version 6.2018 Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

TARGETED THERAPY FOR ADVANCED OR METASTATIC DISEASE

Subsequent Therapy
- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks. Timing of CT scans within Guidelines parameters is a clinical decision.

Sensitizing *EGFR* Mutation
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Gefitinib[3,4]
  - Osimertinib[5]
- Subsequent therapy
  - Osimertinib[6]

***ALK* Rearrangement**
- First-line therapy
  - Alectinib[7,8]
  - Ceritinib[9]
  - Crizotinib[10,11]
- Subsequent therapy
  - Alectinib[12,13]
  - Brigatinib[14]
  - Ceritinib[15]

***ROS1* Rearrangement**
- First-line therapy
  - Ceritinib[16]
  - Crizotinib[17]

***BRAF* V600E Mutation** 1
- First-line therapy
  - Dabrafenib/trametinib[18]
- Subsequent therapy
  - Dabrafenib/trametinib[19,20]

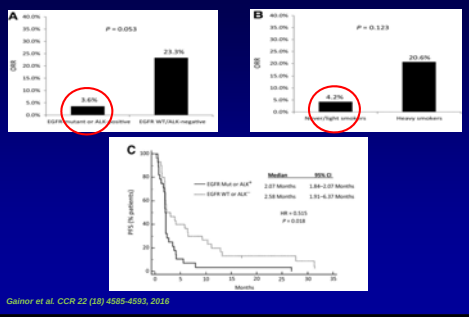
PD-L1 Expression
- First-line therapy
  - Pembrolizumab[21,22]
- Subsequent therapy
  - Atezolizumab[23]
  - Nivolumab[24,25]
  - Pembrolizumab[26]

References

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

NSCL-I
1 OF 2

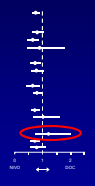
EGFR Mutant or ALK positive NSCLC or Never-smokers have Lower Response Rates to Immunotherapy



Gainor et al. CCR 22 (18) 4585-4593, 2016

CheckMate 057: Treatment Effect on OS in Predefined Subgroups

	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.65 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)

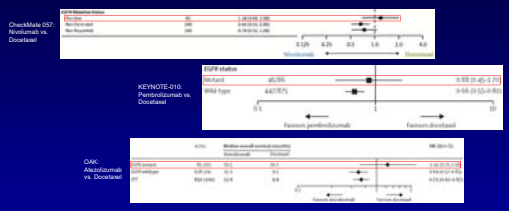


These data suggest that perhaps PD-1 inhibitors are less effective in EGFR-mutated cancers.

Note: EGFR-mutated cancers generally carry low mutational load

Paz-Ares et al., ASCO 2015, abstr LBA109

OS With Immune Checkpoint Inhibitors in Patients With EGFR-mutant Lung Cancers



These data suggest that PD-1 inhibitors are less effective in EGFR-mutated cancers.

Borghaei et al. N Engl J Med. 2015;373:1627
Herbst et al. Lancet. 2016;387:1540
Rittmeyer et al. Lancet. 2017;389:255

Immune Checkpoint Inhibitors Indications

- **PD-1**
  - **Nivolumab**
    - **Previously treated patients with advanced NSCLC, regardless of histology; no requirement for PD-L1 expression testing. Patients with EGFR or ALK mutations should have disease progression on FDA approved therapy for these mutations prior to receiving nivolumab**
  - **Pembrolizumab**
    - **Patients whose disease progresses on or after platinum-based chemotherapy whose tumors express PD-L1 (≥ 1%). Patients with EGFR or ALK mutations should have disease progression on FDA-approved therapy for these mutations**
    - **First line treatment in patients with PD-L1 expression levels ≥50%, with no EGFR or ALK genomic tumor aberrations**
    - **First-line combination therapy with pemetrexed and carboplatin irrespective of PD-L1 expression (conditional approval 5/17) in Non-Squamous NSCLC in absence of EGFR or ALK aberrations**
- **PD-L1**
  - **Atezolizumab**
    - **For patients whose disease progresses during or following platinum-containing chemotherapy, regardless of histology or PDL1 level. Patients with EGFR or ALK mutations should have disease progression on FDA approved therapy for these mutations prior to receiving atezolizumab**
  - **Durvalumab**
    - **Indicated as consolidation post chemo-XRT in pts with stage III NSCLC, independent of histology or EGFR/ALK status, based on superior PFS**

Data from prescribing information; www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm525780.htm

Thank you

Anne S. Tsao, M.D.
Professor
Director, Mesothelioma Program
Director, Thoracic Chemo-XRT Program

October 27, 2018

The University of Texas
MD ANDERSON
CANCER CENTER

Department of Thoracic/Head & Neck Medical Oncology

Discuss Emerging Strategies and Challenges Due to Secondary or Acquired Resistance to Small Molecule TKIs in Patients with ALK-rearranged NSCLC

Vincent Lam, MD

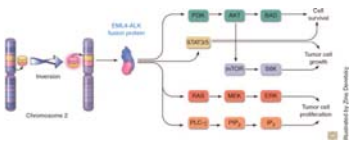
Strategies for Acquired Resistance to ALK TKIs

Vincent Lam, M.D.
Assistant Professor, MD Anderson Cancer Center
Houston, TX

October 27, 2018

ALK fusions are heterogeneous

- Diagnosed by FISH, IHC, RT-PCR, NGS
- More than 20 different *ALK* fusion partners across different cancers
- Multiple variants per given fusion protein
  - *EML4-ALK* has over 10 variants
  - Variants can have different *ALK* TKI sensitivity

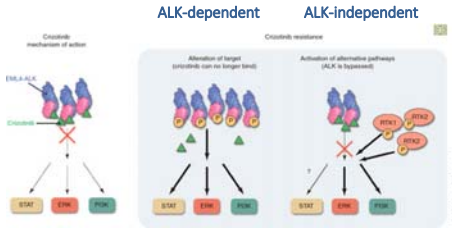


Solomon, Clinical Pharmacology & Therapeutics 2013

Conflict of Interest Disclosure

No relevant financial disclosures

ALK TKI resistance can be grouped into 2 main categories

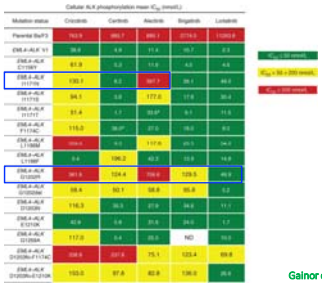


Bypass signaling:
EGFR, HER2, MET, KIT, IGF1R

Lineage changes:
EMT, SCLC

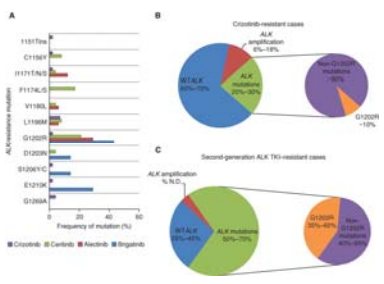
Solomon, Clinical Pharmacology & Therapeutics 2013

ALK TKIs have different sensitivities



Gainor et al, Cancer Discovery 2016

ALK resistance is varied and TKI dependent



Post-crizotinib

- Lower rate of ALK resistance mutations but generally still ALK-dependent
- More potent ALK TKI typically works
- Consider re-biopsy

Post 2nd gen ALK TKI

- Resistance mutation(s) more prevalent
- Re-biopsy!

Lin et al, Ca Discovery 2017

Current post-crizotinib landscape

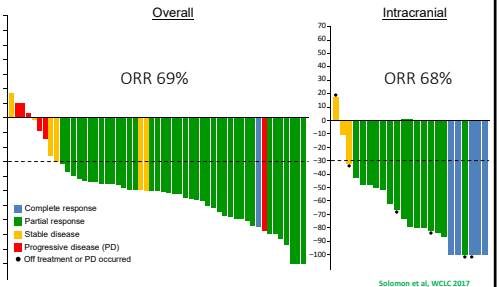
	Ceritinib ASCEND-5 (Ph 3)[1]	Alectinib ALUR (Ph 3)[2]	Brigatinib 180mg ALTA (Ph 2)[3]	Lorlatinib (Ph 1/2)[4]	Ensartinib (Ph 2)[5]
		FDA approval		FDA breakthrough	
ORR	39%	38%	55%	73%	69%
Intracranial ORR	35%	54%	67%	70%	64%
Median PFS	5.4 mo	9.6 mo	16.7 mo	11.1	9.0 mo
Toxicity considerations	GI (diarrhea, nausea, vomiting)	Constipation, fatigue, myalgia	GI, elevated CPK, early onset pulmonary events (6%)	Hypercholesterolemia, hypertriglyceridemia, weight gain, confusion/hallucinations (3%)	Rash, nausea, pruritis
Dose reduction	61%	4%	30%	25%	25%

1. Shaw et al, Lancet Onc 2017 2. Novello et al, Ann Onc, 2018 3. Ahn et al, WCLC 2017 4. Besse et al, ASCO 2018 5. Horn et al, CCR 2018

Lorlatinib – after crizotinib ± chemo

	EXP2+3A (n=59)
ORR, n/N (%) (95% CI)	41/59 (69) (56, 81)
IC ORR, n/N (%) (95% CI)	25/37 (68) (50, 82)
Median DOR, mo (95% CI)	NR (11.1, NR)
DOR ≥6 mo, n[a]/n (%)	20/41 (49)
Median PFS, mo (95% CI)	NR (12.5, NR)

- 37 patients (63%) had brain metastases at baseline.



Solomon et al, WCLC 2017

Crizotinib resistance is generally still *ALK*-dependent

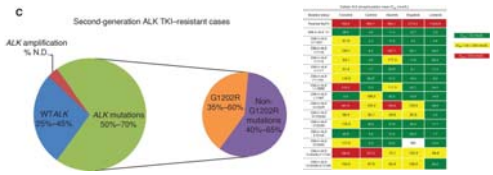
Brigatinib post-crizotinib pooled mutational analysis

	Phase 1/2	ALTA	Total
Patients with baseline NGS data, n	**15[a]**	**17[b]**	**32**
Confirmed ORR, % (n/N)	80 (12/15)	59 (10/17)	69 (22/32)
Patients with secondary ALK mutations at baseline, n	**5**	**4**	**9**
Confirmed ORR, % (n/N)	80 (4/5)	75 (3/4)	78 (7/9)
Patients without secondary ALK mutations at baseline, n	**10[a]**	**13[b]**	**23**
Confirmed ORR, % (n/N)	80 (8/10)	54 (7/13)	65 (15/23)

- **Lower rate of ALK resistance mutations but generally still ALK-dependent**
- **More potent ALK TKI typically works**
- **Consider re-biopsy, but not required**

Gettinger et al, ASCO 2016

2nd gen TKI resistance is more varied



- Resistance mutation(s) and lineage shifts more prevalent
- Re-biopsy!

1. Lin et al, Ca Discovery 2017 2. Gainor et al, Ca Discovery 2016

Current post-alectinib landscape

	Ceritinib ASCEND-9 (Ph 2, n=20)[1]	Brigatinib (retrospective, n=22)[2]	Lorlatinib (Ph 1/2)[3], awaiting FDA approval	Ensartanib (Ph 2)[4], trial on-going
ORR	25%	17%	40%	25%
Intracranial ORR	25%	25%	41%	NR
Median PFS	3.7 mo	4.4 mo	5.5 mo	1.9 mo

- Current Brigatinib FDA label is only for post-*crizotinib* progression
- MDACC clinical trial evaluating Ceritinib + Everolimus (NCT02321501)

1. Hida et al, Cancer Sci 2018 2. Lin et al, JTO 2018 3. Besse et al, ASCO 2018 4. Horn et al, CCR 2018

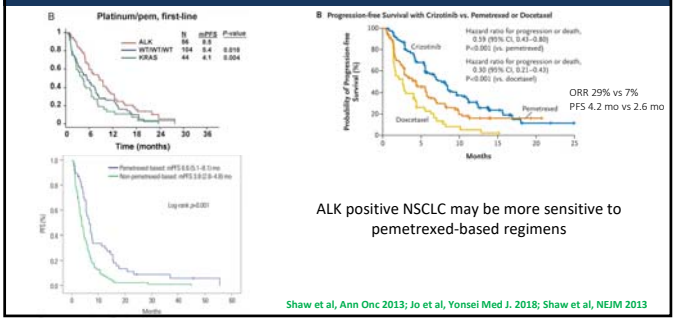
Lorlatinib has broad post-2nd gen TKI activity

Table 3. Efficacy by Last Prior Second-Generation ALK TKI Received (EXP2–5)

	Alectinib	Ceritinib	Brigatinib
OVERALL			
N	62	47	8
ORR			
%	40.3	42.6	37.5
95% CI	28.1–53.6	28.3–57.8	8.5–75.5
DOR,[a] months			
Median	5.6	6.9	NC[b]
95% CI	4.2–24.4	5.6–NR	
Progression-free survival,[a] months			
Median	5.5	7.3	NC[b]
95% CI	4.1–7.1	5.5–11.1	
INTRACRANIAL – Overall			
N	37	35	5
IC ORR			
%	40.5	54.3	40.0

Besse et al, ASCO 2018

Don't forget chemotherapy

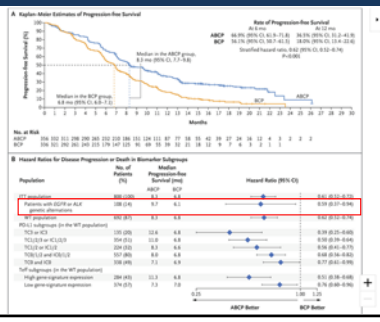


ORR 29% vs 7%
PFS 4.2 mo vs 2.6 mo

ALK positive NSCLC may be more sensitive to pemetrexed-based regimens

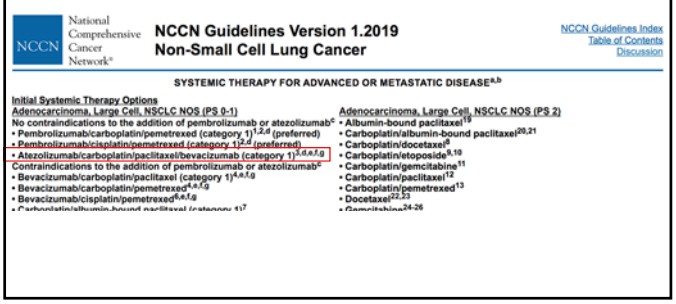
Shaw et al, Ann Onc 2013; Jo et al, Yonsei Med J. 2018; Shaw et al, NEJM 2013

IMpower 150 – a chemoIO option for *ALK*



- **Carboplatin/paclitaxel/ atezolizumab/bevacizumab (ABCP)** vs carboplatin/paclitaxel/ bevacizumab (BCP) in 1L metastatic non-squamous NSCLC
- ORR, PFS, OS benefit
- *EGFR/ALK+* pts received at least one approved TKI
- First IO-based regimen to show clinical benefit for *EGFR/ALK+* pts
- Caution: small *ALK+* subgroup (n=13 in ABCP)

IMpower 150 – NCCN category 1



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE[a,b]

Initial Systemic Therapy Options

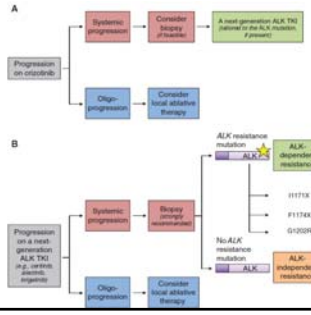
Adenocarcinoma, Large Cell, NSCLC NOS (PS 0-1)

No contraindications to the addition of pembrolizumab or atezolizumab[c]
- Pembrolizumab/carboplatin/pemetrexed (category 1)[1,2,d] (preferred)
- Pembrolizumab/cisplatin/pemetrexed (category 1)[1,2,d] (preferred)
- Atezolizumab/carboplatin/paclitaxel/bevacizumab (category 1)[3,d,e,f,g]

Contraindications to the addition of pembrolizumab or atezolizumab[c]
- Bevacizumab/carboplatin/paclitaxel (category 1)[4,e,f,g]
- Bevacizumab/carboplatin/pemetrexed[4,e,f,g]
- Bevacizumab/cisplatin/pemetrexed[5,e,f,g]
- Carboplatin/albumin-bound paclitaxel (category 1)[17]

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)
- Albumin-bound paclitaxel[19]
- Carboplatin/albumin-bound paclitaxel[20,21]
- Carboplatin/docetaxel[6]
- Carboplatin/etoposide[9,10]
- Carboplatin/gemcitabine[11]
- Carboplatin/paclitaxel[12]
- Carboplatin/pemetrexed[13]
- Docetaxel[22,23]
- Gemcitabine[24-26]

Potential treatment algorithm

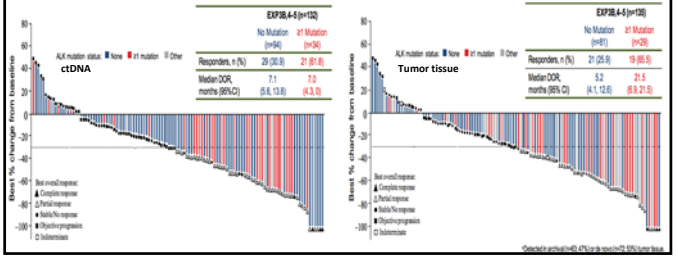


Emerging data may support consideration of lorlatinib too

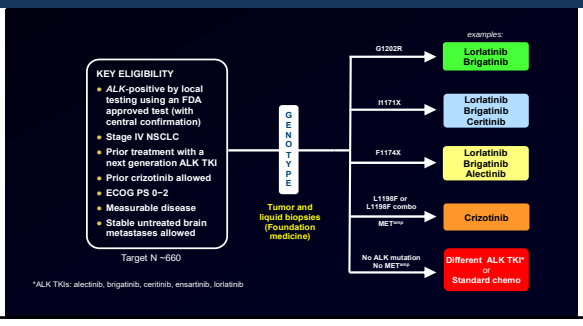
Lin et al, Ca Discovery 2017

Lorlatinib can be effective even without ALK resistance mutations

Lorlatinib response post-next gen ALK TKI



NCI-NRG ALK Master Protocol



Summary

- **Consider local therapy for oligoprogression**
- **Post-crizotinib: next-generation ALK TKIs are very active**
  - **Alectinib/brigatinib preferred (CNS, more potent, resistance mutations)**
  - **Lorlatinib has FDA breakthrough designation**
- **Optimal therapy post-next generation ALK TKI is not well defined, should re-biopsy**
  - **Resistance mechanisms may guide use of another TKI**
  - **Otherwise, platinum/doublet or chemoIO (IMpower 150)**
  - **Lorlatinib FDA approval expected; ensartinib currently in trial**

Thank you

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October 27, 2018

For online registration and more information visit: www.cancernetus.com