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COMPREHENSIVE CANCER CENTER

PATIENT CARE
RESEARCH
EDUCATION
COMMUNITY

Uncommon Mutations/Fusions

EGFRex20, RET, MET, HER2, NRG1

Stephen V. Liu, MD
Associate Professor of Medicine
Georgetown University

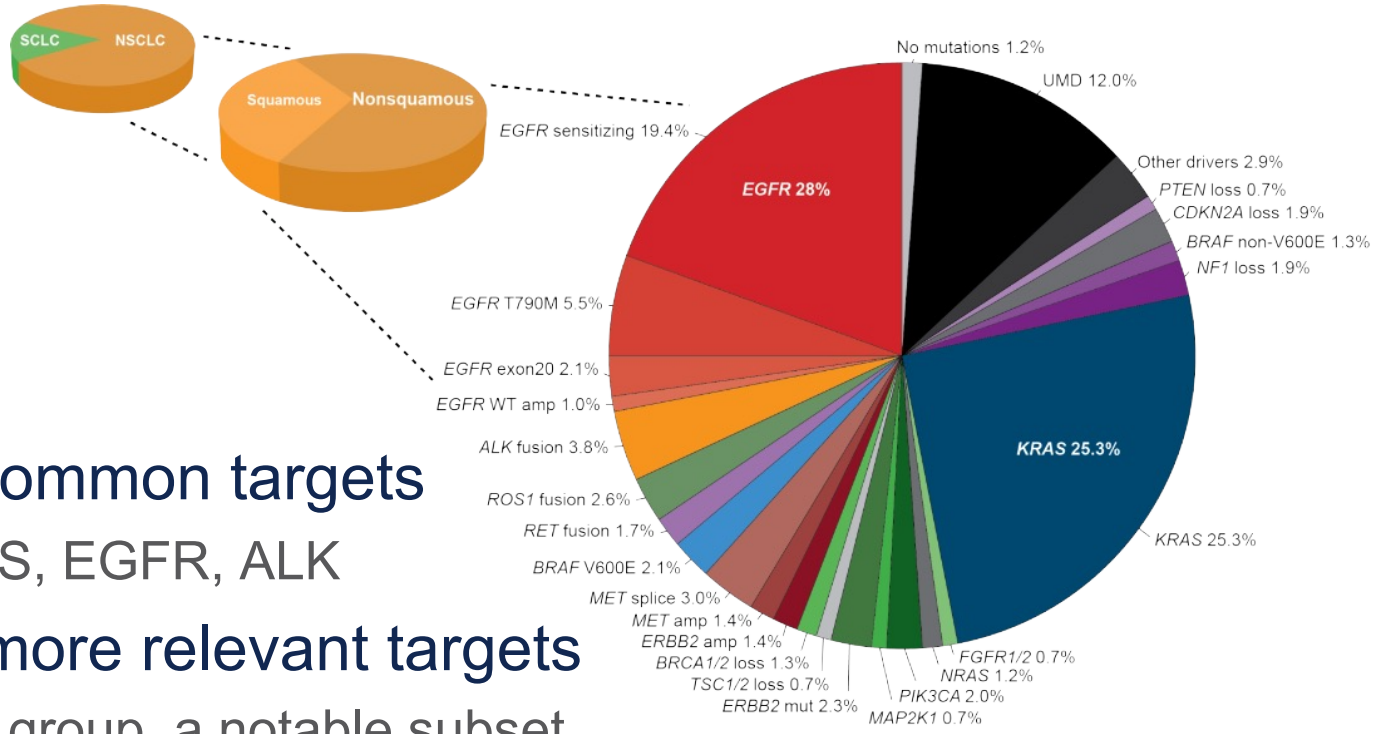
Saturday, April 2, 2022

@StephenVLiu

NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

http://lombardi.georgetown.edu
Lombardi CancerLine: 202.444.4000

Targeted Therapy



- More common targets
  - KRAS, EGFR, ALK
- Many more relevant targets
  - As a group, a notable subset

Jordan, Cancer Disc 2017

Oncology is *Complicated*

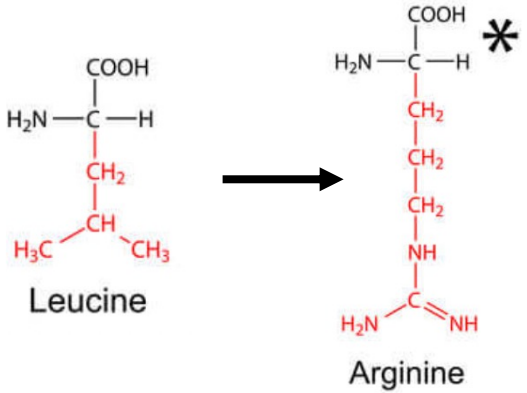
- Expanding roles and responsibilities
  - Medical Oncology
  - Palliative Care
  - Immunology
  - Rheumatology
  - Cardiology
  - Endocrinology
  - Medicinal Chemistry
  - Molecular Pathology

Targeted Therapy

- Details matter!

EGFR

- ”EGFR mutation positive” is *not enough detail*
  - Exon 19 deletion
  - Exon 21 L858R
  - Atypical (G719X, L861Q, S768I)
  - Exon 20 insertion

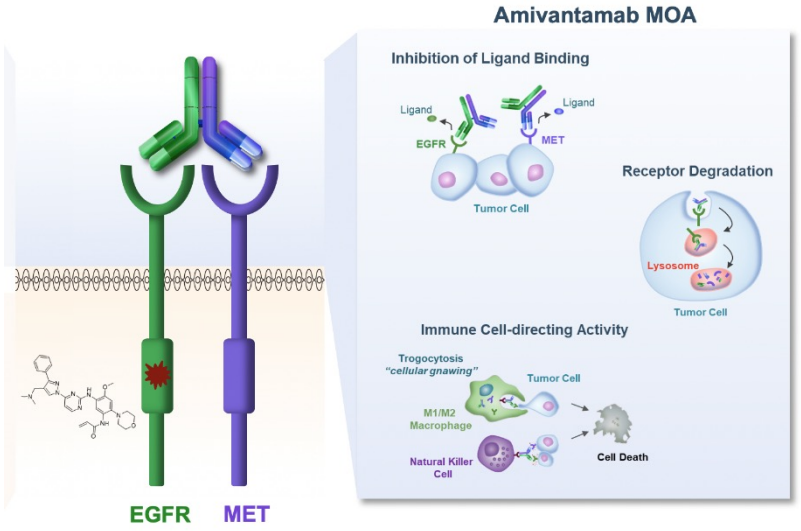


EGFR Exon 20 Insertion

- Easily detected with NGS
- More commonly seen in specific populations
  - Female sex
  - Never smokers
  - Adenocarcinoma histology
- Like del19/L858R, poor responses to immunotherapy
- Unlike del19/L858R, poor responses to standard TKIs
- Standard treatment platinum doublet chemotherapy

Amivantamab

- Bispecific antibody targeting EGFR and MET
  - Intravenous administration
  - Infusion reactions
  - Phase I CHRYSALIS
    - Established RP2D
    - 1050mg (<80kg)
    - 1400mg (≥80kg)
    - Weekly C1
    - Q2W C2+



Bauml, ASCO 2021

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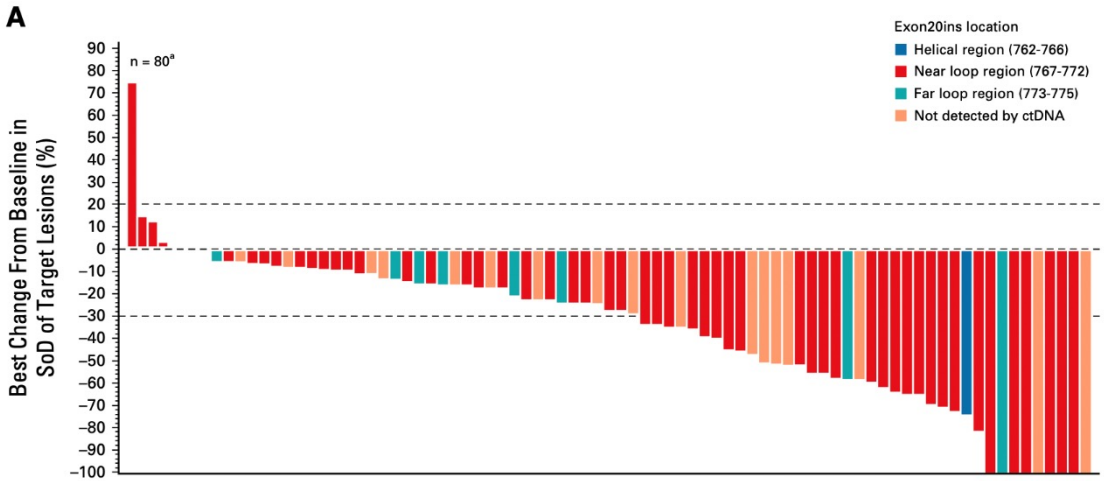
Amivantamab

- EGFR exon 20 insertion after chemotherapy
  - 81 pts
  - RR 40%
  - DOR 11.1m
  - PFS 8.3m
  - OS 22.8m

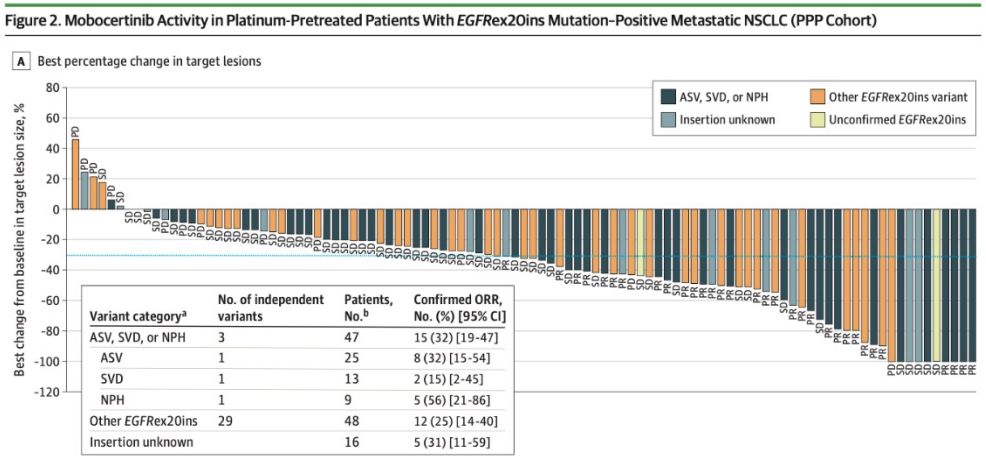


- FDA accelerated approval May 21, 2021

Sabari, WCLC 2020

Mobocertinib (TAK-788)

- Potent irreversible pan-ErbB kinase inhibitor
- Post-platinum based chemotherapy cohort (n=114)
  - IRC RR 28%
  - mPFS 7.3m
  - mDOR 17.5m
  - Toxicity
    - 91% diarrhea
      - 21% G3+
    - 45% rash



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

- FDA accelerated approval Sept 15, 2021

Zhou, JAMA Onc 2021

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RET

- Often altered in medullary thyroid cancer (MEN)
- RET fusions are important drivers in NSCLC
  - Present in ~2% of NSCLC
  - Various fusion partners (KIF5B, CCDC6, NCOA4, others)
  - More common in non-smokers
- Multiple kinase inhibitors have some activity at RET
  - Cabozantinib
  - Vandetanib
  - Sunitinib

RET in NSCLC

- Global retrospective registry of 165 patients with RET fusion positive NSCLC

Table 2. Best Response to RET Inhibitor Therapy

RET Inhibitor	Complete Response	Partial Response	Stable Disease	Disease Progression	Not Evaluable	Missing Data
All agents (n = 53)	2 (4%)	11 (22%)	16 (32%)	20 (40%)	1 (2%)	3
Cabozantinib (n = 21)	1 (5%)	6 (32%)	5 (26%)	7 (37%)	0	2
Vandetanib (n = 11)	0	2 (18%)	3 (27%)	6 (55%)	0	0
Sunitinib (n = 10)	0	2 (22%)	3 (33%)	3 (33%)	1 (11%)	1
Sorafenib (n = 2)	0	0	2	0	0	0
Alectinib (n = 2)	0	0	0	2	0	0
Lenvatinib (n = 2)	0	1	0	1	0	0
Nintedanib (n = 2)	1	0	1	0	0	0
Ponatinib (n = 2)	0	0	2	0	0	0
Regorafenib (n = 1)	0	0	0	1	0	0

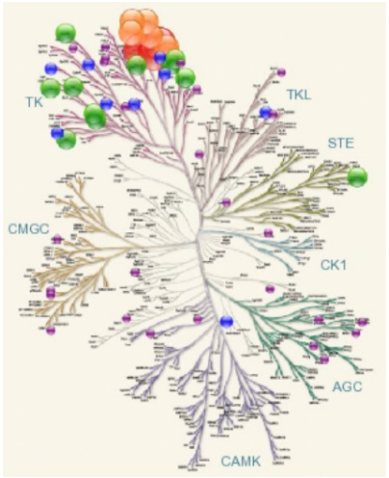
NOTE. The best response to a multikinase inhibitor with activity against RET is summarized for 53 patients with advanced *RET*-rearranged lung cancers.

Gautschi, JCO 2017

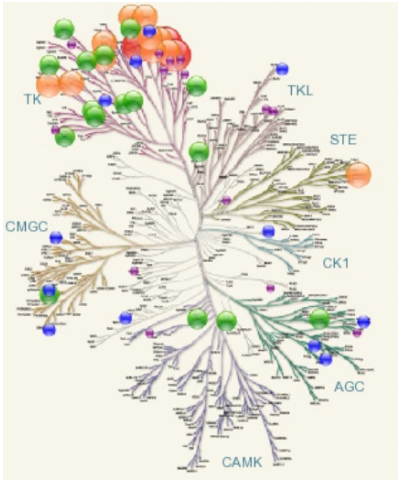
RET in NSCLC

- Selective RET inhibitors – wider therapeutic window

Lenvatinib

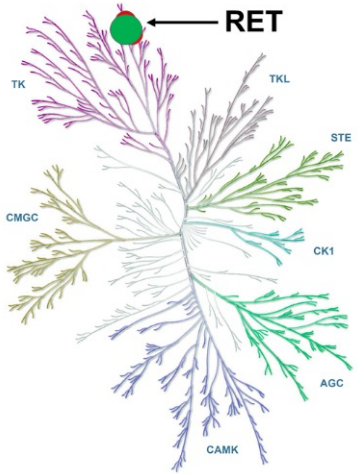


Sunitinib

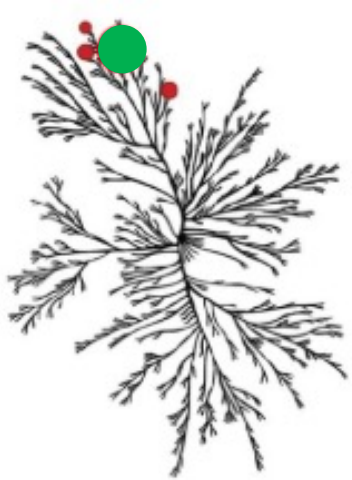


Multikinase Inhibitors

Selpercatinib



Pralsetinib

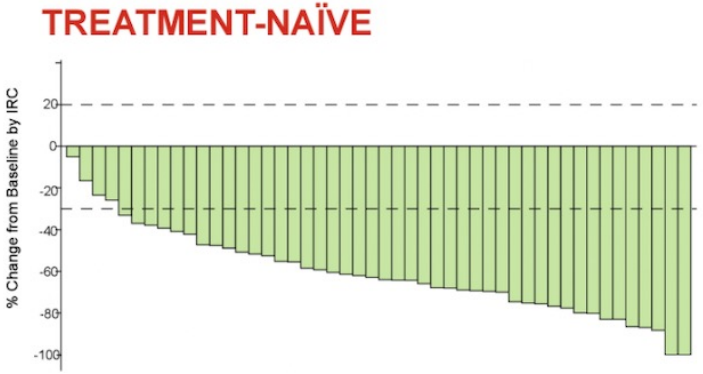


Selective RET Inhibitors

Gautschi, JCO 2017; Gainor, ASCO 2019; Drilon, WCLC 2019; Stjepanovic, Biologics 2014

Selpercatinib (LOXO-292)

- Selpercatinib (LOXO-292) 160mg twice daily
- Phase I/II LIBRETTO trial
  - 105 pts with prior chemo
    - RR 64%, DOR 17.5m, PFS 19.3m
  - 48 treatment naïve
    - RR 85%, DOR NR, PFS 13.0m

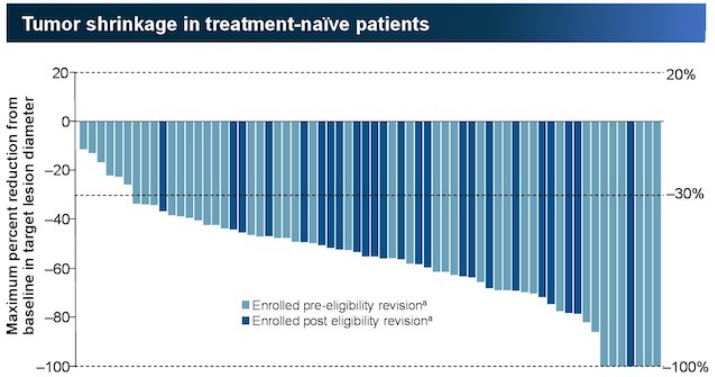


- FDA accelerated approval May 8, 2020

Besse, ASCO 2021

Pralsetinib (BLU-667)

- Pralsetinib (BLU-667) 400mg once daily
- Phase I/II ARROW trial
  - 126 pts with prior chemo
    - RR 62%, DOR 22.3m, PFS 16.5m
  - 68 treatment naïve
    - RR 79%, DOR NR, PFS 13.0m
  - 25 treatment naïve (eligible)
    - RR 88%, DCR 96%, DOR NR, PFS NR



- FDA accelerated approval Sept 4, 2020

Curigliano, ASCO 2021

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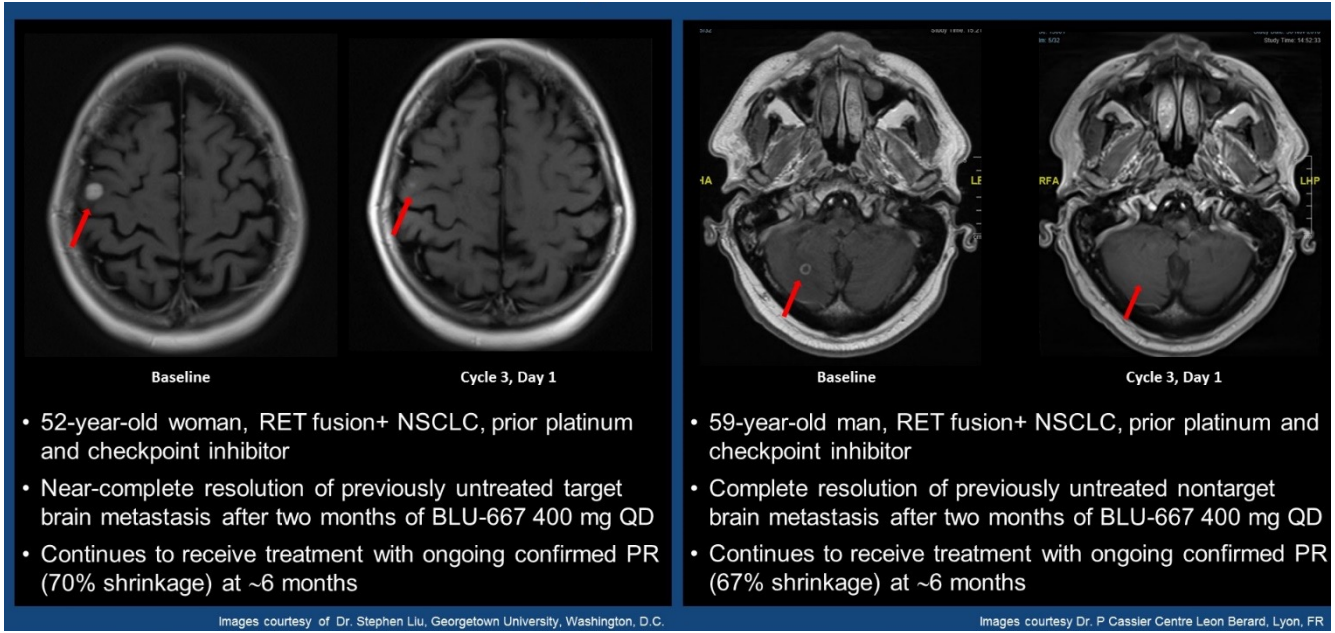
Selective RET Inhibitors

- Pralsetinib and selpercatinib have CNS efficacy



Gainor, ASCO 2019

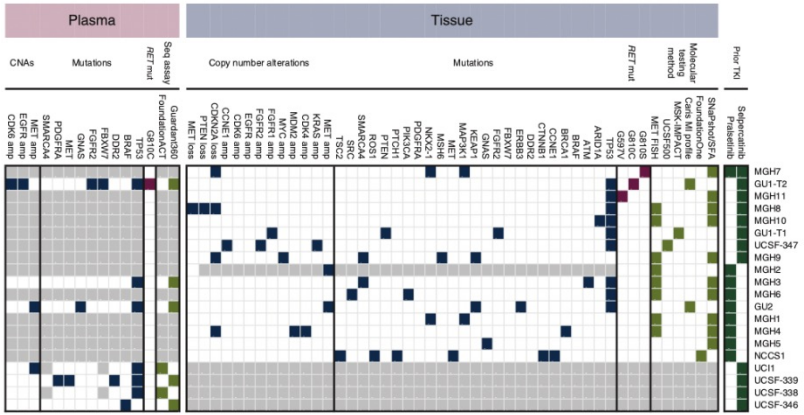
Selective RET Inhibitors

- Pralsetinib and selpercatinib very well tolerated
  - Only 2-6% discontinue due to adverse event
- Selpercatinib toxicity noted after immunotherapy
  - Hypersensitivity reactions noted in LIBRETTO
    - Rash, fever, arthralgias, myalgias, thrombocytopenia, LFT elevation
    - Less commonly: hypotension, tachycardia, creatinine elevation
  - Occurred in 19/125 patients with prior IO therapy (12.5%)
  - Management: hold therapy, start steroids, rechallenge at 40mg bid and escalate as tolerated

McCoach, JTO 2022; Curigliano, ASCO 2021; Besse, ASCO 2021

Acquired Resistance

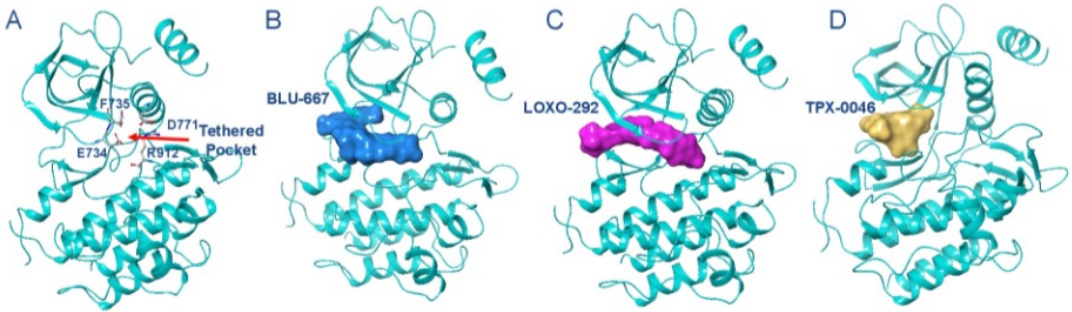
- Early analysis of acquired resistance (n=23)
  - RET G810X mutations (10%)
  - MET amplification (10%)
  - KRAS amplification
- Late resistance may differ
- Biopsy important
  - Histology check



Lin, Ann Oncol 2020

Next Generation RET Inhibitors

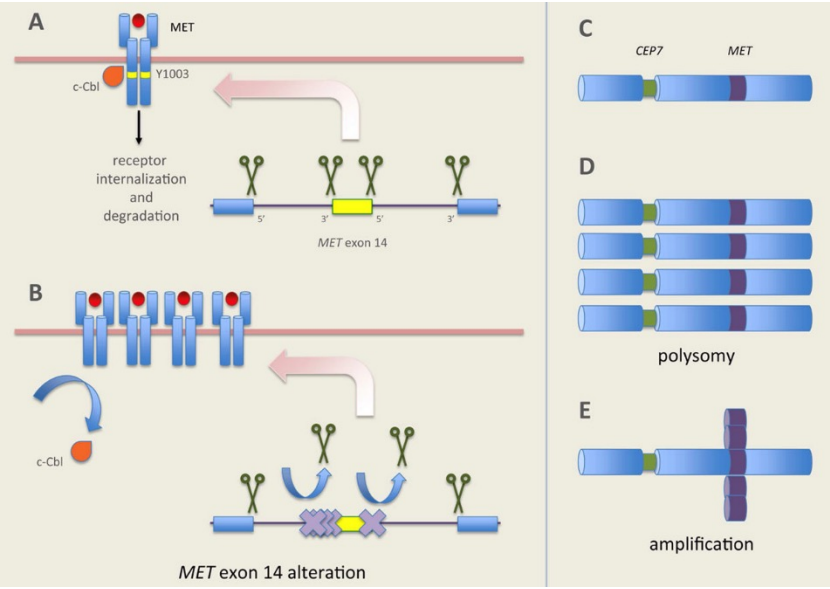
- TPX-0046
  - Retains potency with G810X solvent front mutations
  - Phase I study
- BOS172738
  - Phase I study



Drilon, ASCO 2020

MET Exon 14 Skipping Mutations

- Present in 3-5% of NSCLC
  - Diverse family of mutations that promote MET signaling



Drilon, JTO 2017

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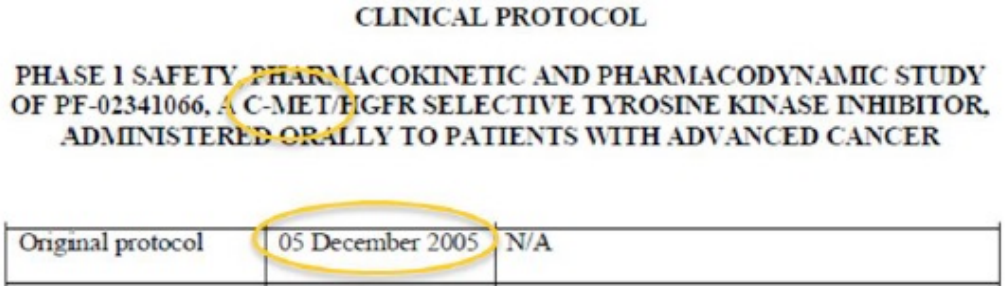
MET Exon 14 Skipping Mutations

- Initial development plan for crizotinib



CLINICAL PROTOCOL

PHASE 1 SAFETY, PHARMACOKINETIC AND PHARMACODYNAMIC STUDY OF PF-02341066, A C-MET/HGFR SELECTIVE TYROSINE KINASE INHIBITOR, ADMINISTERED ORALLY TO PATIENTS WITH ADVANCED CANCER

Original protocol	05 December 2005	N/A

Drilon, ASCO 2016

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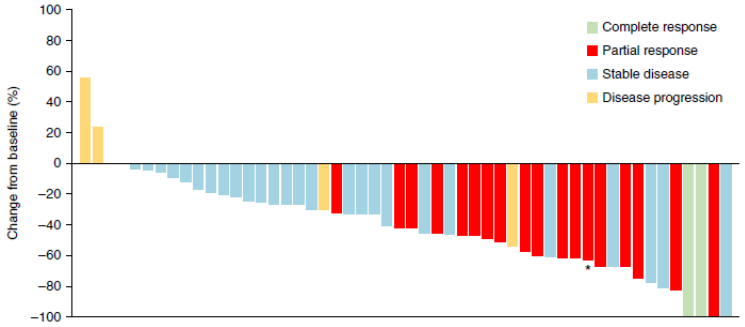
Crizotinib for METex14

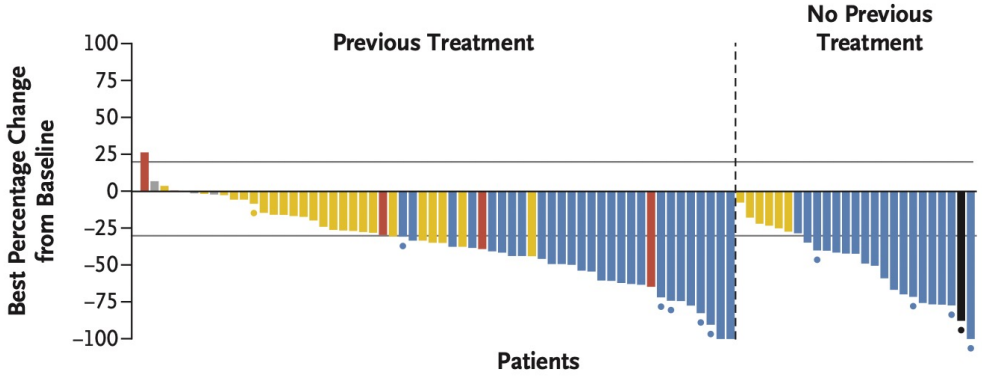
- PROFILE 1001
- 69 patients with METex14 NSCLC
  - 84% adenocarcinoma, 9% sarcomatoid
  - 62% smokers, 38% never-smokers
  - RR 32%, mDOR 9.1m
  - mPFS 7.3m, mOS 20.5m
  - Not FDA approved



Drilon, Cancer Med 2020

Capmatinib for METex14

- Phase II GEOMETRY trial
  - Previously treated (n=100)
    - RR 44%, mDOR 9.7m, mPFS 5.5m
  - Treatment naïve (n=60)
    - RR 67%, mDOR 12.6m, mPFS 12.3m



FDA accelerated approval May 6, 2020

Wolf, NEJM 2020

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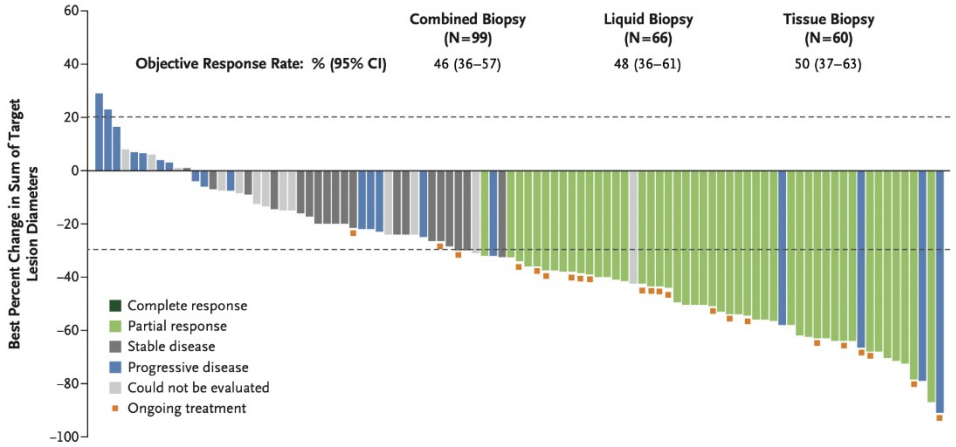
Tepotinib for METex14

- Phase II VISION trial
  - 152 pts with METex14 NSCLC
  - RR 46%, mDOR 11.1m
  - Liquid bx: RR 48%; tissue bx: RR 50%



FDA accelerated approval Feb 3, 2020

Paik, NEJM 2020

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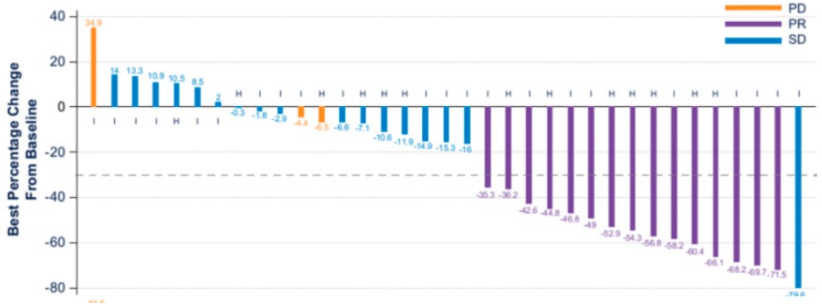
METex14

- Capmatinib and tepotinib
  - Approved, effective targeted agents
  - Similar toxicities
    - Peripheral edema
    - Nausea, vomiting
    - Increased creatinine
  - Capmatinib
    - 23% dose reduction, 11% discontinued due to adverse event
  - Tepotinib
    - 33% dose reduction, 11% discontinued due to adverse event

Wolf, NEJM 2020; Paik, NEJM 2020

Telisotuzumab vedotin (Teliso-V)

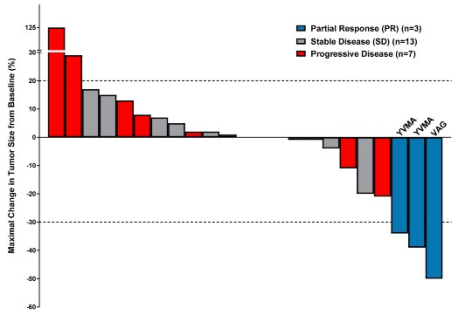
- Antibody drug conjugate, 1.9mg/kg q2w IV
- Phase II trial
  - MET by IHC (SP44)
  - Non-sq, EGFR wt, RR 35%
    - MET high RR 54%
    - MET in RR 25%
  - Non-sq, EGFR mt, RR 13%
  - Squamous NSCLC, RR 14%
- FDA Breakthrough Designation
  - NSCLC with high c-MET overexpression

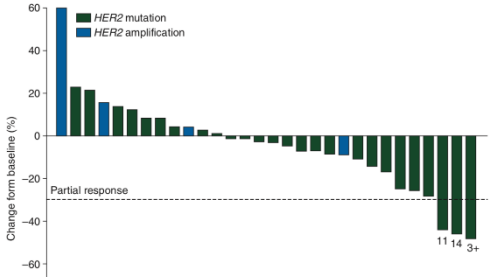


Wolf, NEM 2020; Paik, NEJM 2020

HER2 Mutant NSCLC

- HER2 mutations present in ~3% of NSCLC
  - Mutation relevant in NSCLC, not expression/amplification
  - Agents used in other cancers not necessarily effective
  - Afatinib
    - Retrospective
    - 23 HER2 mt, RR 23%
  - Dacomitinib
    - Prospective
    - 26 HER2 mt, RR 12%

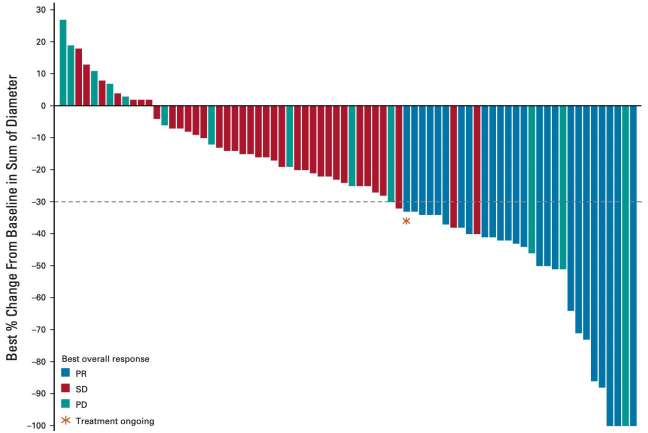




Lai, Eur J Cancer 2019;
Kris, Ann Oncol 2015

Poziotinib in HER2mt

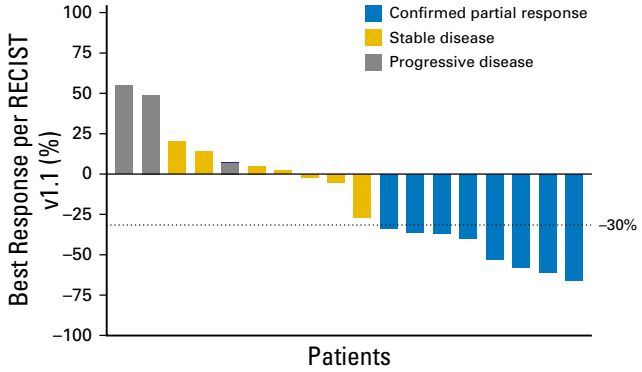
- Poziotinib is an irreversible pan-ErbB inhibitor
  - ZENITH20 trial
    - HER2 mutant NSCLC
    - Previously treated
    - RR 27.8%, DCR 70%
    - mPFS 5.5m, mDOR 5.1m
  - Toxicities largely EGFR related
    - 77% dose reduction rate
    - G3+ TRAEs
      - Rash (49%), diarrhea (26%), stomatitis (RR 24%)
  - FDA Breakthrough Designation



Le, JCO 2022

Trastuzumab Emtansine in HER2mt

- Trastuzumab emtansine (T-DM1)
  - Antibody-drug conjugate
- Prospective phase II study
  - 18 HER2 mutant NSCLC
  - RR 44%, mPFS 5m



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Le, JCO 2022

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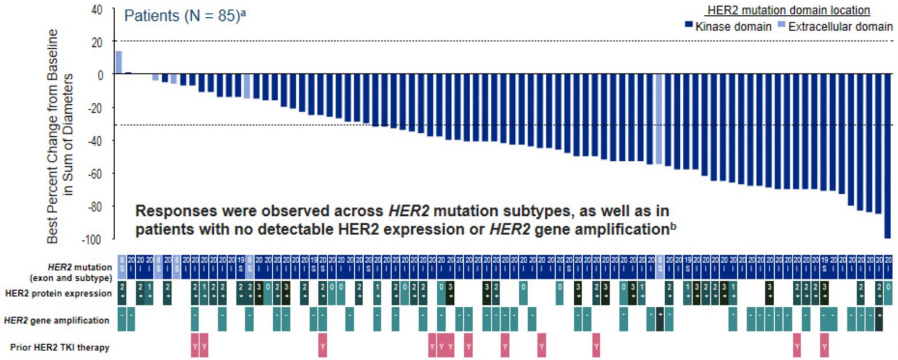
Trastuzumab Deruxtecan in HER2mt

- Trastuzumab deruxtecan (TDxD) 6.4mg/kg q3w
  - Antibody-drug conjugate (HER2, topoisomerase I, DAR ~8)
- DESTINY-Lung01
  - Cohort 2 (HER2 mutant)
  - 91 patients
  - RR 50%, DCR 92%
  - DOR 9.3m
  - PFS 8.2m, OS 17.8m
- FDA Breakthrough Designation



Li, NEJM 2021

Trastuzumab Deruxtecan in HER2mt

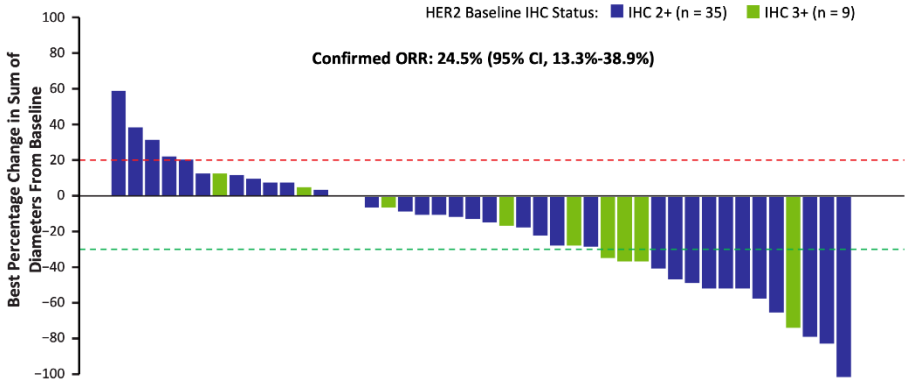
- Trastuzumab deruxtecan 6.4mg/kg q3w
- DESTINY-Lung01
  - 34% dose reduction
  - 25% discontinuation
  - 2% fatal adverse event
  - 18.7% G3 NTP
  - 26.4% pneumonitis
    - 4.4% G3
    - 2.2% G5

n (%)	Any grade	Grade ≥3
Patients with ≥1 drug-related TEAEs	88 (96.7)	42 (46.2)
Drug-related TEAEs with ≥20% incidence in all patients		
Nausea	66 (72.5)	8 (8.8)
Fatigue[a]	48 (52.7)	6 (6.6)
Alopecia	42 (46.2)	0
Vomiting	36 (39.6)	3 (3.3)
Neutropenia[b]	32 (35.2)	17 (18.7)
Anemia[c]	30 (33.0)	9 (9.9)
Diarrhea	29 (31.9)	3 (3.3)
Decreased appetite	27 (29.7)	0
Leukopenia[d]	21 (23.1)	4 (4.4)
Constipation	20 (22.0)	0

Li, NEJM 2021

Trastuzumab Deruxtecan in HER2+

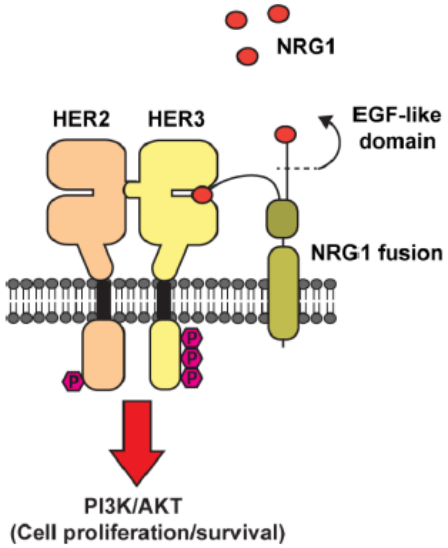
- Trastuzumab deruxtecan (TDxD) 6.4mg/kg q3w
  - Antibody-drug conjugate (HER2, topoisomerase I, DAR ~8)
- DESTINY-Lung01
  - Cohort 1 (HER2 IHC)
  - 49 patients
  - RR 24.5%
  - PFS 5.4m, OS 11.3m
  - 55% G3+ AEs
  - ILD in 16.3%



Li, NEJM 2021

NRG1 Fusions

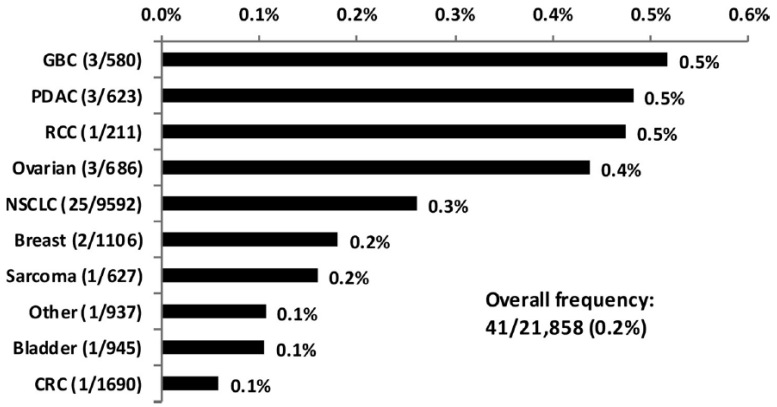
- Neuregulin 1 (NRG1)
  - EGF-like domain serves as ligand for HER3
  - Promotes heterodimerization (HER2)
  - Activates downstream PI3K/AKT/MAPK
- NRG1 fusions
  - Low incidence across tumors
  - Preserves EGF-like domain



Schram, WCLC 2020

NRG1 Fusions

- NRG1 fusions
  - Difficult to detect
  - Large intronic regions
  - Multiple fusion partners
  - RNA-seq more sensitive
- Seen across tumor types
  - 0.3% NSCLC



Jonna, CCR 2019

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NRG1 Fusions

- eNRGy1 Global Registry
  - 110 NRG1+ NSCLC cases
  - Primarily non-smokers, adenocarcinoma
  - Poor outcomes with standard therapy

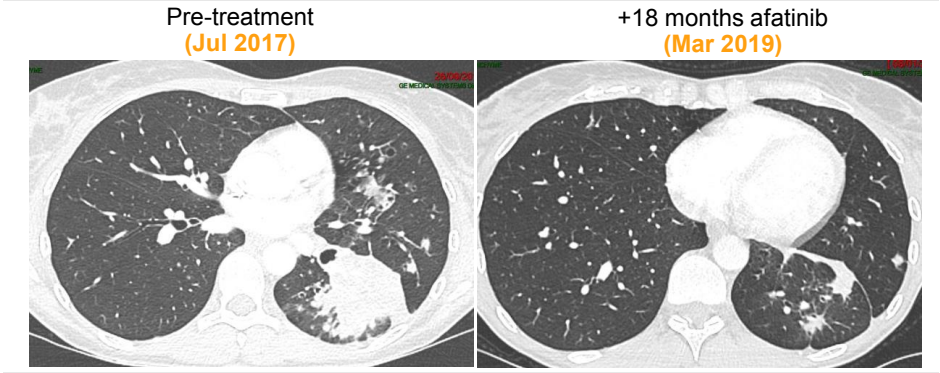
Response	Platinum-Doublet–Based Chemotherapy	Taxane-Based Chemotherapy	Combined Chemotherapy and Immune Therapy	Single-Agent Immunotherapy	Targeted Therapy With Afatinib
Response rate, %	13	14	0	20	25
CR, % (n/N)	0 (0/15)	0 (0/7)	0 (0/9)	0 (0/5)	0 (0/20)
PR, % (n/N)	13 (2/15)	14 (1/7)	0 (0/9)	20 (1/5)	25 (5/20)
SD, % (n/N)	47 (7/15)	14 (1/7)	44 (4/9)	20 (1/5)	15 (3/20)
PD, % (n/N)	40 (6/15)	71 (5/7)	56 (5/9)	60 (3/5)	60 (12/20)
Median PFS (95% CI), range	5.8 months (2.2 to 9.8), 0.7-12.1	4.0 months (0.8 to 5.3), 0.8-5.5	3.3 months (1.4 to 6.3), 1.4-15.2	3.6 months (0.9 to undefined), 0.9-11.2	2.8 months (1.9 to 4.3), 0.3-25.3

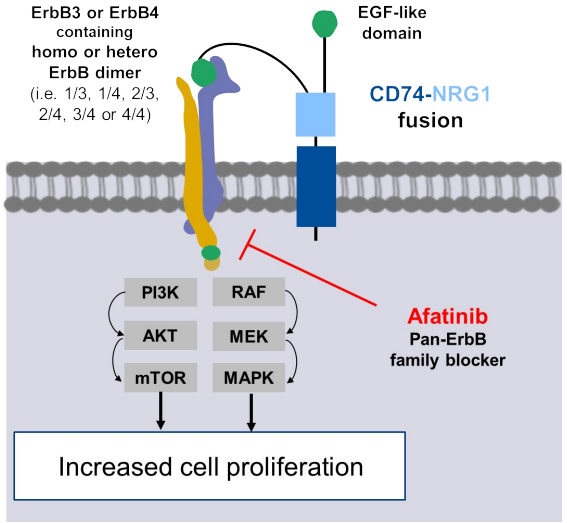
Abbreviations: CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Drilon, JCO 2021

Afatinib and NRG1

- Afatinib
  - Irreversible pan-ErbB kinase inhibitor
  - Multiple case series showing activity
  - Prospective TAPUR study ongoing

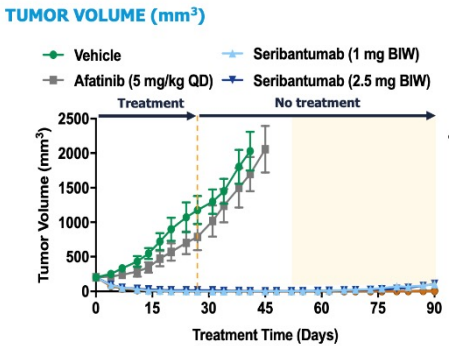


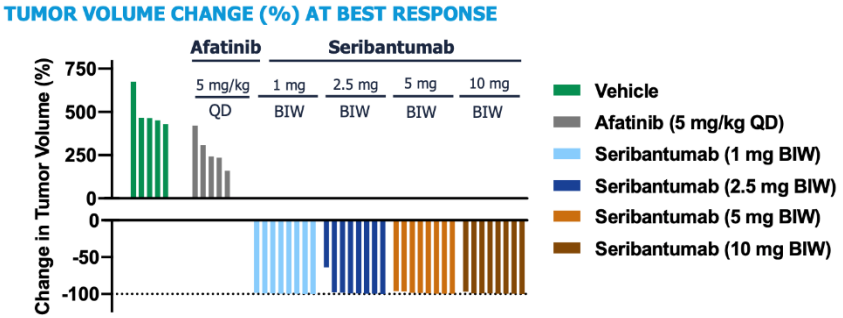


Liu, ESMO 2019, Duruisseaux, WCLC 2019

Seribantumab and NRG1

- Seribantumab
  - HER3 monoclonal antibody
  - Blocks ligand-dependent activation of HER3
  - Blocks heterodimerization
  - Tumor agnostic phase II CRESTONE study ongoing



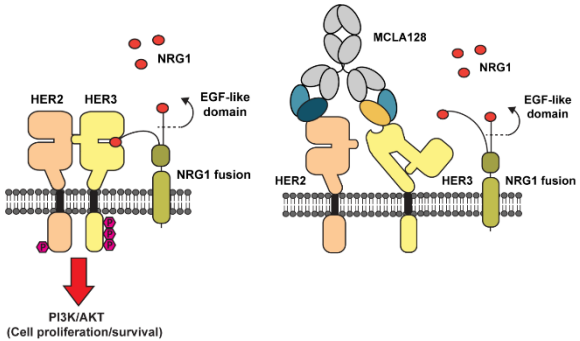


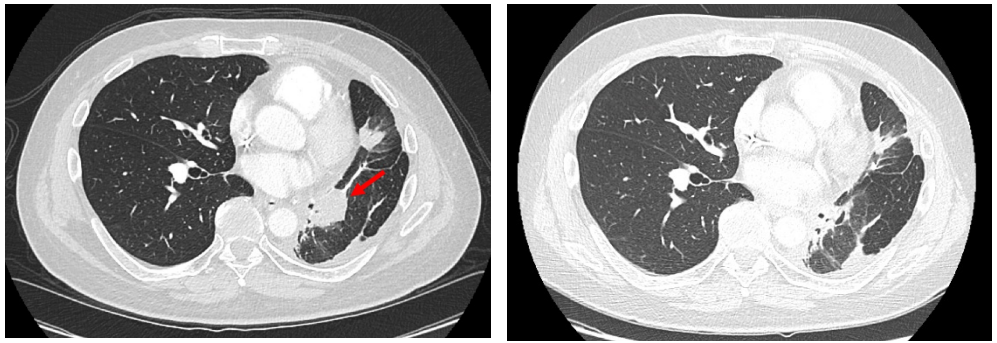
Odintsov, ENA 2020

Georgetown | Lombardi

Zenocutuzumab and NRG1

- Zenocutuzumab (MCLA-128)
  - Bispecific antibody targeting HER2 and HER3 with ADCC
  - Blocks NRG1 binding to HER3
  - FDA Fast Track Designation





Schram, ENA 2019

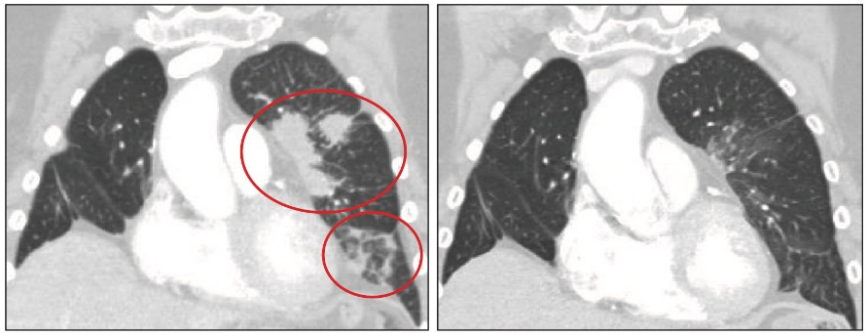
Acquired Resistance

- Presence of actionable drivers guides initial therapy
- Many of the same drivers mediate resistance
  - MET amplification
  - KRAS mutations
  - RET fusions
  - BRAF mutations/fusions
  - ALK fusions
  - NRG1 fusions

Acquired Resistance

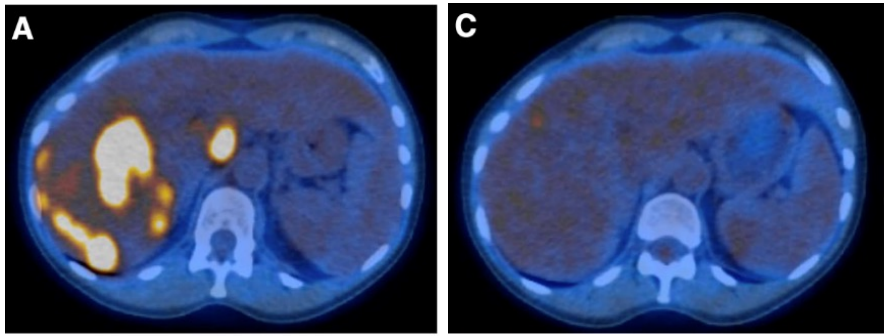
- Biopsies at resistance can guide therapy
  - Histologic transformation (SCLC, squamous NSCLC)
  - New actionable resistance alteration

Response to Osimertinib + Pralsetinib in Patient With *EGFR*+ NSCLC and a *RET* Fusion Post Afatinib/Cetuximab



Baseline **Wk 8**

Response to Osimertinib + Selpercatinib in Patient With *EGFR*+ NSCLC and a *RET* Fusion Post Osimertinib



Baseline **Mo 1**

Piotrowska, Cancer Disc 2018; Rehman, JCO Precis Oncol 2021

Driver+ and Immunotherapy

- IMMUNOTARGET
  - Retrospective analysis of IO monotherapy in driver+ NSCLC

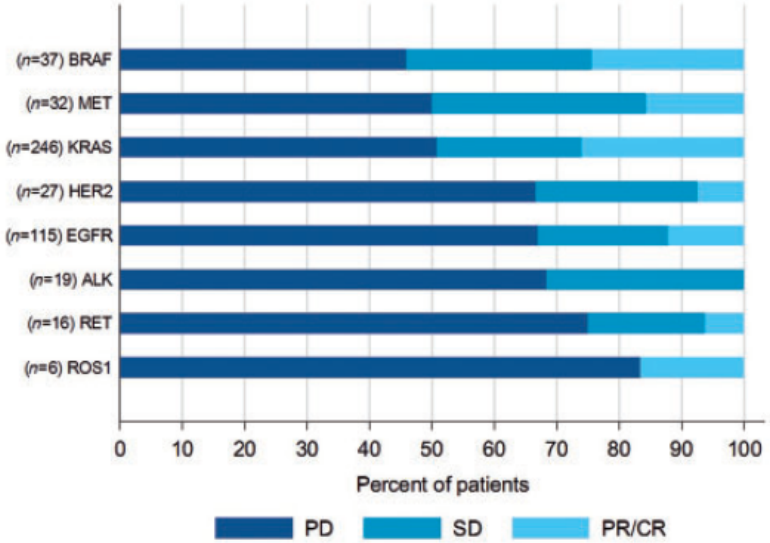


Table 2. PFS according to primary oncogenic driver from initiation of ICI

	EVT/*N*	Median PFS [95% CI] (months)
KRAS	208/271	3.2 [2.7; 4.5]
EGFR	117/125	2.1 [1.8; 2.7]
BRAF	34/43	3.1 [1.8; 4.6]
HER2	23/29	2.5 [1.8; 3.5]
MET	26/36	3.4 [1.7; 6.2]
ALK	21/23	2.5 [1.5; 3.7]
ROS1	–	–
RET	15/16	2.1 [1.3; 4.7]

EVT, event; *N*, number.

Mazieres, Ann Oncol 2019

Biomarker Testing

- Growing number of relevant targets in NSCLC
- Testing rates in the US remain suboptimal
- MYLUNG Consortium
  - Analysis of US hospitals biomarker testing in NSCLC
  - Collected testing rates for those with access to testing
  - Looked only at EGFR, ALK, BRAF, ROS1 and PDL1
  - Only 46% of patients with advanced NSCLC were tested for all 5 markers
- Advantages of DNA & RNA-based testing

Robert, ASCO 2021

Unanswered Questions

- Optimal initial strategy
  - Targeted therapy, if so – which one
  - Chemotherapy
  - Combination therapy
- Overcoming, preventing resistance
- Significance of co-mutations
- CNS tropism and efficacy
- Adjuvant and consolidation therapy
- Role of immunotherapy

Summary

- Effective new targeted therapies for smaller, genomically-defined subsets of NSCLC
  - EGFRex20 (amivantamab, mobocertinib)
  - RET (pralsetinib, selpercatinib)
  - MET (capmatinib, tepotinib)
  - HER2 (pending poziotinib, pending TDxD)
  - NRG1 (investigational)
- Important to obtain biomarker testing for all patients
  - At diagnosis and consider at progression