Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

What are new approaches for NSCLC patients with driver mutations?

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Disclosures

- Research support from AstraZeneca and Boehringer Ingelheim.
- Consultant/advisor/speaker fees from Amgen, AstraZeneca, Blueprint Medicine, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo, Genentech, Janssen, Regeneron, Sanofi Genzyme, and Takeda.
- I will be discussing non-FDA approved indications during my presentation.

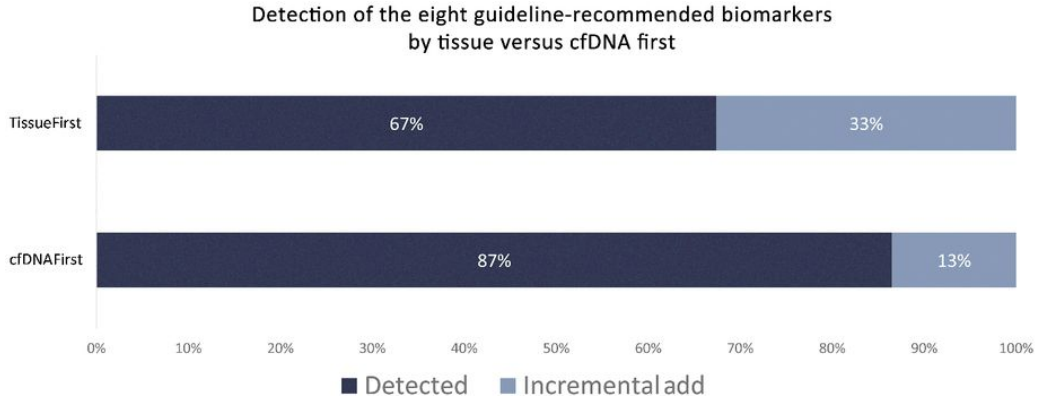
Overview

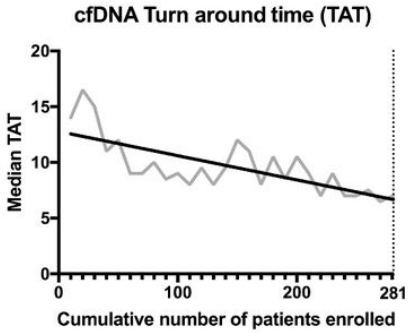
- Diagnosis – when to use liquid biopsies
- Targeted therapies for advanced NSCLC
  - New agents
  - Use in first vs second line
- Progression on TKIs
  - Management of oligoprogression
  - When to repeat a liquid/tissue biopsy
  - Role of targeted therapy, chemotherapy, and immunotherapy
- Early-stage and locally advanced NSCLC with driver mutations

Use of ctDNA analysis to identify actionable biomarkers

- ctDNA is complementary to tissue testing
  - Nile Study:
    - 282 patients with NSCLC underwent ctDNA analysis AND standard-of-care tumor tissue testing, with the primary objective of demonstrating noninferiority of ctDNA-based vs SOC tumor tissue-based genotyping

Guideline-recommended biomarker positivity by sample type		Tissue		
		Positive	Negative	Total
cfDNA	Positive	48	29	77
	Negative	12	193	205
	Total	60	222	282





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Leighl NB, et al. CCR 2019

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Targeted Therapies for NSCLC

EGFR Sensitizing:
Osimertinib

EGFRex20ins:
Amivantamab
Mobocertinib

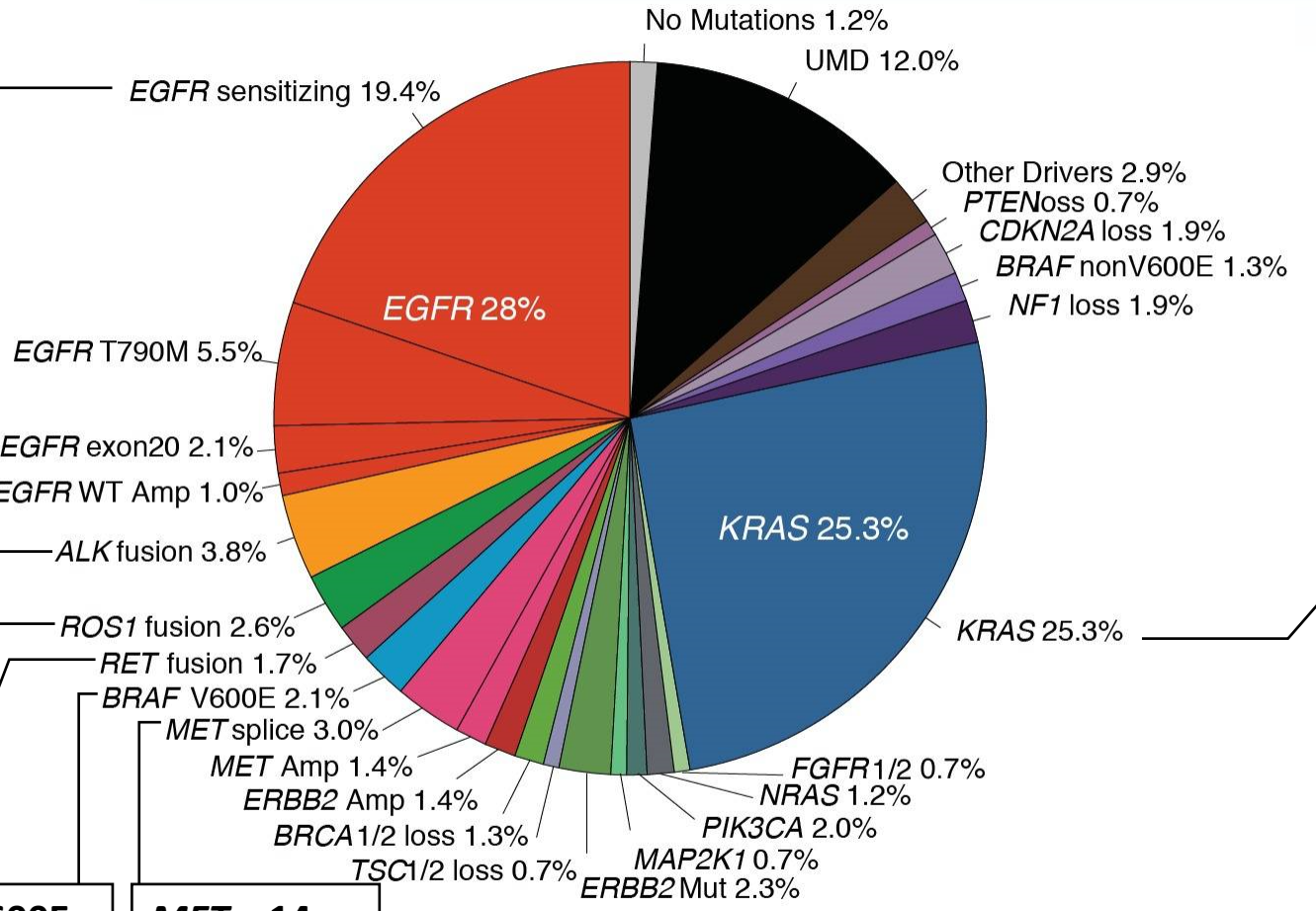
ALK:
Alectinib
Brigatinib
Lorlatinib

ROS1:
Crizotinib
Entrectinib

RET fusion:
Selpercatinib
Pralsetinib

BRAF V600E:
Dabrafenib + trametinib

_MET_ex14:
Capmatinib
Tepotinib



KRAS^{G12C}:
Sotorasib

HER2:
Trastuzumab deruxtecan

NTRK fusion:
Entrectinib
Larotrectinib

Jordan EJ, et al. Cancer Discov 2017

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Targeted Therapies for NSCLC

First-line treatments

EGFR Sensitizing:
Osimertinib

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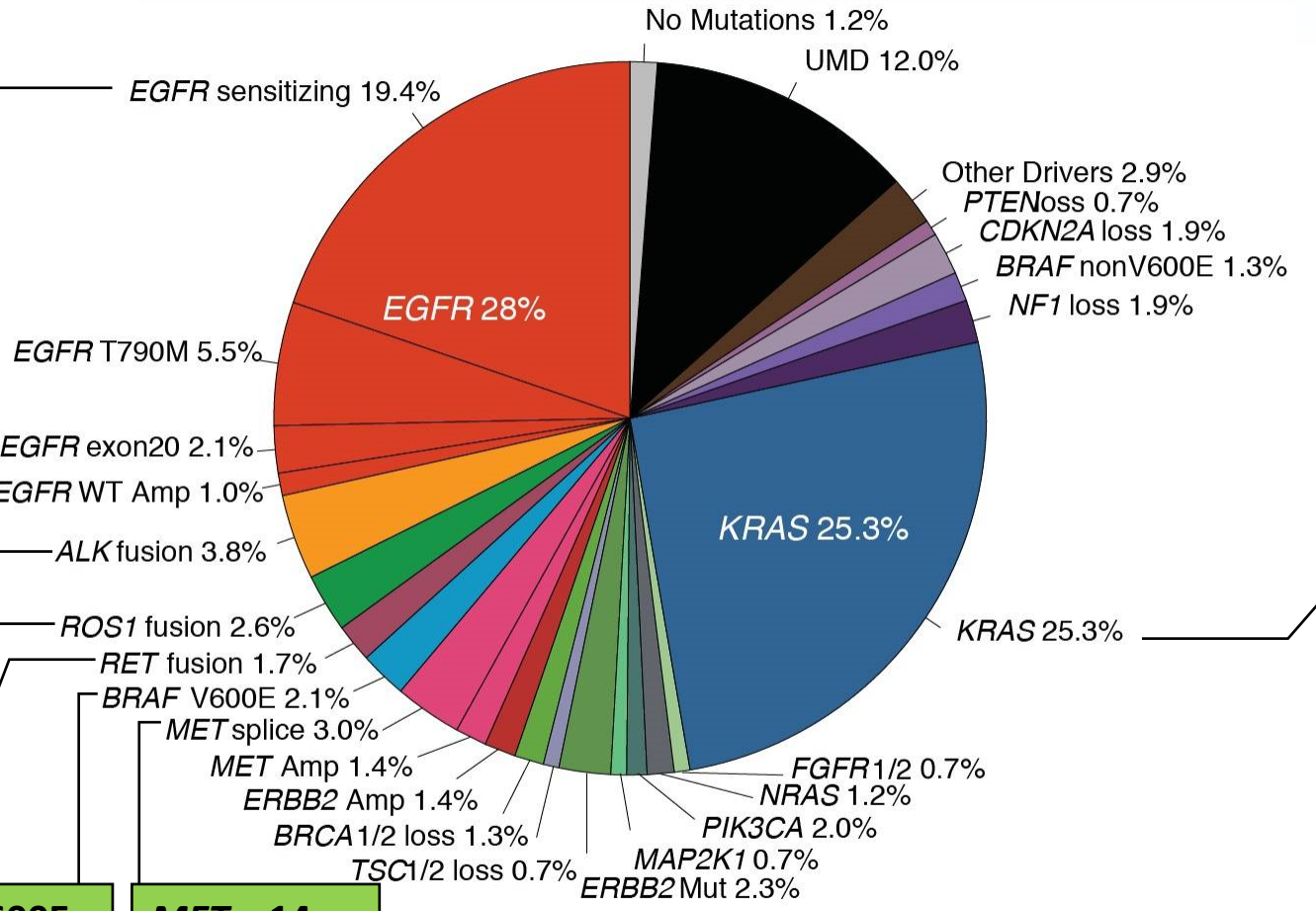

Jordan EJ, et al. Cancer Discov 2017

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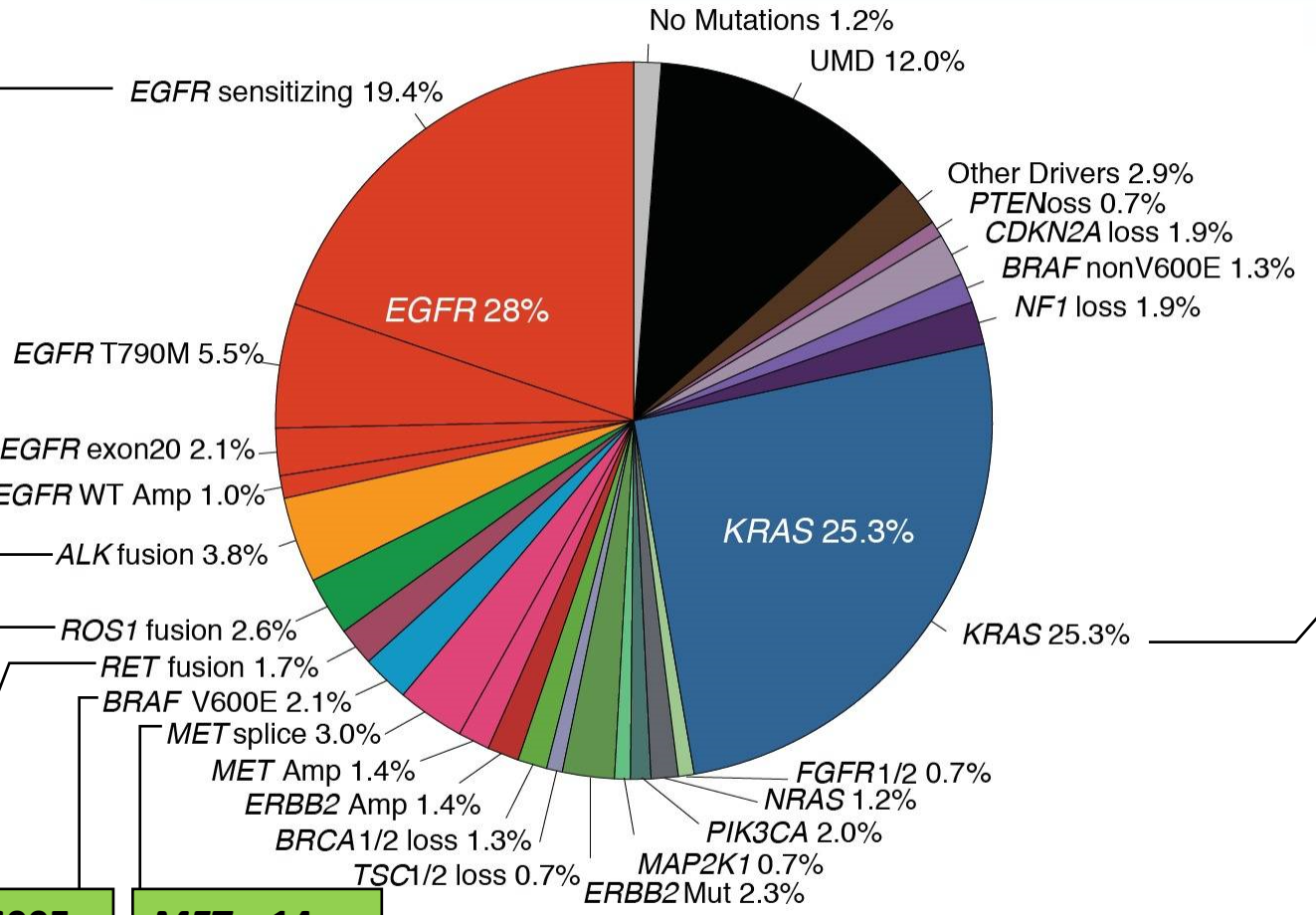
Targeted Therapies for NSCLC

First-line treatments

Second-line treatments



***EGFR* Sensitizing:**
Osimertinib

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Jordan EJ, et al. Cancer Discov 2017

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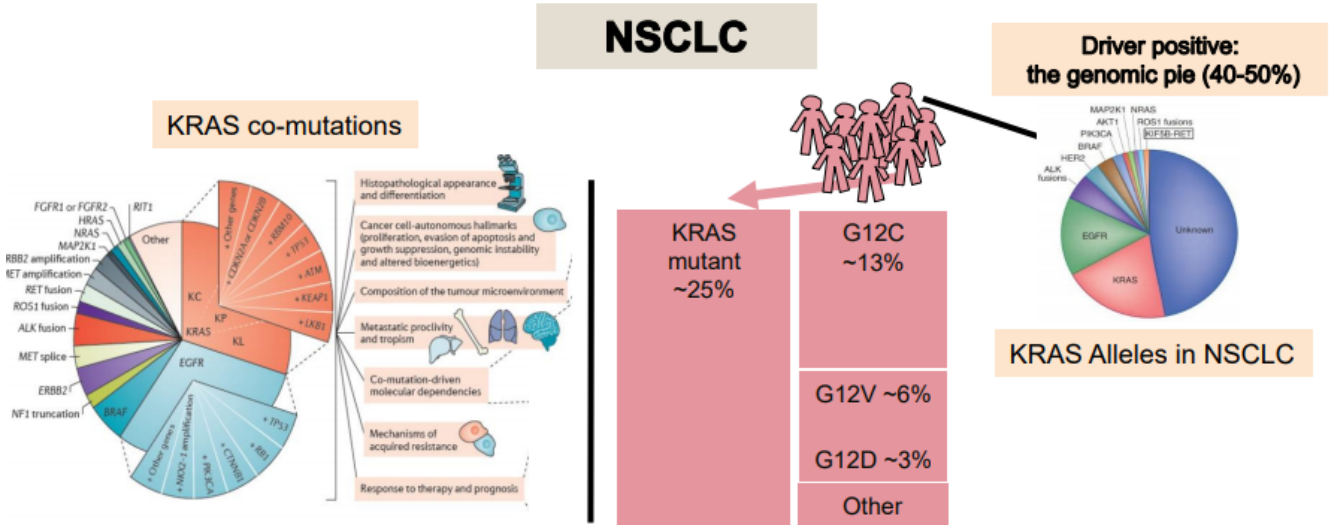
New treatments for EGFR exon 20 insertion mutations

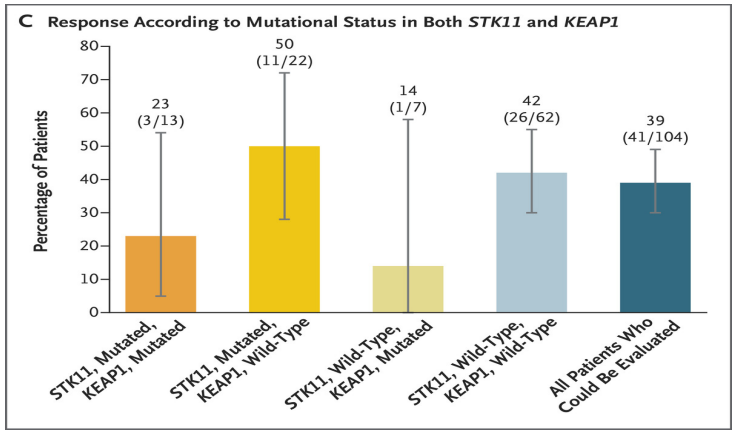
	Amivantamab	Mobocertinib
MoA	▪ Fully humanized, bispecific IgG1 Ab targeting EGFR and MET	▪ Irreversible EGFR TKI that targets EGFR ex20ins mutations
Administration	IV	Oral
Efficacy ▪ ORR, % ▪ mDoR, mo ▪ mPFS, mo ▪ mOS, mo	(N = 81; postplatinum population) 40 11.1 8.3 22.8	(N = 114; platinum-pretreated cohort) 28 17.5 7.3 24.0
Toxicities	Infusion-related reactions (in 66% of patients, most grade 1-2), rash, edema	Diarrhea, rash, nausea

- Both FDA approved for treatment of advanced NSCLC with *EGFR* ex20ins mutations with disease progression on or after platinum-based chemotherapy

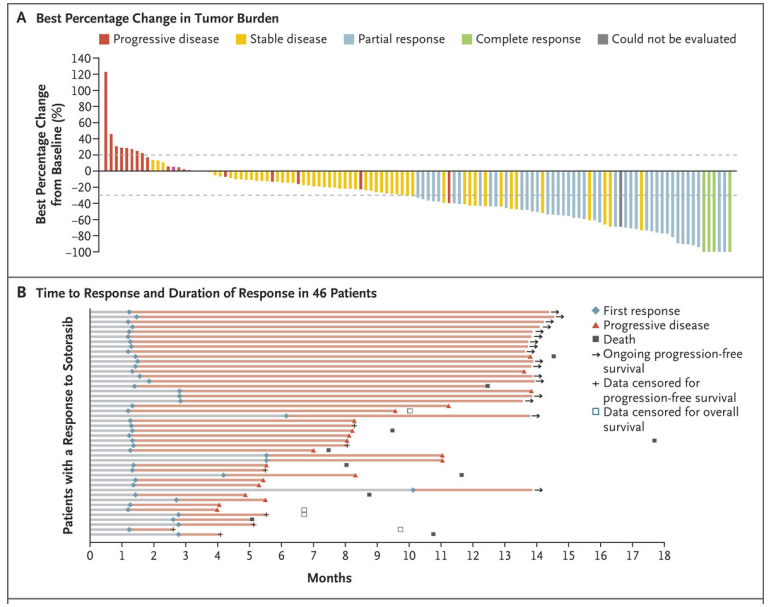
Park et al. JCO 2021.
Zhou et al. JAMA Oncol 2021.

Targeted therapy for KRAS G12C mutant NSCLC





CodeBreaK100: Phase 2 trial of sotorasib, a small molecule inhibitor of KRAS G12C



ORR 37.1%
DCR 80.6%
Median DOR 11.1m

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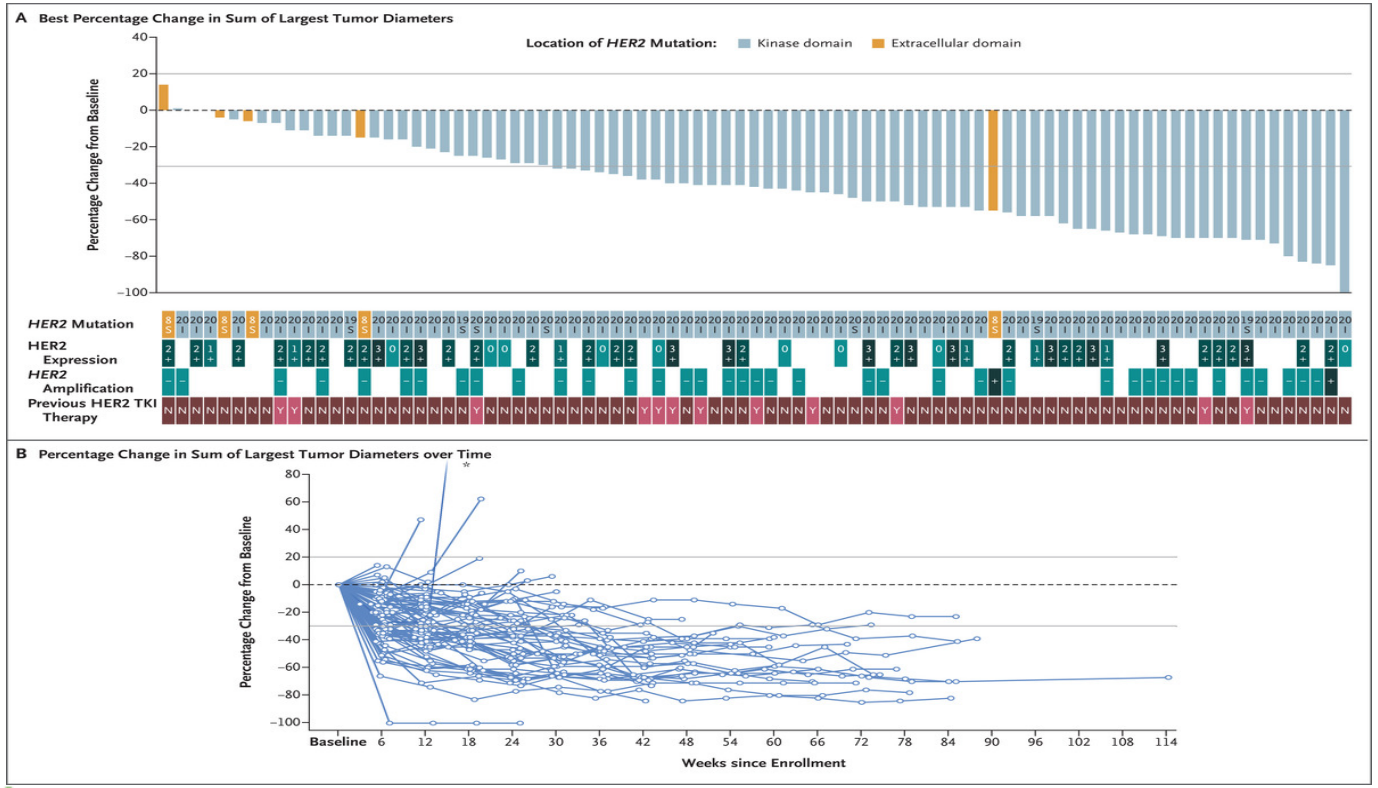
Skoulidis et al. Nat Rev Cancer 2019
Skoulidis et al. NEJM 2021

Treatment of HER2-mutant NSCLC

DESTINY-Lung01: Phase 2 trial of trastuzumab deruxtecan, an antibody-drug conjugate of an anti-HER2 antibody linked to a topoisomerase I inhibitor



- ORR 55% (50/91 patients
- Median DOR 9.3 months
- Median PFS 8.2 months
- Median OS 17.8 months

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BT Li et al. N Engl J Med 2022.

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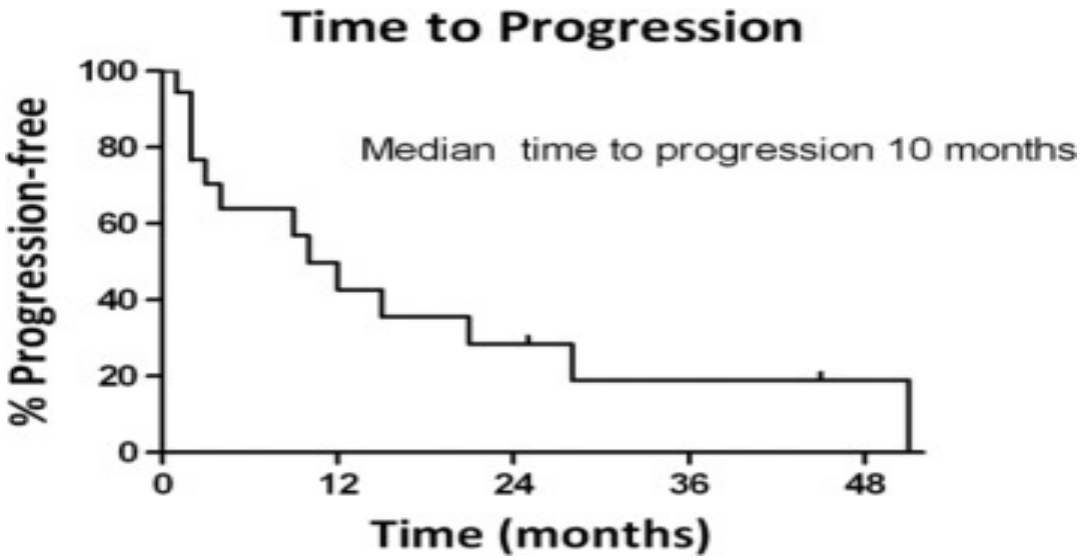
Treatment of oligoprogression

Local therapy for oligoprogression in EGFR-mutant and ALK-rearranged lung cancer

Site of first progression	Number of patients	PFS1 (months) (CI)	PFS2 (months)(CI)	Site of 2nd progression	
CNS	10	10.9 7.3 – 18.3	7.1 1.7 – 11.3	2 (20%)	no prog
				3 (30%)	CNS
				5 (50%)	eCNS
eCNS*	15	9.0 6.5 – 13.8	4.0 2.7 –7.4	4 (27%)	no prog
				3 (20%)	CNS
				8 (53%)	eCNS
All patients	**25**	**9.8** **8.8 – 13.8**	**6.2** **3.7 – 8.0**	**6 (24%)**	**no prog**
				7 (28%)	**CNS**
				12 (48%)	**eCNS**



- Can be a strategy in asymptomatic patients with one or a few sites of progression
- Is this still relevant in the setting of newer agents?

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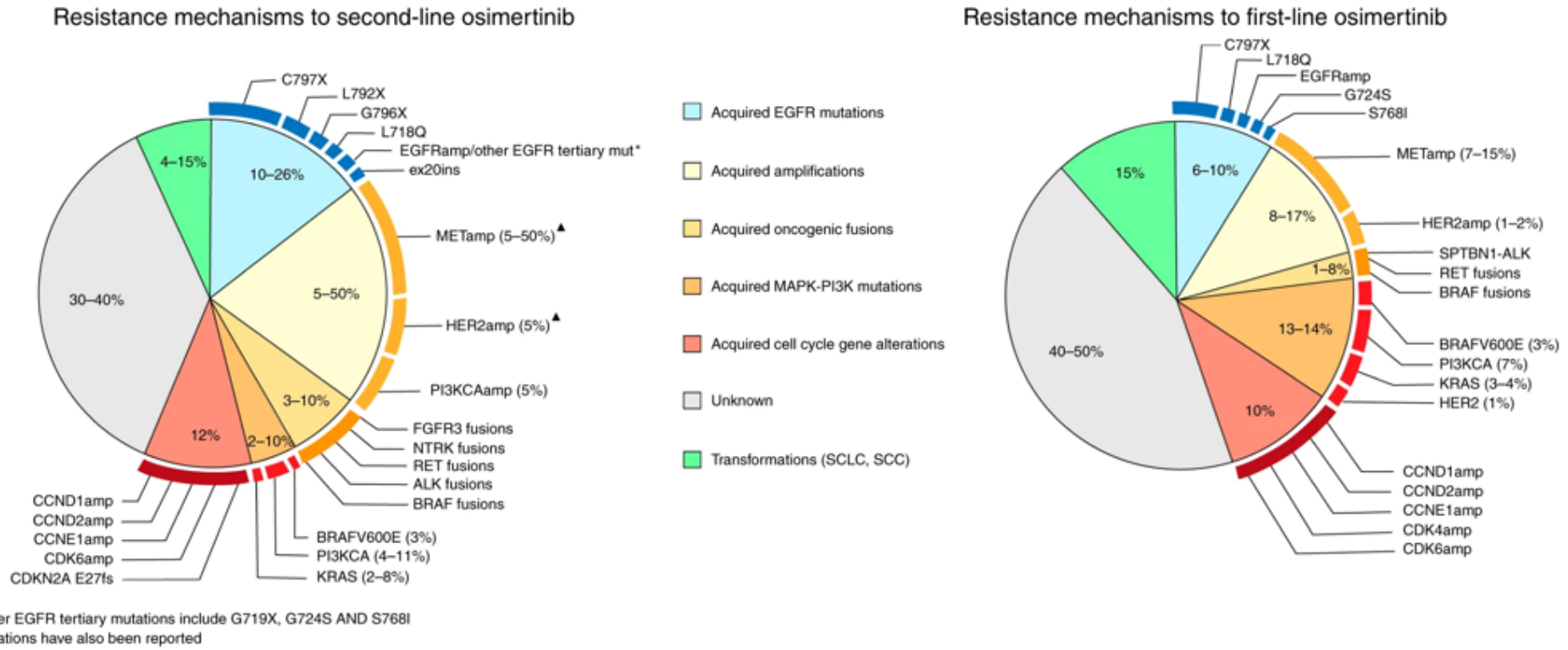
Weickhardt AJ, et al. J Thorac Oncol 2012
Yu, H et al. J Thorac Oncol 2013

What can we learn from molecular analysis (from tissue or blood) at resistance to osimertinib?

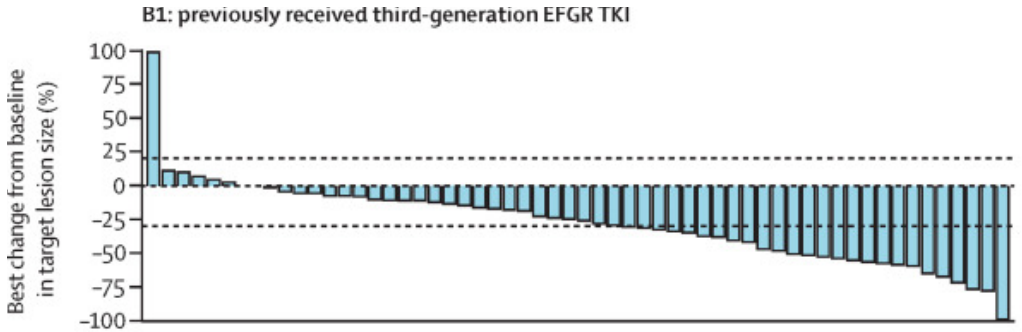


* Other EGFR tertiary mutations include G719X, G724S AND S768I
▲Mutations have also been reported

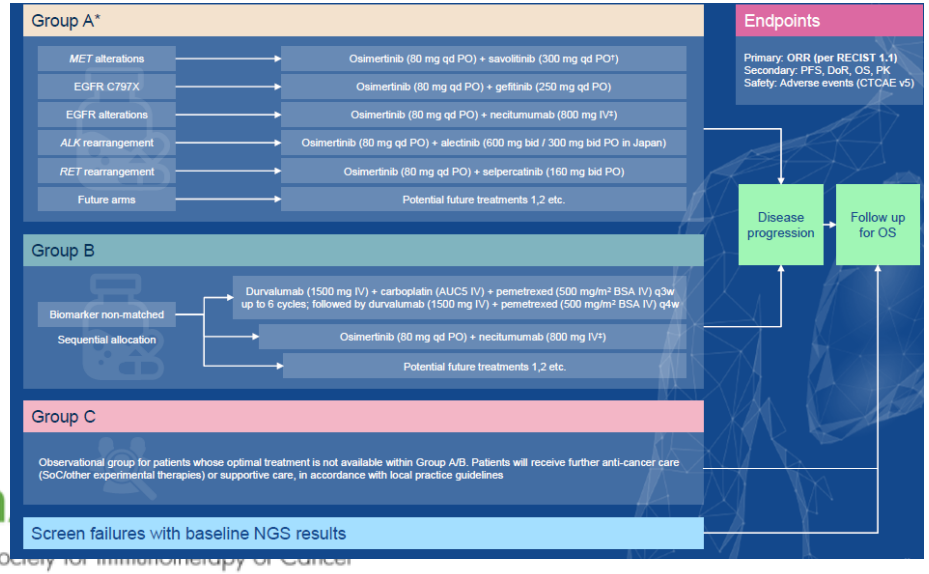
Leonetti A, et al. BJC 2019

Targeted therapy after EGFR TKI resistance

Osimertinib plus savolitinib for patients with MET amp after progression on an EGFR TKI

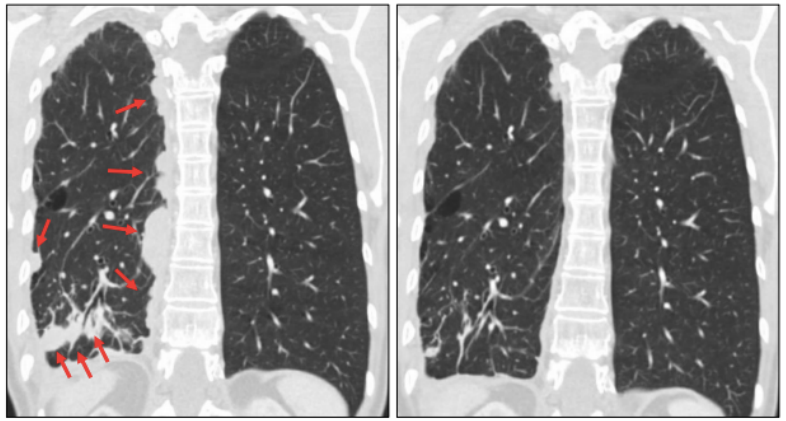


Orchard Trial Schema



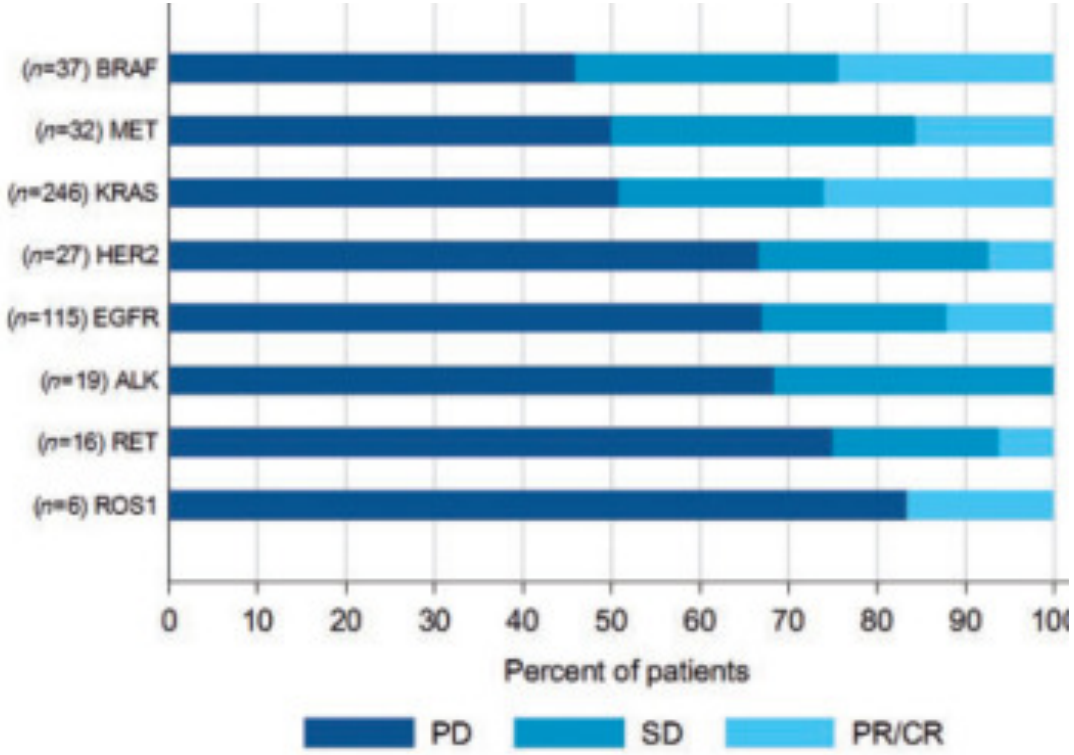
Osimertinib plus pralsetinib for RET-fusion-mediated EGFR TKI resistance

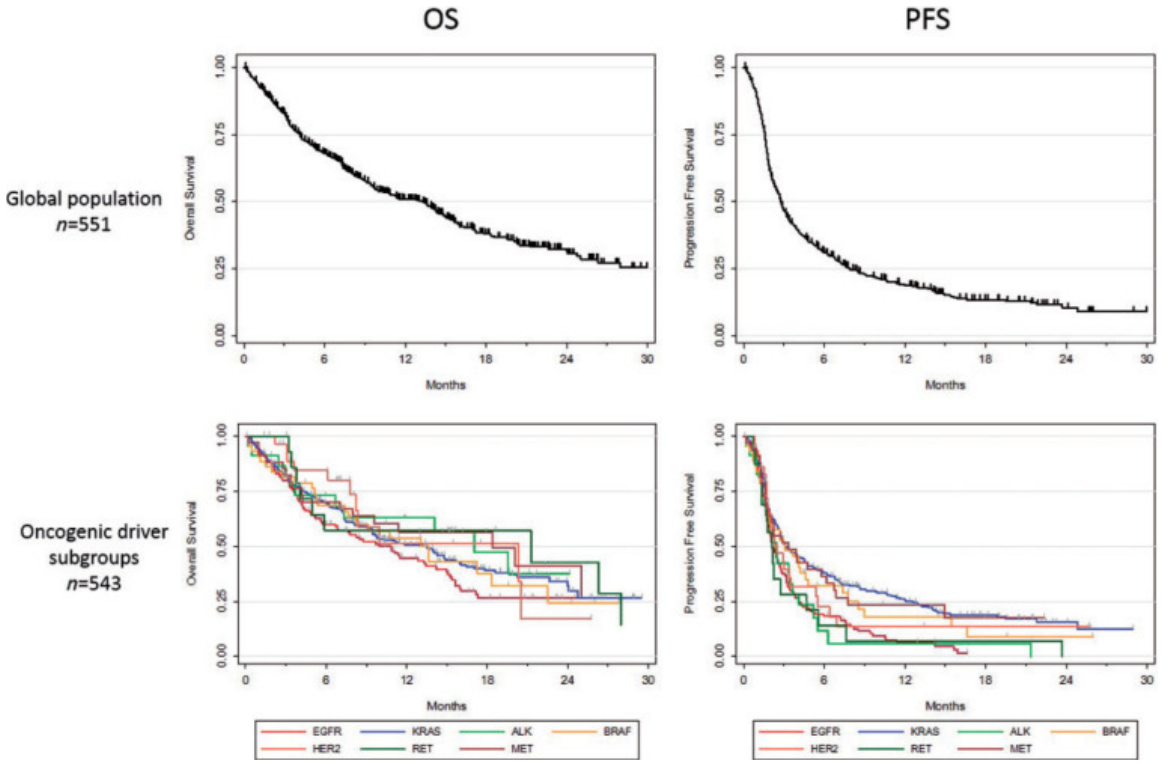
- RET fusion at progression on 2nd-line osimertinib identified as a mechanism of resistance (CCDC6-RET)
- Treated with osimertinib plus pralsetinib with a partial response ongoing at 4 months



Sequist L, et al. Lancet Oncol 2020
Piotrowska Z, et al, Cancer Discovery 2018

Immunotherapy for molecular subsets of NSCLC

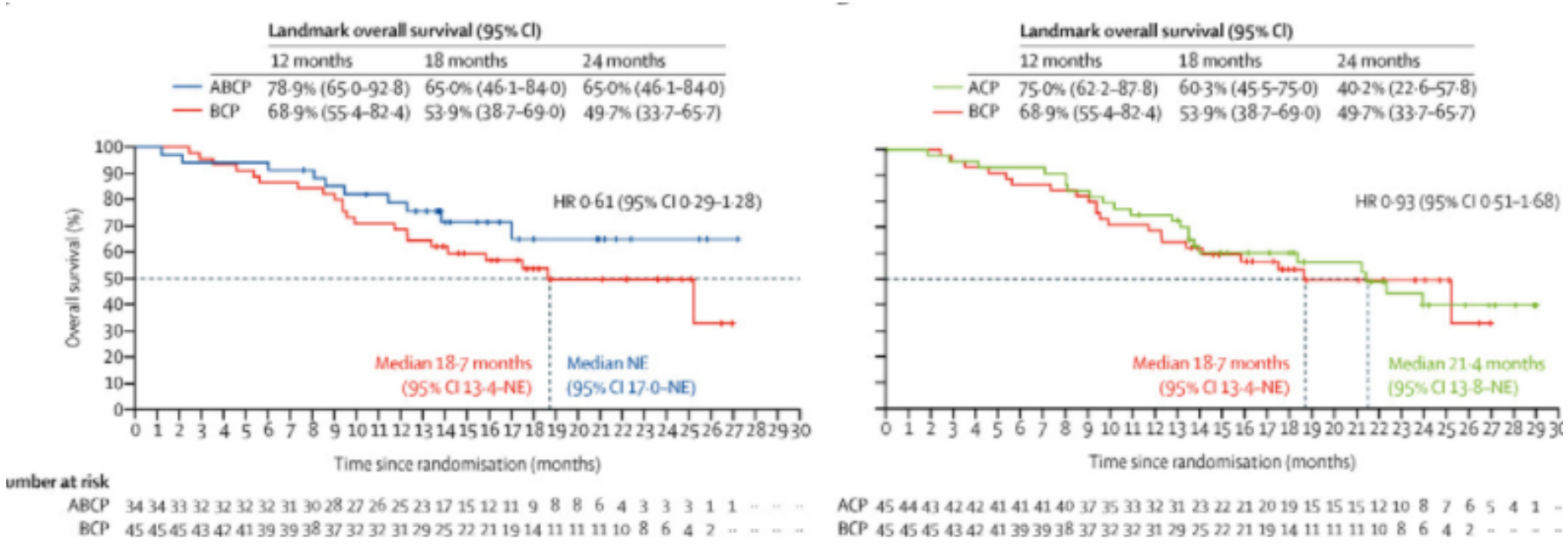




Mazieres J, et al. Annals of Oncology 2019.

Chemotherapy plus immunotherapy for EGFR-mutant NSCLC

- IMpower150: Randomized phase 3 trial of atezolizumab/bevacizumab/carboplatin/paclitaxel (ABCP) vs atezo plus carbo/paclitaxel (ACP) vs bev/carbo/paclitaxel (BCP)
- Allowed patients with EGFR mutations or ALK translocations after disease progression on one or more approved TKIs



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Reck M, et al. Lancet Respiratory Medicine 2019.

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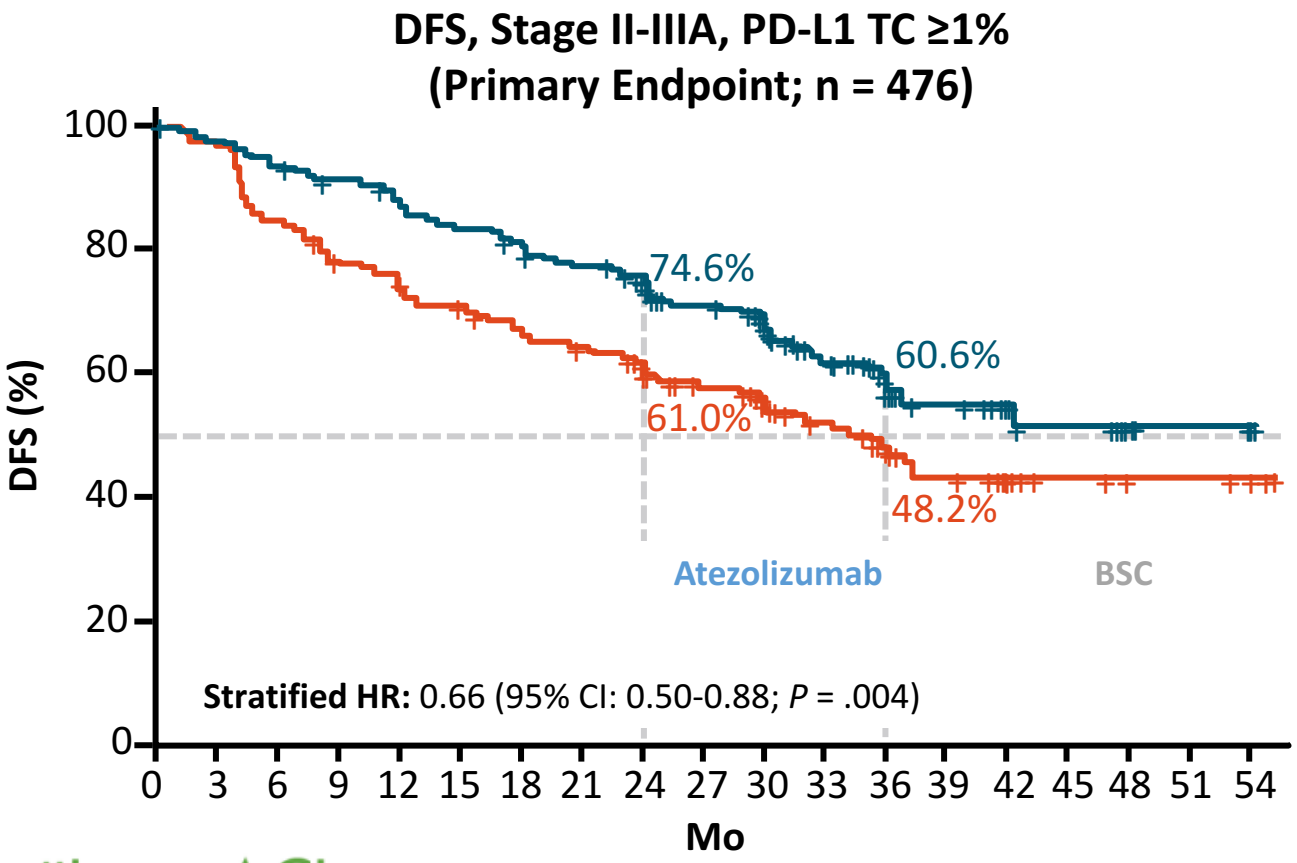
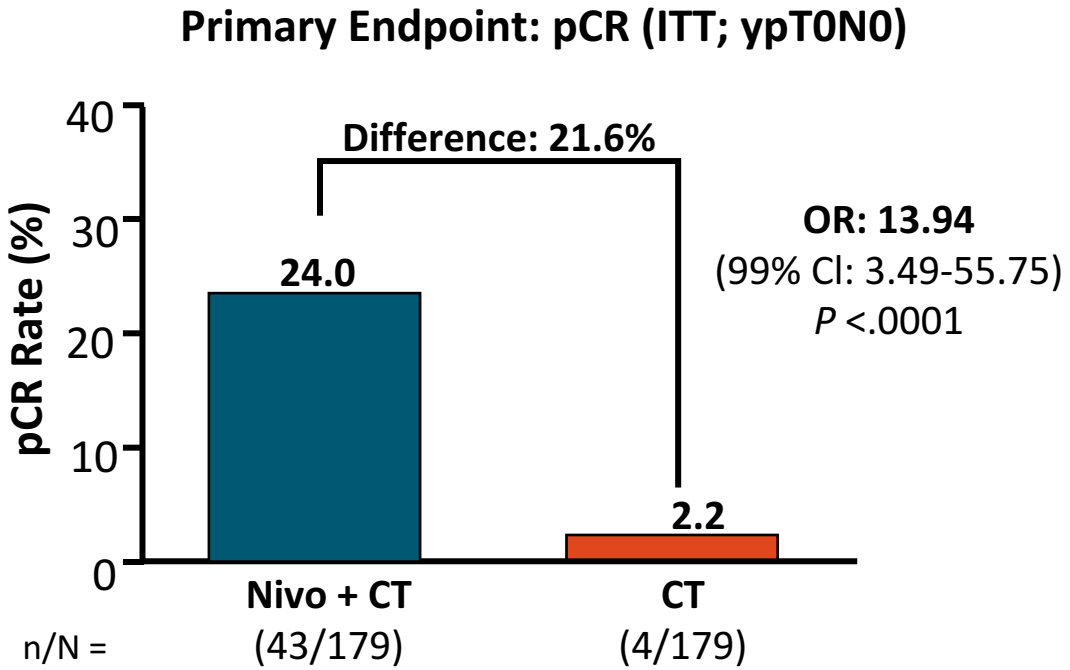
Immunotherapy for early-stage NSCLC

IMpower010: Adjuvant atezo



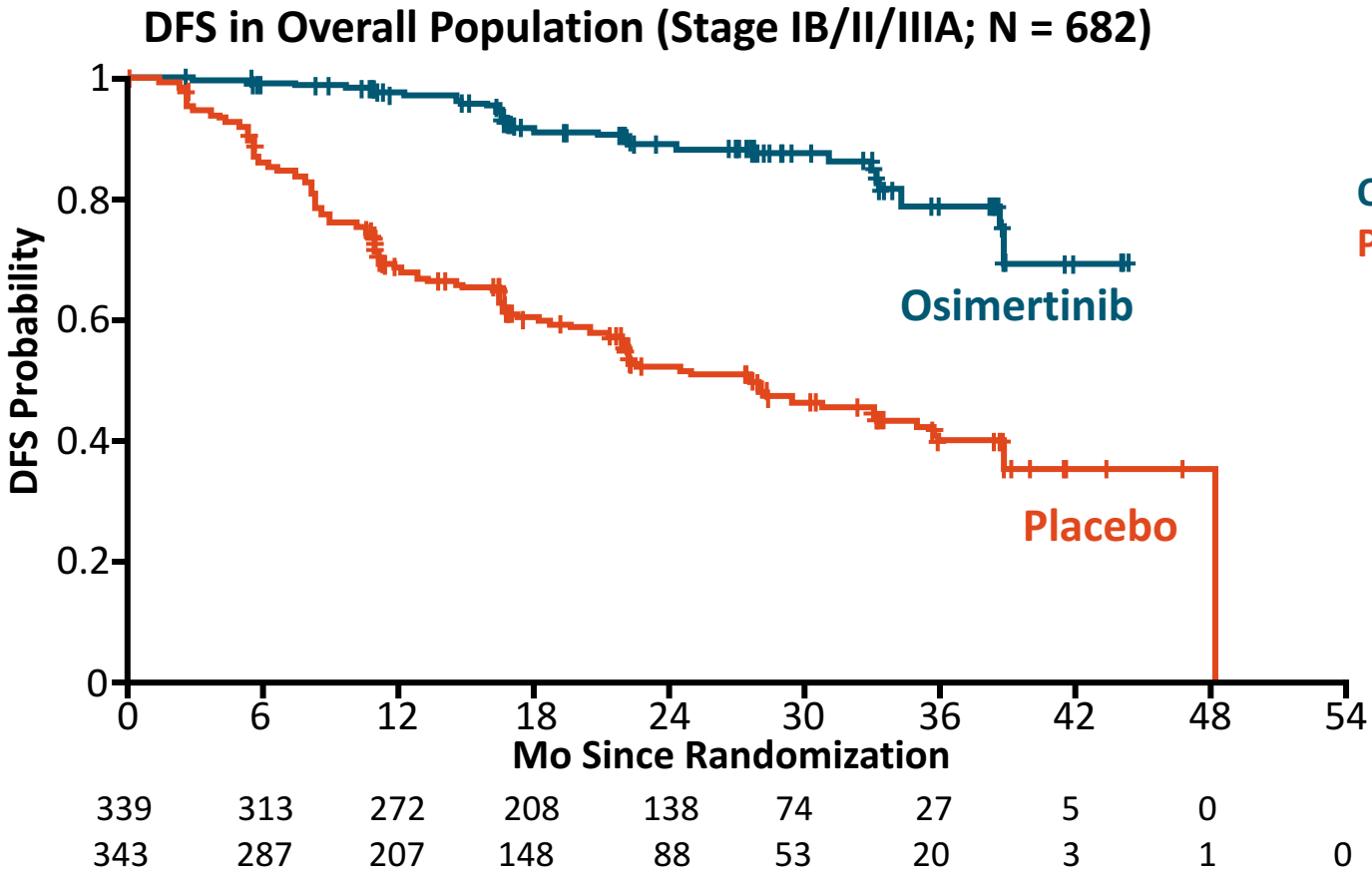
CheckMate 816: Neoadjuvant chemo/nivo



Are these studies applicable to driver-mutation positive NSCLC?

Wu, et al. NEJM. 2020.
Forde, et al. AACR 2021

Adjuvant osimertinib for early-stage EGFR-mutant NSCLC



	Median DFS, Mo	24-Mo DFS,%
Osimertinib	NR	89
Placebo	27.5	52

HR: 0.20 (95% CI: 0.14-0.30; *P* <.001)

Maturity: 33% (osimertinib: 11%; placebo: 55%)

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Wu, et al. NEJM. 2020.

Immunotherapy for locally advanced NSCLC

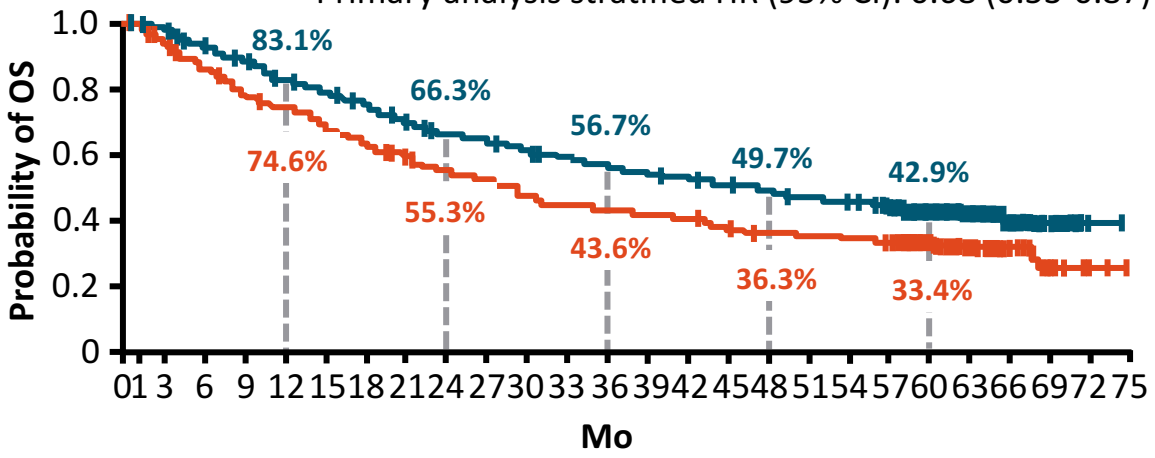
Pacific: Consolidation durvalumab after chemo/RT

5-Yr OS (ITT)

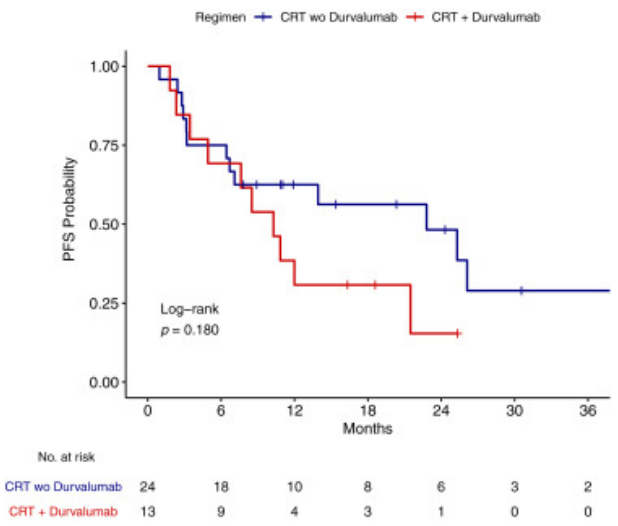
	Median OS, Mo (95% CI)
Durvalumab (n = 476)	47.5 (38.1-52.9)
Placebo (n = 237)	29.1 (22.1-35.1)

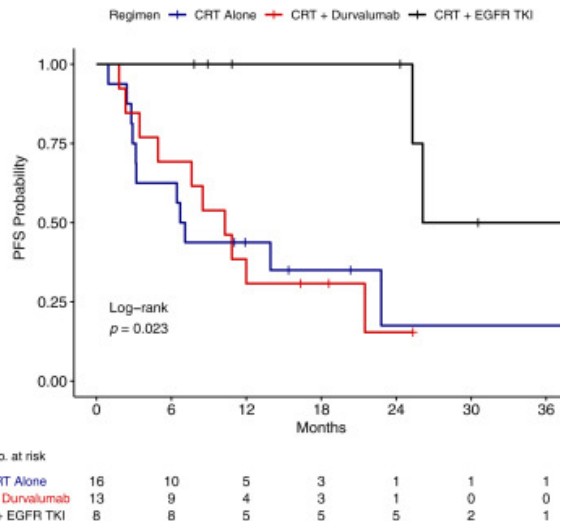
5-yr stratified HR (95% CI): 0.72 (0.59-0.89)

Primary analysis stratified HR (95% CI): 0.68 (0.53-0.87)



Durvalumab after chemo/RT in EGFR-mutant NSCLC





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Spigel et al. ASCO 2021
Aredo JV, et al. JTO 2021

Summary

- ctDNA analysis can increase the detection of driver oncogenes which is critical to determining the best treatment strategy for patients with advanced NSCLC
- Most targeted therapies are used as first-line treatment, but some are reserved for second line (i.e. therapies for EGFR exon 20 and KRAS G12C)
- Treatment options at progression on targeted therapy include local therapy for oligoprogression or chemotherapy +/- immunotherapy
  - Repeat biopsy (tissue or blood) may identify a potentially actionable mechanism of resistance
- The benefit of immunotherapy for early-stage or locally advanced driver-mutation positive NSCLC is unclear