Targeting KRAS and HER2 in advanced NSCLC

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DISCLOSURES

Commercial Interest	Relationship(s)
AstraZeneca, Novartis, Takeda, Roche, Medimmune, Mirati, Spectrum	Research Funding
Amgen, Oncocyte	Consulting
Bayer, Blueprints Medicine	Advisory Board

Abstracts:

PS01.07 – CodeBreaK 100: Registrational Phase 2 Trial of Sotorasib in **KRAS p.G12C** Mutated Non-small Cell Lung Cancer (Bob Li)

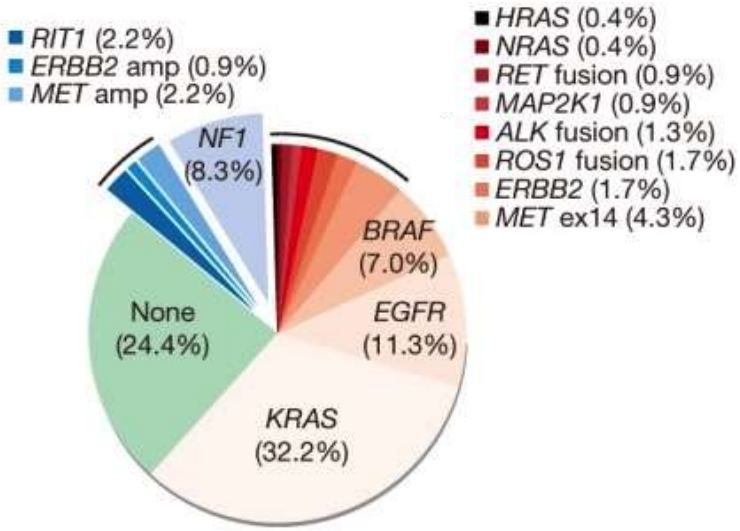
OA04.05 – Destiny-Lung01: Trastuzumab Deruxtecan in **HER2-Overexpressing** Metastatic NSCLC (K. Nakagawa).

MA11.04 – Poziotinib in previously treated **HER2 exon 20** NSCLC patients (R. Cornelissen)

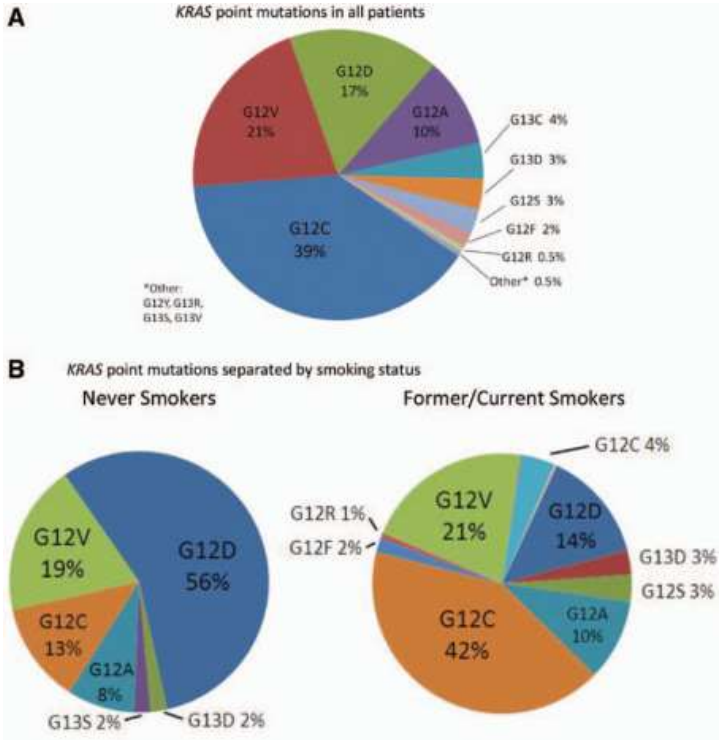
FP14.15 – Neratinib-Based Combination Therapy in **HER2-Mutant** Lung Adenocarcinomas (Bob Li)

KRAS p.G12C is found in ~ 13% of lung adenocarcinomas

Oncogenic drivers in lung adenocarcinoma

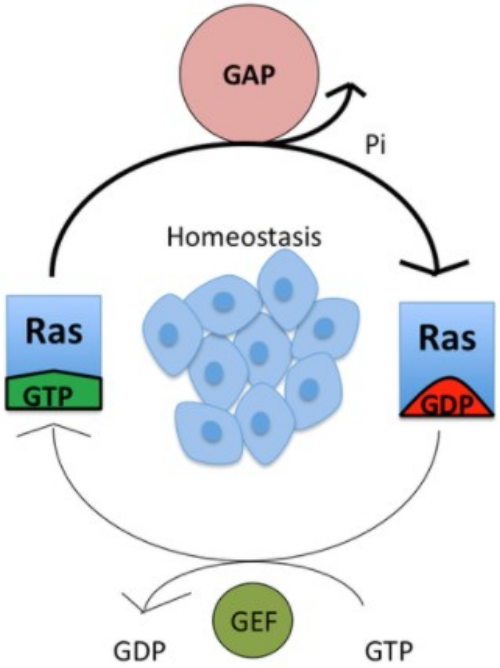


EA Collisson *et al. Nature* **000**, 1-8 (2014) doi:10.1038/nature13385

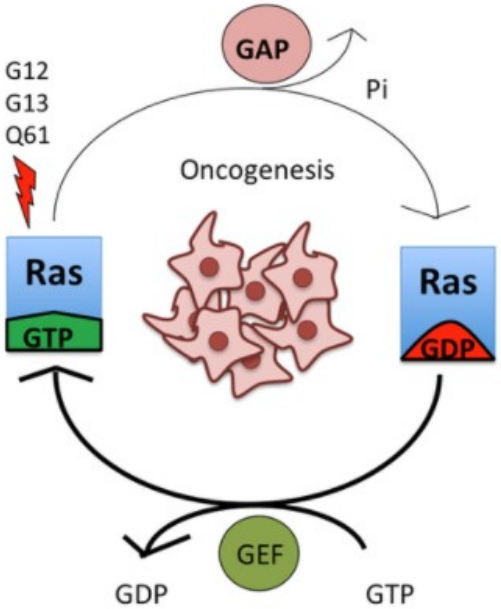


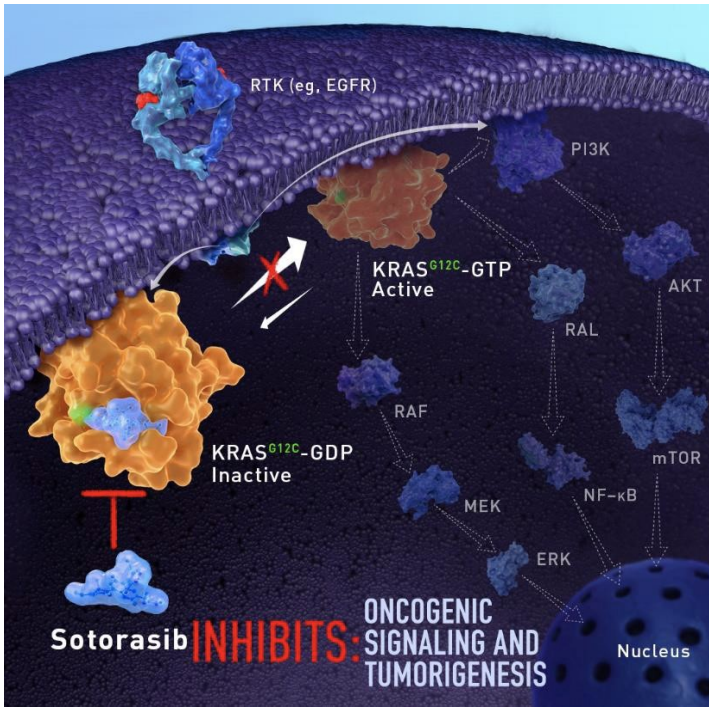
KRAS p.G12C shift the equilibrium to an active GTP-bound state

Normal Cells

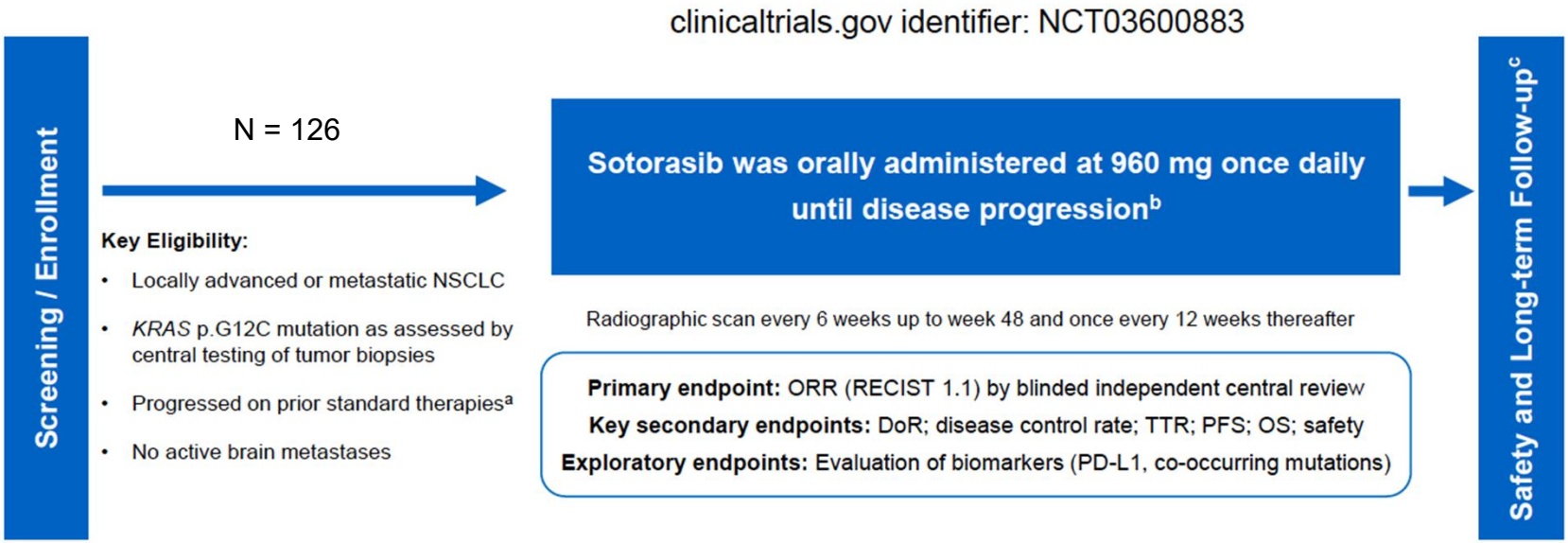


Cancer Cells





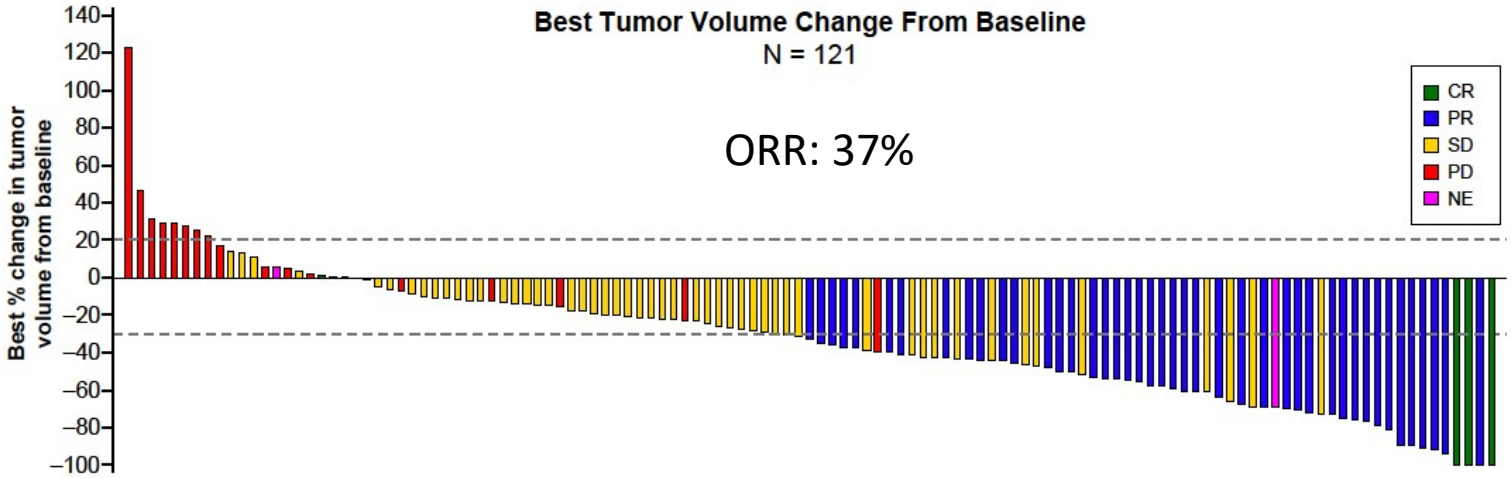
Trial Design



Li et al. WCLC 2020

Depth of Tumor Response

Tumor shrinkage of any magnitude was observed in 81% of patients (101/124)
Median percentage of best tumor shrinkage among all responders was 60%



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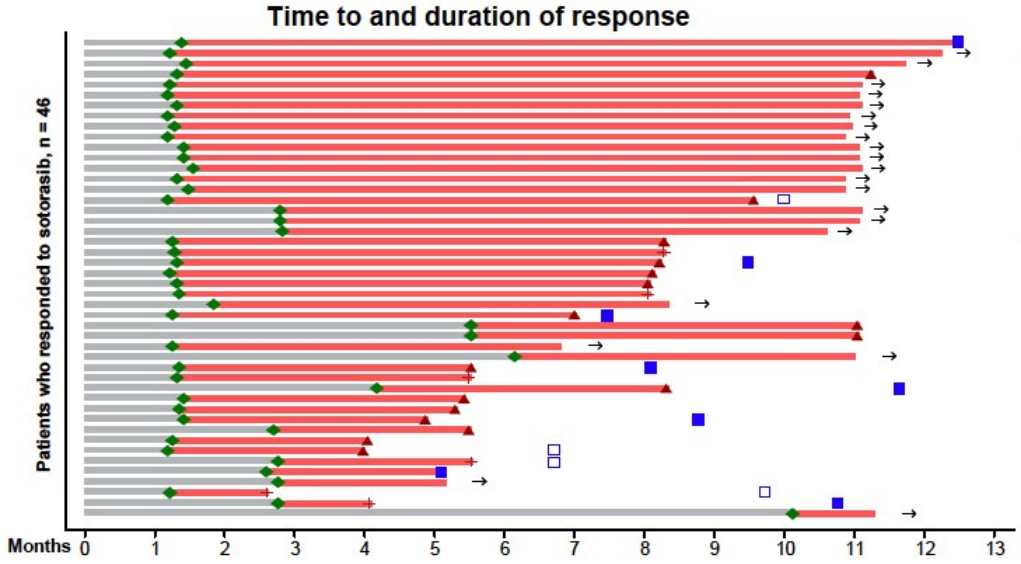
Durability of Tumor Response

Responses to sotorasib were durable; 72% were seen at the first assessment

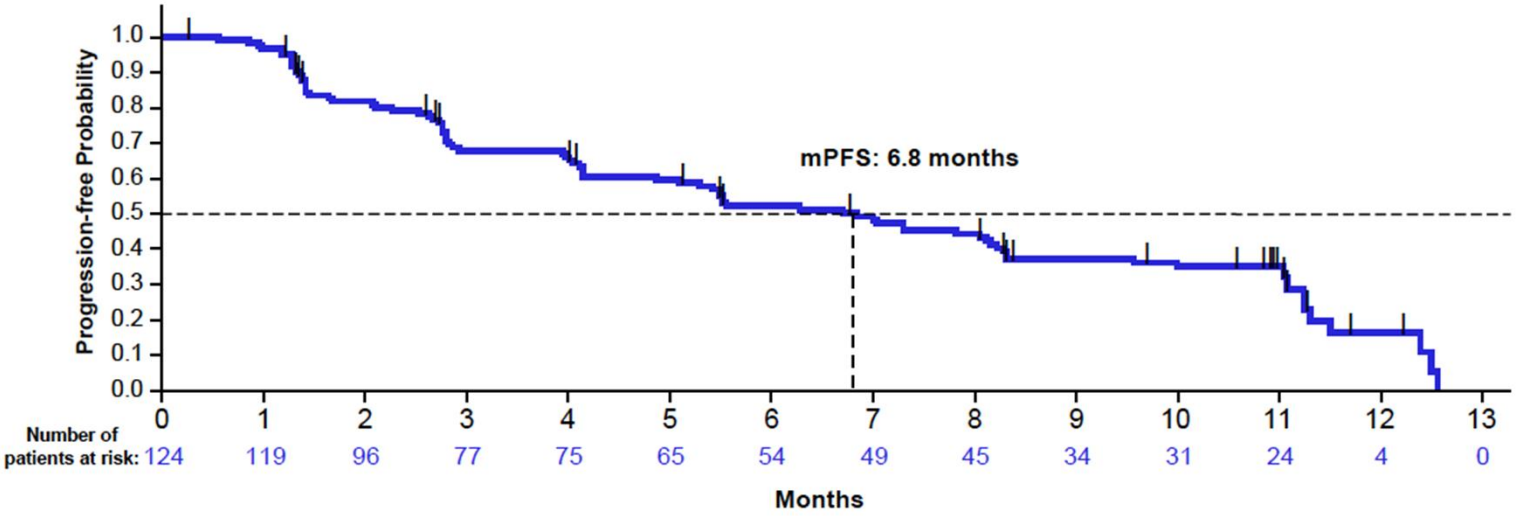


- Median duration of response: **10.0 months** (95% CI: 6.9, 11.1)
- Median time to objective response: **1.4 months**
- **43%** (20/46) of responders remained on treatment without progression as of the data cutoff

Li et al. WCLC 2020

Progression-Free Survival

Median progression-free survival was 6.8 months (95% CI: 5.1, 8.2)



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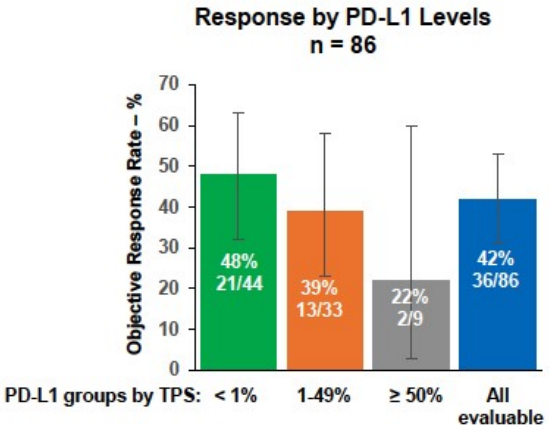
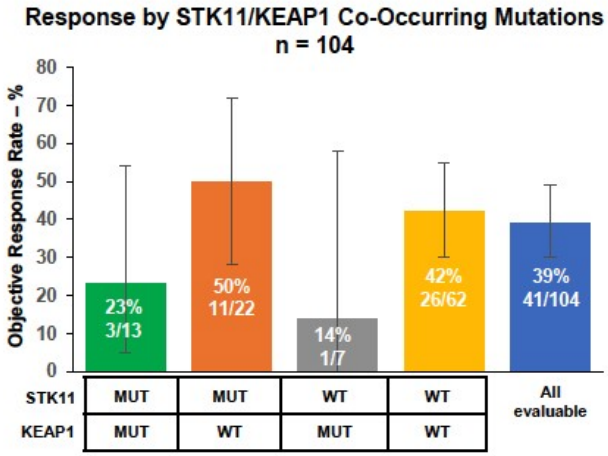
Tumor Response by PD-L1 Levels and STK11/KEAP1 Co-Occurring Mutations

In the exploratory biomarker analyses, responses to sotorasib were observed across the range of PD-L1 expression levels and STK11/KEAP1 co-occurring mutations





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Clinical Data to date on KRAS G12C Inhibitors

Drug	Trial	N	RR	DOR	PFS
Sotorasib	Phase I	59	32.2%	10.9 months	6.3 months
Adagrasib	Phase I/II	51	45%	TBD	TBD
Sotorasib	Phase II	126	37.1%	10.0 months	6.8 months

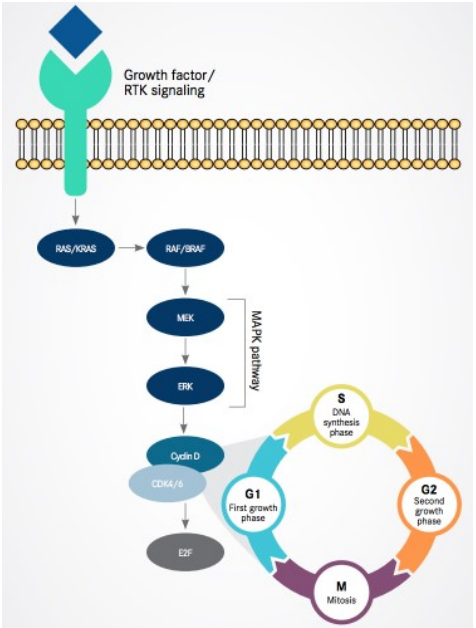
- Most common TRAEs are GI toxicities (nausea, vomiting, diarrhea, ALT/AST increases)
- Most TRAEs are grade 1 and 2
- TRAEs leading to discontinuations < 10%

Hong et al., NEJM 2020; Jänne et al. ENA 2020; Li et al. WCLC 2020

Janne, WCLC 2020

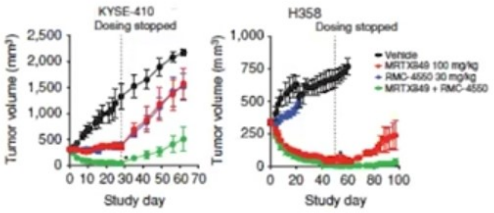
Why is sotorasib ORR < 40% when TKIs are 70-80-%

1. More tumor heterogeneity/higher TMB in KRASG12C compared to EGFR/ALK.
2. More potential upstream and downstream bypass tracks.
3. KRAS-mutant tumors may be less oncogene-dependent.
4. Sotorasib may be a less effective KRAS inhibitor than osimertinib is an EGFR inhibitor.

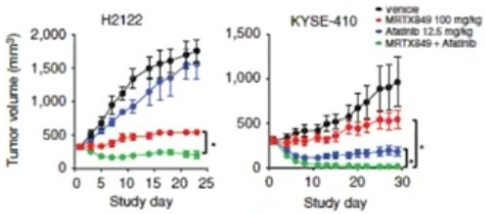


This illustration depicts the synergy between KRAS signaling and the cyclin-dependent kinases. KRAS is a member of the RAS family, which can activate the MAPK pathway and interact with the cell cycle through the cyclin-dependent kinases (CDKs). E2F indicates transcription factors of the *E2F* gene.

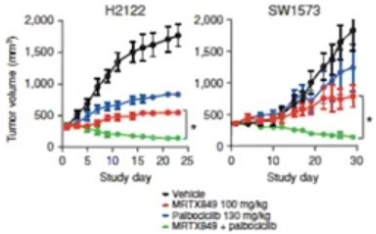
Preclinical and Clinical Combination Studies with KRAS G12C Inhibitors



SHP2 inhibitor combination



Afatinib combination



Palbociclib combination

Multiple combinations in clinical development…..

Adagrasib/afatinib
Adagrasib/TNO155
Adagrasib/Palbociclib
Adagrasib/pembrolizumab
Adagrasib/BI 1701963 (SOS1 inhibitor)
Adagrasib/cetuximab (CRC)

Sotorasib/pembrolizumab
Sotorasib/RMC-4630
Sotorasib/trametinib
Sotorasib/afatinib

Janne, WCLC 2020

Conclusions

- Sotorasib is a first-in-class $KRAS^{G12C}$ inhibitor and demonstrates clinical activity in advanced $KRAS^{G12C}$ mutated NSCLC: ORR: 37%, DOR: 10.0 months, PFS: 6.8 months.
- Patients with STK11 mutated tumors may have better response to sotorasib, while those with KEAP1 mutations may have worse.
- Viable 2nd line therapy option for patients with $KRAS^{G12C}$ mutated NSCLC, but chemo + ICI should still be given first.
- Acquired resistance is a significant concern and resistance mechanisms need to be identified.
- Several combination therapy trials are planned or underway.

Treatment options for *HER2*-altered NSCLC

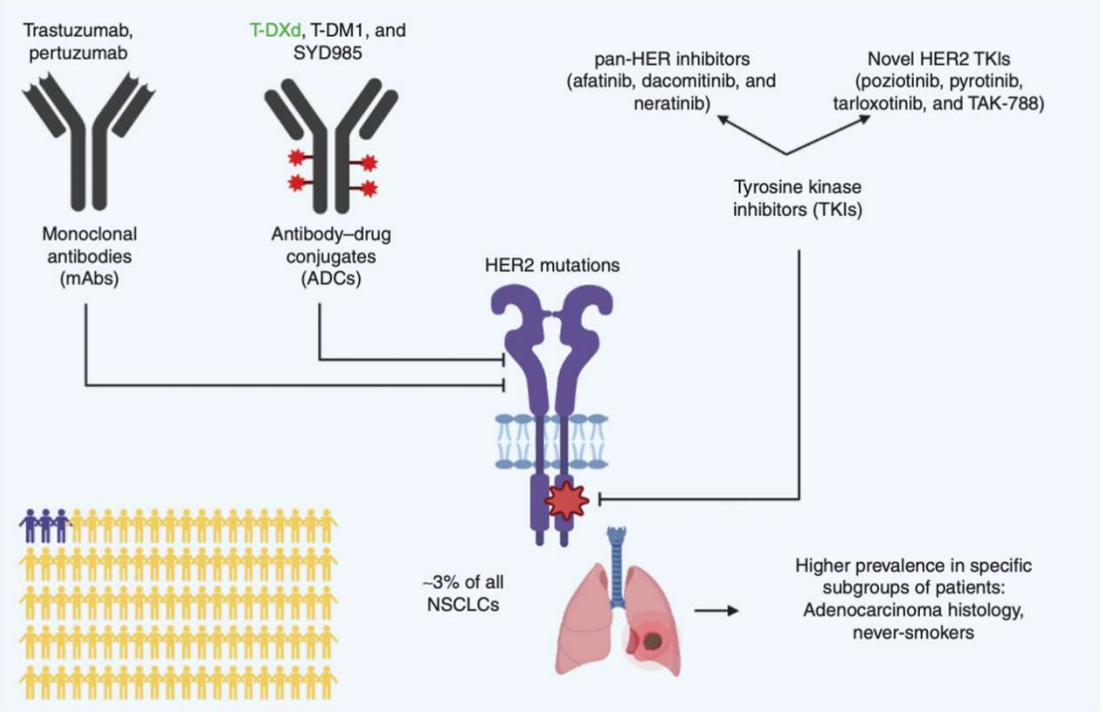
Prevalence of HER2 alterations in NSCLC:

Activating mutation: 2-4%

Amplification: 10-20%

Overexpression: 2.4 - 38%

Not mutually exclusive

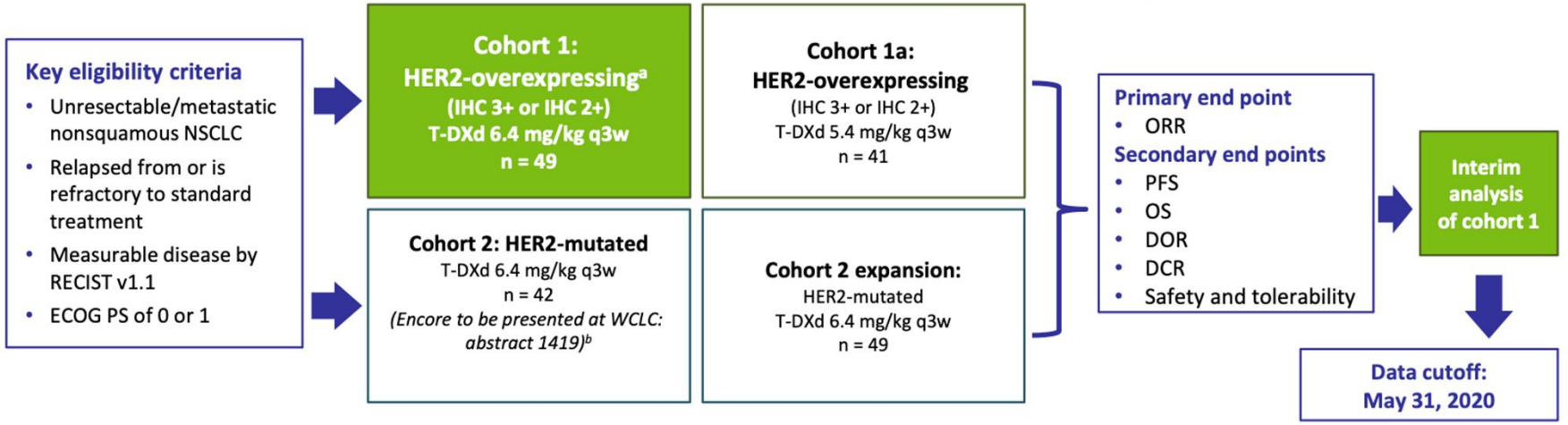


Rolfo and Russo, Cancer Discovery, 2020

DESTINY-Lung01 Study Design

Trastuzumab-Deruxtecan (T-DXd)

Phase 2 study of T-DXd, a novel antibody-drug conjugate, in patients with HER2-overexpressing or HER2-mutated metastatic NSCLC (NCT03505710)

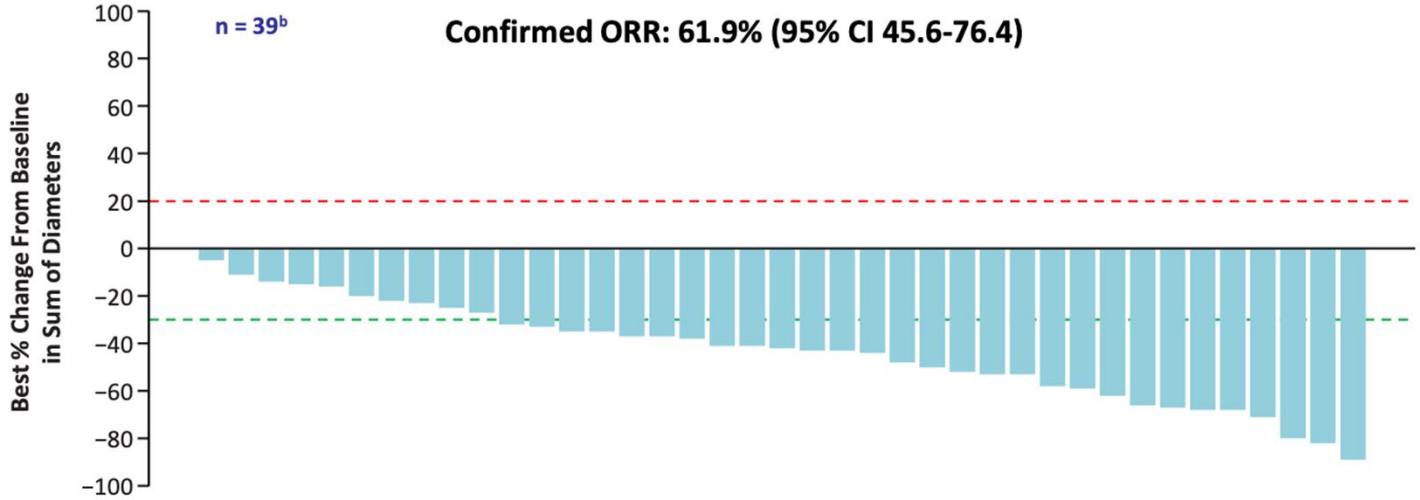


- In cohort 1, 11 patients remained on treatment, and 38 patients had discontinued treatment primarily because of PD (n = 22) or AEs (n = 9)[c]
- Median treatment duration was 18.0 weeks (range, 3.0-57.1 weeks)

K. Nakagawa et al.

DESTINY-Lung01 HER2-Mutated NSCLC

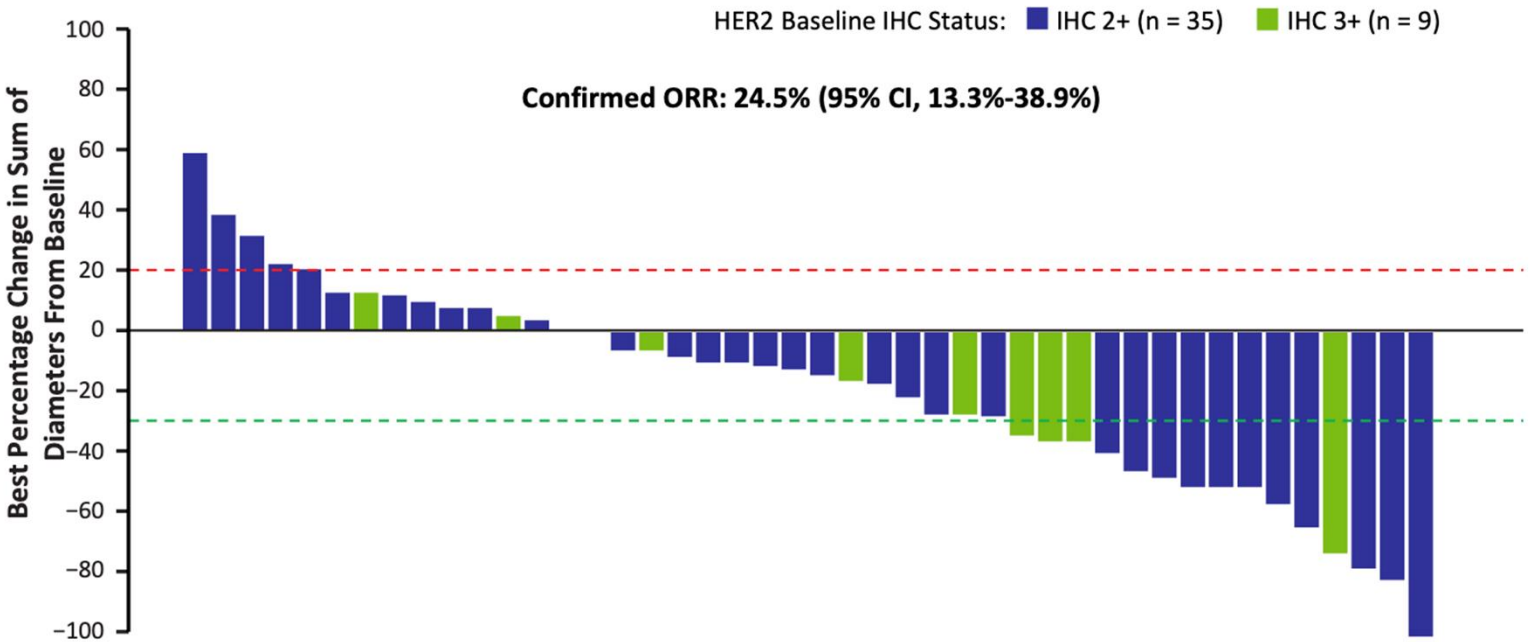
Best Percentage Change in Tumor Size[a] With T-DXd



Smit et al.

DESTINY-Lung01 HER2-Overexpressing NSCLC

Best Percentage Change in Tumor Size[a] With T-DXd

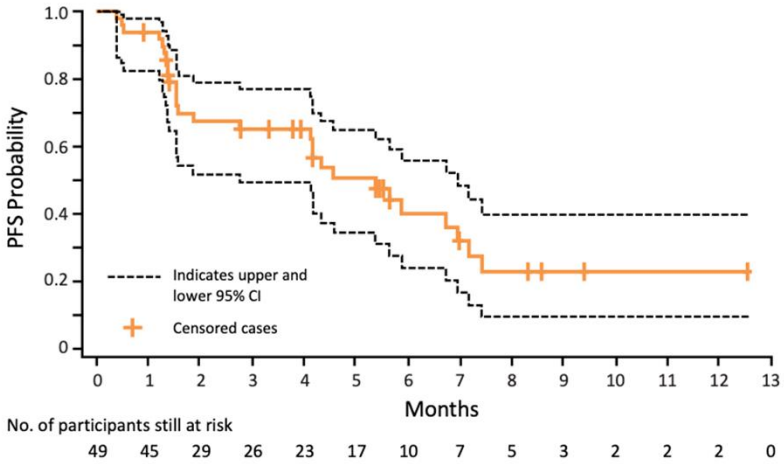


K. Nakagawa et al.

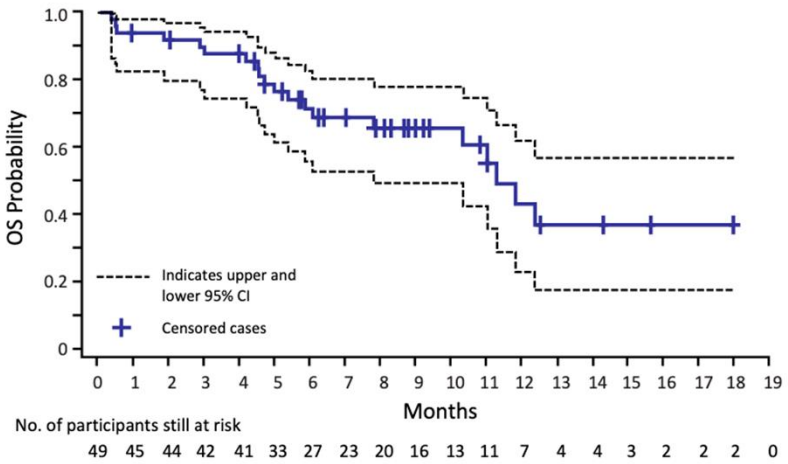
DESTINY-Lung01 HER2-Overexpressing NSCLC

PFS and OS With T-DXd

PFS (N = 49)
Median: 5.4 months (95% CI, 2.8-7.0 months)



OS (N = 49)
Median: 11.3 months (95% CI, 7.8-NE)



K. Nakagawa et al.

Update on poziotinib for the treatment of previously treated HER2 exon 20 mutated NSCLC

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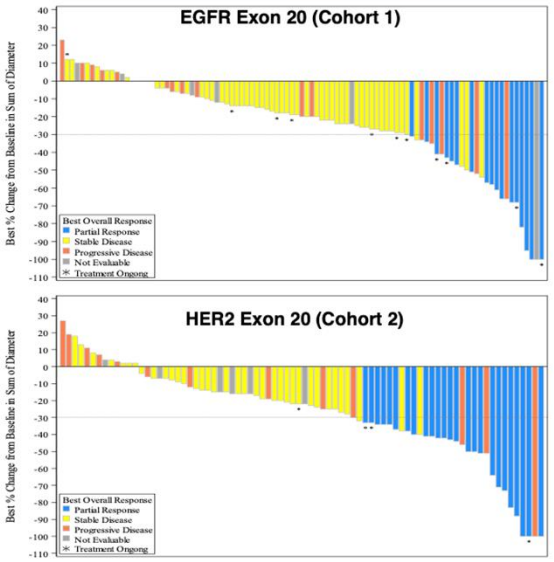
CONQUERING THORACIC CANCERS WORLDWIDE

Primary Efficacy and Safety

- Cohort 2 (2L HER2 exon 20) primary endpoint was met
- Median age 61yrs; median prior therapy = 2 (1-9); 66% females; 67% non-smokers; 13% stable brain metastases at entry
- Common Grade 3 TRAEs: Diarrhea (26%), Rash (29%), mucosal inflammation (10%)

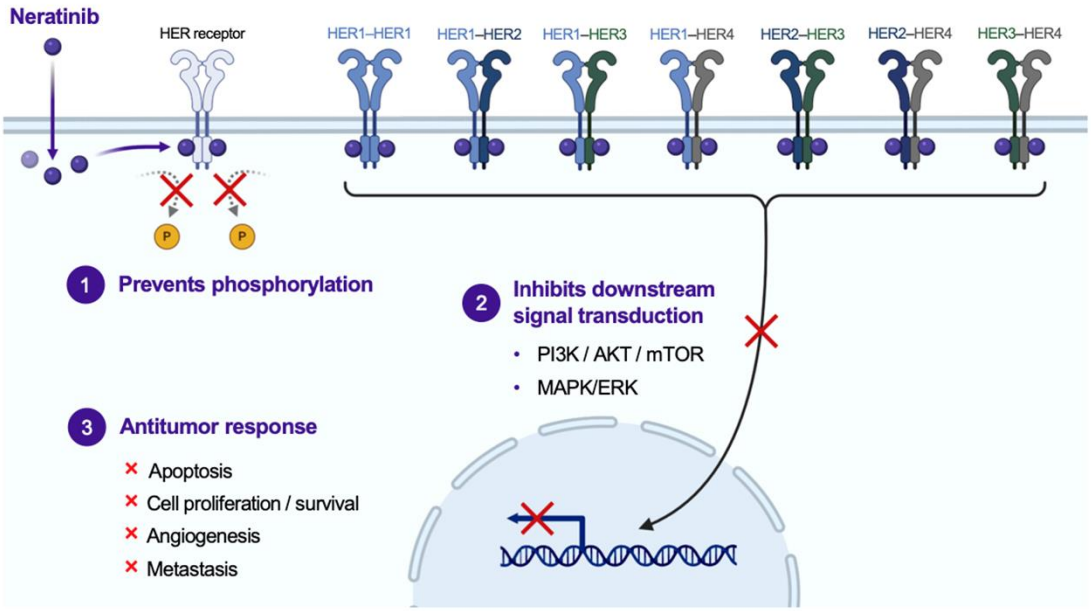
	2L EGFR Exon 20 (N=115)	2L HER2 Exon 20 (N=90)
ORR (n), [95% CI]	**14.8%** (17) [8.9, 22.6%]	**27.8%** (25) [18.9, 38.2%]
Unconfirmed ORR (n), [95% CI]	**19.1%** (22) [12.4, 27.5%]	**31.1%** (28) [21.8, 41.7%]
DCR (n), [95% CI]	**68.7%** (79) [59.4, 77.0%]	**70.0%** (63) [59.4, 79.2%]
DoR, median (months), [95% CI]	**7.4** [3.7, 9.7]	**5.1** [4.2, 5.5]
PFS, median (months), [95% CI]	**4.2** [3.7, 6.6]	**5.5** [3.9, 5.8]



R Cornelissen et al.

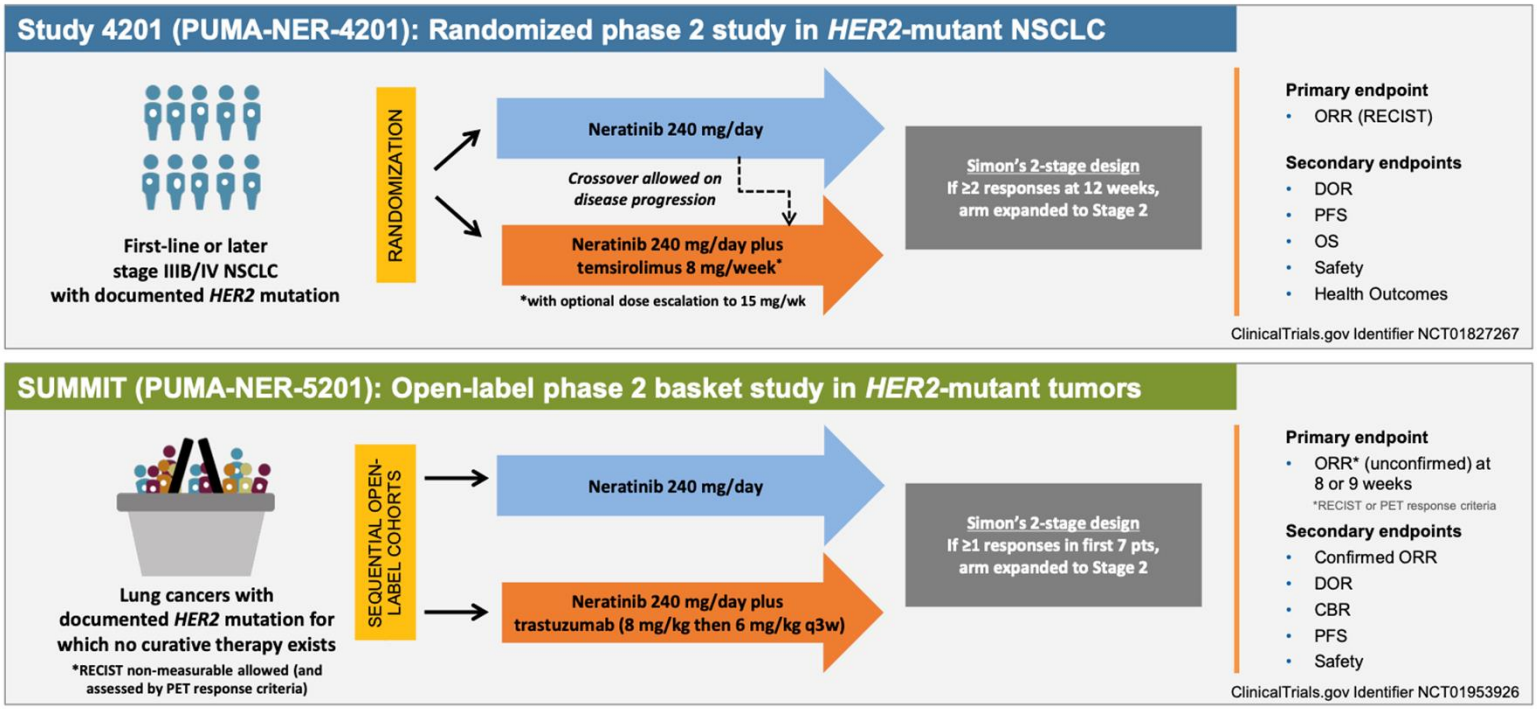
Neratinib: mechanism of action

- Oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), and HER4 (ERBB4)[1]
- Potent inhibition of intracellular signaling, cell proliferation and colony formation of *HER2*-mutant and amplified breast tumor cell lines *in vitro*[2,3]



Li et al. WCLC 2020

Study design: Phase 2 trials of neratinib in *HER2*-mutated lung cancers



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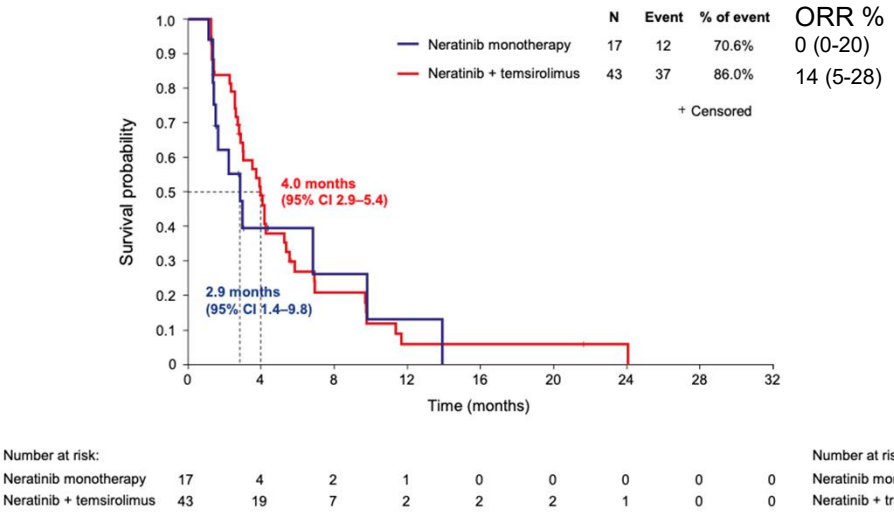
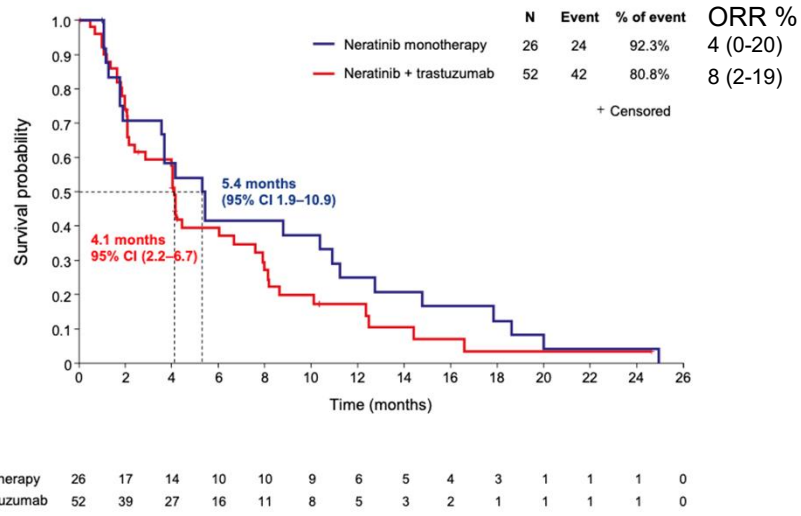
Progression-free survival

Study PUMA-NER-4201[1]



Study PUMA-NER-5201 (SUMMIT)[2]



Li et al. WCLC 2020

Trastuzumab Deruxtecan is superior to other HER2-directed therapies in cross-trial comparisons

Why are antibody-drug conjugates more effective against HER2 mutated than overexpressing NSCLC?

Possible explanations:

- Cancer is not dependent on HER2 overexpression, but is dependent on HER2 mutation.
- Better antibody binding to mutated HER2?

	ORR: HER2 mutated	ORR: HER2 overexpression
Trastuzumab + pertuzumab	21% (3/21)	Not assessed
T-DM1 (Ado-Trastuzumab + anti-microtubule)	44% (8/18)	8% (4/49)
T-DXd (Trastuzumab + TOPO-I inhibitor)	62% (24/39)	24.5% (12/49)
Poziotinib	27.8% (25/90)	Not assessed
Afatinib	19% (5/28)	Not assessed
Dacomitinib	12% (3/26)	Not assessed
Neratinib	2.3% (1/43)	Not assessed
Neratinib + temsirolimus	14%(6/43)	Not assessed
Neratinib + traztuzumab	8% (4/52)	Not assessed

Adapted from Rolfo and Russo, Cancer Discovery, 2020

Conclusions

- HER2 activating mutations occur in 2-4% of lung adenocarcinomas, while amplification or overexpression may occur in over 30% of lung adenocarcinomas.
- Antibody-drug conjugates T-DM1 and T-DXd are emerging as effective therapy for HER2-mutated lung cancers, but have limited activity in HER2 overexpressing lung cancers.
- Poziotinib demonstrates increased activity against HER2-mutated lung cancer compared to historic data for other TKIs.
- HER2 is emerging as a targetable oncogenic driver in NSCLC.