2020 Year In Review: Early Stage and Targeted Therapy in NSCLC

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Agenda

Early-Stage Disease

-- ADAURA: Osimertinib in resected EGFR-mutated NSCLC

-- ADJUVANT/CTONG 1104: Gefitinib vs chemotherapy for Stage II-IIIA NSCLC with an EGFR activating mutation

EGFR-Mutated

-- RELAY: Ramucirumab + erlotinib in patients with untreated, EGFR-mutated advanced NSCLC

-- FLAURA: Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC

-- ECOG-ACRIN 5162: A Phase II study of osimertinib 160 mg for NSCLC with EGFR exon 20 insertions

-- Amivantamab for NSCLC with EGFR exon 20 insertions

-- Patritumab deruxtecan for EGFR-mutated NSCLC

-- Osimertinib + savolitinib in patients with EGFR mutation-positive, MET-amplified NSCLC after progression on EGFR TKIs

MET Exon 14 Skipping

-- GEOMETRY mono-1: Capmatinib in MET exon 14-mutated or MET-amplified NSCLC

-- Tepotinib in NSCLC with MET exon 14 skipping mutations

RET Fusion

-- ARROW: Pralsetinib in patients with advanced RET fusion-positive NSCLC

-- Efficacy of selpercatinib in RET fusion-positive NSCLC

Courtesy of Joel W Neal, MD, PhD

ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC
Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Max. interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

NCT02511106; ADAURA data cut-off: January 17, 2020. *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶Stage IB / II / IIIA.
CT, computed tomography; Ex19del, exon 19 deletion;
IDMC, Independent Data Monitoring Committee; WHO, World Health Organization.

Herbst RS, et al. ASCO 2020. Abstract LBA5.

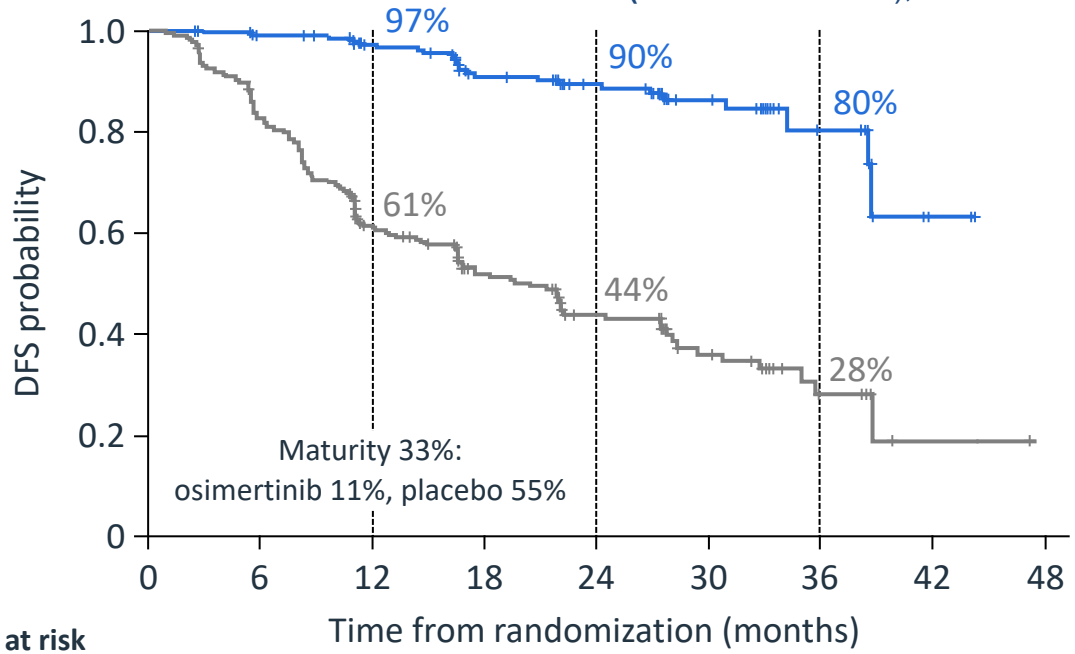
Courtesy of Joel W Neal, MD, PhD

ADAURA: Disease-free survival (DFS)

Primary endpoint: DFS in patients with Stage II/IIIA disease

	Median DFS, mo (95% CI)
Osimertinib	NR (38.8–NR)
Placebo	20.4 (16.6–24.5)

HR 0.17 (95% CI 0.12–0.23); *P*<0.0001

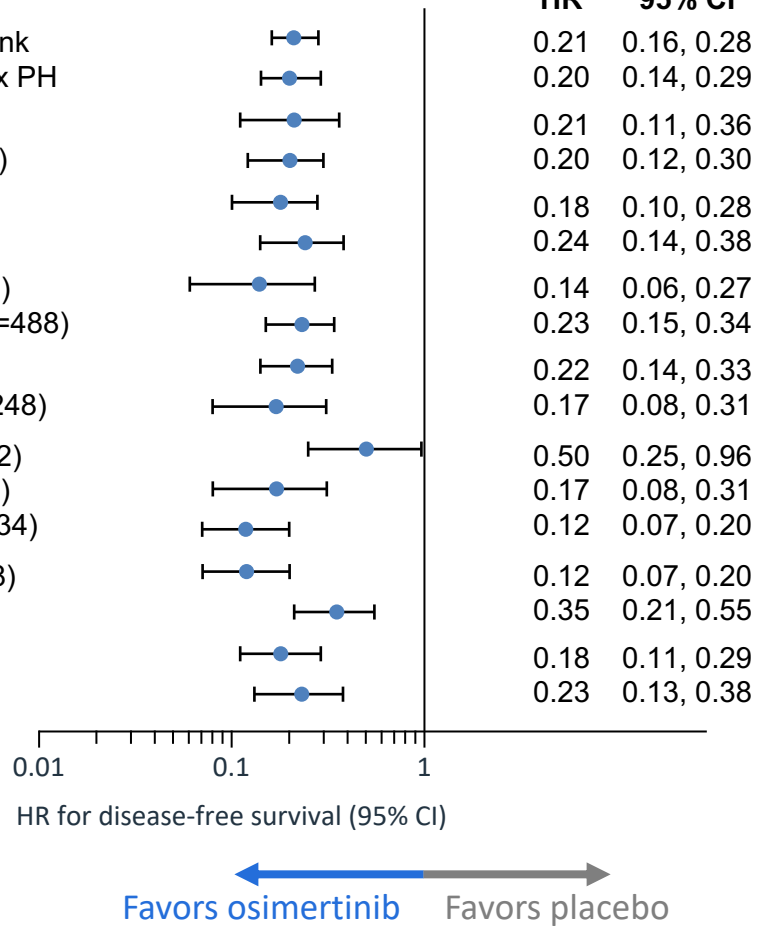


No. at risk

Osimertinib	233	219	189	137	96	51	17	2
Placebo	237	190	128	82	51	27	9	1

DFS across subgroups in the overall population

Subgroup		HR	95% CI
Overall (N=682)	Stratified log-rank	0.21	0.16, 0.28
	Unadjusted Cox PH	0.20	0.14, 0.29
Sex	Male (n=204)	0.21	0.11, 0.36
	Female (n=478)	0.20	0.12, 0.30
Age	<65 (n=380)	0.18	0.10, 0.28
	≥65 (n=302)	0.24	0.14, 0.38
Smoking status	Smoker (n=194)	0.14	0.06, 0.27
	Non-smoker (n=488)	0.23	0.15, 0.34
Race	Asian (n=434)	0.22	0.14, 0.33
	Non-Asian (n=248)	0.17	0.08, 0.31
Stage	Stage IB (n=212)	0.50	0.25, 0.96
	Stage II (n=236)	0.17	0.08, 0.31
	Stage IIIA (n=234)	0.12	0.07, 0.20
*EGFR*m	Ex19del (n=378)	0.12	0.07, 0.20
	L858R (n=304)	0.35	0.21, 0.55
Adjuvant chemotherapy	Yes (n=378)	0.18	0.11, 0.29
	No (n=304)	0.23	0.13, 0.38

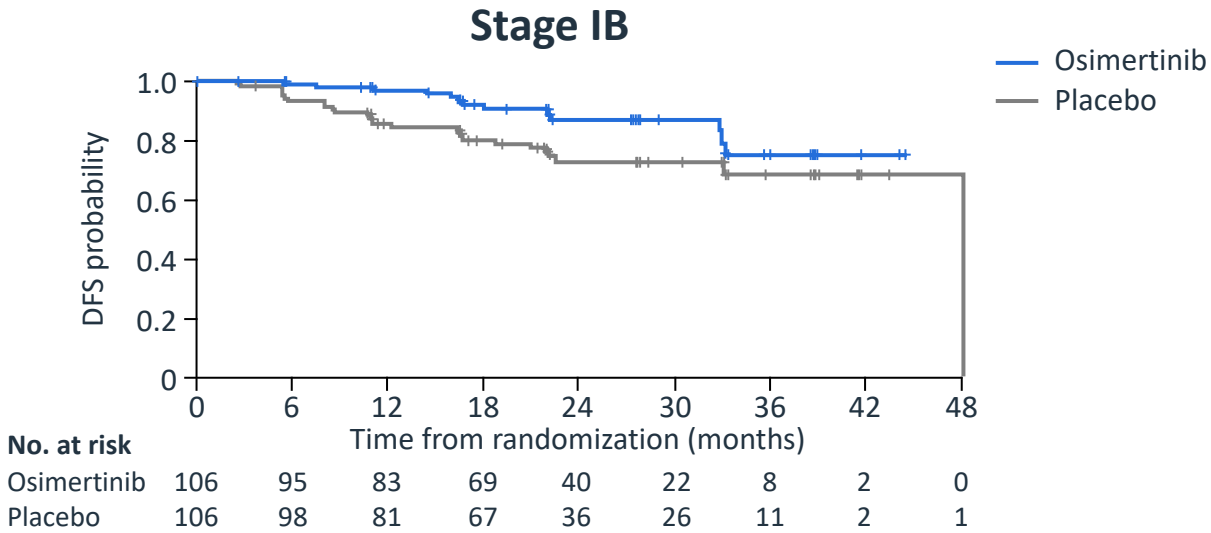


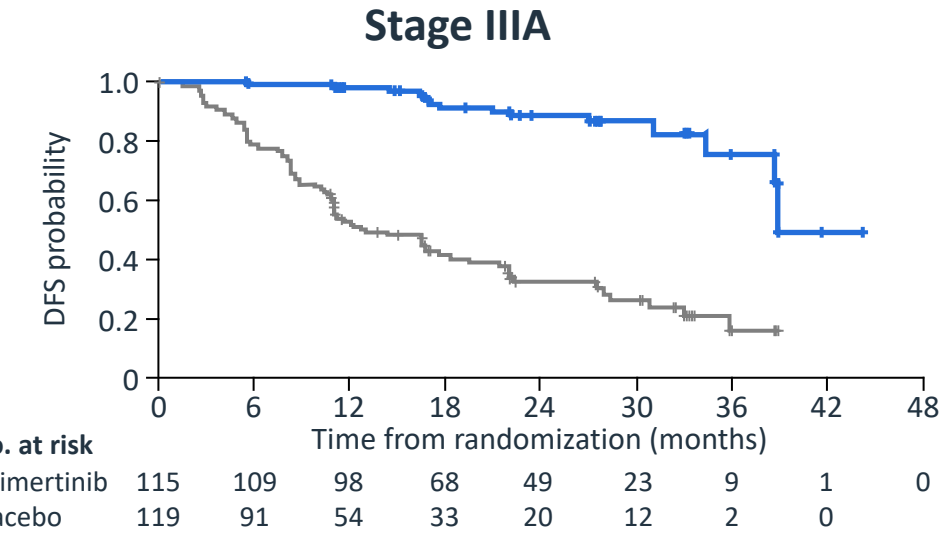
Data cutoff: January 17, 2020. NR, not reached

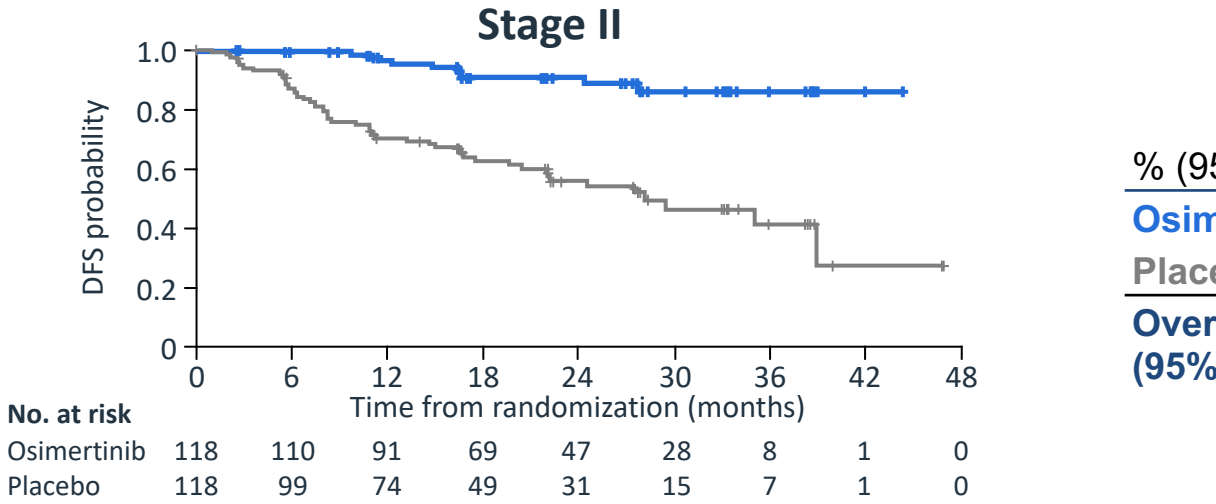
Herbst RS, et al. ASCO 2020. Abstract LBA5.

Courtesy of Joel W Neal, MD, PhD

ADAURA: Disease-free survival by stage







2 Year DFS rate

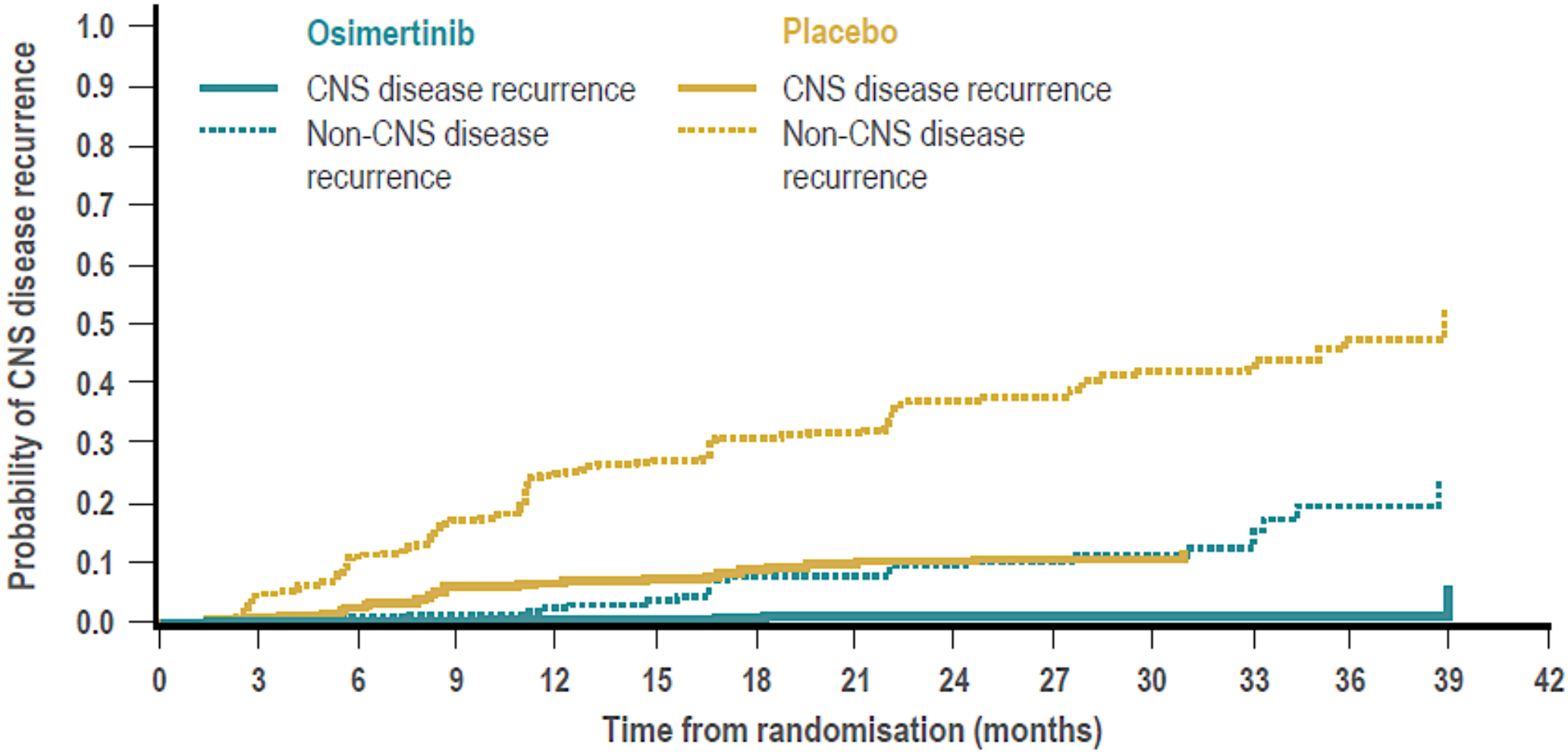
% (95% CI)	Stage IB	Stage II	Stage IIIA
Osimertinib	87 (77–93)	91 (82–95)	88 (79–94)
Placebo	73 (62–81)	56 (45–65)	32 (23–42)
Overall HR (95% CI)	**0.50 (0.25–0.96)**	**0.17 (0.08–0.31)**	**0.12 (0.07–0.20)**

Data cutoff: January 17, 2020.

Herbst RS, et al. ASCO 2020. Abstract LBA5.

Courtesy of Joel W Neal, MD, PhD

ADAURA: CNS Recurrence Risk



Tsuboi M ESMO 2020; Abstract LBA1

Courtesy of Joel W Neal, MD, PhD

ADJUVANT CTONG 1104 study design (NCT01405079)

Completely resected pathological stage II-IIIA (N1-N2) NSCLC

EGFR activating mutation (exon 19 deletion or exon 21 L858R)

ECOG PS 0-1

Age ≥18 years & <75 years

n=220

Stratification factors:

EGFR mutation

N stage

R 1:1

Gefitinib 250 mg/day for 24 months or until disease progression or unacceptable toxicity

Vinorelbine (25 mg/m^2 Days 1 & 8) plus cisplatin (75 mg/m^2 Day 1) every 3 weeks, for up to 4 cycles

DFS

Primary endpoint:

- DFS

Secondary endpoints:

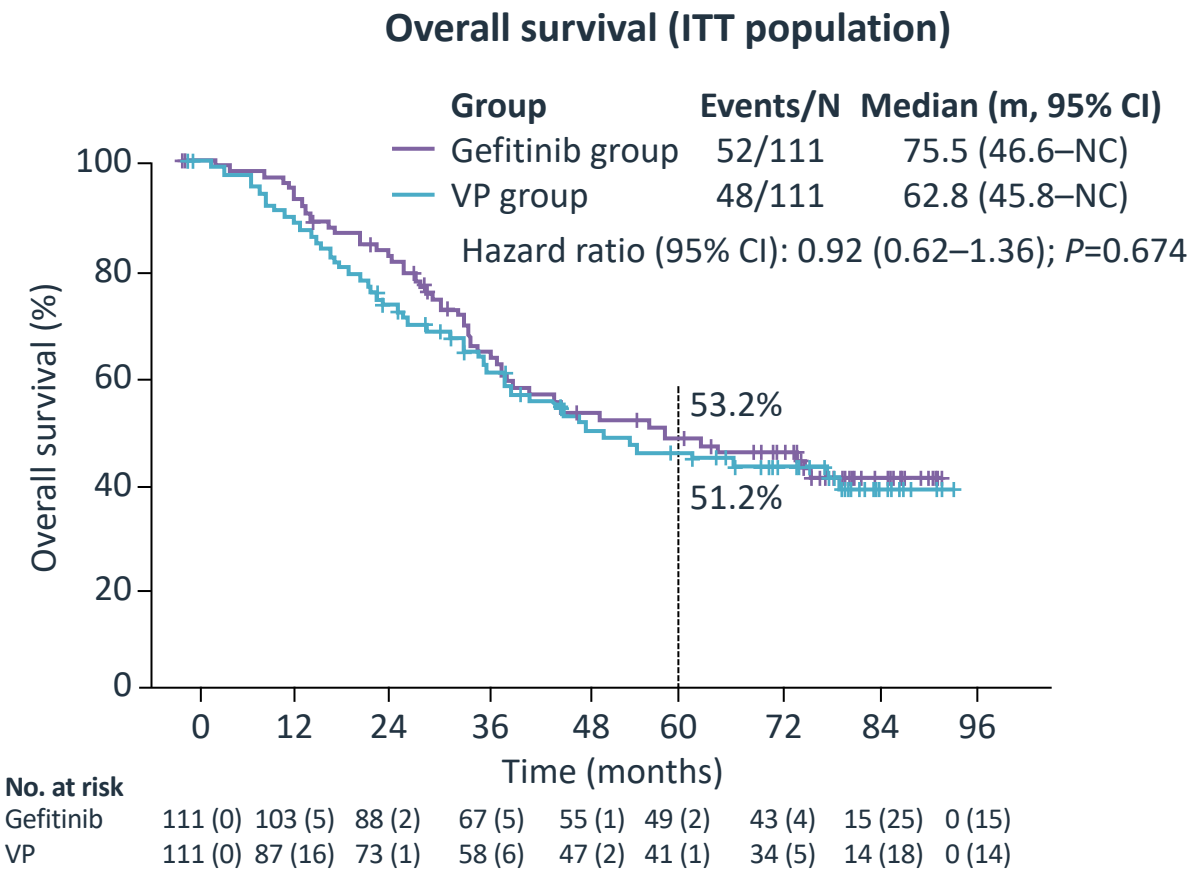
3-year DFS rate, 5-year DFS rate, OS, 5-year OS rate, safety, HRQoL (FACT-L, LCSS, TOI), exploratory biomarker analyses

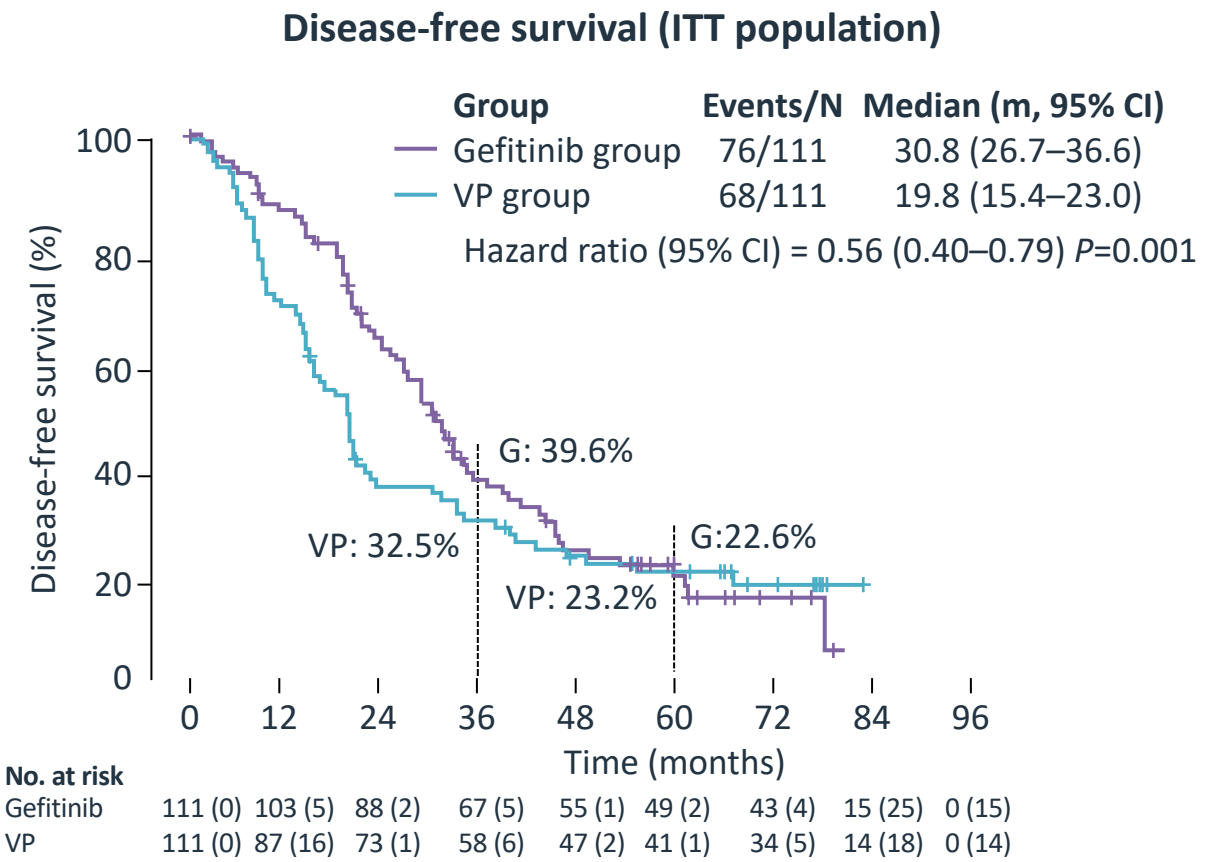
ECOG PS, Eastern Cooperative Oncology Group Performance Status; DFS，disease-free survival; FACT-L, Functional Assessment of Cancer Therapy – Lung; HRQoL, health-related quality of life; LCSS, Lung Cancer Symptom Scale; OS, overall survival; R, randomization; TOI, Trial Outcome Index

Wu Y-L, et al. ASCO 2020. Abstract 9005

Courtesy of Joel W Neal, MD, PhD

CTONG1104/ADJUVANT: Overall survival and disease-free survival





ITT, intention-to-treat; VP, vinorelbine plus cisplatin

Wu Y-L, et al. ASCO 2020. Abstract 9005.

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- ADAURA shows striking DFS benefit with osimertinib (with optional chemo), now FDA approved and SOC (I would use in stage II and above after adjuvant chemotherapy, and have discussion for stage I pts)
- ADJUVANT provided DFS benefit with gefitinib in N2 disease (instead of chemo) but no OS improvement

Future Directions:

- Await ADAURA overall survival results (particularly in stage IB disease)
- Unclear role in Stage III chemo-radiation – Locally Advanced “LAURA” study

Courtesy of Joel W Neal, MD, PhD

RELAY: Erlotinib + Ramucirumab

~450 patients with EGFR mutant NSCLC randomized to first line:
Erlotinib + Ramucirumab vs Erlotinib:

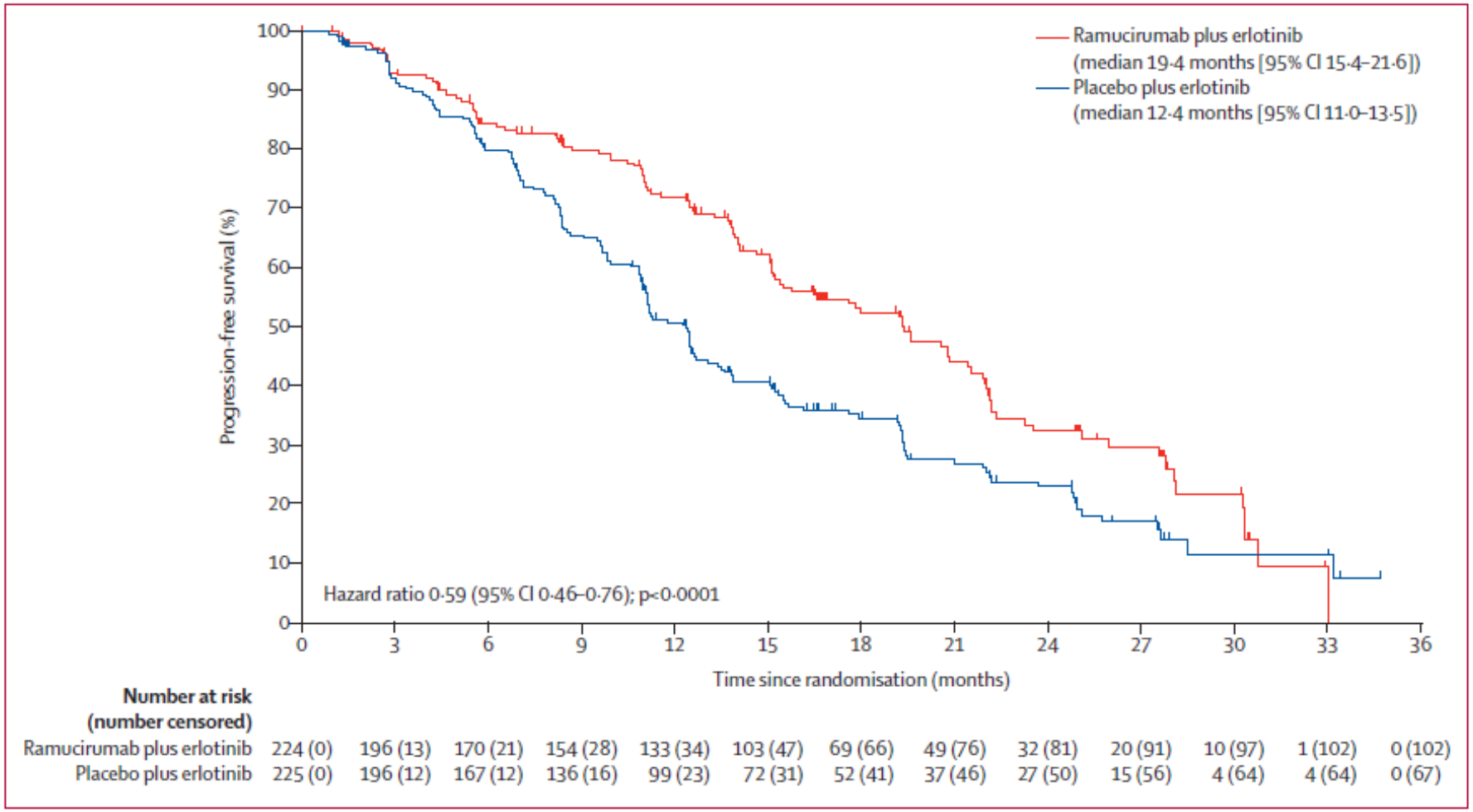


Figure 2: **Kaplan-Meier estimates of investigator-assessed progression-free survival**

PFS 19.4 vs 12.4 months
RR 76% vs 75%
2-year OS 83% vs 79%

Nakagawa et al Lancet Oncology 2019

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- FDA approved option for first line treatment of EGFR+ NSCLC
- Unclear role in first line setting because osimertinib is SOC (relatively equivalent PFS 18.9 months) but probably has better CNS penetration
- Anti-angiogenic therapy active in EGFR+ NSCLC and should be incorporated for some line of therapy

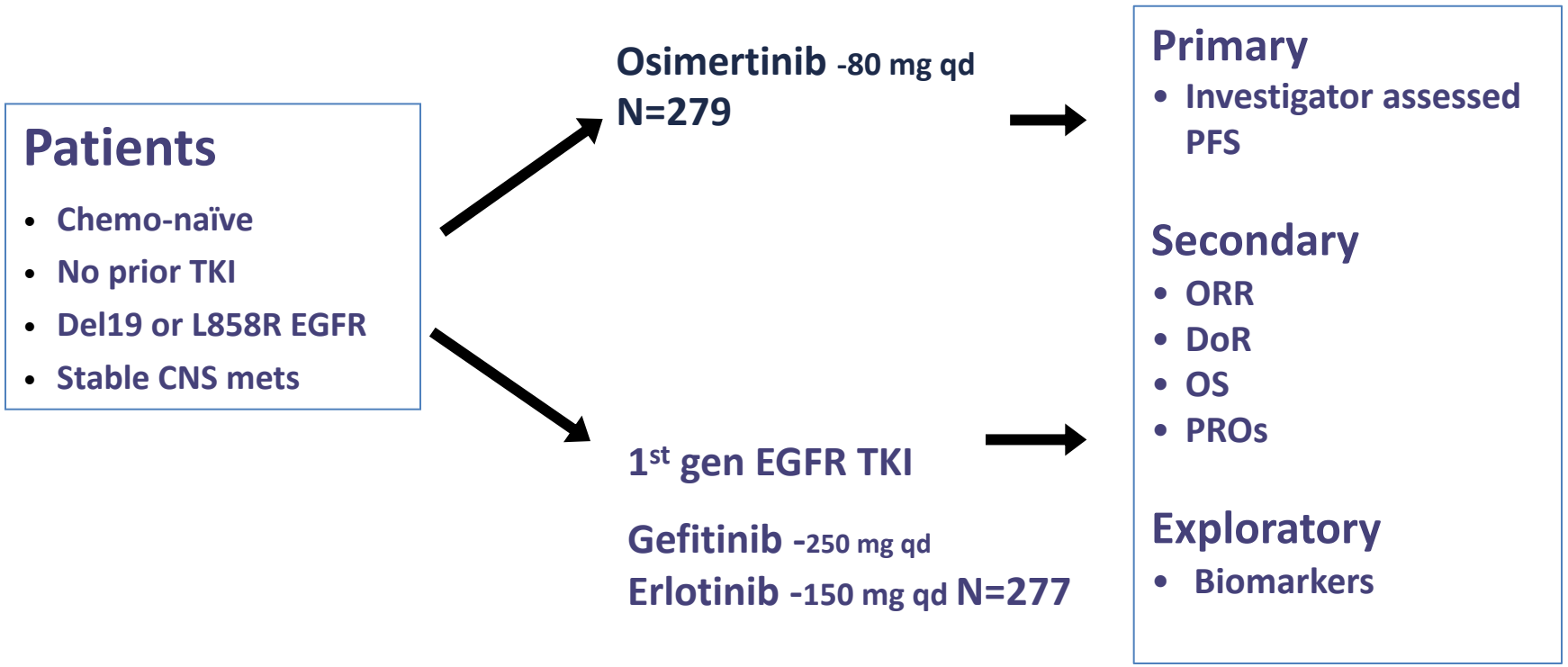
Future Directions:

- What is the role of ramucirumab and/or bevacizumab together with osimertinib in first line treatment of NSCLC?
- Is anti-angiogenic therapy more active with EGFR TKI, or chemo +/- anti PD-1/PD-L1 therapy?

Courtesy of Joel W Neal, MD, PhD

FLAURA:

~550 patients with EGFR mutant NSCLC randomized to first line:
Osimertinib vs Gefitinib or Erlotinib



Ramalingam SS et al, *N Engl J Med.* 2020

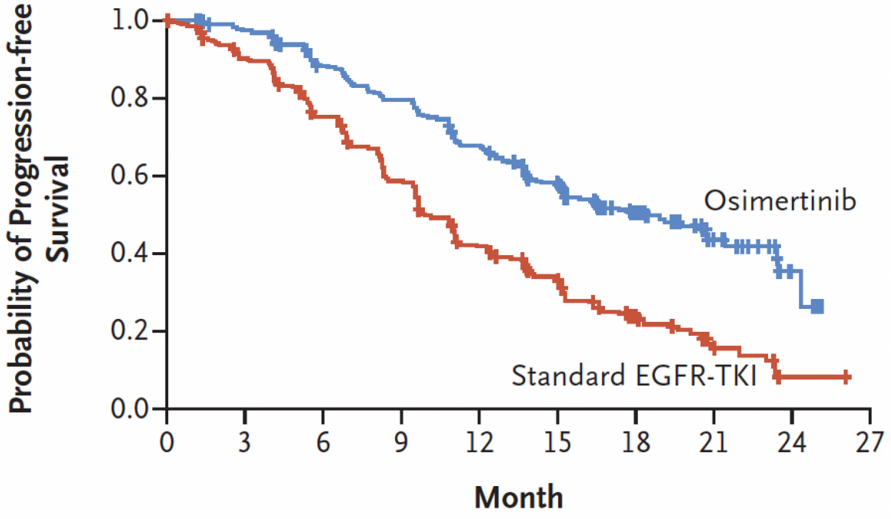
Courtesy of Joel W Neal, MD, PhD

FLAURA:

Progression-free Survival in Full Analysis Set

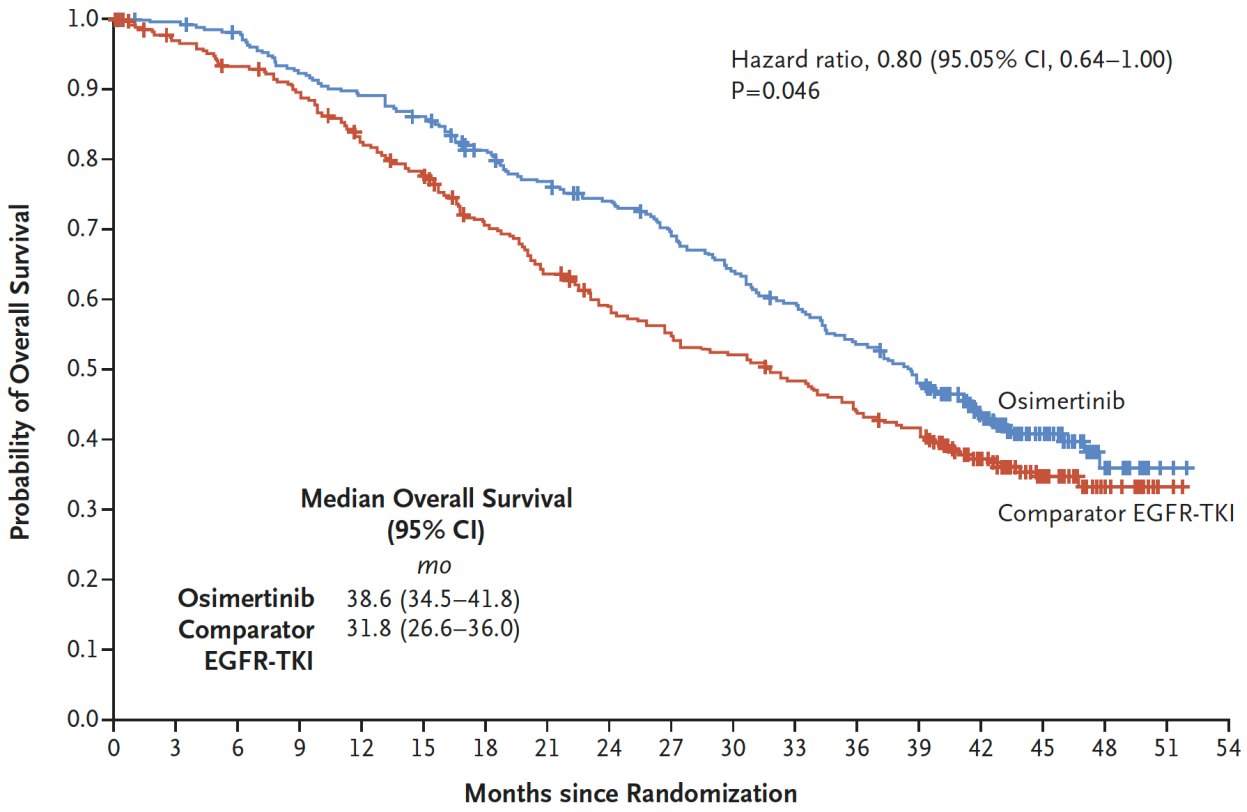
	No. of Patients	Median Progression-free Survival (95% CI)
		mo
Osimertinib	279	18.9 (15.2–21.4)
Standard EGFR-TKI	277	10.2 (9.6–11.1)

Hazard ratio for disease progression or death, 0.46 (95% CI, 0.37–0.57)
P<0.001



No. at Risk

Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0



No. at Risk

Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Response rates 80% vs 76%

Soria JC et al, *N Engl J Med*. 2018, Ramalingam SS et al, *N Engl J Med.* 2020

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- Osimertinib remains the first-line standard of care for EGFR+ NSCLC
- Expected median overall survival for newly diagnosed pts >3 years

Future Directions:

- Combination therapy with osimertinib (Chemo with FLAURA2, anti-angiogenics, MET inhibitors, etc).
- Given high rates of pneumonitis and other IRAE's, AVOID combinations of osi+anti-PD-1/PD-L1.

Courtesy of Joel W Neal, MD, PhD

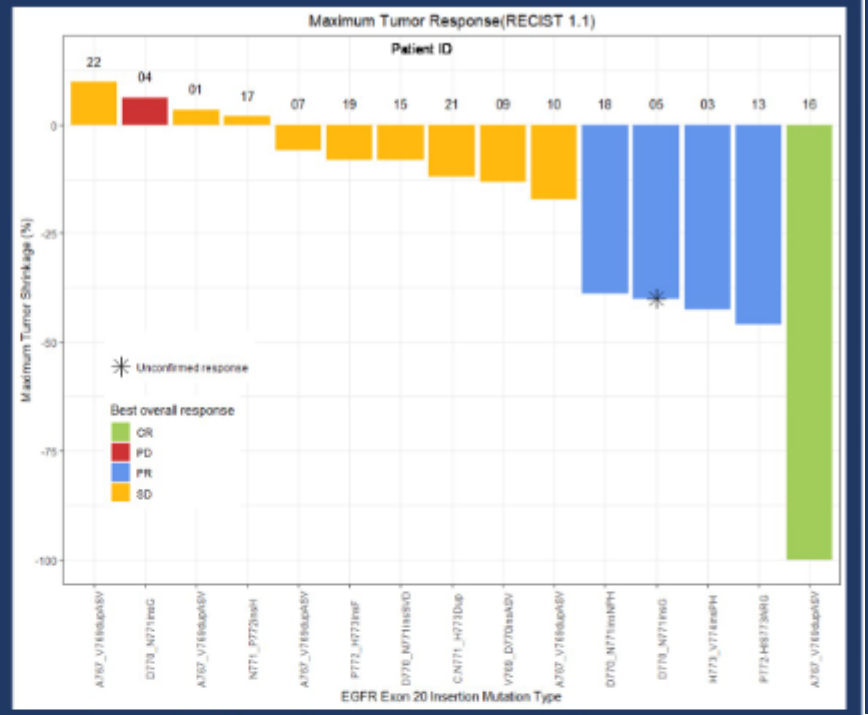
Osimertinib in EGFR Exon 20 insertion NSCLC

Exon 20 NSCLC comprises ~4% of EGFR+ NSCLC and is resistant to 1st and 2nd generation EGFR TKI therapy (Afatinib PFS ~3 months)

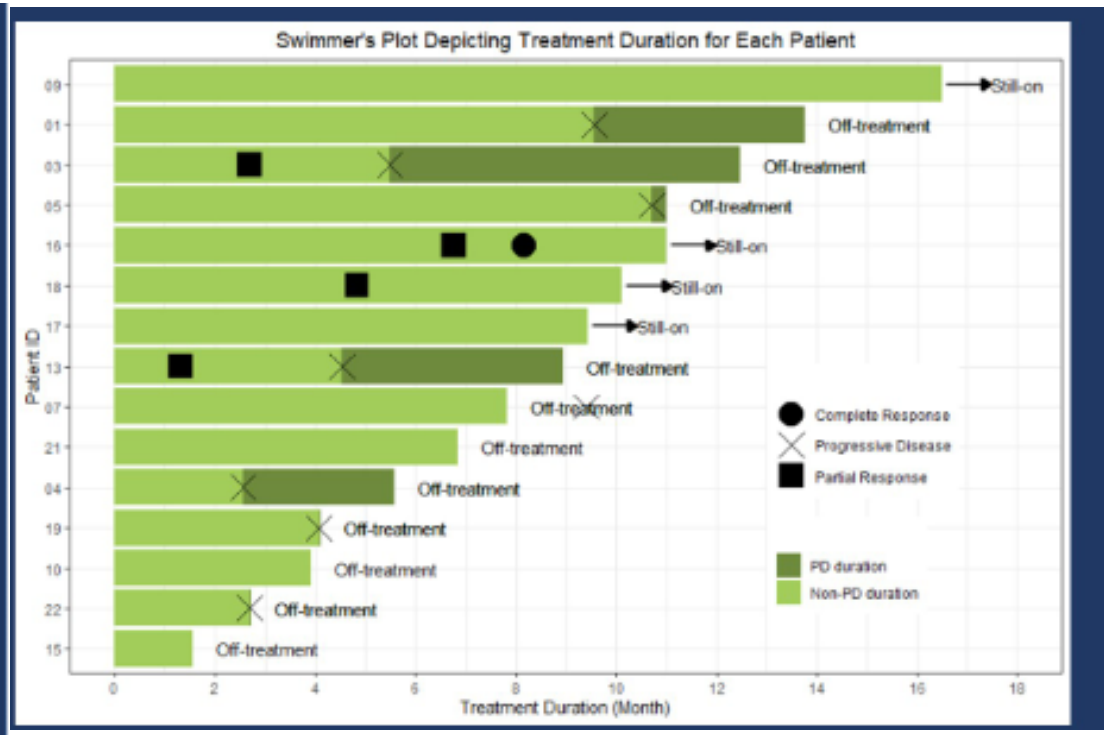
Fig 1. Waterfall Plot

OVERALL EFFICACY:

- **Confirmed ORR:** 4/17, 24%
- **DCR:** 14/17, 82%
- **mPFS:** 9.6 mo (95% CI, 4.1, 10.7)
- **mDOR:** NA (95% CI, 4.7, NA)



PR- partial response, SD- stable disease, PD- progressive disease, NA- not evaluable



Pietrowska ASCO 2020 Abstract 9513

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- Osimertinib has modest efficacy in EGFR Exon 20 NSCLC
- I still recommend first line carbo/pemetrexed +/- bevacizumab
- This could be considered 2nd line or beyond if clinical trials not available

Future Directions:

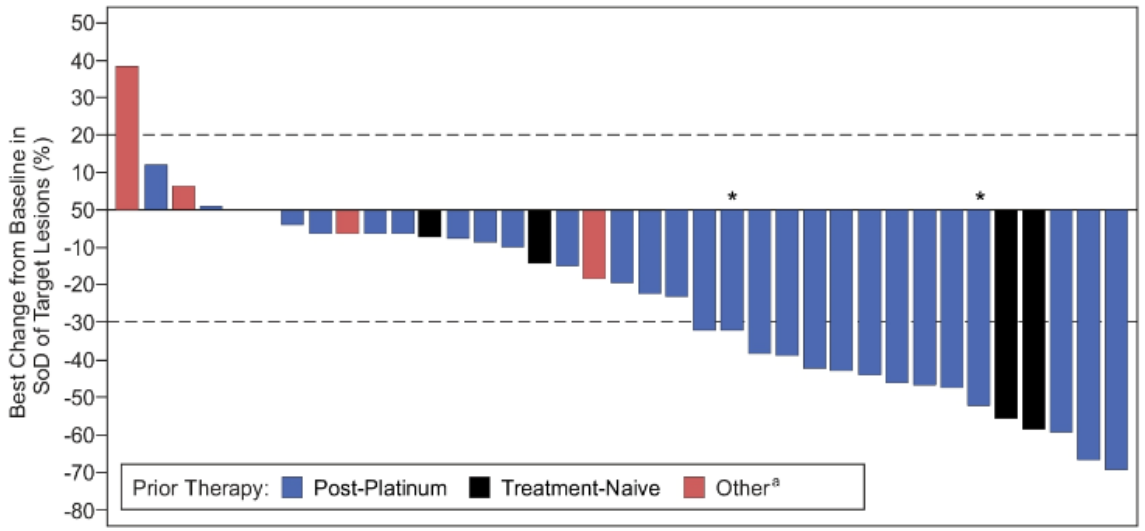
- Many more promising clinical trial agents: mobocertinib (TAK788), tarloxotinib, poziotinib, amivantamab which may be a better option in the 1st line or beyond setting if accessible

Courtesy of Joel W Neal, MD, PhD

Amivantamab in EGFR Exon 20 insertion NSCLC

Amivantamab is an EGFR/MET bispecific antibody
39 patients – RR 36% and PFS 8.3 months

Figure 2. Best Percentage Change from Baseline in Sum of Target Lesion Diameters

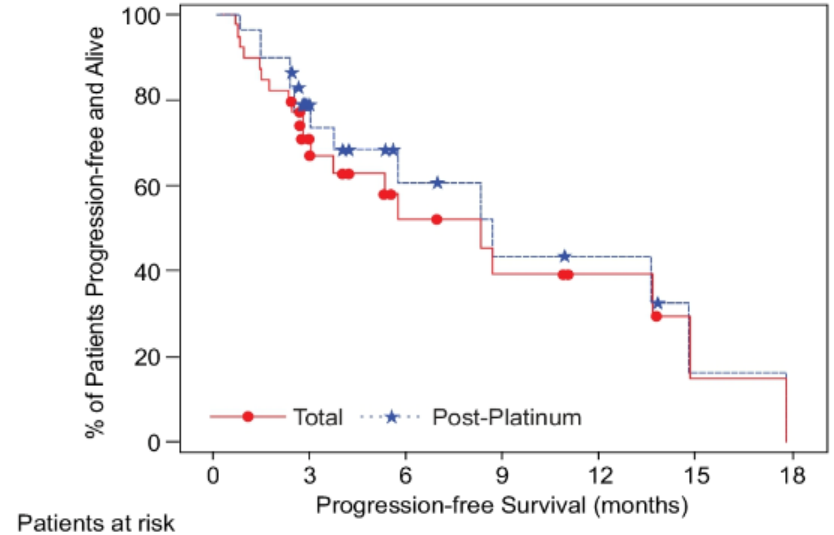


*Unconfirmed partial response. [a]2 patients treated with EGFR TKIs, 1 with bevacizumab plus radiation therapy, 1 with adjuvant immuno-oncology chemotherapy. 2 patients did not have post-baseline disease assessments and are not included in the plot. SoD=sum of diameters

- The overall response rate (ORR), confirmed responses only, was 36% (95% confidence interval [CI], 21–53), with 14/39 patients achieving a partial response.
- The ORR in post-platinum patients was 41% [95% CI, 24–61]).
- The clinical benefit rate (partial response or better or stable disease of at least 12 weeks [2 disease assessments]) was 67% (95% CI, 50–81) for all patients and 72% (95% CI, 53–87) for post-platinum patients.

- Median progression-free survival (mPFS) was 8.3 months (95% CI, 3.0–14.8) among all patients, with significant early censoring.
- Post-platinum patients had mPFS of 8.6 months (95% CI, 3.7–14.8).

Figure 5. Progression-free Survival



Park ASCO 2020 Abstract 9512

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- Unavailable for clinical use at this time, but appears active and tolerable as single agent (infusion reactions very common)

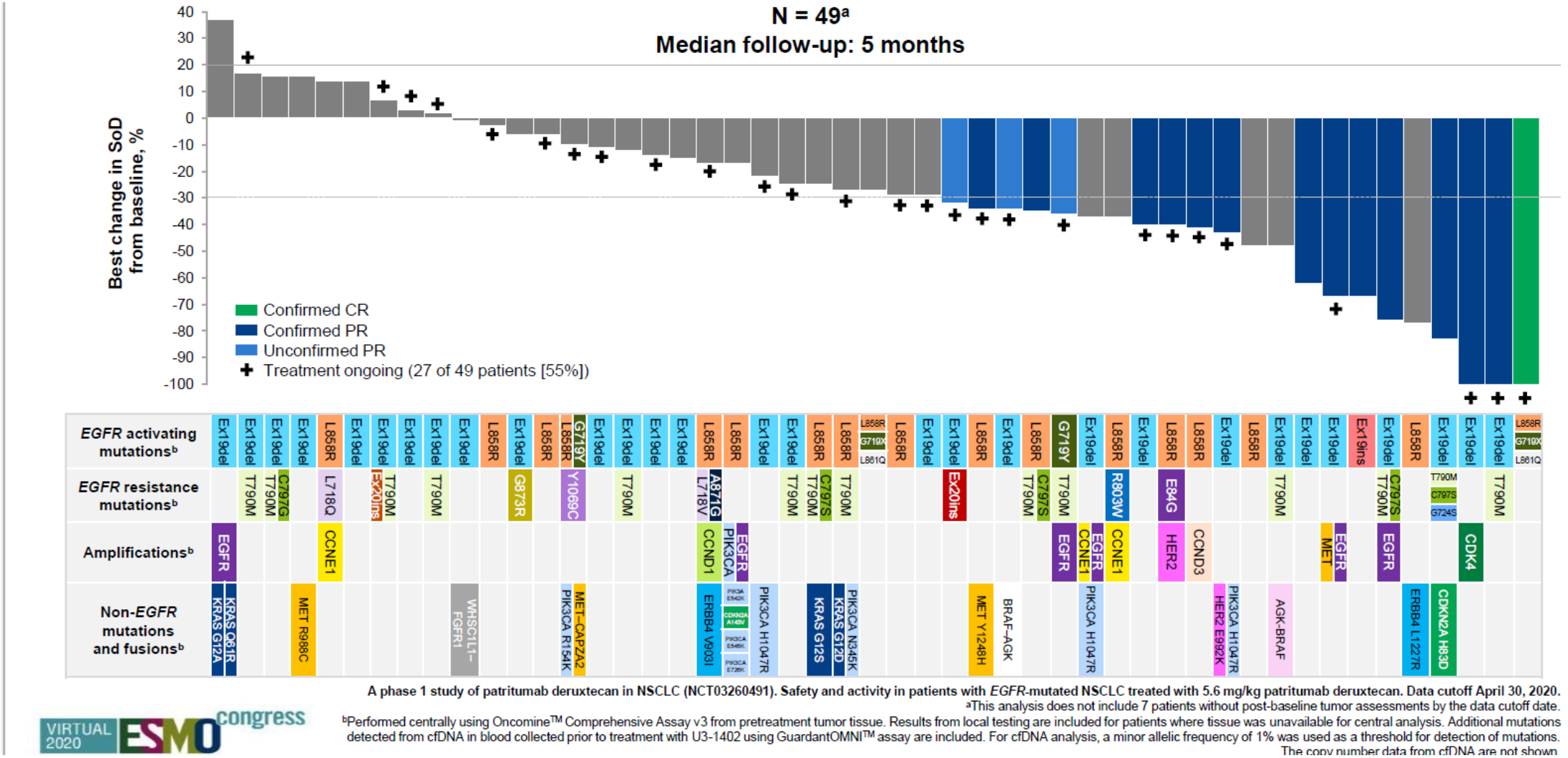
Future Directions:

- Other active EGFR Exon 20 TKI's could potentially be combined with amivantamab to increase RR and PFS

Courtesy of Joel W Neal, MD, PhD

Patritumab Deruxtecan in EGFR mutant NSCLC

This is a HER3 directed antibody-drug conjugate
Tested in 49 pts with EGFR+ NSCLC resistant to prior therapy



A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

[a]This analysis does not include 7 patients without post-baseline tumor assessments by the data cutoff date.

[b]Performed centrally using Oncomine™ Comprehensive Assay v3 from pretreatment tumor tissue. Results from local testing are included for patients where tissue was unavailable for central analysis. Additional mutations detected from cfDNA in blood collected prior to treatment with U3-1402 using GuardantOMNI™ assay are included. For cfDNA analysis, a minor allelic frequency of 1% was used as a threshold for detection of mutations. The copy number data from cfDNA are not shown.

VIRTUAL 2020 ESMO congress

Yu ESMO 2020 LBA62

Courtesy of Joel W Neal, MD, PhD

Patritumab Deruxtecan in EGFR mutant NSCLC

AE's appear generally tolerable

Patritumab deruxtecan continued to demonstrate a manageable safety profile

- The most common grade ≥3 TEAEs were thrombocytopenia (16 patients [28%]) and neutropenia (11 patients [19%])
- TEAEs associated with discontinuation (9%) included fatigue (n = 2), decreased appetite (n = 1), ILD (n = 1), pneumonitis (n = 1), and URTI (n = 1)
  - There were no discontinuations due to thrombocytopenia or neutropenia
- Three (5.3%) ILD events were adjudicated by an independent central review committee as being related to treatment
- There were no treatment-related TEAEs associated with death

TEAEs (regardless of causality), n (%)	N = 57
TEAEs	57 (100)
Grade ≥3	38 (67)
Associated with discontinuation	5 (9)
Associated with dose reduction	10 (18)
Associated with dose interruption	17 (30)
Associated with death	3 (5)
Treatment-emergent SAEs	21 (37)
Grade ≥3	18 (32)
Treatment related	11 (19)

TEAEs in ≥20% of patients, n (%)	N = 57	
	All grades	Grade ≥3
Fatigue	33 (58)	5 (9)
Nausea	31 (54)	2 (4)
Thrombocytopenia[a]	30 (53)	16 (28)
Decreased appetite	20 (35)	1 (2)
Neutropenia[b]	19 (33)	11 (19)
Vomiting	17 (30)	1 (2)
Alopecia	17 (30)	NA
Anemia[c]	15 (26)	5 (9)
Constipation	14 (25)	0

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Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- Appears active and tolerable in this population, but not available for clinical use
- May overcome a variety of resistance mechanisms

Future Directions:

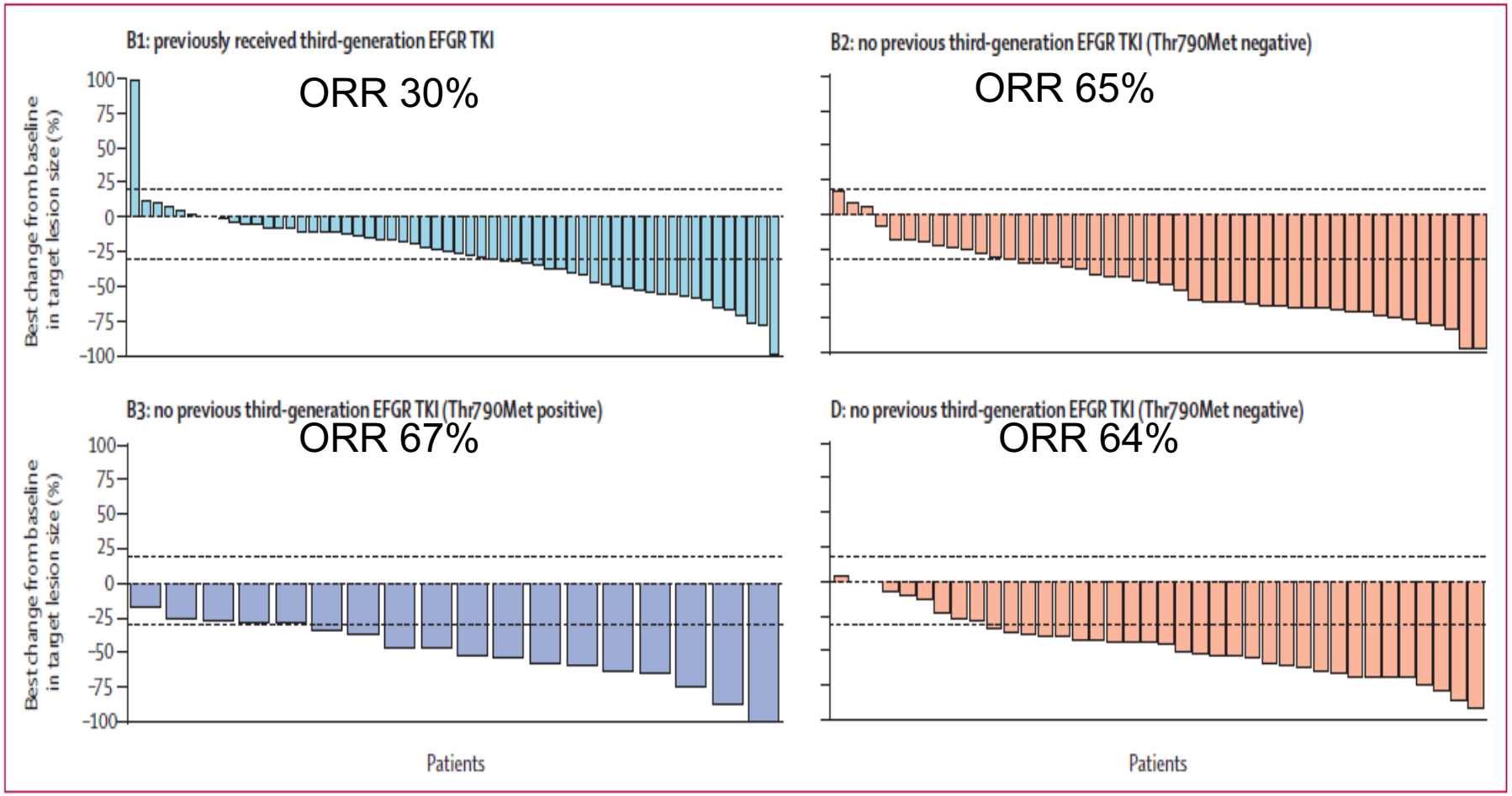
- Phase 2 study ongoing
- Could envision combinations with EGFR-TKI therapy

Courtesy of Joel W Neal, MD, PhD

Savolitinib plus osimertinib in EGFR mutant NSCLC

Savolitinib is a MET TKI
186 Patients with MET positive resistance to prior treatments:

- Had prior third gen EGFR TKI
- No prior 3rd gen TKI, with or without T790M



Part B:
PFS 7.6 months

Part D:
PFS 9.1 months

Sequist Lancet Oncology 2020

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- If MET is detected as mechanism of EGFR resistance (by FISH or DNA NGS) then combination MET + EGFR TKI therapy is reasonable
- Savolitinib not approved but 300 mg dose better tolerated than 600 mg (anorexia, fatigue, edema, vomiting, diarrhea)

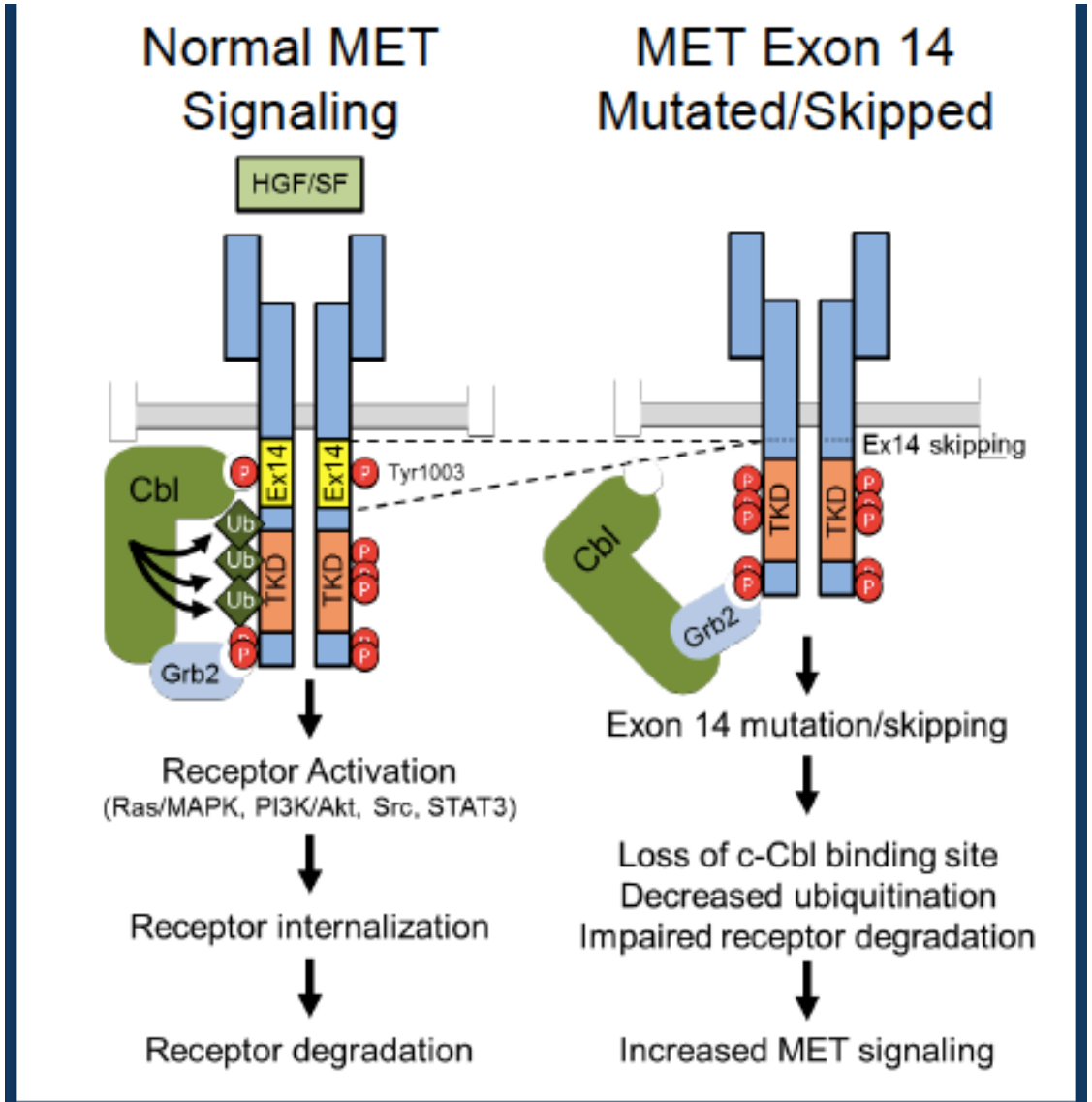
Future Directions:

- Unclear tolerability/safety of other MET inhibitors with osimertinib and other 3rd gen TKIs
- Amivantamab (EGFR/MET mAb) may also be active in this population

Courtesy of Joel W Neal, MD, PhD

Met Exon 14 NSCLC

MET exon 14 alterations are present in 3-4% of NSCLC
Best detected with DNA NGS or RNA-based assays

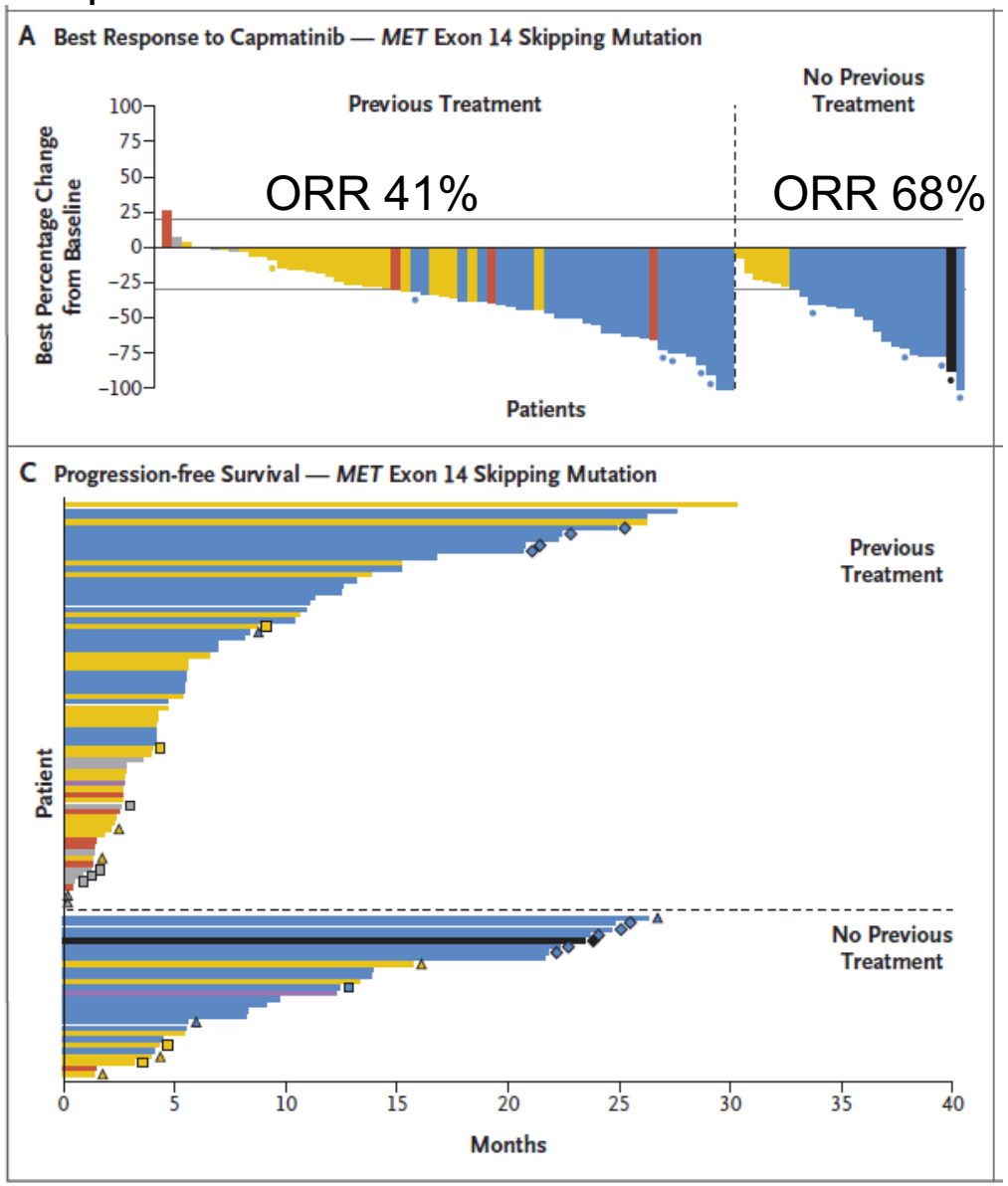


TCGA, *Nature*. 2014 Jul 31;511(7511):543-50.
Awad MM, et al, *J Clin Oncol*. 2016 Mar 1;34(7):721-30.
Paik PK, et al, *Cancer Discov*. 2015 Aug;5(8):842-9.
Frampton GM, et al, *Cancer Discov*. 2015 Aug;5(8):850-9.
Awad MM, et al, J Clin Oncol. 2016 Mar 10;34(8):879-81.

Courtesy of Joel W Neal, MD, PhD

Capmatinib in Met Exon 14 NSCLC

364 patients across all cohorts



PFS
1L: 12.4 mos
2L/3L: 5.4 mos

54% (7/13) with intracranial response

Wolf NEJM. 2020

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- Capmatinib is FDA approved for MET+ NSCLC – First line standard of care
- Better CNS penetration than crizotinib
- Tolerable side effects – note peripheral edema

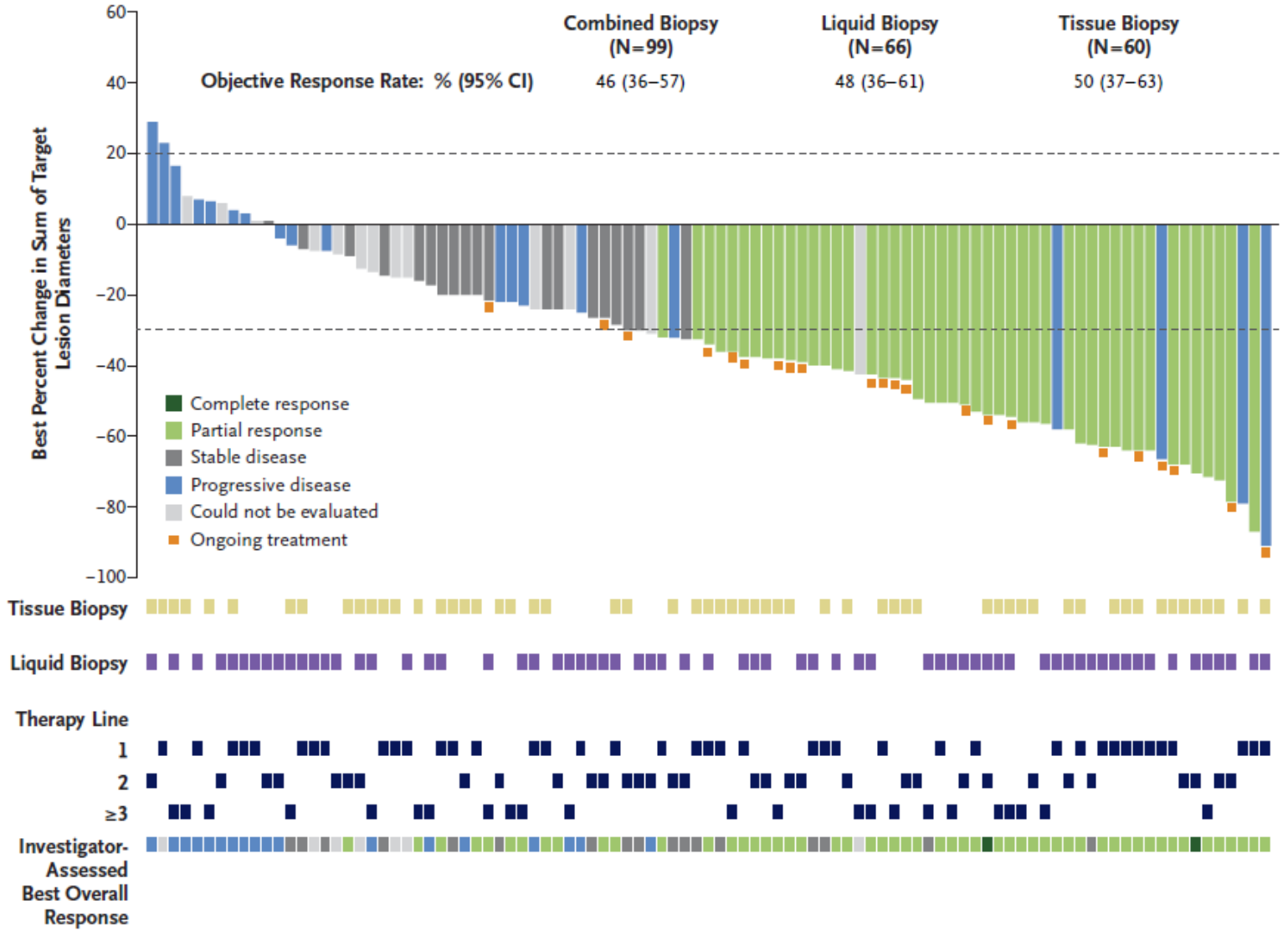
Future Directions:

- Consider combination strategies, other agents are emerging

Courtesy of Joel W Neal, MD, PhD

Tepotinib in Met Exon 14 NSCLC

152 patients across all cohorts, 99 pts for efficacy analysis



46% ORR (independent)

PFS 8.5 months

55% (6/11) with intracranial response

	Tepotinib, all (n=146)	Tepotinib no plat (n=71)	Tepotinib, prior plat (n=72)
Response Rate*	45%	42%	50%
Median DOR*	11.1 mo	10.8 mo	12.4 mo
Median PFS*	8.9 mo	8.5 mo	11.0 mo

Paik. NEJM. 2020

Mazieres NACLC 2020 Oral abstract

Courtesy of Joel W Neal, MD, PhD

Conclusions:

Clinical Implications:

- Tepotinib is a compelling alternative to capmatinib in the first line setting but not yet FDA approved
- No clear distinguishing factors from capmatinib

Future Directions:

- If approved, consider combination strategies, head-to-head comparison to determine superiority?

Courtesy of Joel W Neal, MD, PhD

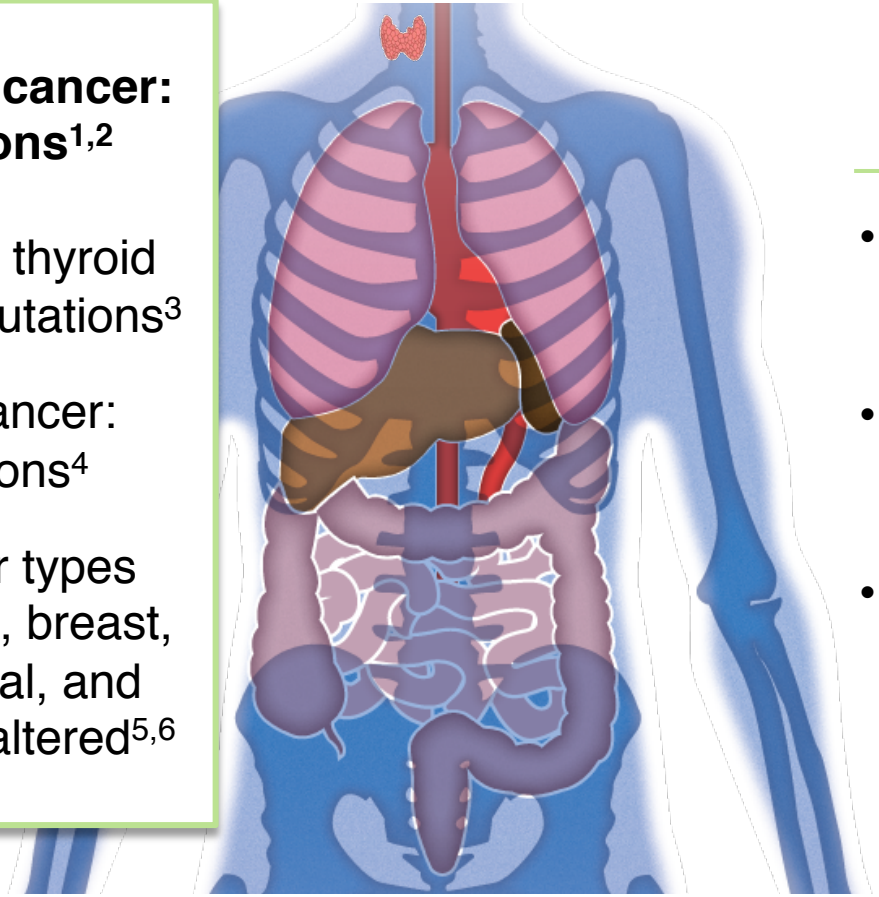
RET Alterations: Diverse Oncogenic Drivers Lacking Targeted Therapeutic Approach

Non-small cell lung cancer: ~1-2% RET fusions[1,2]

Advanced medullary thyroid cancer: ~90% RET mutations[3]

Papillary thyroid cancer: ~20% RET fusions[4]

Multiple other tumor types including esophageal, breast, melanoma, colorectal, and leukemia: <1% RET-altered[5,6]



NSCLC patients with RET fusions have not significantly benefited from existing therapy

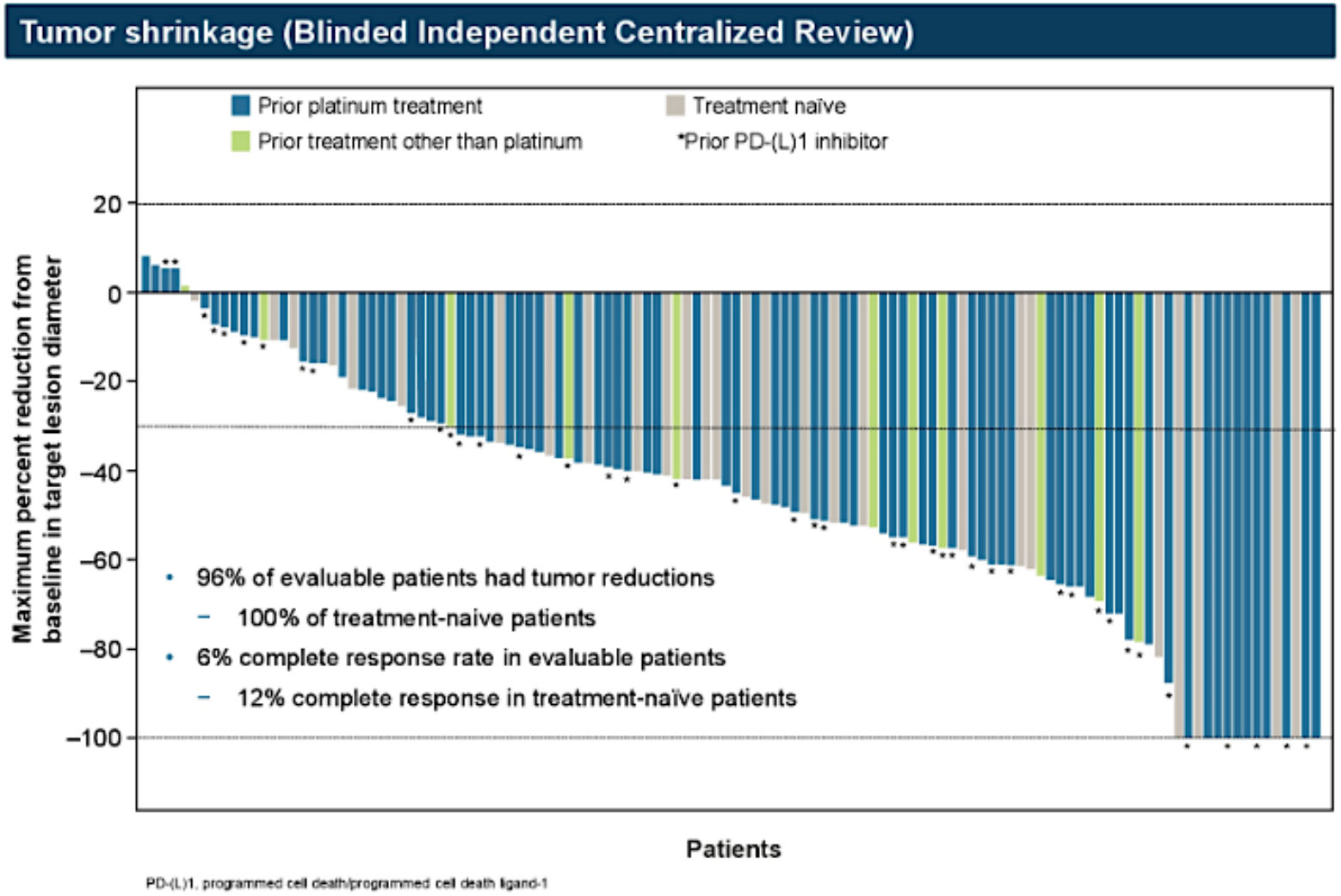
- Chemotherapy: nonspecific, low response rates, significant toxicity
- Checkpoint inhibition: Preliminary evidence for lack of benefit in RET-altered NSCLC[7]
- Multikinase inhibitors: ↓ activity, ↑ off-target toxicity[8,9]

NSCLC, non-small cell lung cancer; 1. Lipson, et al. *Nat Med* 2012; 2. Takeuchi, et al. *Nat Med* 2012; 3. Romei, et al. *Oncotarget* 2018; 4. Santoro, et al. *J Clin Invest* 1992; 5. Kato, et al. *Clin Cancer Res* 2017; 6. Ballerini, et al. *Leukemia* 2012; 7. Mazieres, et al. *JCO* 2018; 8. Drillon, et al. *Lancet* 2017; 9. Yoh, et al. *Lancet Respir Med* 2017

Courtesy of Joel W Neal, MD, PhD

Pralsetinib in RET+ NSCLC

RET rearrangements are present in 1-2% of NSCLC
Best detected with FISH, DNA NGS or RNA-based assays



65% ORR (independent)

Median PFS not reached

56% (5/9) pts with intracranial response

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Pralsetinib in RET+ NSCLC

Note Transaminitis and pneumonitis

Treatment-related adverse events in ≥10% of patients (N=354, all tumor types)		
AE preferred term	**All patients (n=354)**	
	Any grade	**Grade ≥3**
AST increased	31%	2%
Anemia	22%	8%
ALT increased	21%	1%
Constipation	21%	1%
Hypertension	20%	10%
Neutropenia	19%	10%
Diarrhea	14%	1%
White blood cell count decreased	14%	3%
Dysgeusia	13%	0%
Blood creatinine increased	12%	0%
Fatigue	12%	1%
Neutrophil count decreased	12%	4%
Dry mouth	11%	0%
Hyperphosphatemia	11%	<1%
Asthenia	10%	1%

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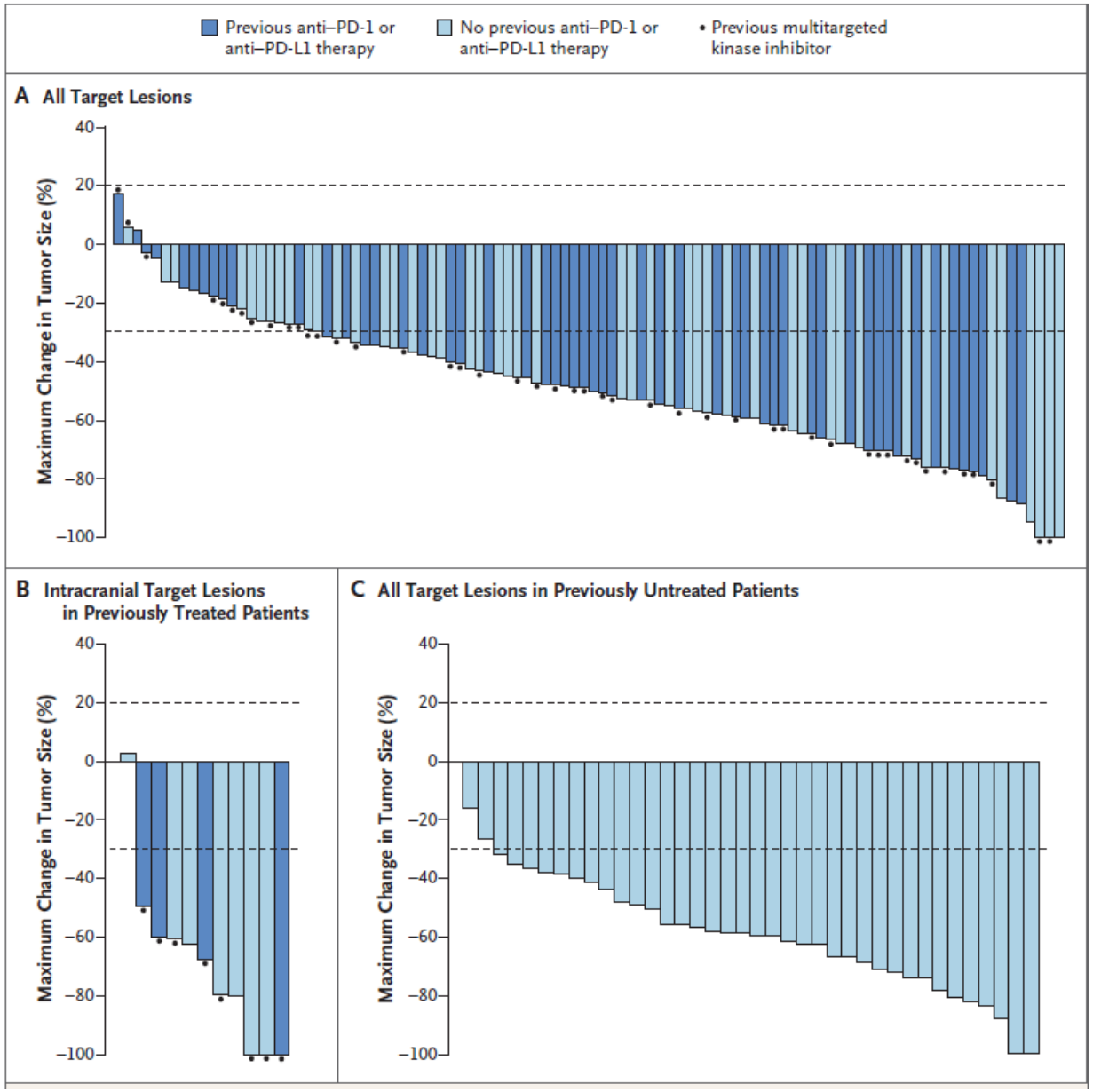
Courtesy of Joel W Neal, MD, PhD

Selpercatinib in RET+ NSCLC



Prior therapy:
64% ORR
PFS 16.5 mo

1st line:
85% ORR
PFS NR (?>18 mo)

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Selpercatinib in RET+ NSCLC

Note QT prolongation

Table 3. Adverse Events in 144 Patients with *RET* Fusion–Positive NSCLC Who Received Selpercatinib.*

Adverse Event	Adverse Events, Regardless of Attribution (N=144)					Treatment-Related Adverse Events (N=144)		
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4	Any Grade
	number of patients (percent)							
Any adverse event	8 (6)	47 (33)	69 (48)	14 (10)	144 (100)	39 (27)	2 (1)	131 (91)
Diarrhea	46 (32)	18 (12)	5 (3)	0	69 (48)	2 (1)	0	36 (25)
Dry mouth	48 (33)	11 (8)	0	0	59 (41)	0	0	52 (36)
Hypertension	3 (2)	22 (15)	20 (14)	0	45 (31)	13 (9)	0	25 (17)
Increased aspartate aminotransferase level	18 (12)	11 (8)	12 (8)	2 (1)	43 (30)	7 (5)	1 (1)	32 (22)
Fatigue	26 (18)	16 (11)	0	0	42 (29)	0	0	19 (13)
Increased alanine aminotransferase level	14 (10)	6 (4)	15 (10)	3 (2)	38 (26)	11 (8)	2 (1)	29 (20)
Constipation	33 (23)	3 (2)	2 (1)	0	38 (26)	1 (1)	0	16 (11)
Nausea	32 (22)	5 (3)	1 (1)	0	38 (26)	0	0	14 (10)
Peripheral edema	29 (20)	6 (4)	0	0	35 (24)	0	0	19 (13)
Urinary tract infection	4 (3)	21 (15)	7 (5)	0	32 (22)	0	0	0
Headache	21 (15)	7 (5)	2 (1)	0	30 (21)	0	0	6 (4)
Rash	20 (14)	6 (4)	2 (1)	0	28 (19)	2 (1)	0	17 (12)
Abdominal pain	18 (12)	8 (6)	1 (1)	0	27 (19)	0	0	5 (3)
Cough	24 (17)	3 (2)	0	0	27 (19)	0	0	3 (2)
Increased blood creatinine level	21 (15)	3 (2)	0	0	24 (17)	0	0	13 (9)
Dyspnea	15 (10)	6 (4)	3 (2)	0	24 (17)	0	0	4 (3)
Vomiting	17 (12)	6 (4)	1 (1)	0	24 (17)	1 (1)	0	5 (3)
Prolonged QT on electrocardiography	9 (6)	7 (5)	7 (5)	0	23 (16)	3 (2)	0	14 (10)
Pyrexia	14 (10)	8 (6)	1 (1)	0	23 (16)	1 (1)	0	8 (6)
Dry skin	19 (13)	3 (2)	0	0	22 (15)	0	0	13 (9)
Thrombocytopenia	13 (9)	6 (4)	3 (2)	0	22 (15)	2 (1)	0	15 (10)

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Conclusions:

Clinical Implications:

- Pralsetinib and selpercatinib are both approved for RET+ NSCLC in the first line setting
- Pralsetinib has apparent higher rate of pneumonitis while selpercatinib has QT prolongation

Future Directions:

- Consider combination strategies or head-to-head comparison to determine superiority (but both agents are excellent!)

Courtesy of Joel W Neal, MD, PhD

Thank you!

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