Later lines of treatment in metastatic NSCLC:
opportunities to move the needle

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≥ 2nd line options - mNSCLC*

Oncogenic driver mutation

KRAS G12C†: Sotorasib, adagrasib
EGFR Exon 20†: Amivantamab
HER2†: Trastuzumab deruxtecan (T-Dxd)

Treatment adaptation to on-target resistance mechanism identified. Examples below
- EGFR C797S → 4th generation EGFR TKI trial
- ALK G1202R → lorlatinib (or ALK TKI trial)
- *MET* amp → clinical trial with MET inhibitors (ideally in combination with parent TKI)

Enroll into clinical trials with novel agents
- ADCs
- Phase 1/2 immuno-oncology agents
- Novel small molecule combinations

Carboplatin + pemetrexed (+/- parent TKI)
Docetaxel +/- ramucirumab (2nd line)
Gemcitabine
Paclitaxel (or nab-paclitaxel)
Vinorelbine

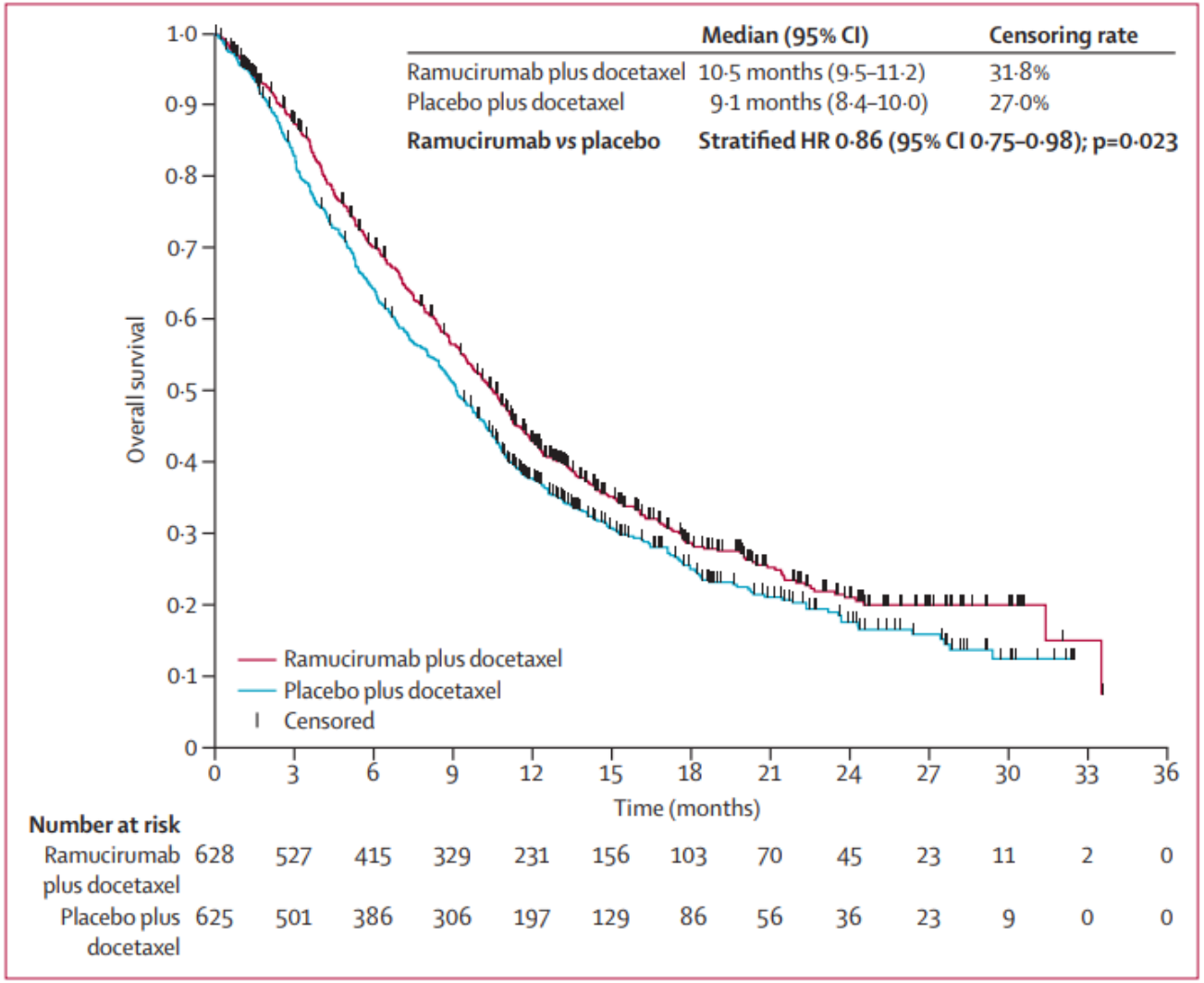
No actionable driver mutation

Enroll into clinical trials with novel agents
- ADCs
- Phase 1/2 immuno-oncology agents
- Novel small molecule combinations

Docetaxel +/- ramucirumab (2nd line)
Gemcitabine
Paclitaxel (or nab-paclitaxel)
Vinorelbine
Immune checkpoint inhibitor (if not given first line)

After progression on first line therapy for NSCLC, please strongly consider referral for a clinical trial

Current standard of care for 2nd line in mNSCLC



- Multi-center, double-blind, phase 3 RCT (n = 1253) with (1:1) randomization
  - Docetaxel 75mg/m2 +/- ramucirumab 10mg/kg (DR)
  - Docetaxel 75mg/m2 + placebo (DP)
- Efficacy endpoints
  - OS (primary): HR 0.86, 95% CI 0.75 – 0.98
    - DR – 10.5 months
    - DP – 9.1 months
  - PFS (secondary): HR 0.76, 95% CI 0.68 – 0.86
    - DR – 4.5 months
    - DP – 3.0 months
  - Investigator ORR (secondary): OR 1.89, 1.41-2.54
    - DR – 23%
    - DP – 14%
- Safety endpoints
  - Dose modifications: 33% (DR) vs 23% (DP)
  - Serious AEs: 43% vs 42%

Garon *Lancet Oncol* 2014

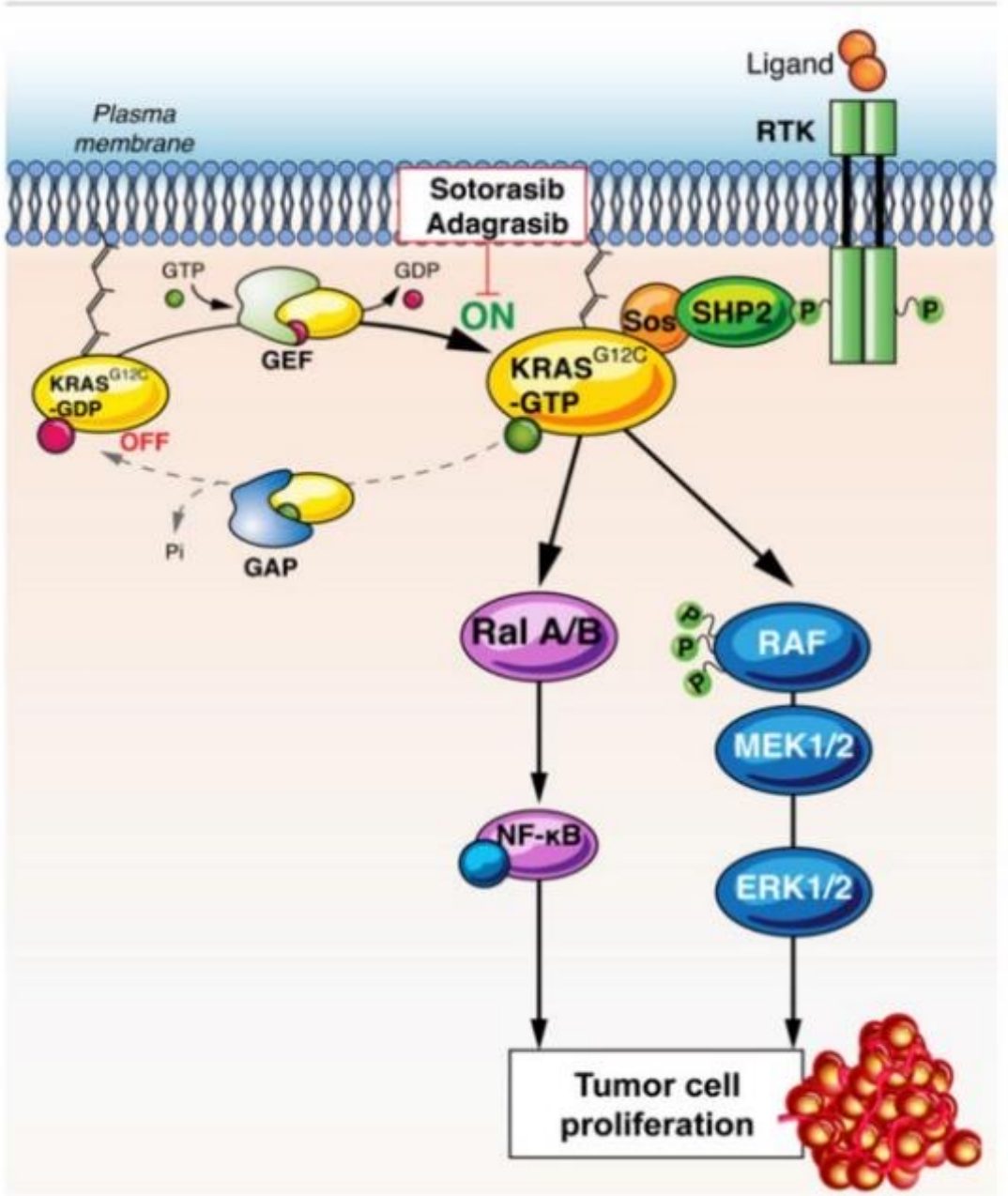
What is the benchmark for a 2nd line agent?

- **OS:** 9-10 months
- **PFS:** 3-4 months
- **ORR:** 14-20%
- **Safety:** < 33% dose modifications
- **SAEs:** < 42%

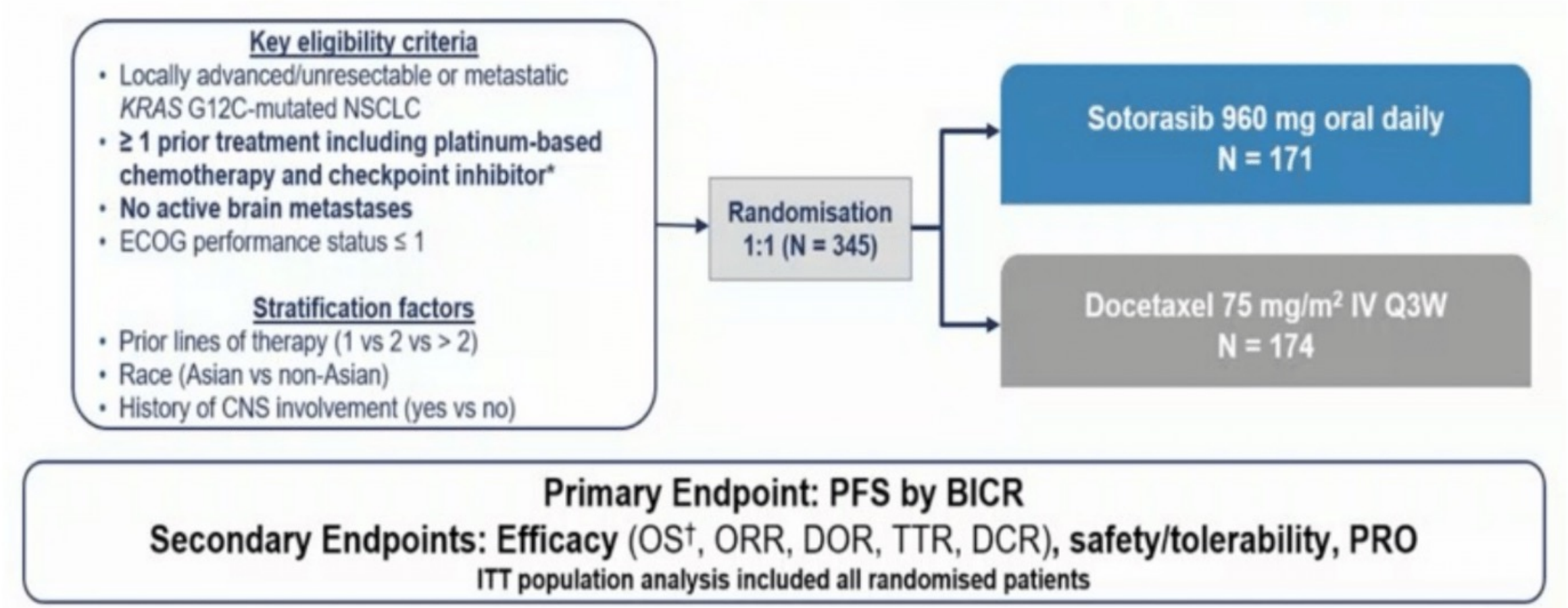
Later line treatments for KRAS G12C

Ras signaling pathway

- KRAS proto-oncogenes → Ras-Raf-Mek-Erk pathway
  - GTP-bound = active
  - GDP-bound = inactive
- Missense mutations in codon 12, 13 and 61 hinder GTP hydrolysis → activation
- Sotorasib (and adagrasib)
  - Irreversibly bind mutant cysteine via a covalent bond
  - Binding the switch pocket II → locks KRAS G12C in the GDP "off" state
  - Inhibits Raf signaling → Reduce MEK/ERK signaling



CodeBreak 200 - sotorasib



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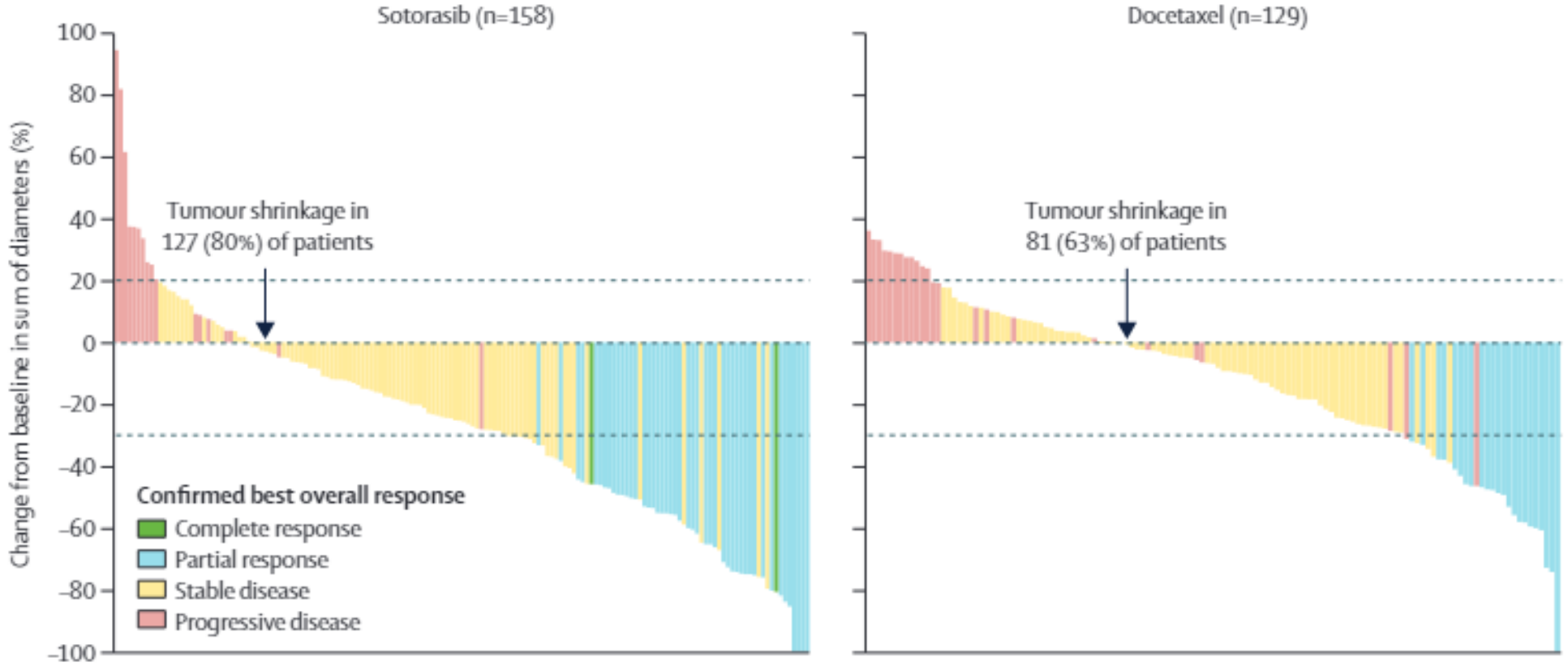
A

	Sotorasib	Docetaxel
Overall response rate (95% CI)	28·1 (21·5–35·4)	13·2 (8·6–19·2)
Disease control rate (95% CI)	82·5 (75·9–87·8)	60·3 (52·7–67·7)
Median duration of response, months (95% CI)	8·6 (7·1–18·0)	6·8 (4·3–8·3)



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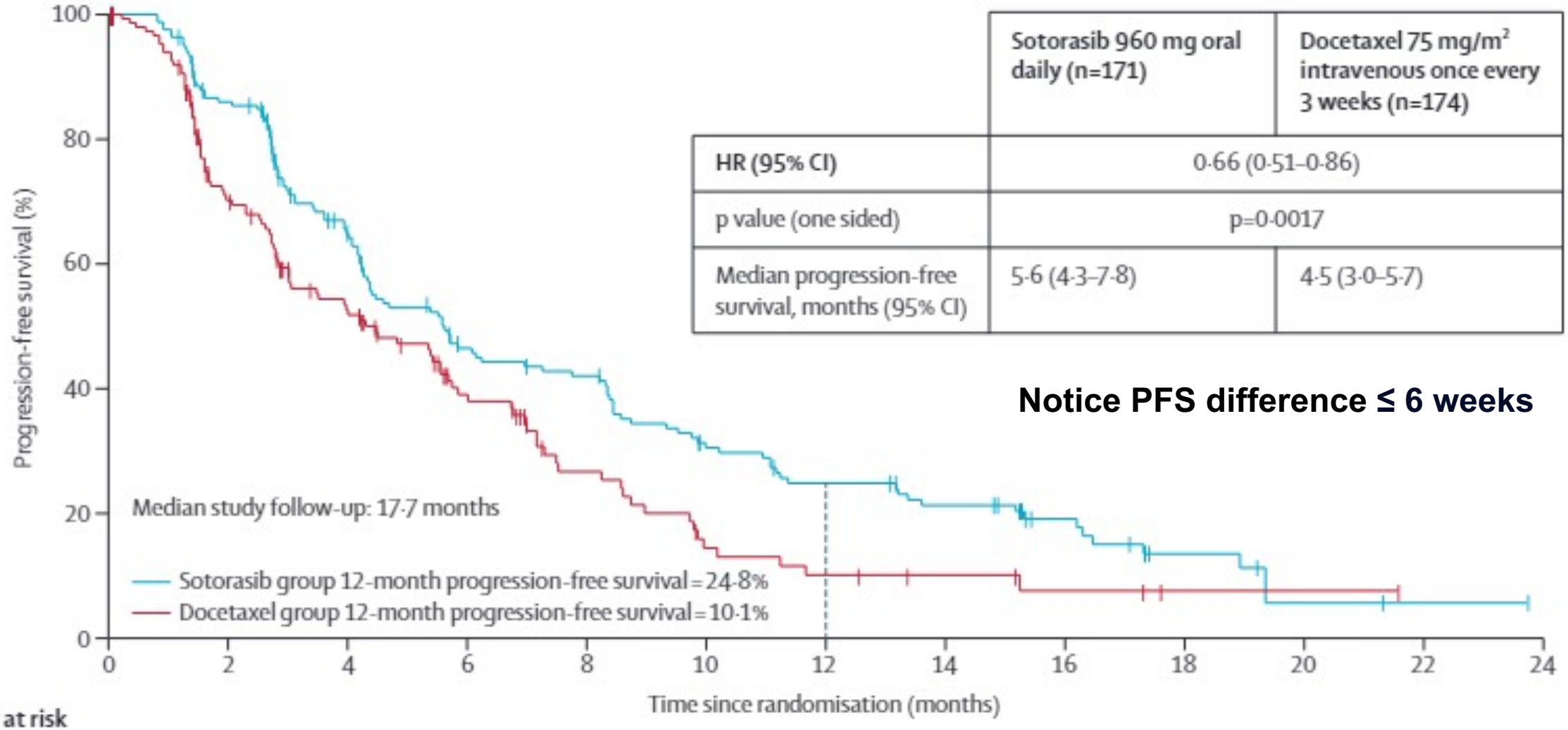
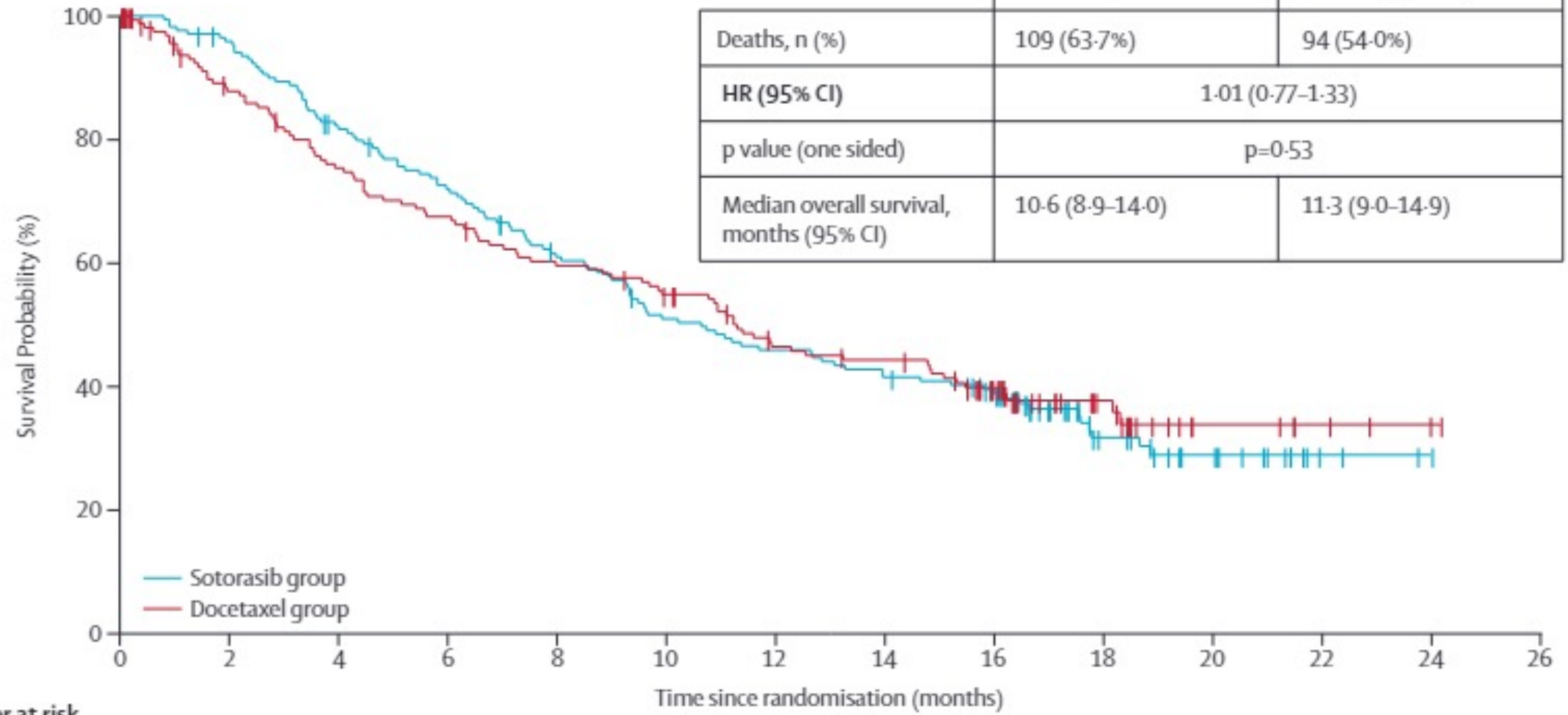


	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
HR (95% CI)	0·66 (0·51–0·86)	
p value (one sided)	p=0·0017	
Median progression-free survival, months (95% CI)	5·6 (4·3–7·8)	4·5 (3·0–5·7)

Notice PFS difference ≤ 6 weeks

Number at risk (number censored)												
Sotorasib group	171 (0)	139 (9)	93 (14)	63 (4)	56 (1)	38 (3)	30 (1)	24 (2)	14 (8)	6 (4)	2 (1)	1 (1)	0 (1)
Docetaxel group	174 (0)	93 (39)	62 (9)	36 (12)	20 (6)	10 (1)	7 (0)	5 (2)	3 (1)	1 (2)	1 (0)	0 (1)	..

	Sotorasib 960 mg oral daily (n=171)	Docetaxel 75 mg/m² intravenous once every 3 weeks (n=174)
Deaths, n (%)	109 (63·7%)	94 (54·0%)
HR (95% CI)	1·01 (0·77–1·33)	
p value (one sided)	p=0·53	
Median overall survival, months (95% CI)	10·6 (8·9–14·0)	11·3 (9·0–14·9)



Number at risk (number censored)													
Sotorasib group	171 (0)	162 (2)	137 (2)	119 (1)	98 (3)	81 (1)	73 (0)	66 (0)	56 (6)	25 (24)	15 (8)	3 (12)	0 (3)	..
Docetaxel group	174 (0)	135 (20)	115 (1)	103 (0)	90 (1)	81 (2)	65 (4)	61 (1)	44 (11)	20 (22)	7 (11)	4 (3)	1 (3)	0 (1)

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Other safety signals

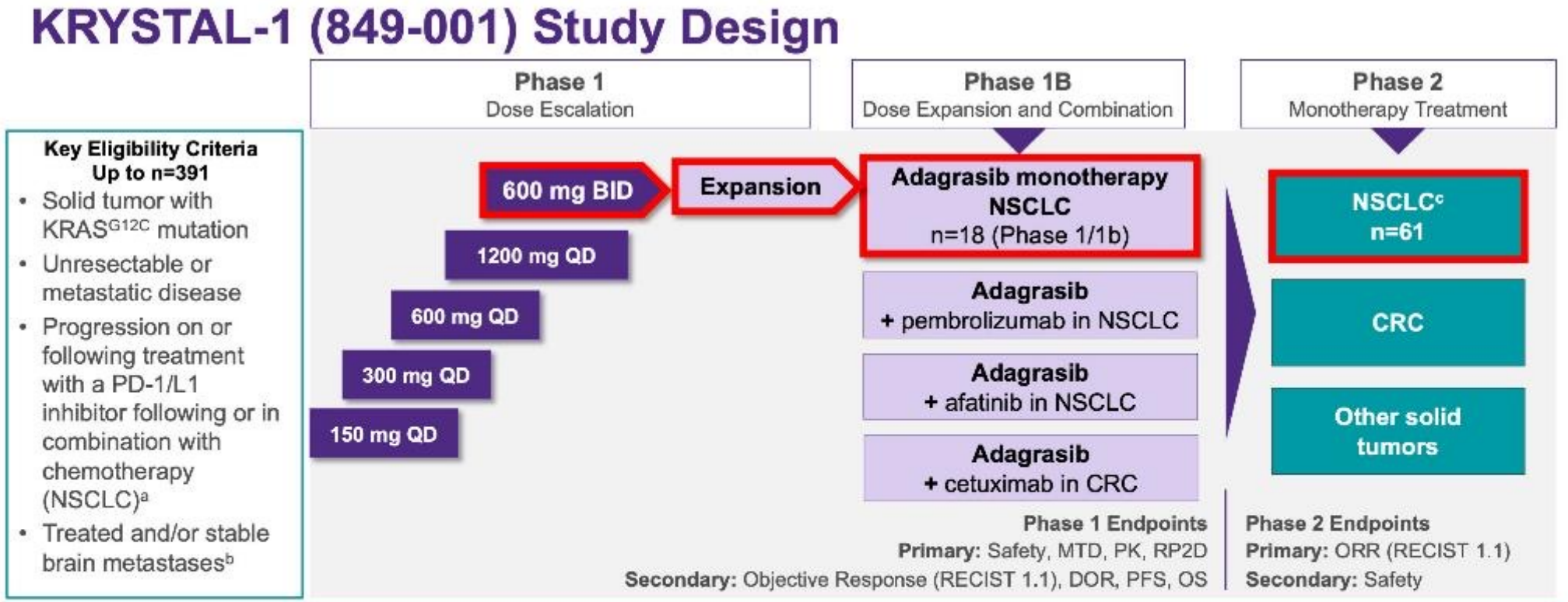
	Sotorasib (n=169)		Docetaxel (n=151)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhoea	57 (34%)	20 (12%)	28 (19%)	3 (2%)
Fatigue	11 (7%)	1 (1%)	38 (25%)	9 (6%)
Alopecia	2 (1%)	0	31 (21%)	0
Nausea	24 (14%)	2 (1%)	30 (20%)	1 (1%)
Anaemia	5 (3%)	1 (1%)	27 (18%)	5 (3%)
Decreased appetite	18 (11%)	3 (2%)	21 (14%)	0
Stomatitis	1 (1%)	0	17 (11%)	2 (1%)
Constipation	5 (3%)	0	16 (11%)	0
Asthenia	7 (4%)	1 (1%)	16 (11%)	4 (3%)
Alanine aminotransferase increased	17 (10%)	13 (8%)	0	0
Aspartate aminotransferase increased	17 (10%)	9 (5%)	0	0
Neutropenia	2 (1%)	0	20 (13%)	18 (12%)
Neuropathy peripheral	0	0	15 (10%)	1 (1%)
Oedema peripheral	0	0	14 (9%)	1 (1%)
Dysgeusia	4 (2%)	0	13 (9%)	0
Myalgia	3 (2%)	0	13 (9%)	2 (1%)
Vomiting	8 (5%)	0	10 (7%)	0
Arthralgia	2 (1%)	0	10 (7%)	1 (1%)
Mucositis	1 (1%)	0	10 (7%)	2 (1%)
Alkaline phosphatase increased	11 (7%)	5 (3%)	1 (1%)	0
Malaise	2 (1%)	1 (1%)	9 (6%)	1 (1%)
Febrile neutropenia	0	0	8 (5%)	8 (5%)
Abdominal pain	9 (5%)	2 (1%)	6 (4%)	0
Pyrexia	1 (1%)	0	8 (5%)	0
Pneumonia	0	0	7 (5%)	5 (3%)

Data are n (%). Adverse events were graded with the use of the Common Terminology Criteria for Adverse Events (version 5.0), which incorporates certain elements of *Medical Dictionary for Regulatory Activities* terminology.

Table 3: **Treatment-related adverse events of any grade (occurring in ≥5% of patients) or of grade ≥3 (occurring in ≥3% of patients)**

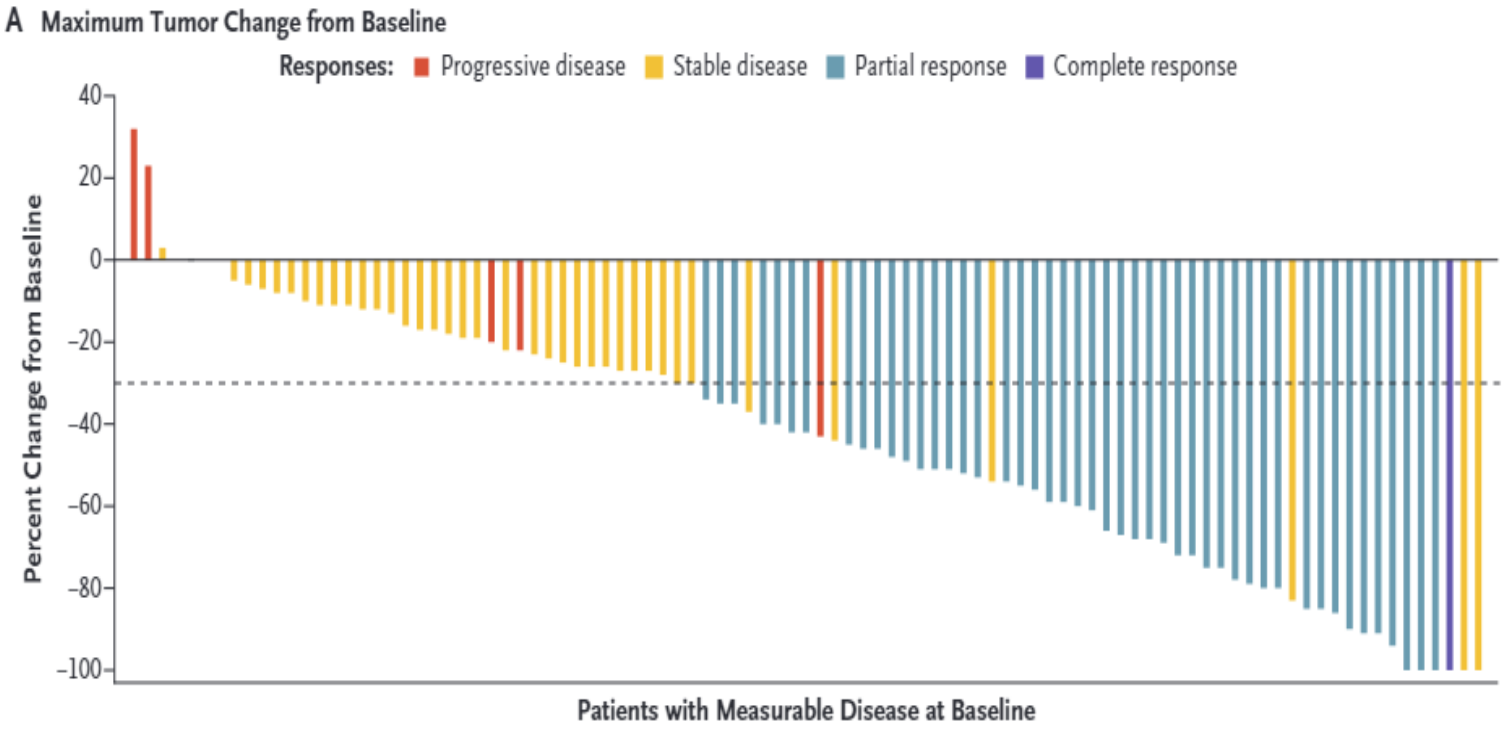
	Sotorasib N = 169	**Docetaxel N = 151**
Grade ≥ 3 AEs	94 (56)	84 (56)
Fatal TEAEs	11 (7)	11 (7)
Serious TEAEs	64 (38)	60 (40)
Discontinuation	22 (13)	22 (15)
Dose reduction	26 (15)	42 (28)
Dose interruption	83 (49)	40 (26)

KRYSTAL-1 – adagrasib monotherapy

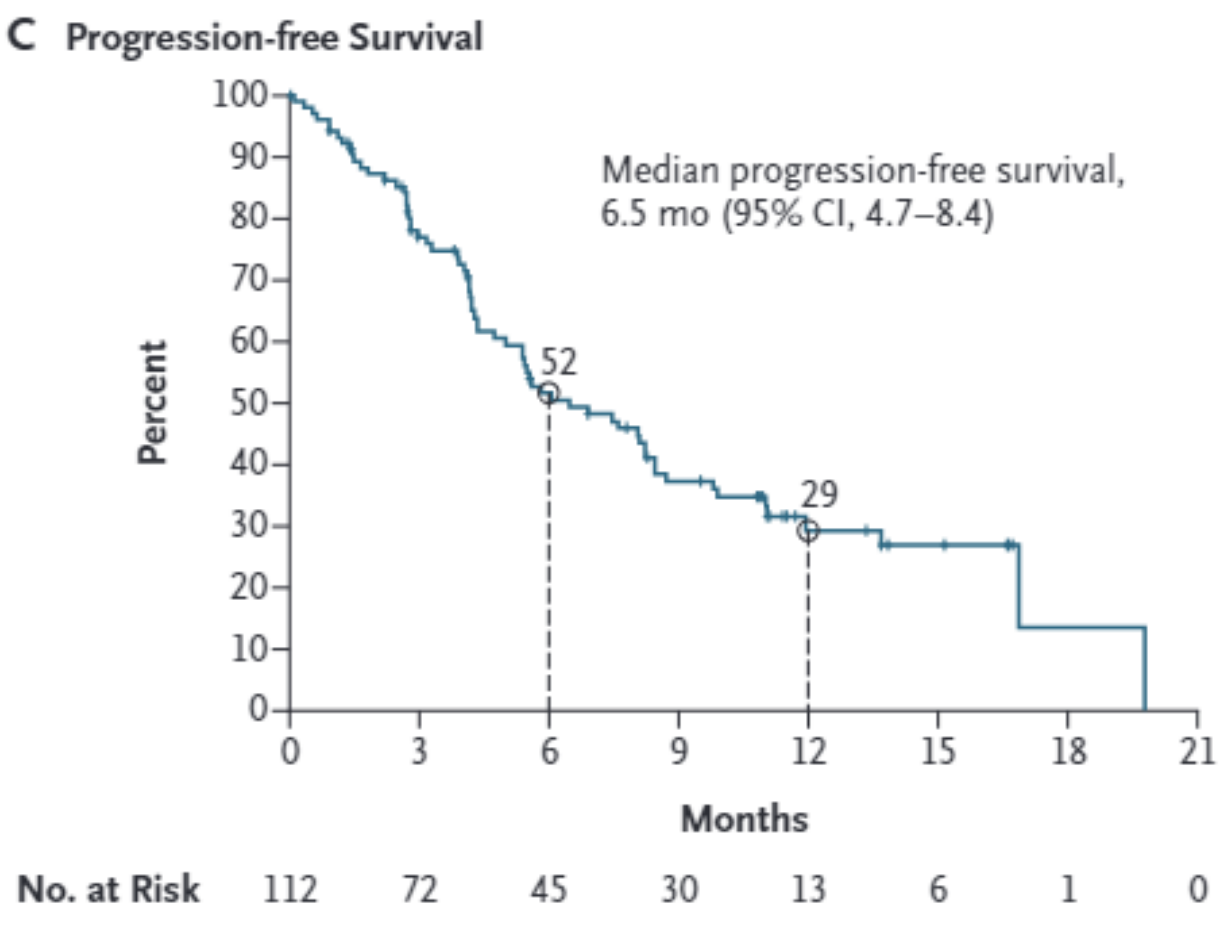


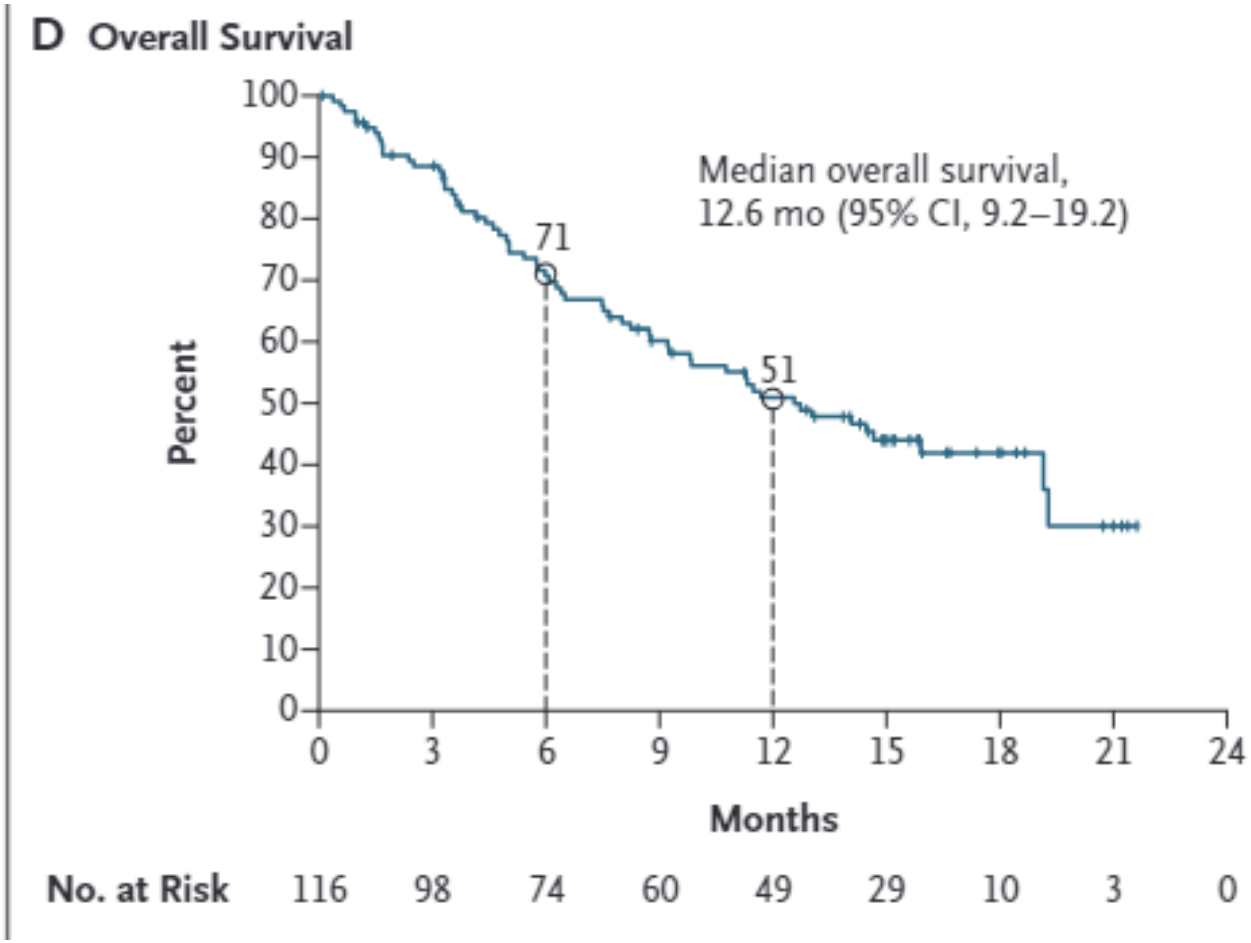
- Previously reported data from Phase 1 demonstrated clinical activity with adagrasib (MRTX849) in patients with pretreated KRASG12C NSCLC and CRC
- 600 mg BID was chosen as the RP2D
- Here we report data for 79 patients evaluating adagrasib 600 mg BID in patients with previously treated NSCLC in Phase 1/1b (n=18, median follow-up, 9.6 mo) and Phase 2 (n=61); pooled (n=79) median follow-up, 3.6 mo
- Data cut-off date: 30 August 2020

[a]Applies to the majority of NSCLC cohorts. [b]Most cohorts allow patients with brain metastases if adequately treated and stable; additional phase 1/1b cohort allows limited brain metastases. [c]Primary NSCLC cohort eligibility based on a tissue test; KRASG12C testing for entry was performed locally or centrally using a sponsor pre-approved test. ClinicalTrials.gov. NCT03785249.



Variable	Cohort A (N=112)†
Objective response‡	
No. of patients	48
Percent (95% CI)	42.9 (33.5–52.6)
Best overall response — no. (%)	
Complete response	1 (0.9)
Partial response	47 (42.0)
Stable disease	41 (36.6)
Progressive disease	6 (5.4)
Not evaluable	17 (15.2)
Disease control	
No. of patients	89
Percent (95% CI)	79.5 (70.8–86.5)
Median duration of response (95% CI) — mo	8.5 (6.2–13.8)
Median progression-free survival (95% CI) — mo	6.5 (4.7–8.4)
Median overall survival (95% CI) — mo§	12.6 (9.2–19.2)


C Progression-free Survival
Median progression-free survival, 6.5 mo (95% CI, 4.7–8.4)
Percent
100
90
80
70
60
50
40
30
20
10
0
52
29
0 3 6 9 12 15 18 21
Months
No. at Risk 112 72 45 30 13 6 1 0


D Overall Survival
Median overall survival, 12.6 mo (95% CI, 9.2–19.2)
Percent
100
90
80
70
60
50
40
30
20
10
0
71
51
0 3 6 9 12 15 18 21 24
Months
No. at Risk 116 98 74 60 49 29 10 3 0

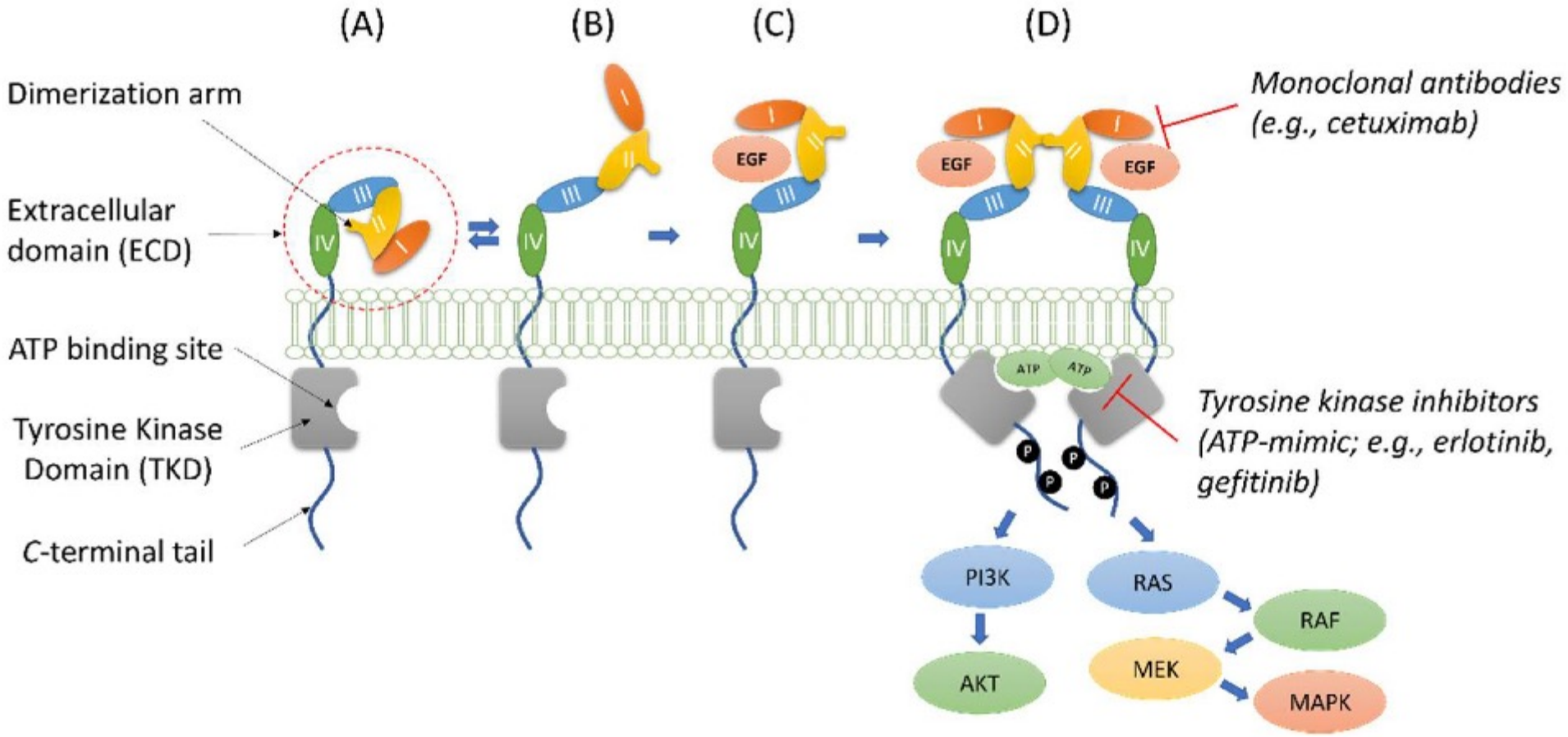
Event	Any Grade	Grade ≥3
	no. of patients (%)	
Any adverse event	116 (100)	95 (81.9)
Adverse event leading to dose reduction or interruption	96 (82.8)	—
Adverse event leading to discontinuation of therapy	18 (15.5)	—
Adverse event of any grade that occurred in >10% of patients or that was grade ≥3 in >1 patient†		
Diarrhea	82 (70.7)	1 (0.9)
Nausea	81 (69.8)	5 (4.3)
Fatigue	69 (59.5)	8 (6.9)
Vomiting	66 (56.9)	1 (0.9)
Anemia	42 (36.2)	17 (14.7)
Dyspnea	41 (35.3)	12 (10.3)
Blood creatinine increased	40 (34.5)	1 (0.9)
Decreased appetite	37 (31.9)	5 (4.3)
ALT increased	33 (28.4)	6 (5.2)
Edema peripheral	33 (28.4)	0
AST increased	31 (26.7)	6 (5.2)
Constipation	27 (23.3)	0
Hyponatremia	27 (23.3)	10 (8.6)

KRAS TKIs – where do we go from here?

- ORR for sotorasib and adagrasib (across Phase 1, 2 and 3 trials) is relatively consistent ranging from 28.1 – 42.9%
- PFS benefit is lower than scan interval frequency (6 weeks) for sotorasib
  - Early warning sign that might not be an OS benefit!
- Patient preferences may play role here, but KRAS TKIs do have important side effects and dose reductions common
- CNS predominant disease – may favor KRAS G12C TKI
- **Key message – highlights importance of selecting optimal and *tolerable* dose when determining RP2D**

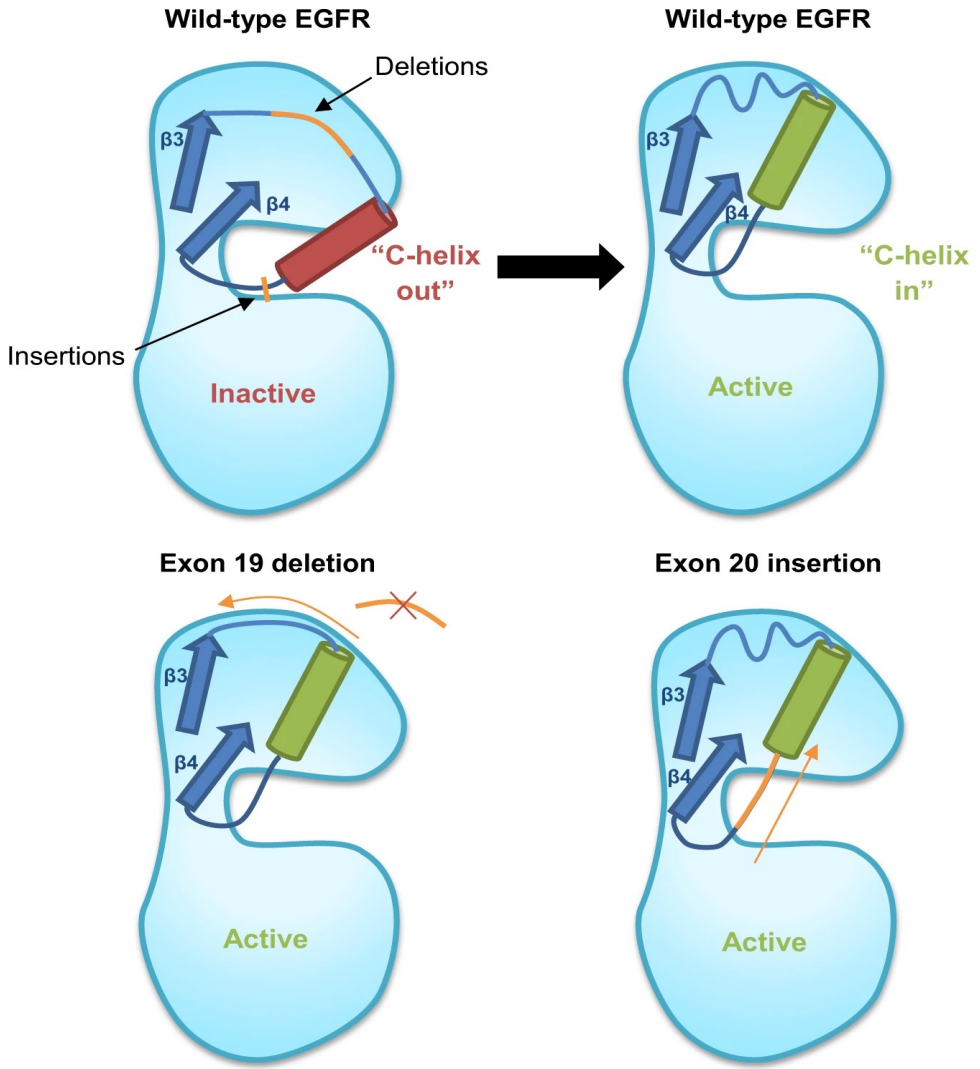
Later line treatments for EGFR Exon 20 insertion mutations

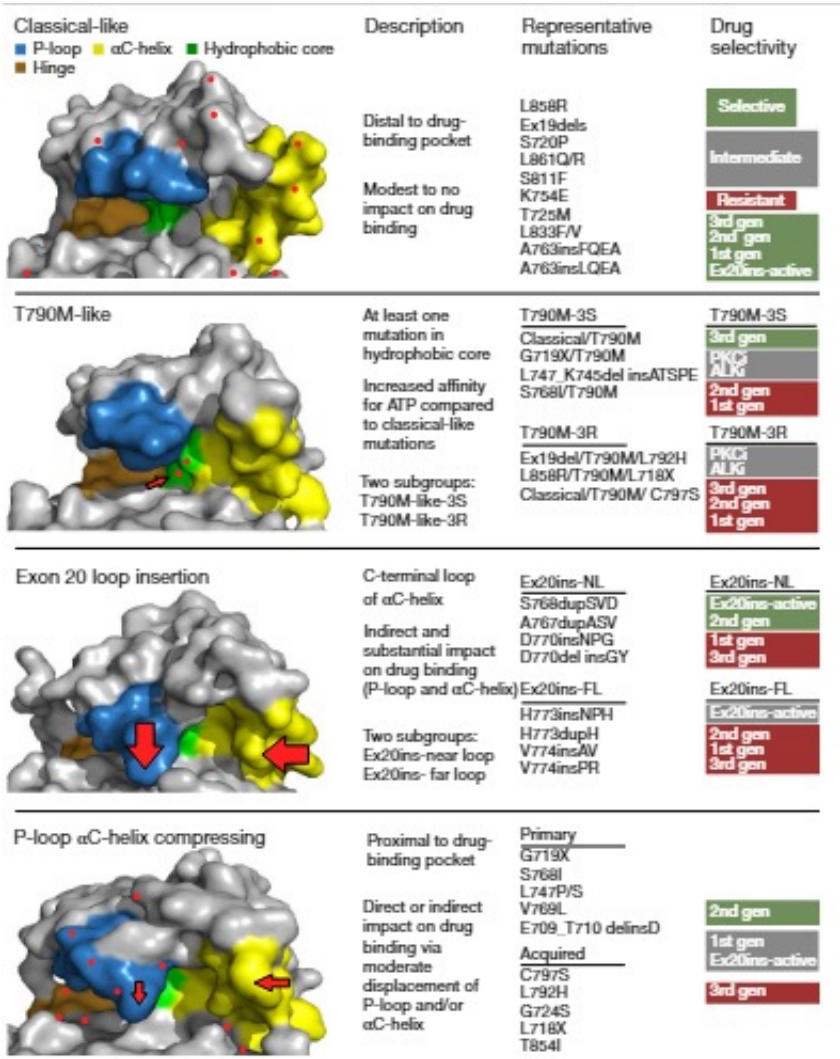
EGFR (ERBB1) dimerization



***Note:** EGF-like ligand more accurate given variety of signaling substrates

EGFR mutations





Knowing that your patient is EGFR positive is **not** enough!

You need to know which mutations are sensitizing to EGFR TKIs

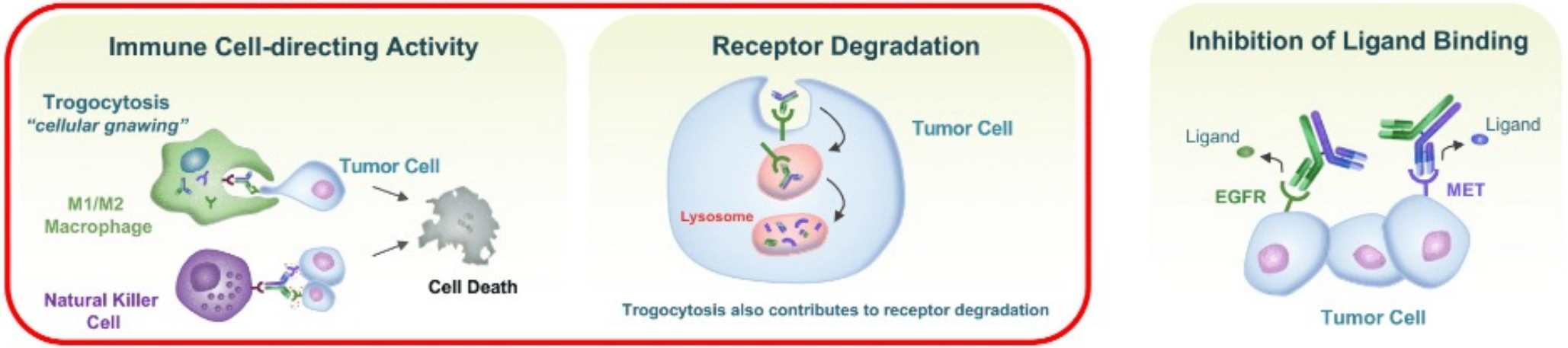
- *Drug-sensitive*:
  - Exon 19 del, L858R
- *Partially drug-sensitive*:
  - G719, L861Q
- *Insensitive*:
  - Exon 20 insertions (except FQEA)

[1]Vyse & Huang *Nature* 2019
[2]Roblchaux *Nature* 2021

Amivantamab: EGFR-MET Bispecific Antibody

- Fully human EGFR-MET bispecific antibody with immune cell-directing activity[1-2]
- Targets activating and resistance EGFR mutations and MET mutations and amplifications[3-4]
- Demonstrated monotherapy activity in patients with diverse EGFRm disease including EGFR Exon19del, L858R, T790M, C797S, Exon20ins, and MET amplification[3-4]

MOA Relevant to EGFR Exon20ins-mutated NSCLC



[1]Vijayaraghavan *Mol Cancer Ther* 19(10):2044. [2]Yun *Cancer Discov* 10(8):1194. [3]Haura *JCO* 37(15_suppl):9009. [4]Park *JCO* 38(15_suppl):9512
EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutant; MET, mesenchymal-epithelial transition; NSCLC, non-small cell lung cancer

CHRYSALIS Study Design: Post-platinum Exon20ins Population

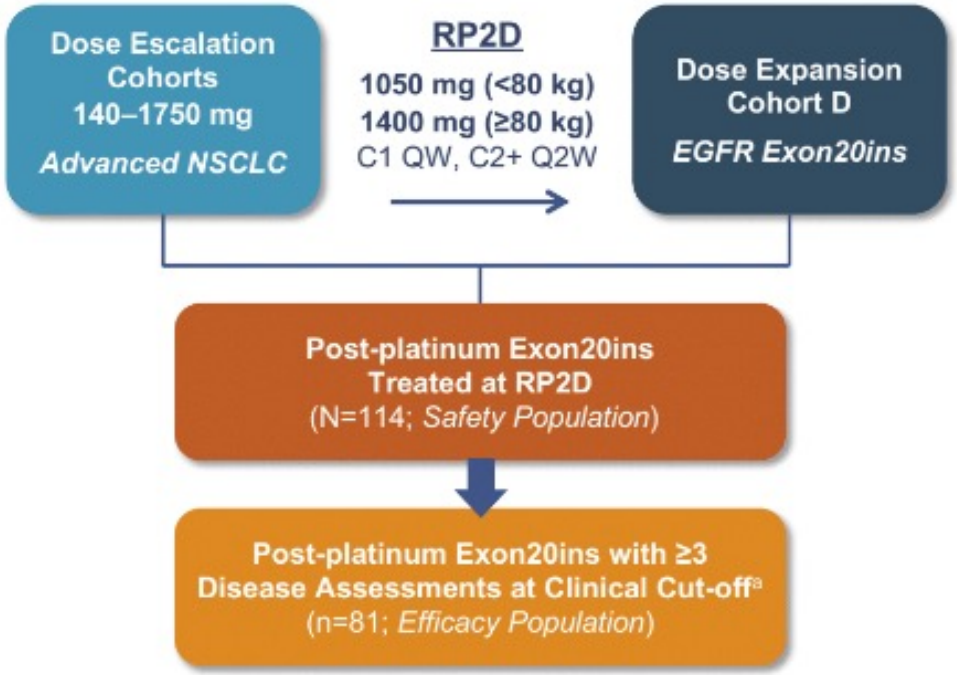
NCT02609776

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy



Efficacy End Points

Primary

- Overall response rate per RECIST v1.1

Key Secondary

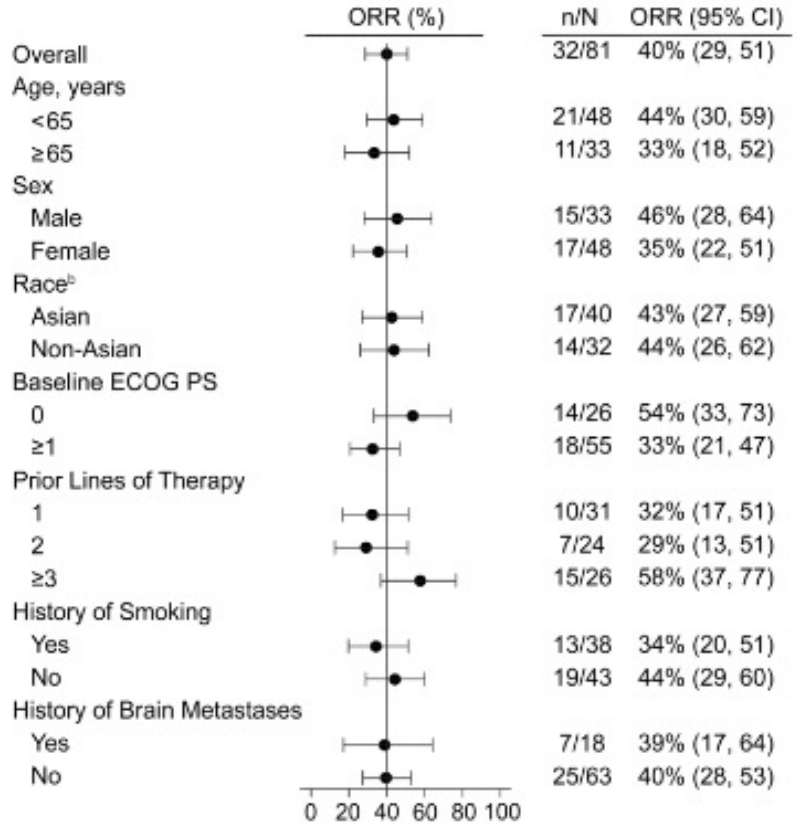
- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

[a]Post-platinum patients treated at the RP2D and had ≥3 scheduled disease assessments or discontinued, progressed, or died prior to the 3rd postbaseline assessment at the time of clinical cut-off (June 8, 2020). By October 8, 2020, all responders in the efficacy population had ≥6 months of follow-up from their first disease assessment.
C, cycle; Q2W, every other week; QW, weekly; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose

Amivantamab: Efficacy by BICR

BICR-assessed Response	Efficacy Population (n=81)
Overall response rate	**40%** (95% CI, 29–51)
Median duration of response	**11.1 months** (95% CI, 6.9–NR)
Best response, n (%)	
Complete response	3 (4)
Partial response	29 (36)
Stable disease	39 (48)
Progressive disease	8 (10)
Not evaluable	1 (1)
Clinical benefit rate[a]	74% (95% CI, 63–83)

Median follow-up: 9.7 months (range, 1.1–29.3)

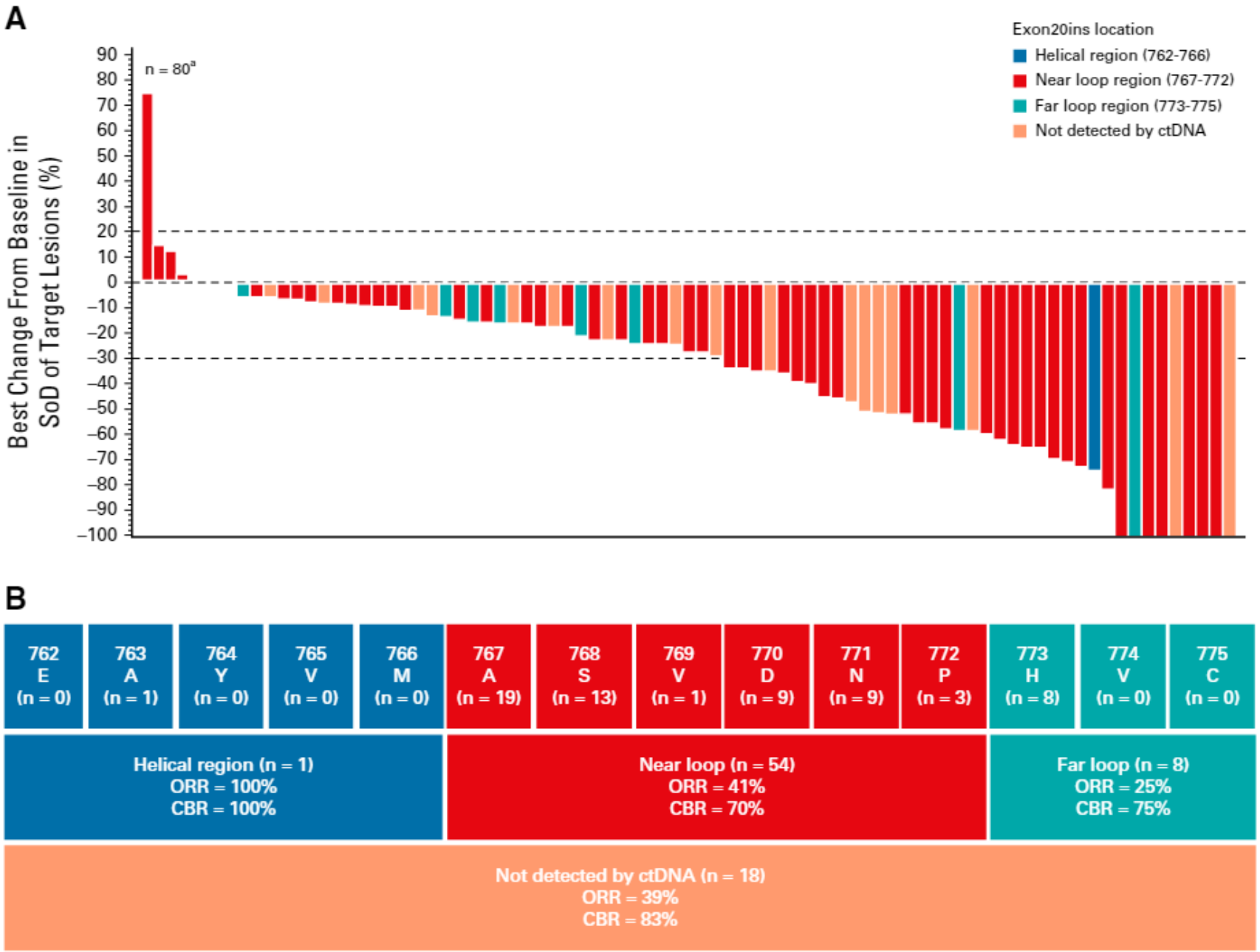


8 October 2020 efficacy data cut. [a]Clinical benefit rate (CBR) defined as complete response or partial response or stable disease for at least 2 disease assessments. [b]Does not include 9 patients with race not reported and multiple race.
BICR, blinded independent central review; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; NR, not reached; ORR, overall response rate

TABLE 2. Summary of AEs

Event	Safety Population (n = 114), No. (%)	Patients Treated at the RP2D (n = 258), No. (%)
Any AE	113 (99)	257 (100)
Grade ≥ 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption[a]	40 (35)	88 (34)

	Safety Population (n = 114), No. (%)				Patients Treated at the RP2D (n = 258), No. (%)			
Most Common AE (≥ 10%)	Total	Grade 1	Grade 2	Grade ≥ 3	Total	Grade 1	Grade 2	Grade ≥ 3
Rash[b]	98 (86)	43 (38)	51 (45)	4 (4)	202 (78)	101 (39)	94 (36)	7 (3)
Infusion-related reaction	75 (66)	9 (8)	63 (55)	3 (3)	167 (65)	21 (8)	140 (54)	6 (2)
Paronychia	51 (45)	28 (25)	22 (19)	1 (1)	104 (40)	50 (19)	51 (20)	3 (1)
Hypoalbuminemia	31 (27)	6 (5)	22 (19)	3 (3)	63 (24)	21 (8)	38 (15)	4 (2)
Constipation	27 (24)	18 (16)	9 (8)	0	58 (23)	36 (14)	22 (9)	0
Nausea	22 (19)	17 (15)	5 (4)	0	55 (21)	40 (16)	14 (5)	1 (0.4)
Dyspnea	22 (19)	12 (11)	8 (7)	2 (2)	52 (20)	28 (11)	13 (5)	11 (4)
Stomatitis	24 (21)	11 (10)	13 (11)	0	50 (19)	33 (13)	17 (7)	0
Peripheral edema	21 (18)	20 (18)	1 (1)	0	50 (19)	43 (17)	5 (2)	2 (1)
Pruritus	19 (17)	11 (10)	8 (7)	0	49 (19)	40 (16)	9 (4)	0
Fatigue	21 (18)	15 (13)	4 (4)	2 (2)	47 (18)	29 (11)	16 (6)	2 (1)
Cough	16 (14)	11 (10)	5 (4)	0	40 (16)	25 (10)	15 (6)	0
Decreased appetite	16 (14)	7 (6)	9 (8)	0	39 (15)	23 (9)	16 (6)	0
Dry skin	18 (16)	18 (16)	0	0	33 (13)	32 (12)	1 (0.4)	0

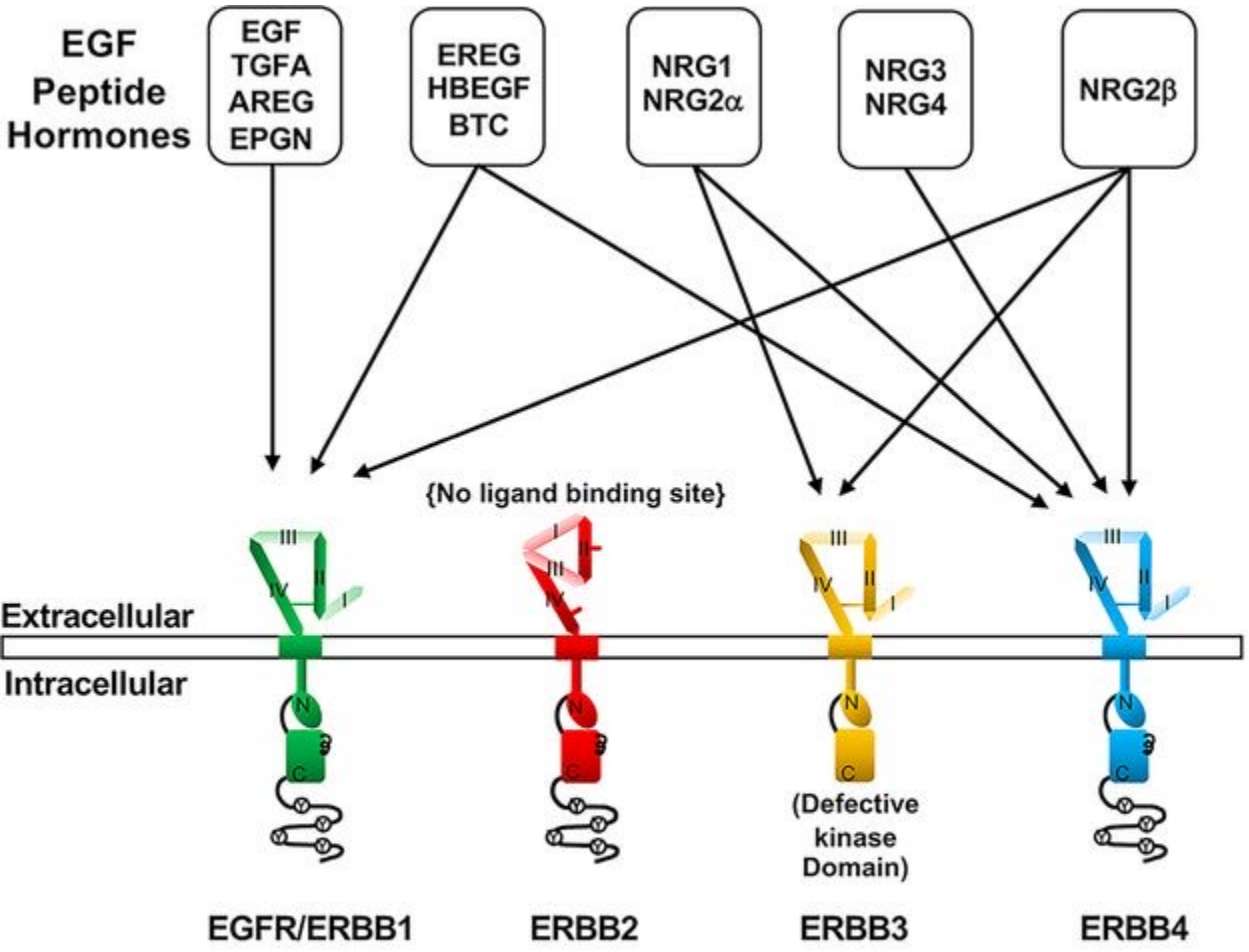

A
Exon20ins location
Helical region (762-766)
Near loop region (767-772)
Far loop region (773-775)
Not detected by ctDNA
n = 80[a]
Best Change From Baseline in SoD of Target Lesions (%)
90
80
70
60
50
40
30
20
10
0
−10
−20
−30
−40
−50
−60
−70
−80
−90
−100
B
762 E (n = 0)
763 A (n = 1)
764 Y (n = 0)
765 V (n = 0)
766 M (n = 0)
767 A (n = 19)
768 S (n = 13)
769 V (n = 1)
770 D (n = 9)
771 N (n = 9)
772 P (n = 3)
773 H (n = 8)
774 V (n = 0)
775 C (n = 0)
Helical region (n = 1)
ORR = 100%
CBR = 100%
Near loop (n = 54)
ORR = 41%
CBR = 70%
Far loop (n = 8)
ORR = 25%
CBR = 75%
Not detected by ctDNA (n = 18)
ORR = 39%
CBR = 83%

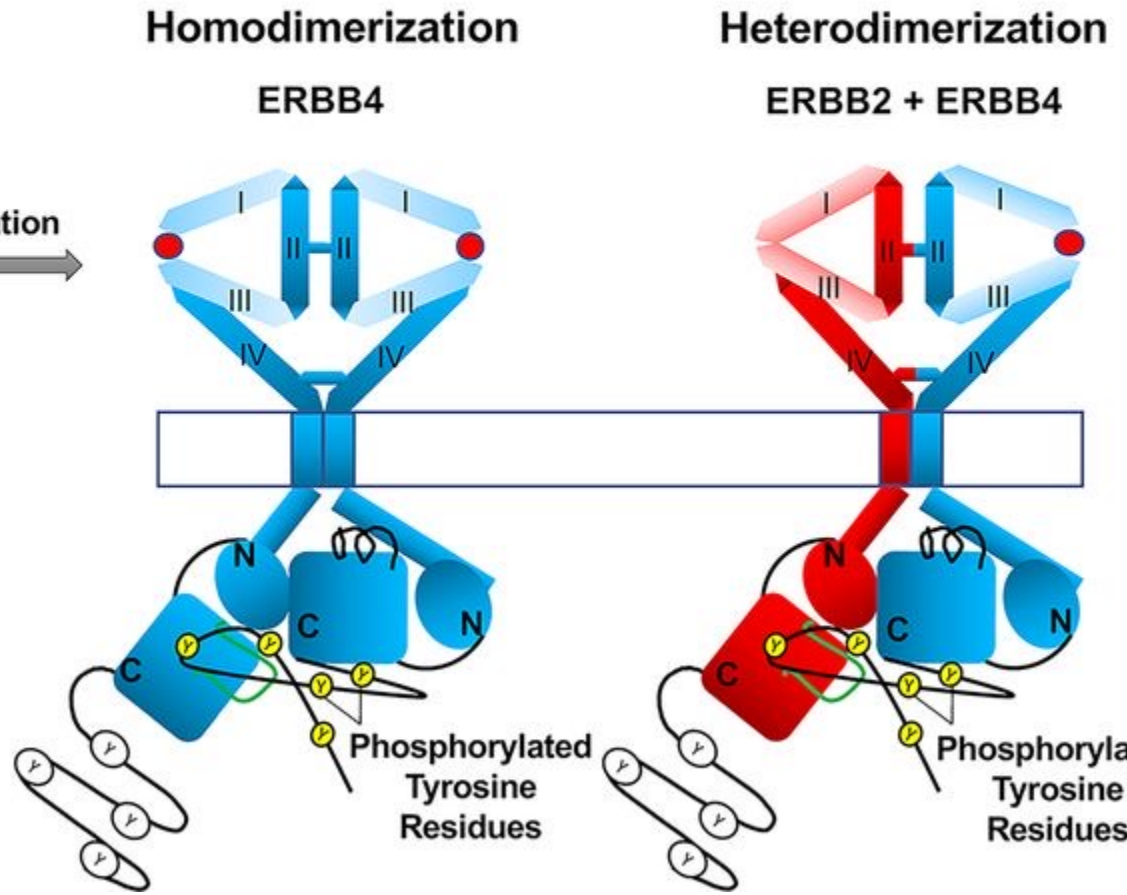
EGFR Exon 20 therapies – what's next

- Amivantamab is available for patients with EGFR Exon 20 insertion mutations who progress on 1st line platinum chemotherapy
  - *Open question whether to include ICI or bevacizumab with doublet*
  - *Takeda has voluntarily removed mobocertinib from market*
- Amivantamab has very real side effects including IRR, rash, diarrhea, and peripheral edema
  - *Grade ≥ 3 AEs (30%), dose reduction (10%), dose discontinuation (34%) when treated at RP2D*
- Future directions
  - Amivantamab + lazertinib + chemotherapy combination studies
  - Structural variants of EGFR Exon 20 may matter (far loop vs near loop)

Later line treatments – antibody drug conjugates (ADCs)

Receptor tyrosine kinases and dimerization





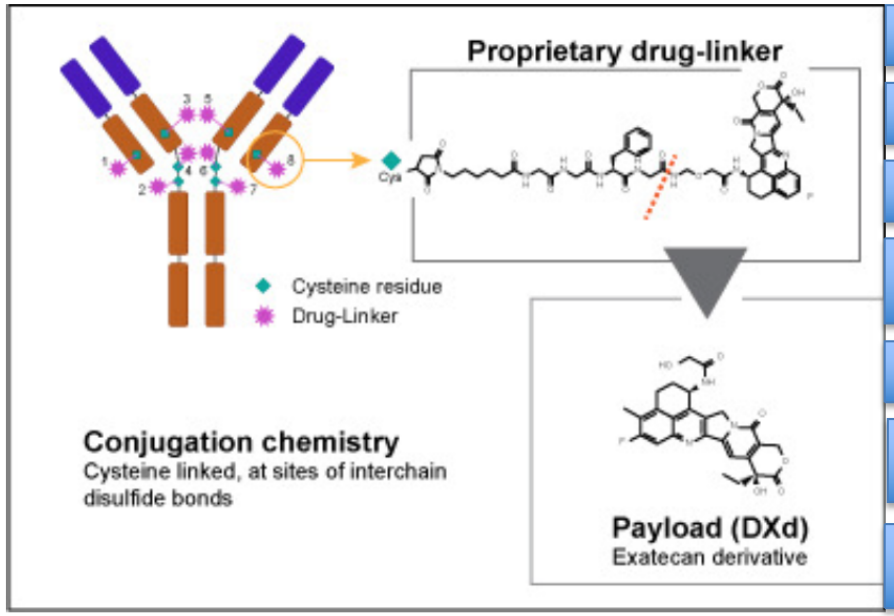
Vyse & Huang *Nature* 2019

HER2 mutations, amplifications, overexpression

ERBB2 Mutations	*ERBB2* Gene Amplifications	HER2 Protein Overexpression
~2%-3% of lung adenocarcinomas	~2%-5% of lung adenocarcinomas	~2.4%-38% of NSCLCs
NGS, RT-PCR Most common: exon 20	FISH HER2/CEP17 ratio ≥2.0	IHC 2+ or 3+

Trastuzumab deruxtecan (T-DXd)

Designed with the goal of improving clinical attributes of an ADC



- Novel payload
- High potency
- Bystander effect
- Short systemic half-life payload
- Stable linker-payload
- Tumor selective cleavable-linker
- High drug-to-antibody ratio

Drug Design Attributes

DS-8201	T-DM1	Clinical Implications
Topoisomerase-1 inhibitor	Tubulin inhibitor	**Validated topo-1 mechanism**
High: 7-8	Low: 3-4	**More drug delivered, greater tumor cell killing**
Highly membrane permeable → "bystander effect"	Membrane impermeable → no "bystander effect"	**Kills neighboring heterogenous non-HER2 tumor cells (pH-dependent topo-1 potency)**

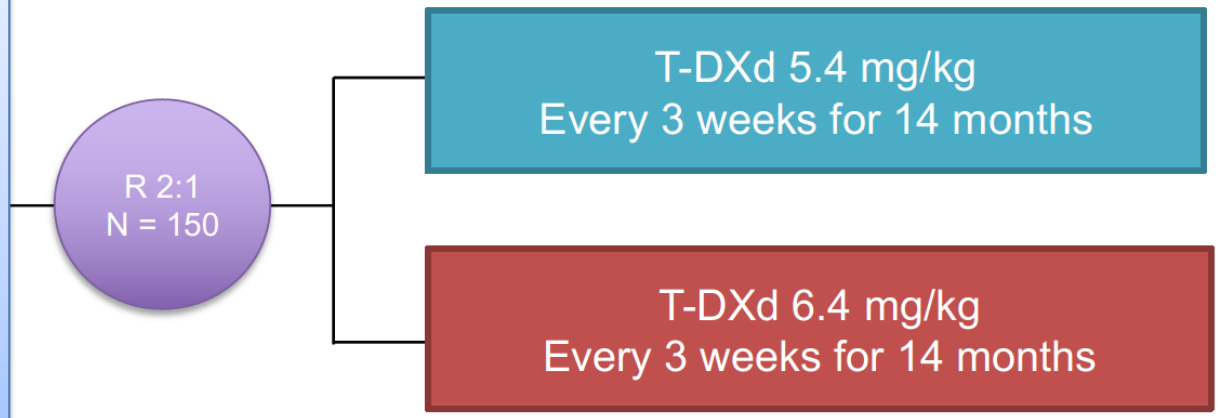
[Fam-] trastuzumab deruxtecan is an antibody-drug conjugate with a HER2 antibody, peptide-based cleavable linker, and a novel topoisomerase I inhibitor payload

DESTINY-Lung 02

HER2+ NSCLC, Second Line

Key Eligibility Criteria

- Confirmed metastatic NSCLC with activating HER2 mutation
- Progression after 1 previous line of platinum-containing therapy
- Absence of *EGFR*, *BRAF* mutations and *ALK*, *ROS1* fusions
- ECOG PS 0 or 1
- LVEF ≥ 50% within 28 days before randomization
- No history of non-infections ILD requiring steroids or active ILD



Primary End Point

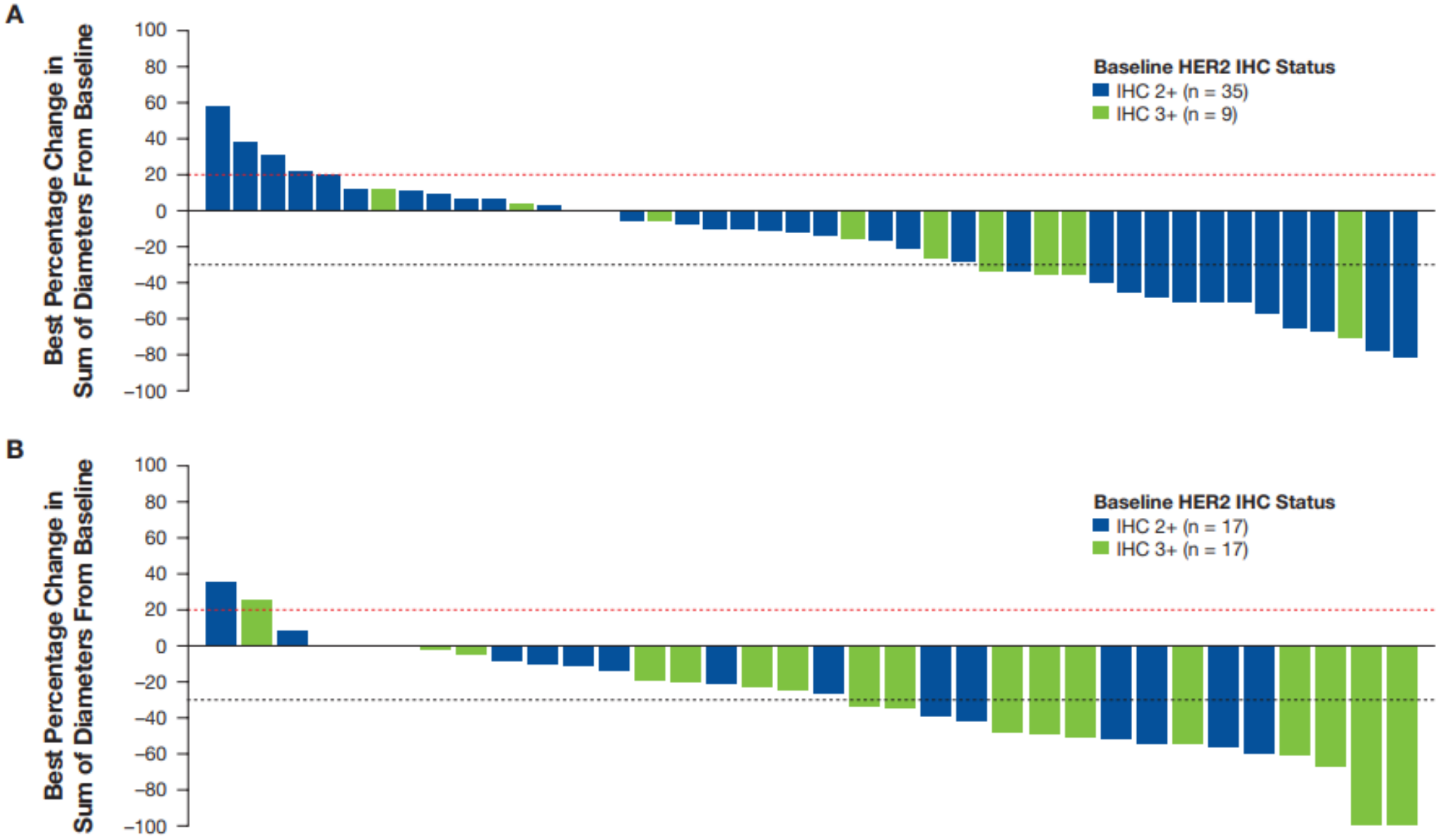
- ORR (RECIST v1.1 per BICR)

Key Secondary End Points

- ORR (RECIST v1.1 per investigator)
- DCR, DOR, and PFS (RECIST v1.1 per BICR), OS, Safety

DL-02 Efficacy

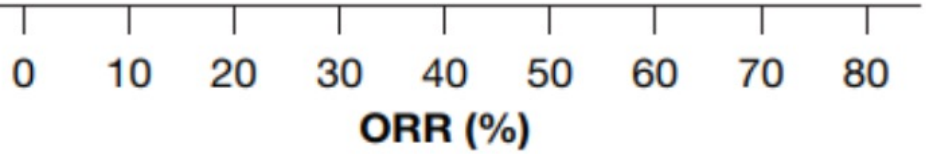
Response Assessment by BICR	Prespecified early cohort	
	T-DXd 5.4 mg/kg n = 52	T-DXd 6.4 mg/kg n = 28
Confirmed ORR,[a] n (%) [95% CI]	28 (53.8) [39.5, 67.8]	12 (42.9) [24.5, 62.8]
Best overall response, n (%)		
CR	1 (1.9)	1 (3.6)
PR	27 (51.9)	11 (39.3)
SD	19 (36.5)	14 (50.0)
PD	2 (3.8)	1 (3.6)
NE[b]	3 (5.8)	1 (3.6)
DCR,[c] n (%) [95% CI]	47 (90.4) [79.0, 96.8]	26 (92.9) [76.5, 99.1]
Median DoR, months [95% CI]	NE [4.2, NE]	5.9 [2.8, NE]
Median TTIR, months [range]	1.4 [1.2-5.8]	1.4 [1.2-3.0]
Median follow-up, months [range]	5.6 (1.1-11.7)	5.4 (0.6-12.1)



Best (minimum) percentage change from baseline in the sum of diameters for all target lesions, based on ICR. Baseline was last measurement taken before enrollment. Red line at 20% indicates PD, and black line at −30% indicates PR (when considering only target lesions). Full analysis set data are shown.

Figure 2. Response to T-DXd by HER2 IHC Status

	No. of responders	Confirmed ORR (95% CI)	Confirmed ORR (95% CI)
Cohort 1 (all patients)	13/49	26.5 (15.0-41.1)	
HER2 IHC 3+	2/10	20.0 (2.5-55.6)	
HER2 IHC 2+	11/39	28.2 (15.0-44.9)	
Cohort 1a (all patients)	14/41	34.1 (20.1-50.6)	
HER2 IHC 3+	9/17	52.9 (27.8-77.0)	
HER2 IHC 2+	5/24	20.8 (7.1-42.2)	



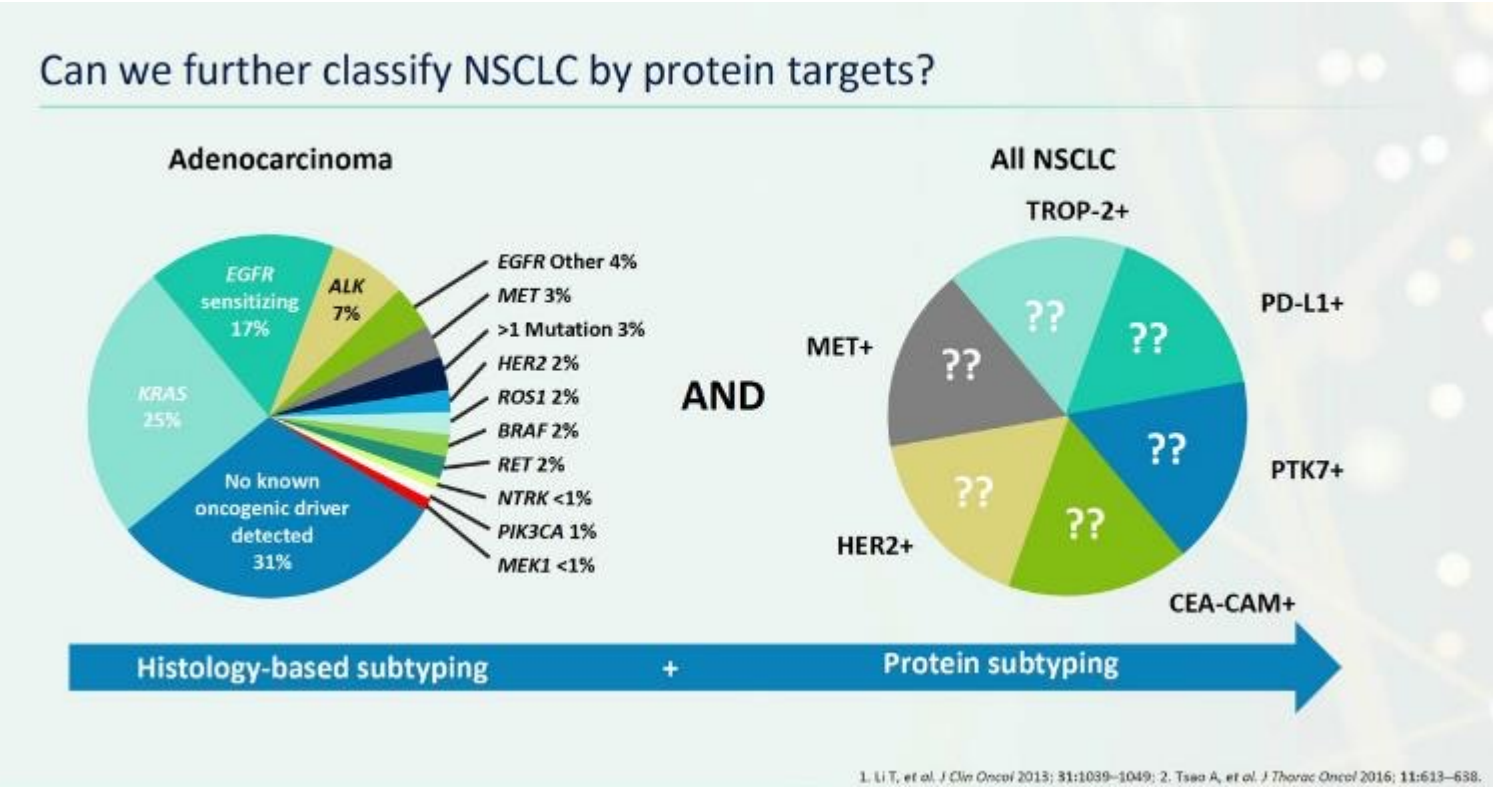
ILD lower in 5.4 mg/kg

Adjudicated Drug-Related ILD

	Safety analysis set[b]		Prespecified early cohort[c]	
Adjudicated as drug-related ILD[a]	T-DXd 5.4 mg/kg n = 101	T-DXd 6.4 mg/kg n = 50	T-DXd 5.4 mg/kg n = 51	T-DXd 6.4 mg/kg n = 28
Any grade, n (%)	**6 (5.9)**	**7 (14.0)**	**4 (7.8)**	**5 (17.9)**
Grade 1	3 (3.0)	1 (2.0)	3 (5.9)	1 (3.6)
Grade 2	2 (2.0)	6 (12.0)	1 (2.0)	4 (14.3)
Grade 3	1 (1.0)	0	0	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0
Cases resolved, n (%)	3 (50.0)	1 (14.3)	1 (25.0)	1 (20.0)
Median time to onset of first adjudicated ILD, days (range)	67.5 (40-207)	41.0 (36-208)	104.5 (40-207)	43.0 (36-208)

- Most cases of adjudicated drug-related ILD were low grade (grade 1/2)
- The rate of adjudicated drug-related ILD was lower in the T-DXd 5.4 mg/kg arm compared with the 6.4 mg/kg arm

Future directions for ADCs



- How to prioritize sequencing? (genomic vs protein subtyping)
- How to sequence payloads? (MMAE vs topoisomerase)
- How to combine with TKIs? Which patients would benefit?
- How to combine with immunotherapy? What PDL1 subtypes?
- What dose is appropriate?
- Biomarker restricted or broad?

Summary

- Docetaxel +/- ramucirumab current 2nd line chemotherapy option
- Sotorasib and adagrasib are options for KRAS G12C NSCLC, but limited single agent activity and toxicity.
  - Newer trials in development with KRAS TKI and KRAS combinations
- Amivantamab is an option for EGFR Exon 20 NSCLC
  - Newer trials include novel EGFR Exon 20 TKIs and amivantamab combinations
- Trastuzumab deruxtecan an option for HER2 altered NSCLC
  - ILD and neutropenia are class toxicities
  - Response rates modest and unclear relationship between HER2 IHC expression
- **After progression on first line treatment for NSCLC, please strongly consider referral for a clinical trial**

THANK YOU

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