TARGETED THERAPY FOR NSCLC IN 2023

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DISCLOSURES

Advisory board/Consultancy*

- Abbvie

Honoraria

- None

Research support to institution

- Astra Zeneca, Amgen, Advaxis, BMS, Merck, GSK, Takeda

*24 Months reporting period

NSCLC TARGETS WITH FDA APPROVED THERAPIES

- EGFR- classical (exon 19 /21)
- EGFR- atypical (G719, L861, S768)
- EGFR Exon 20 insertion
- ALK fusion
- ROS1 fusion
- RET fusion
- NTRK fusion
- MET exon 14 mutation
- HER2 mutation
- KRAS G12C

24 agents approved across these indications

NGS for all patients with non-squamous histology prior to treatment initiation

ADJUVANT EGFR INHIBITION

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ADAURA PHASE III 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§
Maximum 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 continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

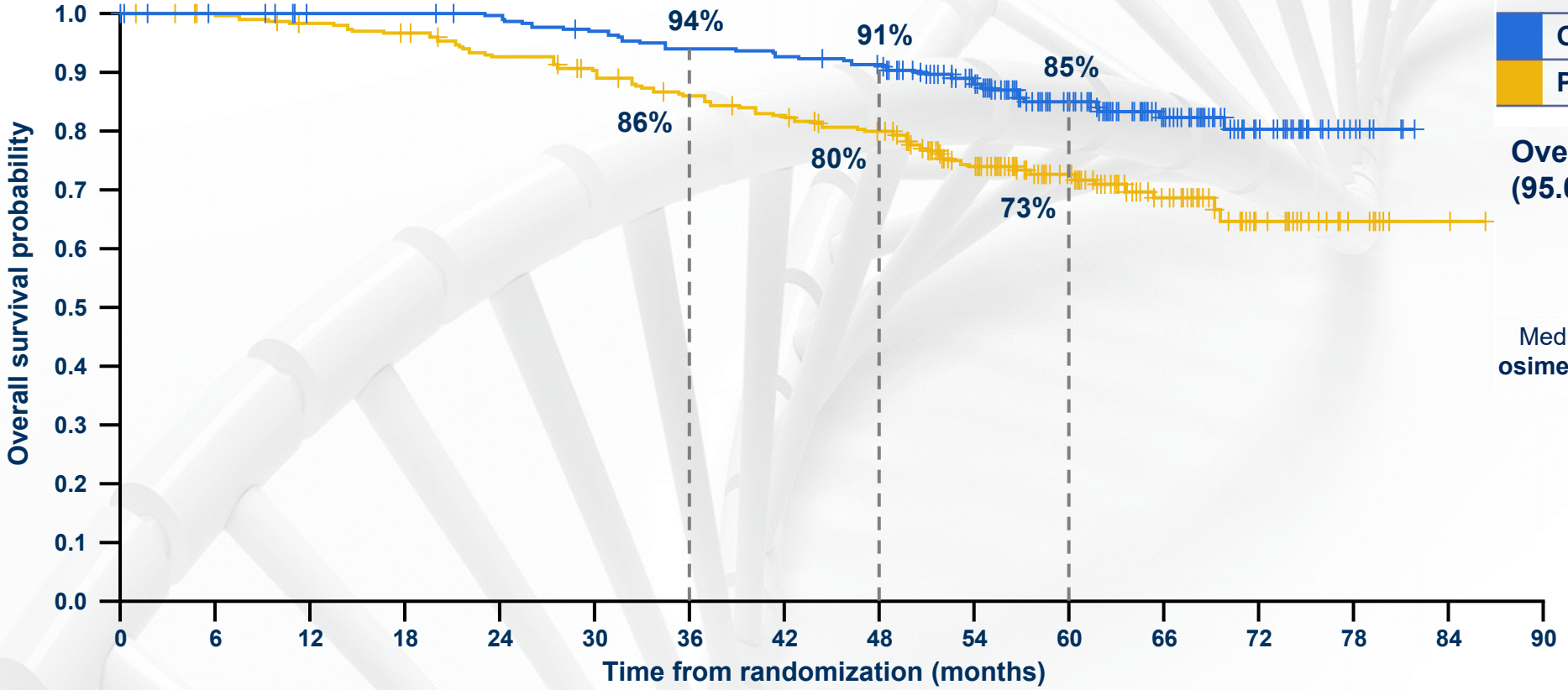
Follow-up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

Herbst R et al, ASCO 2023.

OVERALL SURVIVAL: PATIENTS WITH STAGE II / IIIA DISEASE

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the primary population of stage II–IIIA disease



5-year OS rate, % (95% CI)	
Osimertinib (n=233)	85 (79, 89)
Placebo (n=237)	73 (66, 78)

Overall OS HR (95.03% CI) **0.49 (0.33, 0.73); p=0.0004**

Maturity: 21%
osimertinib 15%, placebo 27%

Median follow-up for OS* (censored patients):
osimertinib 61.7 months, placebo 60.4 months

No. at risk

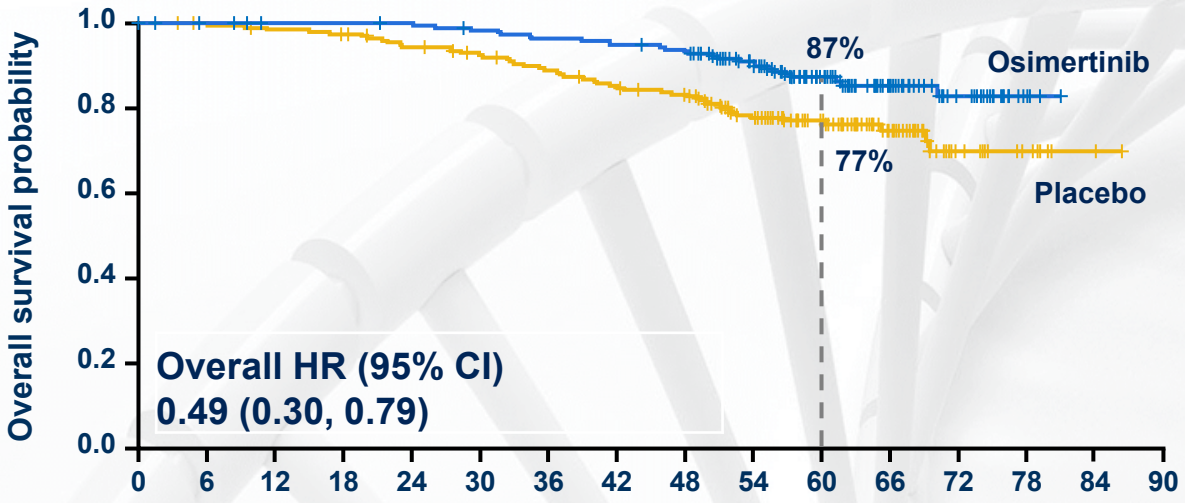
Osimertinib	233	229	224	224	221	214	208	205	200	170	115	69	33	9	0	-
Placebo	237	232	226	221	210	202	190	182	171	138	94	53	25	8	2	0

Herbst R et al, ASCO 2023.

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 59.9 months, placebo 56.2 months.

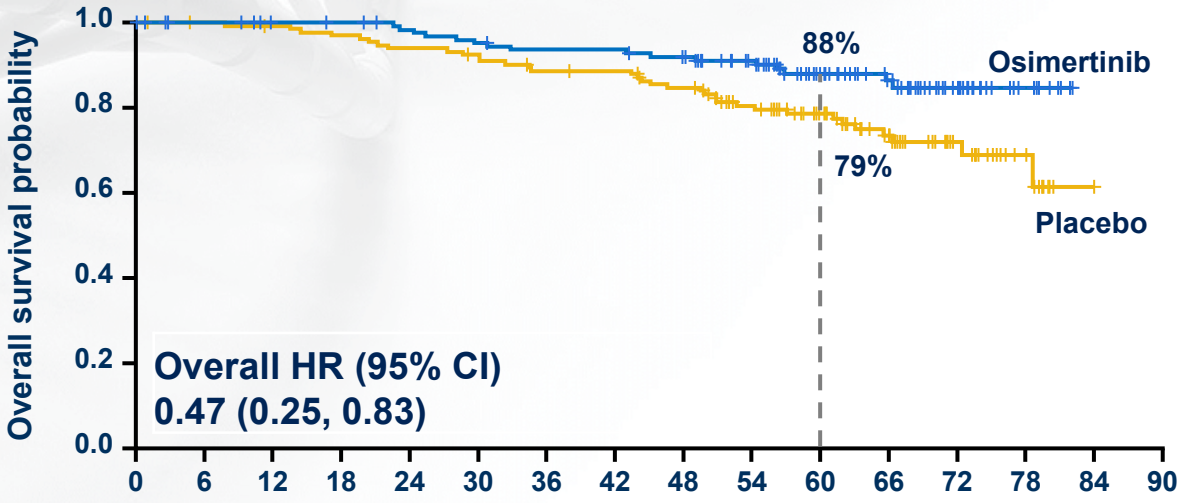
OS in patients with and without adjuvant chemotherapy: patients with stage IB / II / IIIA disease

With adjuvant chemotherapy



No. at risk																
Osimertinib	203	200	197	197	196	192	188	185	182	155	104	58	25	7	0	-
Placebo	207	204	200	197	189	182	174	166	159	133	92	48	19	7	2	0

Without adjuvant chemotherapy



No. at risk																
Osimertinib	136	132	128	127	123	119	116	116	112	97	72	50	25	8	0	-
Placebo	136	134	132	129	125	122	116	115	108	90	72	49	25	10	1	0

Herbst R et al, ASCO 2023.

Data cut-off: January 27, 2023.
Overall population: stage IB / II / IIIA. Tick marks indicate censored data.
Use of adjuvant chemotherapy before randomization was allowed but not mandatory; decided by the physician and patient before enrollment.

MECHANISM-BASED NOVEL APPROACHES TO OVERCOME RESISTANCE

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Proposed Management Approach for Advanced *EGFR*+ NSCLC Progressing on Osimertinib

Progression on Osimertinib Suspected?

- **Obtain brain MRI and chest/abdomen/pelvis CT**
- **Radiographic progression confirmed:** Consider whether special circumstances are present → → →
- **Obtain tissue biopsy of progressing lesion and submit for biomarker testing:** Consider liquid biopsy if tissue biopsy not feasible, but less sensitive for fusions/transformations

Special Circumstances at Progression

- **Oligometastatic**: Continue tx with addition of local ablative tx
- **Slow and/or asymptomatic**: Continue tx beyond progression
- **CNS only**: If limited, continue tx with addition of local ablative tx; if diffuse, transition to CNS-penetrant systemic tx

Bypass Pathways

MET Amplification

- Clinical trial of combined EGFR/MET inhibition
- Osimertinib + MET inhibitor (eg, crizotinib, tepotinib, capmatinib)*

Fusions

- Clinical trial
- *RET:* osimertinib + RET inhibitor (eg, pralsetinib, selpercatinib)*
- *ALK*: osimertinib + ALK TKI*
- *ROS1:* osimertinib + ROS TKI*

Histologic Transformation

- *If SCLC:* clinical trial or platinum/etoposide
  - Role of chemo/IO unknown
- *If squamous:* clinical trial or histology-appropriate platinum doublet chemotherapy

EGFR C797S

- Clinical trial
- Consider 1st- or 2nd-gen EGFR TKI†
- Atezolizumab + carboplatin/paclitaxel + bevacizumab‡

Unknown Mechanism

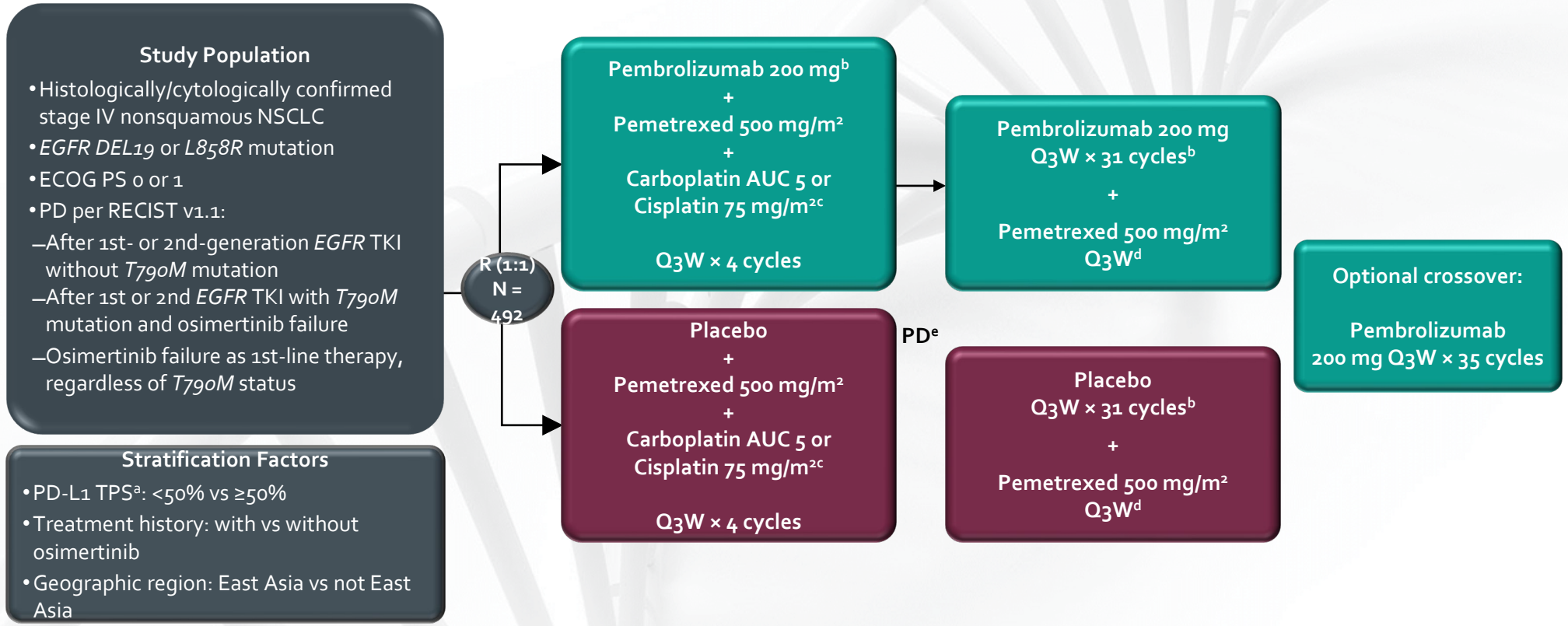
- Clinical trial
- Platinum doublet CT
  - If CNS stable, continue osimertinib (limited data)
- Atezolizumab + carboplatin/paclitaxel + bevacizumab)‡

Piper-Vallillo. JCO. 2020;[Epub].

*Off label/compassionate use. †Erlotinib, gefitinib, afatinib, dacomitinib.
‡IMpower150 regimen; safety concerns regarding future TKI use.

Slide credit: clinicaloptions.com

KEYNOTE-789 (PHASE III): PEMETREXED/PLATINUM ± PEMBROLIZUMAB FOR TKI-RESISTANT, *EGFR*-MUTATED, METASTATIC NSQ NSCLC



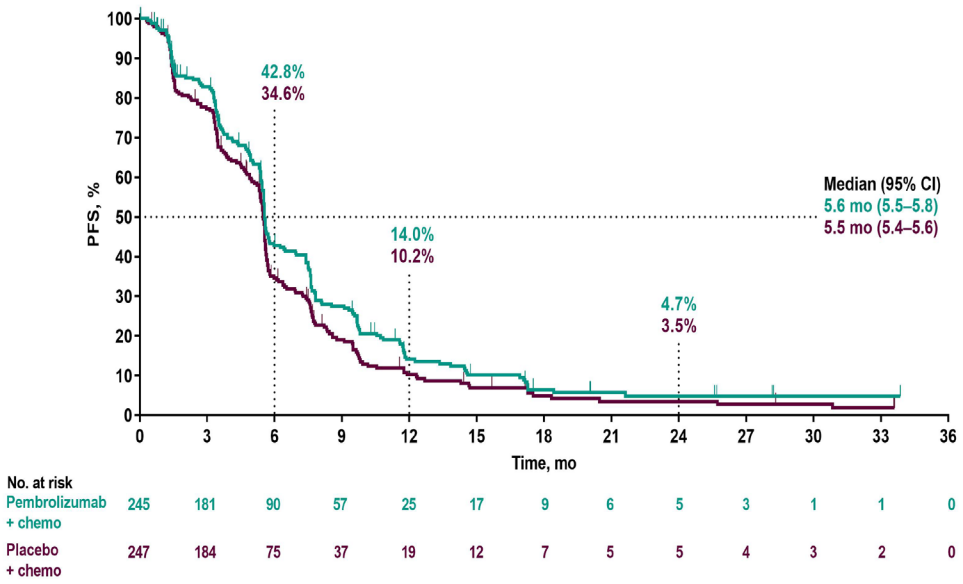
End Points

- **Dual Primary:** PFS per RECIST v1.1 by BICR and OS
- **Secondary:** ORR and DOR per RECIST v1.1 by BICR, safety, and patient-reported outcomes

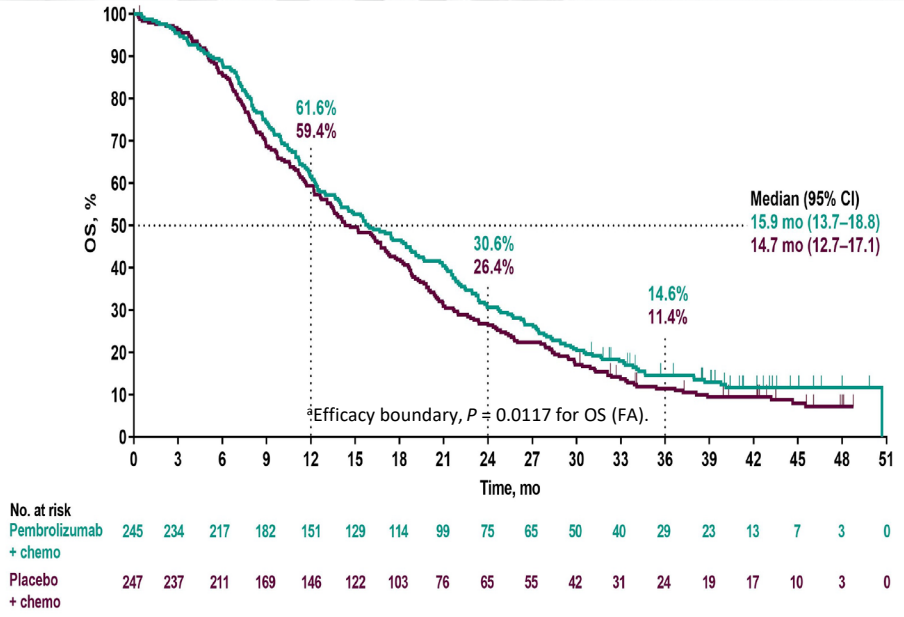
Chih-Hsin Yang J, et al. ASCO 2023. Abstract LBA9000.

NEGATIVE OUTCOME IN PFS AND OS RESPECTIVELY: TINY BENEFIT

PFS



OS



	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	198 (80.8)	0.80 (0.65–0.97)	0.0122
Placebo + chemo	214 (86.6)		

	Events, n (%)	HR (95% CI)	*P* value[a]
Pembrolizumab + chemo	214 (87.3)	0.84 (0.69–1.02)	0.0362
Placebo + chemo	224 (90.7)		

Chih-Hsin Yang J, et al. ASCO 2023. Abstract LBA9000.

4TH GENERATION TKI THERAPY

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SYMPHONY (PHASE 1/2): BLU-945 ± OSIMERTINIB IN PREVIOUSLY TREATED PATIENTS WITH ADVANCED *EGFR*-MUTANT NSCLC

Key eligibility criteria

- Adults with metastatic *EGFR*m NSCLC
- No other known oncogenic tumor drivers
- ECOG status 0-1
- Prior treatment with ≥1 EGFR TKI with activity against T790M; progression on osimertinib as last therapy (part 1B only)

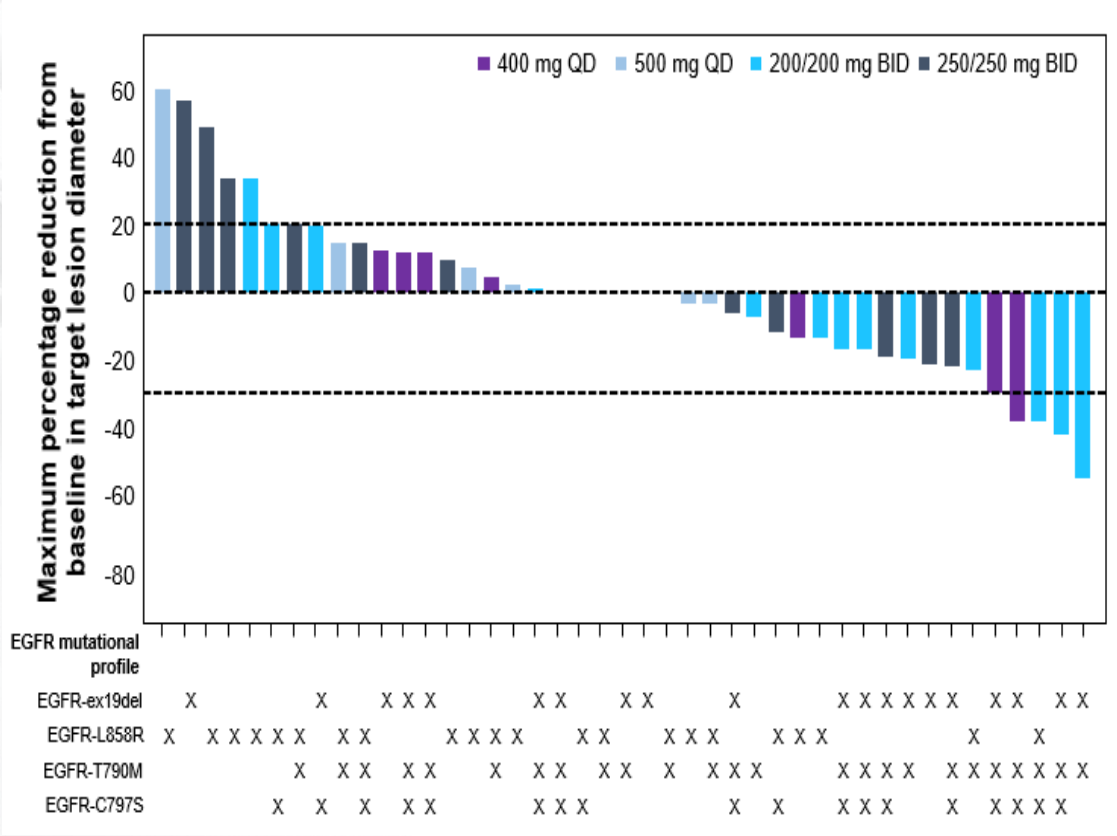
Phase 1 (dose escalation)

Part 1A (N=112)
BLU-945 monotherapy
BOIN design
Starting dose: 25 mg QD[a]
Initiated May 2021

Part 1B (N=55)
BLU-945 + osimertinib (80 mg)
Starting dose:
BLU-945 200 mg QD[a]
Initiated June 2022

All combination patients received osimertinib as last line of therapy without a washout period

Primary endpoints
MTD, RP2D, safety



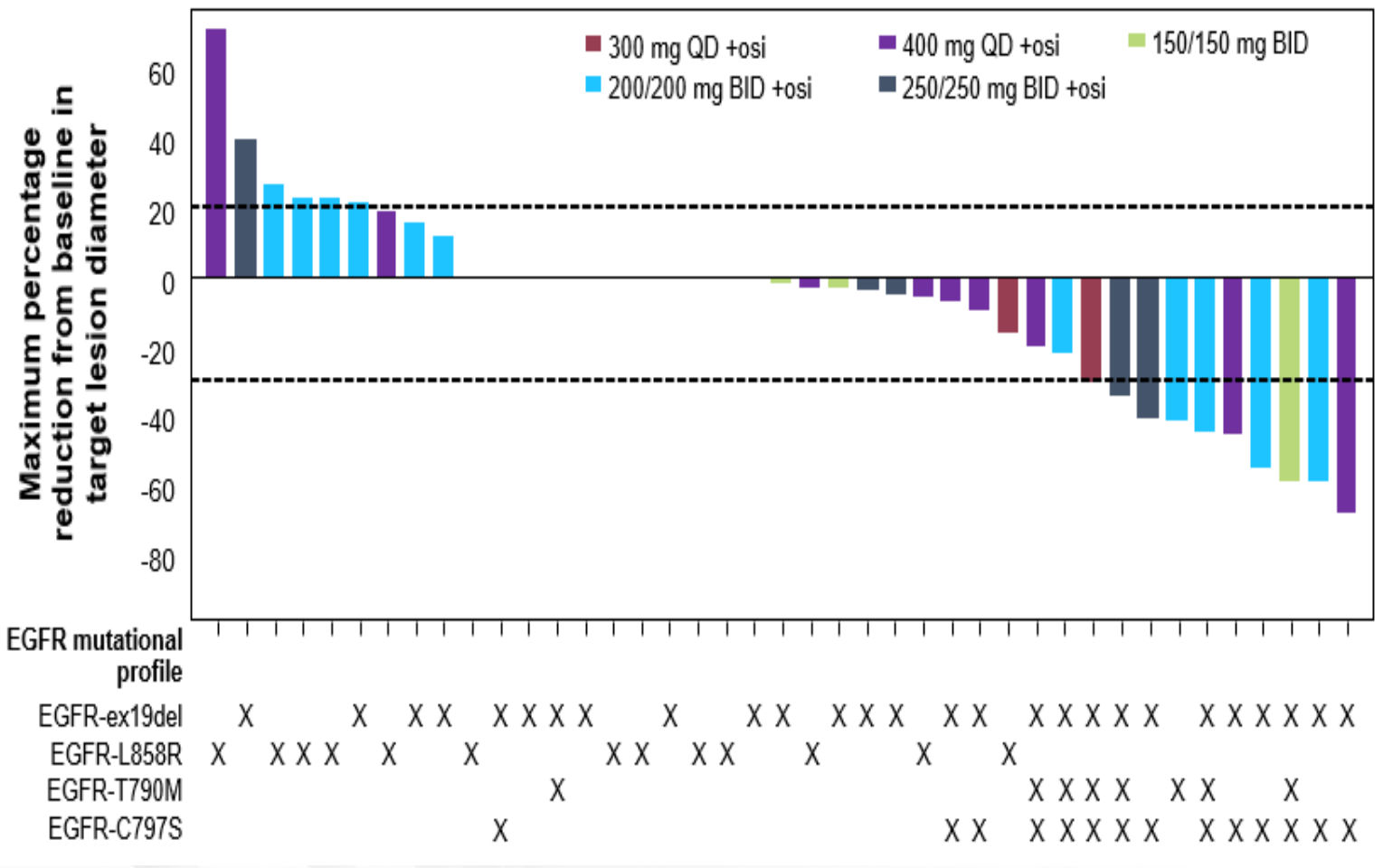
- Patients were heavily pretreated
- 94% of monotherapy and 89% of combination patients had an additional *EGFR* and/or detectable additional genetic alteration

4/18 pts with C797S responded

Elamin YY et al, ASCO 2023.

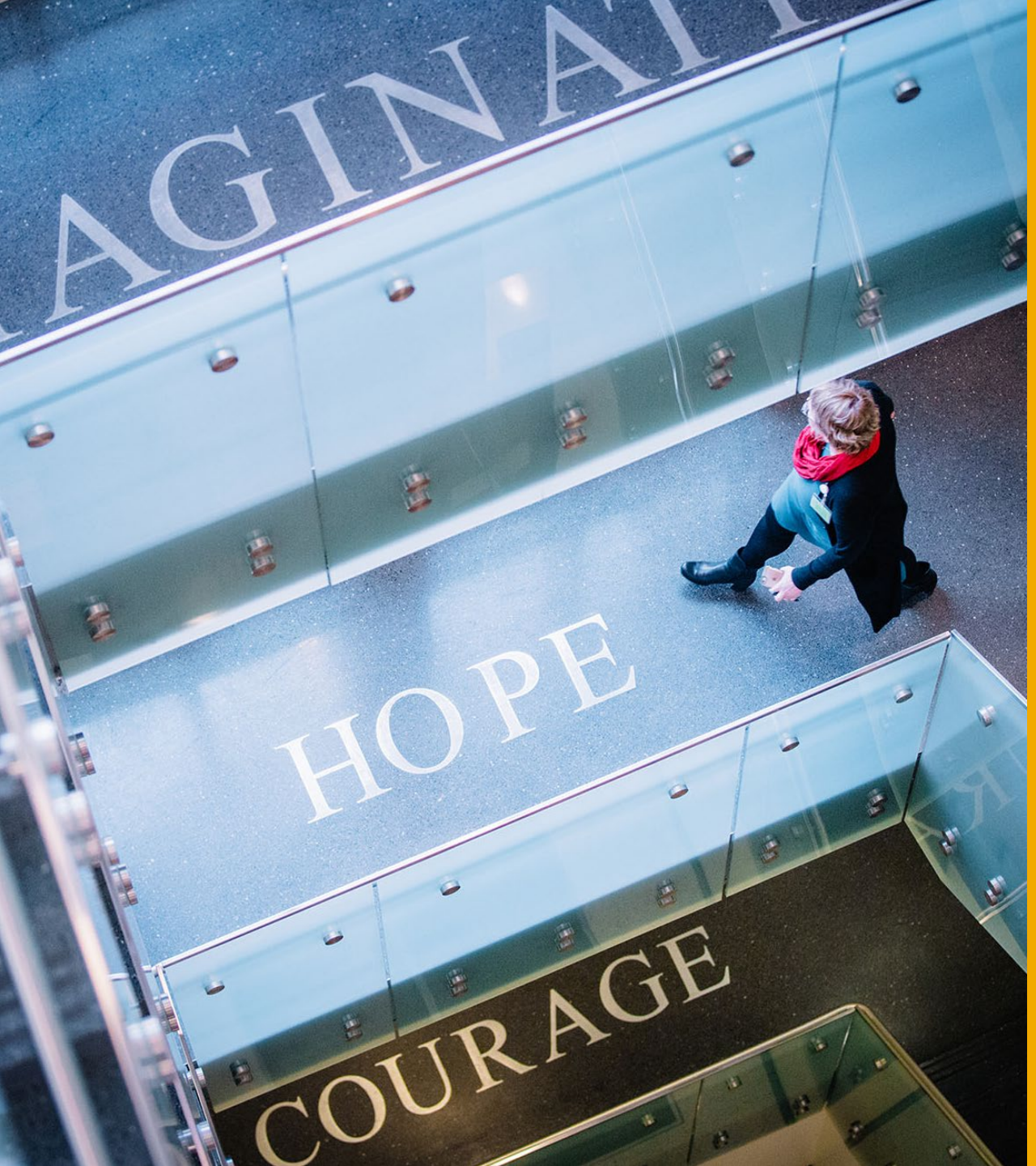
Elamin YY, et al. ASCO 2023. Abstract 9011.

OSIMERTINIB + BLU-945



8/14 pts responded

Elamin YY et al, ASCO 2023.



OTHER NOVEL APPROACHES

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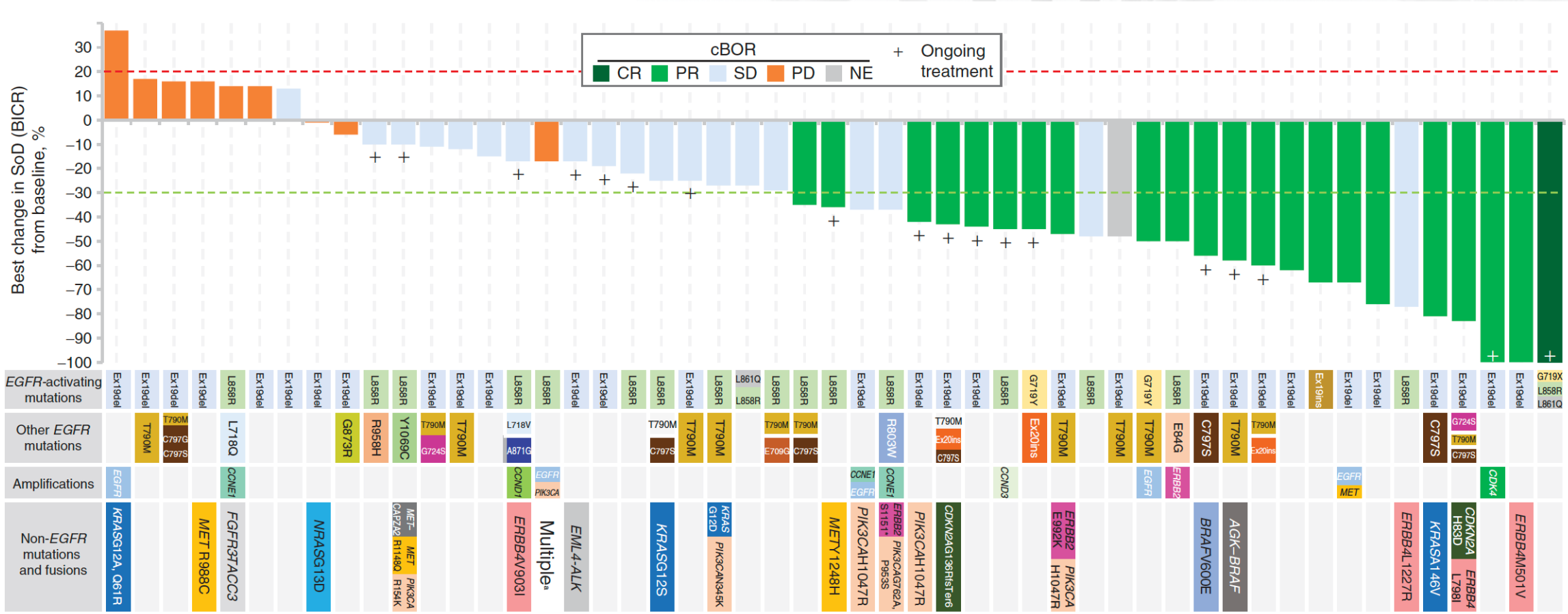
Efficacy and Safety of Patritumab Deruxtecan (HER3-DXd) in EGFR Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer

Pasi A. Jänne[1], Christina Baik[2], Wu-Chou Su[3], Melissa L. Johnson[4], Hidetoshi Hayashi[5], Makoto Nishio[6], Dong-Wan Kim[7], Marianna Koczywas[8], Kathryn A. Gold[9], Conor E. Steuer[10], Haruyasu Murakami[11], James Chih-Hsin Yang[12], Sang-We Kim[13], Michele Vigliotti[14], Rong Shi[14], Zhenhao Qi[14], Yang Qiu[14], Lihui Zhao[14], David Sternberg[14], Channing Yu[14], and Helena A. Yu[15]

Cancer Discovery, 2022.

PATRITUMAB DERUXTECAN: EFFICACY IN EGFR MT NSCLC



Janne P et al, Cancer Discovery, 2022.

EGFR EXON 20 INSERTION

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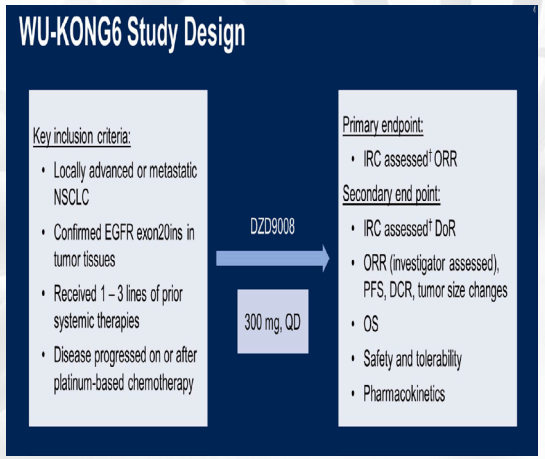
SUNVOZERTINIB FOR EGFR EXON 20 INSERTION

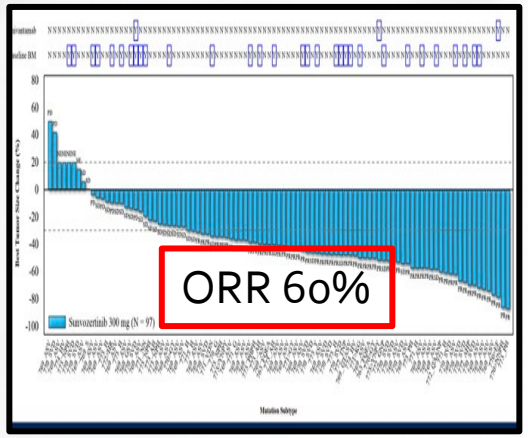
WU-KONG6. Pretreated patients[1]

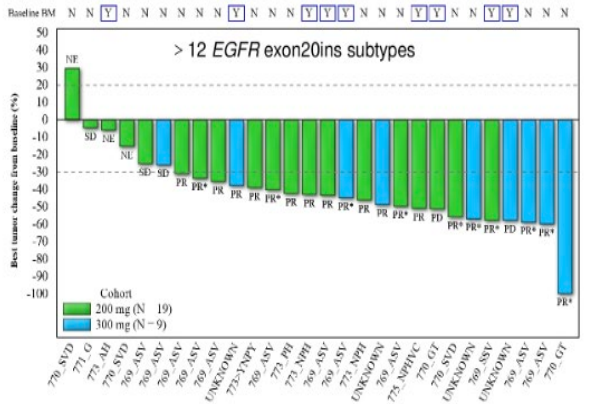
- N 97, brain mets 32%, median prior line 2
- ORR 61% , mDOR 7 m
- Toxicity: diarrhea (67%, G3 7%), CPK increase (57%, G3 17%), and rash.

FIRST LINE[2]

- N 28, brain mets 32%
- ORR 71% (confirmed 36%)
- Toxicity: diarrhea G3 3.6%, CPK increase (G3 14%), rash G3 3% and lipase increase G3 3%.





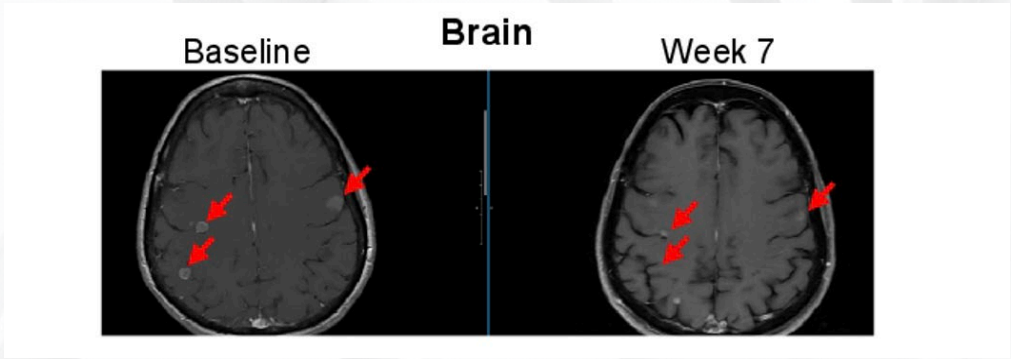


ORR 71,4% (confirmed 35.7%)

[1]Wang M. ASCO 2023, [2] Xu Yan Poster 9073, ASCO2023

BLU-451 PHASE 1 IN ADVANCED NSCLC EGFR EXON 20 INS.

- Oral EGFR TKI
- Phase 1/2 CONCERTO trial *(Nguyen D, ASCO 2023)*
- 48 EGFR Exon 20 ins patients
  - Median number of prior lines 3
  - Baseline brain mets 58%
  - 75% prior EGFR Ex20ins targeted therapy
- TRAEs 69.5%, mostly grade 1-2; no grade 3 diarrhea 0 rash
- Promising activity even in brain mets



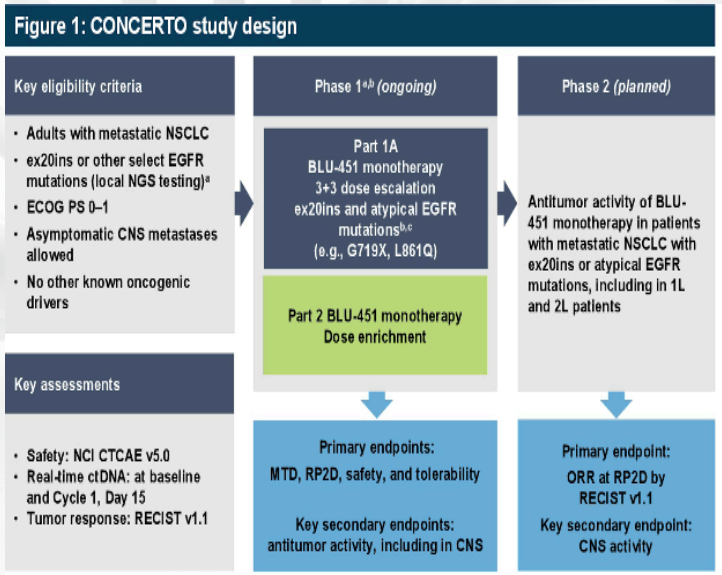
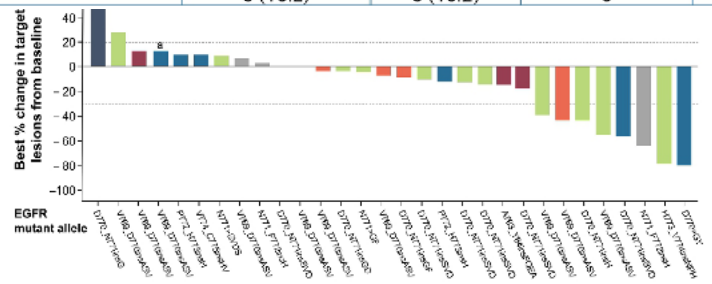


Table 2: Treatment-related adverse events reported in ≥10% of patients in the overall safety population (N=59)

Preferred term, n (%)	Treatment-related adverse events			
	All grade	Grade 1	Grade 2	Grade ≥3
Any adverse event	41 (69.5)	26 (44.1)	12 (20.3)	3 (5.1)
Rash	13 (22.0)	11 (18.6)	2 (3.4)	0
Dermatitis acneiform	9 (15.3)	9 (15.3)	0	0
Fatigue	8 (13.6)	7 (11.9)	1 (1.7)	0
Diarrhea	7 (11.9)	7 (11.9)	0	0
Dry skin	6 (10.2)	6 (10.2)	0	0
Pruritus	6 (10.2)	6 (10.2)	0	0

ORR



ALK POSITIVE NSCLC

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PREFERRED FIRST-LINE ALK INHIBITORS

Study *(ref)*	Treatment	n	RR (%)	PFS (inv, m)	PFS HR
ALEX *Mok, Ann Oncol 2018*	Alectinib 600mg bid Crizotinib 250mg bid	152 151	82.9 75.5	34.8 10.9	0.43 (0.32-0.58)
ALTA 1L *Camidge, JTO 2021*	Brigatinib 180mg qday Crizotinib 250mg bid	137 138	74 62	30.8 9.2	0.43 (0.31-0.58)
CROWN *Solomon, Lancet Respir 2023*	Lorlatinib 100mg qday Crizotinib 250mg bid	149 147	77.2 58.5	NR 9.1	0.19 (0.13-0.27)

SELECTION OF INITIAL ALK THERAPY

Alectinib, brigatinib, lorlatinib

Efficacy

- Rapid, deep, durable responses, intracranial control
  - Lorlatinib with longest first-line PFS

Toxicity

- Different adverse event profiles

Non-clinical factors

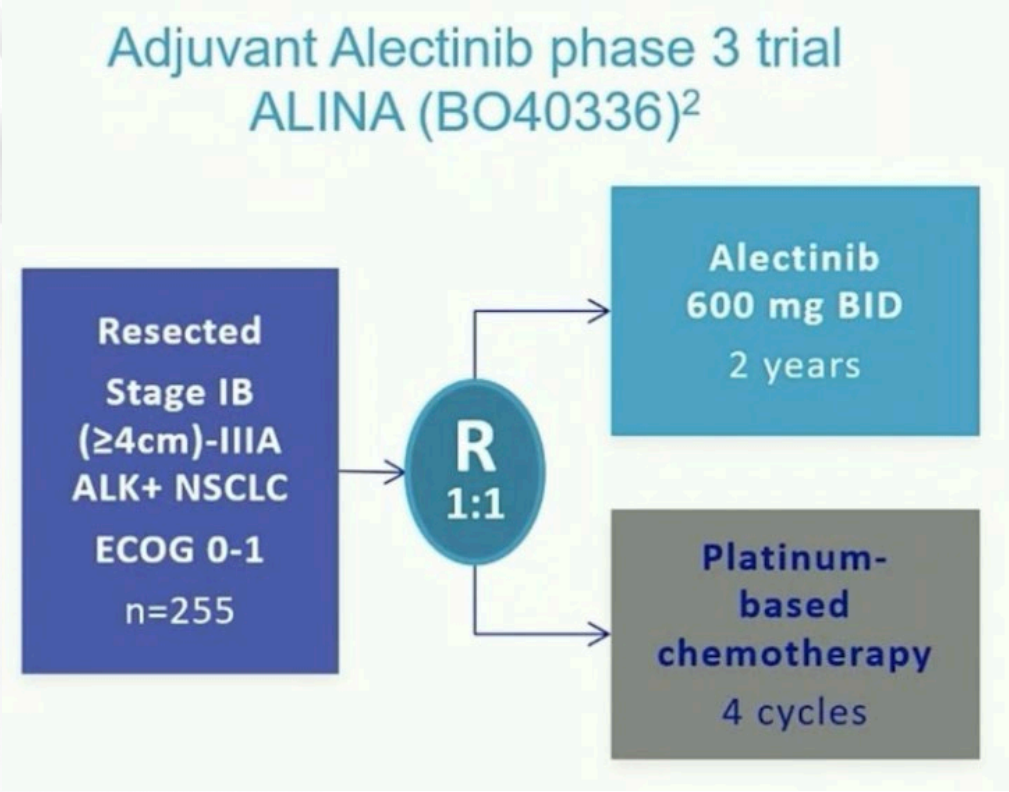
- Comfort, experience
- Access, cost, pill burden

ADJUVANT ALK INHIBITION?

ALINA

- Phase III trial
- Resected ALK+ NSCLC
- Alectinib vs chemotherapy

Based on ADAURA, is it time to offer adjuvant ALK therapy?



Johnson, ELCC 2023

BRAF V600E MUTATION

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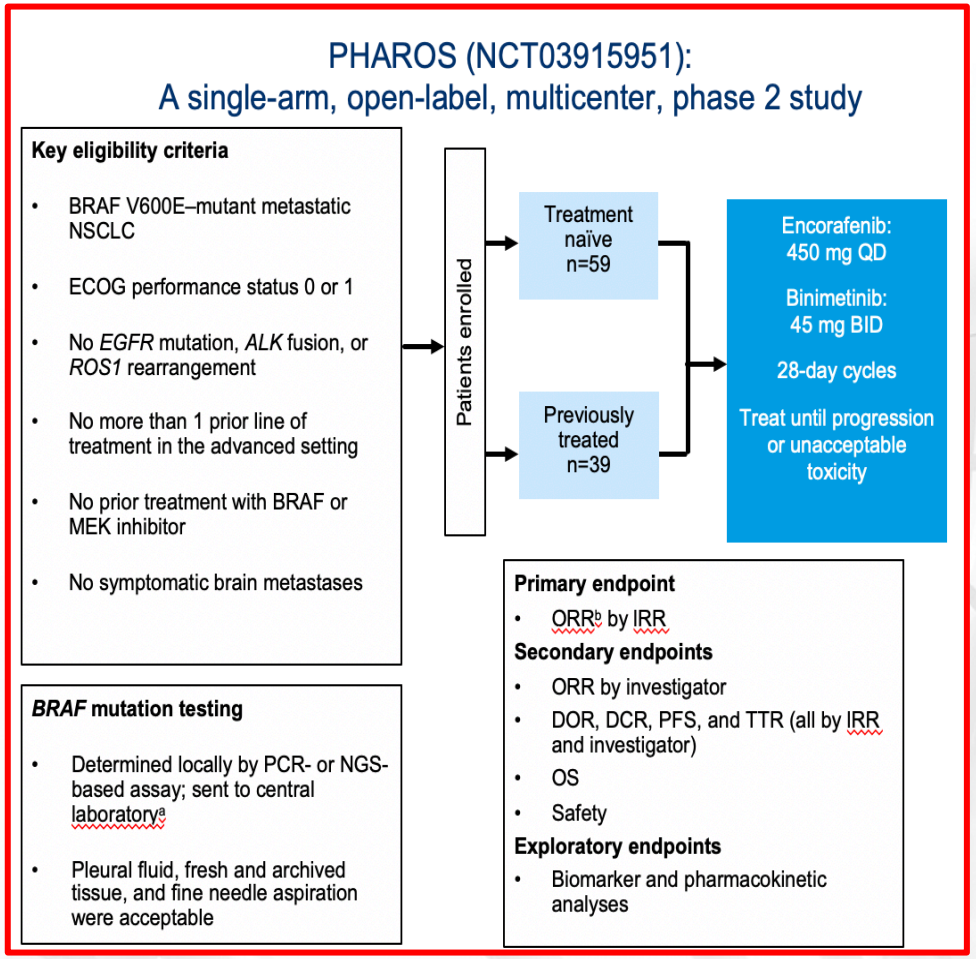
ENCORAFENIB PLUS BINIMETINIB IN BRAF V600E-MUTANT METASTATIC NSCLC

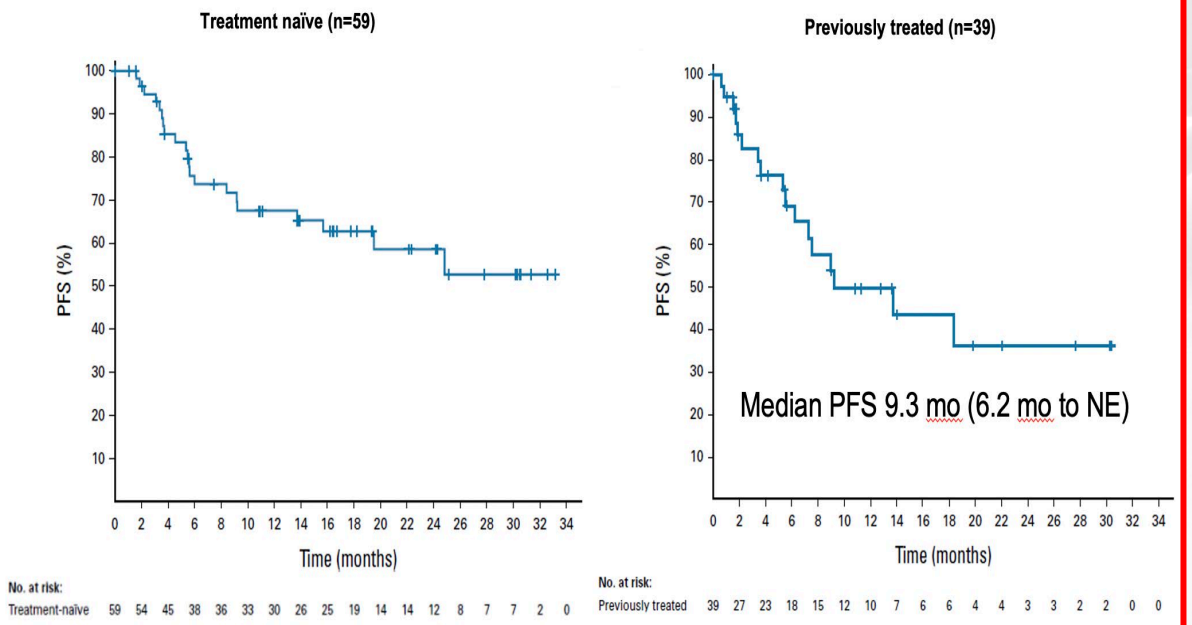


	Treatment naïve (n=59)	Previously treated (n=39)
Objective response rate (95% CI), %[a]	75 (62, 85)	46 (30, 63)
Complete response	9 (15)	4 (10)
Partial response	35 (59)	14 (36)
Stable disease	10 (17)	13 (33)
Progressive disease	2 (3)	3 (8)
Disease control rate at 24 weeks (95% CI), %	64 (51, 76)	41 (26, 58)
Duration of response, median (95% CI), months	NE (23.1, NE)	16.7 (7.4, NE)
Duration of response ≥12 months, n/N (%)	26/44 (59)	6/18 (33)
Time to response, median (range), months	1.9 (1.1-19.1)	1.7 (1.2-7.3)
PFS, months, median (95% CI)	NE (15.7 to NE)	9.3 (6.2 to NE)

Riely G et al, ASCO 2023, JCO 2023

ENCORAFENIB PLUS BINIMETINIB IN BRAF V600E-MUTANT METASTATIC NSCLC

Progression-free survival by IRR



- The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4, 22.3 months) in treatment-naïve patients and 12.8 months (95% CI, 9.0, 19.8 months) in previously treated patients

Incidence of TRAEs of any grade >10% in all patients

	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Riely G et al, ASCO 2023, JCO 2023

Dabrafenib plus Trametinib *vs* Encorafenib plus Binimetinib in *BRAF* ^{V600E} NSCLC : Efficacy

	Dabrafenib/trametinib		Encorafenib/binimetinib	
Study	Single arm phase II		Single arm phase II	
Pts	Treatment naive	Previously treated	Treatment naive	Previously treated
No of Pts	36	57	59	39
Med age	67	64	68	71
Never smoker	28%	28%	31%	28%
Evaluation	Investigator-assess	Investigator-assess	BICR	BICR
Median follow-up	5 yrs	5 yrs	18.2m	12.8m
ORR	64%	68%	75%	46%
DOR	10.2m	9.8m	NE	16.7m
mPFS	10.8m	10.2m	NE	9.3m
OS	17.3m	18.2m	NA	NA

* Due to no head to head comparison, interpretation should be cautious

2023 ASCO ANNUAL MEETING #ASCO23

PRESENTED BY: Myung-Ju Ahn, M.D. Samsung Medical Center

Planchard et al JTO 2022
Reilly et al ASCO 2023

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KNOWLEDGE CONQUERS CANCER

KRAS G12C MUTATION

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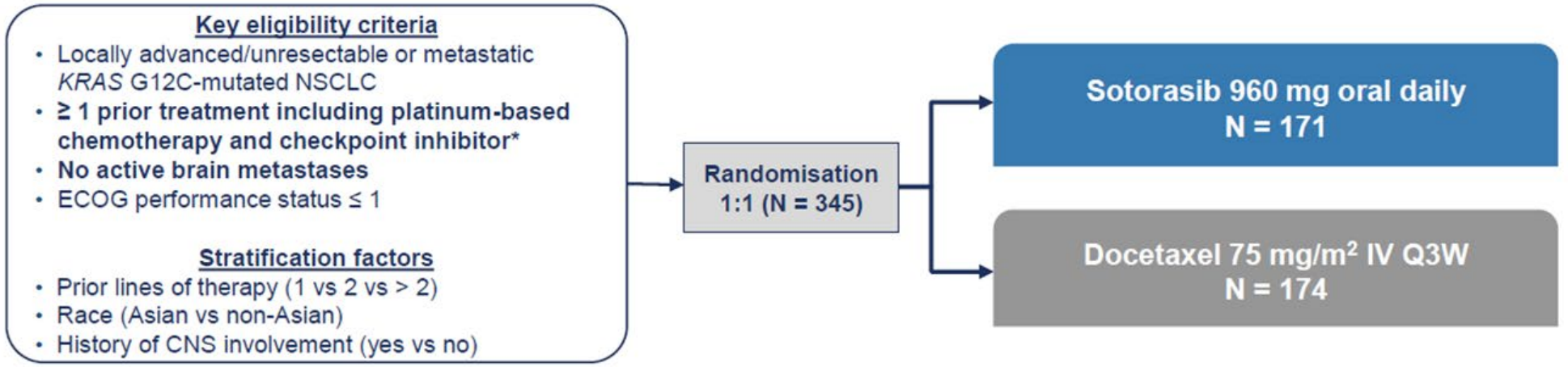
CodeBreaK 200 Phase 3 Study Design



Primary Endpoint: PFS by BICR

Secondary Endpoints: Efficacy (OS†, ORR, DOR, TTR, DCR)**, safety/tolerability, PRO**

ITT population analysis included all randomised patients

Per regulatory guidance, protocol was amended to reduce planned enrolment from 650 to ~330 patients, and crossover from docetaxel to sotorasib was permitted.

Enrollment period: June 4, 2020 to April 26, 2021; protocol amendment: February 15, 2021; data cutoff: August 2, 2022.

NCT04303780; EudraCT: 2019-003582-18.

*Treatment with chemotherapy and checkpoint inhibitor could be concurrent or sequential; patients with medical contraindication to these therapies could be included with approval.

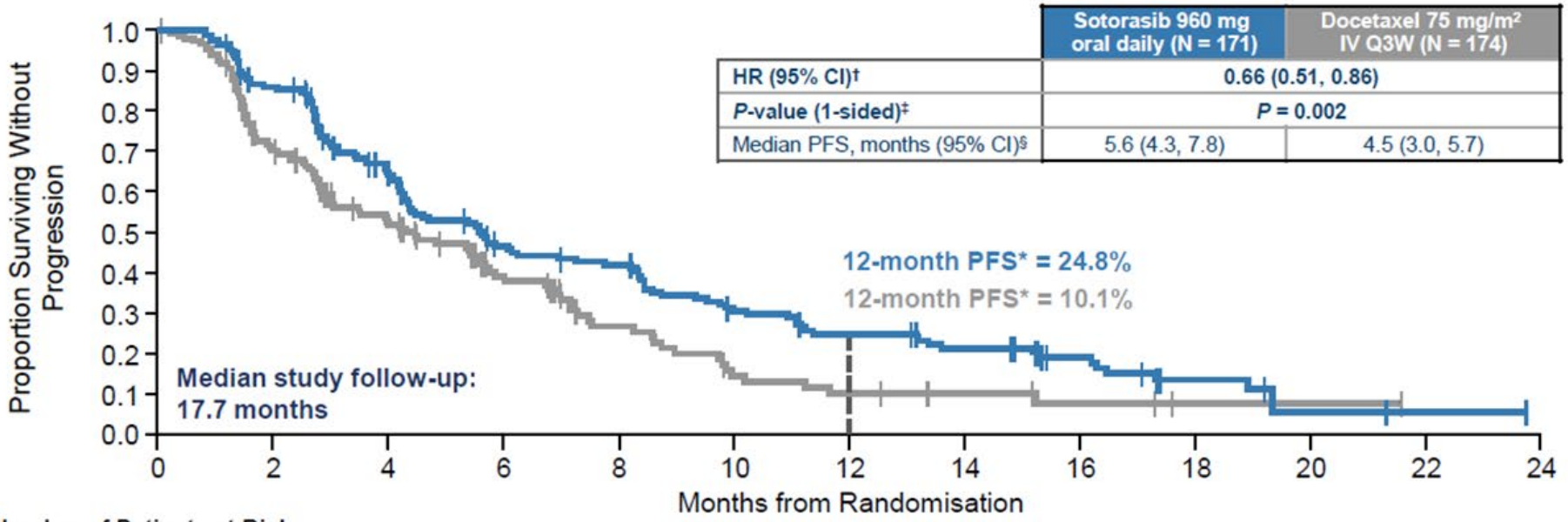
†Analysis of OS planned if PFS was found to be statistically significant and when at least 198 OS events have been reached.

PARIS 2022 ESMO congress

Melissa L. Johnson, MD
Twitter: @MLJohnsonMD2

Primary Endpoint: PFS by BICR

	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
HR (95% CI)†	0.66 (0.51, 0.86)	
P-value (1-sided)‡	*P* = 0.002	
Median PFS, months (95% CI)§	5.6 (4.3, 7.8)	4.5 (3.0, 5.7)



Number of Patients at Risk:

Sotorasib	171	139	93	63	56	38	30	24	14	6	2	1	0
Docetaxel	174	93	62	36	20	10	7	5	3	1	1	0	

CodeBreaK 200 met its primary endpoint with sotorasib demonstrating superior PFS over docetaxel (HR 0.66, *P* = 0.002); 12-month PFS rate was 24.8% for sotorasib and 10.1% for docetaxel

*PFS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model.
‡*P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.

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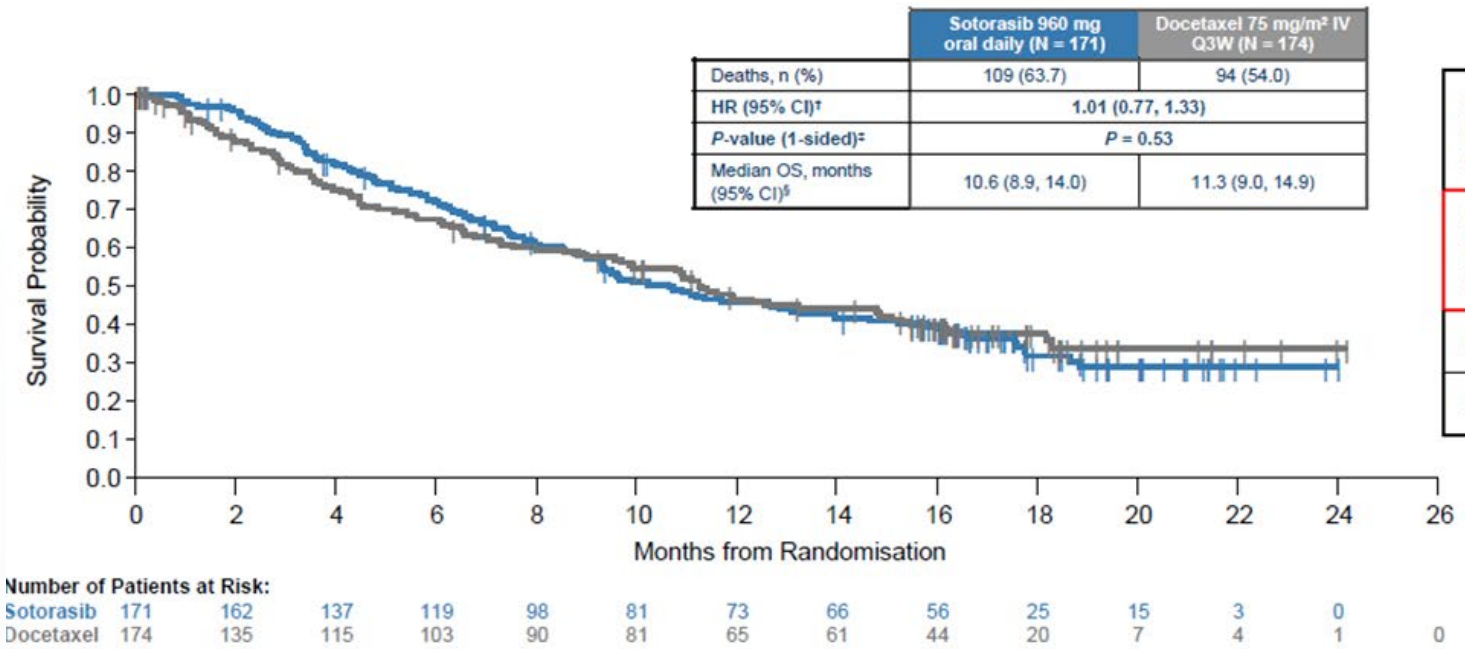
OS: Sotorasib vs Docetaxel*



	Sotorasib 960 mg oral daily (N = 171)	Docetaxel 75 mg/m² IV Q3W (N = 174)
Deaths, n (%)	109 (63.7)	94 (54.0)
HR (95% CI)†	1.01 (0.77, 1.33)	
P-value (1-sided)‡	*P* = 0.53	
Median OS, months (95% CI)§	10.6 (8.9, 14.0)	11.3 (9.0, 14.9)

Number of Patients at Risk:

Sotorasib	171	162	137	119	98	81	73	66	56	25	15	3	0
Docetaxel	174	135	115	103	90	81	65	61	44	20	7	4	1	0

	Sotorasib	Docetaxel
Any subsequent treatment, including crossover**	36%	42%
Subsequent $KRAS^{G12C}$ inhibitor, including crossover	4%	34%
Subsequent chemo	21%	12%
Subsequent IO	9%	6%

*OS rates estimated using Kaplan-Meier method; ITT population.
†HR and 95% CIs estimated using a stratified Cox proportional hazards model
‡ *P*-value calculated using a stratified log-rank test.
§Medians estimated using Kaplan-Meier method; 95% CIs estimated using the method by Klein and Moeschberger with log-log transformation.
**Patients (16.4% in sotorasib arm, 5.2% in docetaxel arm) were treated beyond progression

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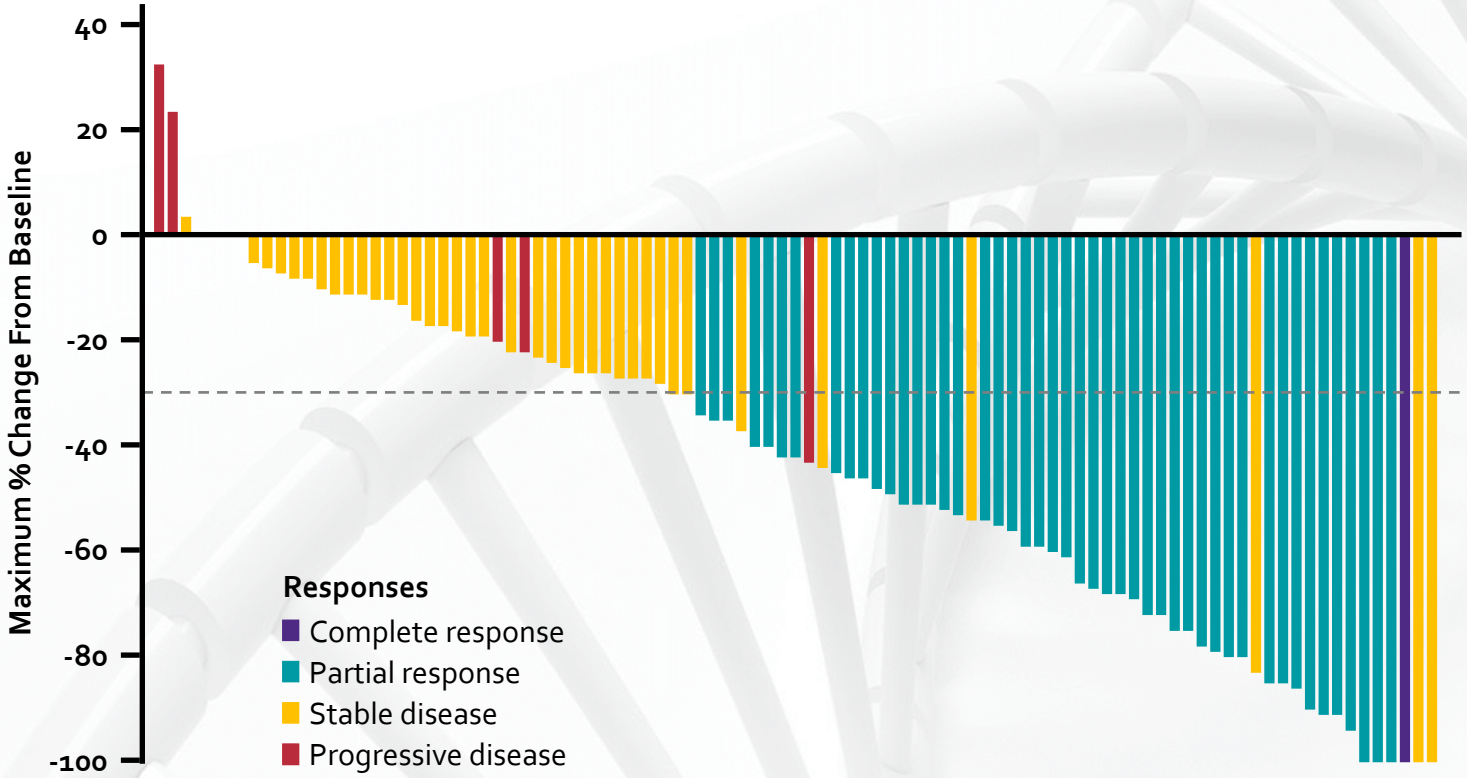
OVERALL RESPONSE RATE WITH ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED KRAS^{G12C}-MUTATED NSCLC



N – 112 patients

ORR: 43%

DCR: 80%

Data as of October 15, 2021. Median follow-up: 12.9 months. Based on BICR. (n=112) evaluable patients

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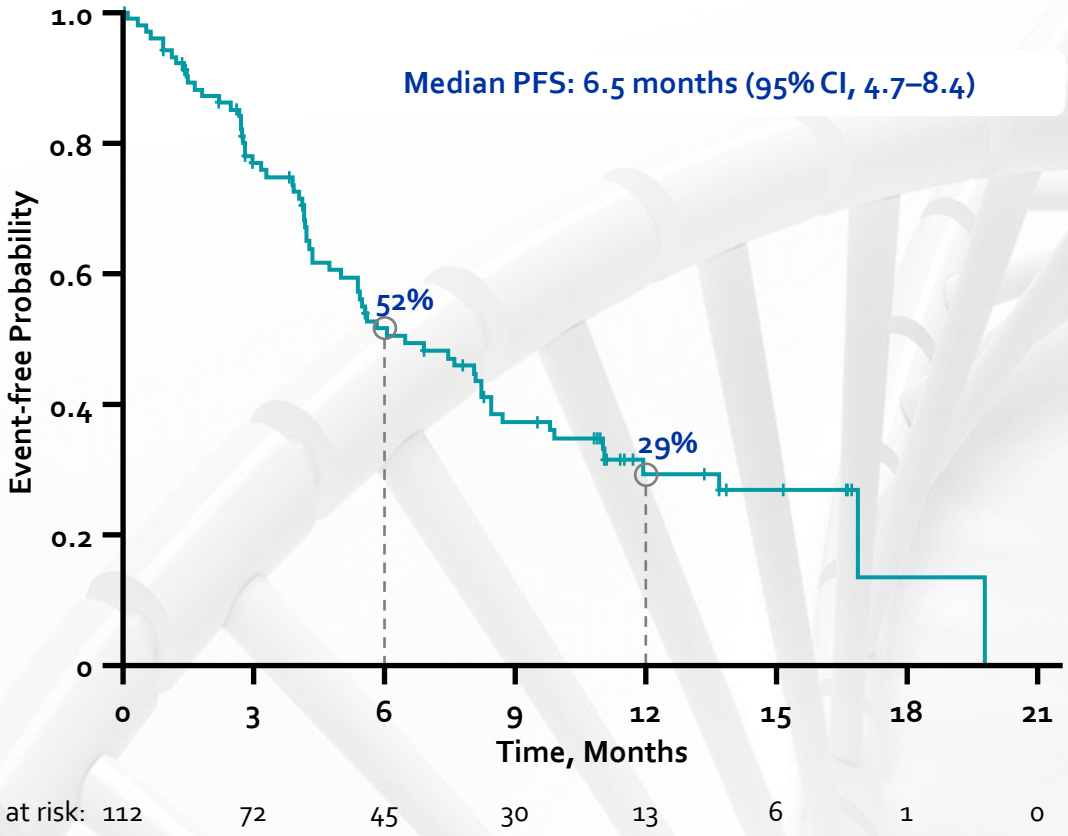
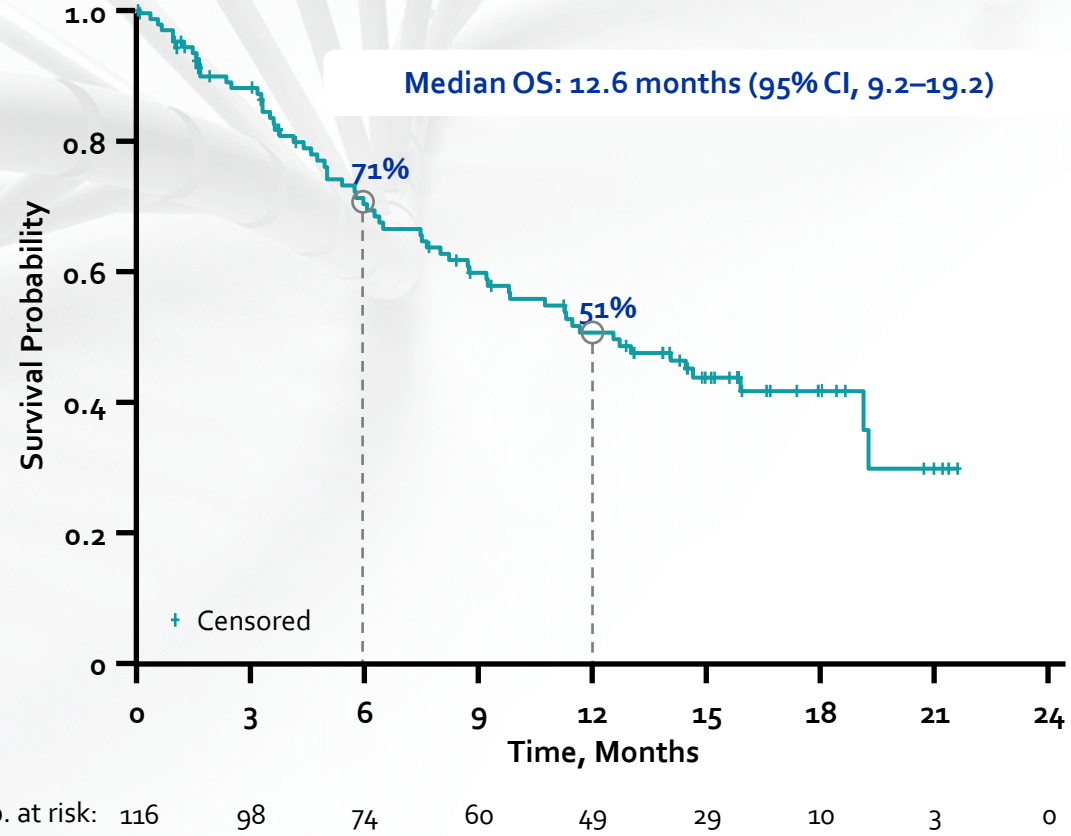
SURVIVAL OUTCOMES WITH ADAGRASIB IN PATIENTS WITH PREVIOUSLY TREATED KRAS^{G12C}-MUTATED NSCLC

Progression-Free Survival[a]



No. at risk:	112	72	45	30	13	6	1	0

Overall Survival[b]



No. at risk:	116	98	74	60	49	29	10	3	0

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OTHER APPROVED TARGETED THERAPIES IN NSCLC

Target	Approved Drugs
HER-2 mutation	Trastuzumab Deruxtecan
MET ex 14 skip mutation	Capmatinib Tepotinib
RET fusion	Selpercatinib Pralsetinib
NTRK fusion	Larotrectinib Entrectinib
ROS1 fusion	Crizotinib Entrectinib