Metastatic Targeted Therapy Updates

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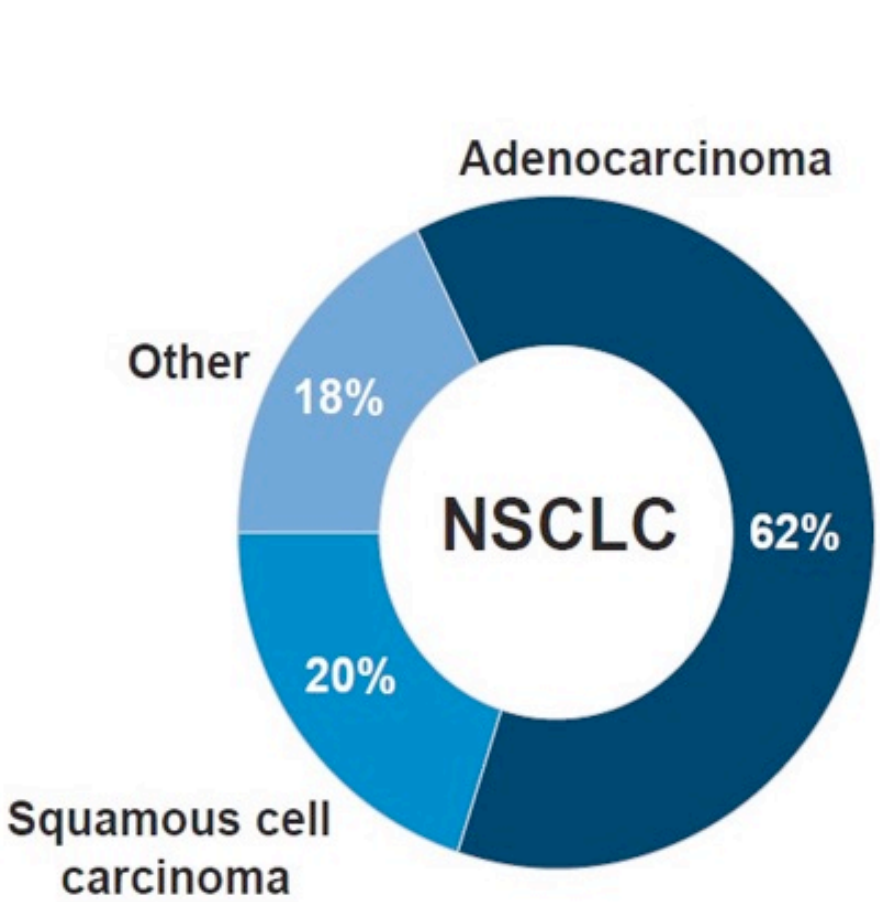
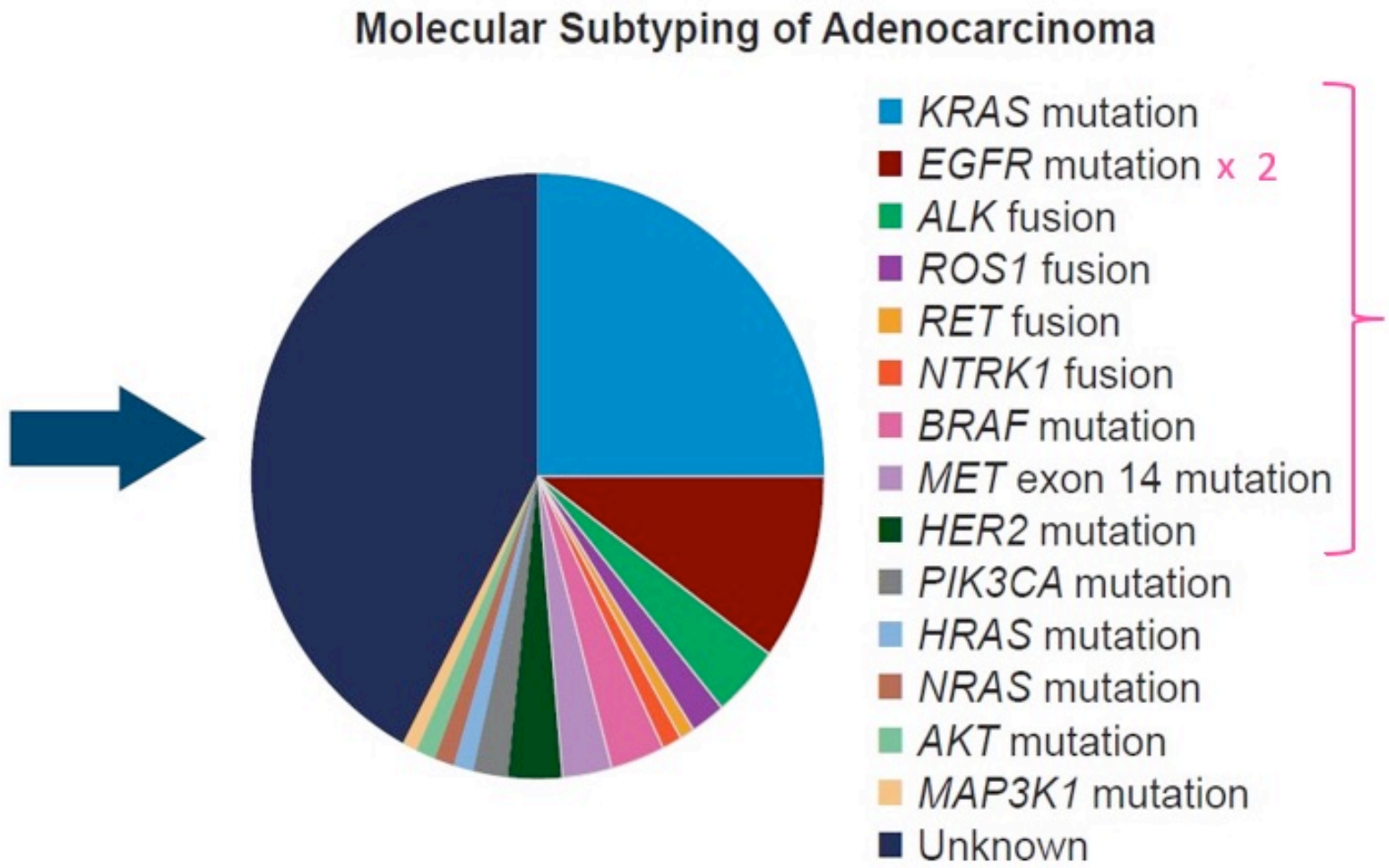
Targeted Therapy in NSCLC





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Targeted Therapy for Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC)

EGFR **Exon 19 Deletion or Exon 21 L858R**
- First-line therapy
  - Afatinib[1]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6]
  - Erlotinib + ramucirumab[7]
  - Erlotinib + bevacizumab[c] (nonsquamous)[8]
- Subsequent therapy
  - Osimertinib[9]

EGFR **S768I, L861Q, and/or G719X**
- First-line therapy
  - Afatinib[1,10]
  - Erlotinib[2]
  - Dacomitinib[3]
  - Gefitinib[4,5]
  - Osimertinib[6,11]
- Subsequent therapy
  - Osimertinib[9]

EGFR **Exon 20 Insertion Mutation**
- Subsequent therapy
  - Amivantamab-vmjw[12]
  - Mobocertinib[13]

KRAS **G12C Mutation**
- Subsequent therapy
  - Sotorasib[14]
  - Adagrasib[15]

ALK **Rearrangement**
- First-line therapy
  - Alectinib[16,17]
  - Brigatinib[18]
  - Ceritinib[19]
  - Crizotinib[16,20]
  - Lorlatinib[21]
- Subsequent therapy
  - Alectinib[22,23]
  - Brigatinib[24]
  - Ceritinib[25]
  - Lorlatinib[26]

ROS1 **Rearrangement**
- First-line therapy
  - Ceritinib[27,28]
  - Crizotinib[29]
  - Entrectinib[30]
- Subsequent therapy
  - Lorlatinib[31]
  - Entrectinib[30]

BRAF **V600E Mutation**
- First-line therapy
  - Dabrafenib/trametinib[32]
  - Dabrafenib[32]
  - Vemurafenib
- Subsequent therapy
  - Dabrafenib/trametinib[33,34]

NTRK1/2/3 **Gene Fusion**
- First-line/Subsequent therapy
  - Larotrectinib[35]
  - Entrectinib[36]

MET **Exon 14 Skipping Mutation**
- First-line therapy/Subsequent therapy
  - Capmatinib[37]
  - Crizotinib[38]
  - Tepotinib[39]

RET **Rearrangement**
- First-line therapy/Subsequent therapy
  - Selpercatinib[40]
  - Pralsetinib[41]
  - Cabozantinib[42,43]

ERBB2 (HER2) **Mutation**
- Subsequent therapy
  - Fam-trastuzumab deruxtecan-nxki[44]
  - Ado-trastuzumab emtansine[45]

NCCN version 3.2023, 04/13/2023

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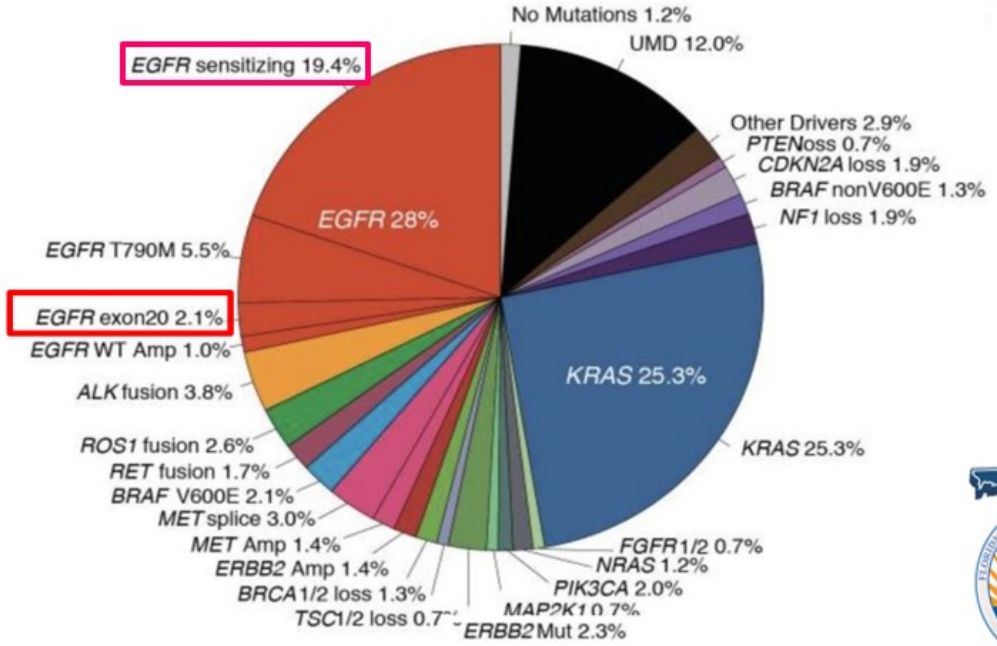
EGFR Pathway



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Lung Cancer Rapid Abstract Session
9011

BLU-945 monotherapy and in combination with osimertinib in previously treated patients with advanced *EGFR*-mutant NSCLC in the phase 1/2 SYMPHONY study

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SYMPHONY (NCT04862780) study design and patient characteristics

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

Characteristic	BLU-945	
	Monotherapy[b] (n=112)	Combination[c] (n=55)
Age, years, median (min, max)	63 (34, 84)	62 (28, 87)
Age group, n (%)		
<65 years	63 (56.3)	32 (58.2)
≥65 years	49 (43.8)	23 (41.8)
Female, n (%)	74 (66.1)	34 (61.8)
CNS metastases at baseline, n (%)	43 (38.4)	17 (30.9)
Prior LOT, median (min, max)	3.5 (1, 13)	2 (1, 7)

- Patients enrolled in the phase 1 dose escalation were heavily pretreated
- 94% of monotherapy and 89% of combination patients had an additional EGFR and/or detectable additional genetic alteration
- Combination dose escalation is ongoing

[a]BID dosing was also evaluated. [b]25–600 mg QD; 100–300 mg BID. [c]200–400 mg QD;100–200 mg BID with OSI 80 mg QD.
BID, twice daily; BOIN, Bayesian optimal interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ex19del, exon 19 deletion; LOT, line of therapy; MTD, maximum tolerated dose; QD, every day; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor.

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BLU-945 monotherapy was generally well tolerated

TRAEs, N=112		
TRAEs, n (%) Safety population	**Any grade**	**Grade ≥3[a]**
Any TRAE	86 (76.8)	37 (33.0)
EGFR-related TRAEs (all patients)		
Rash	11 (9.8)	0
Diarrhea	7 (6.3)	0
Dry skin	4 (3.6)	0
Paronychia	2 (1.8)	0
TRAEs in ≥25% of patients		
ALT	41 (36.6)	25 (22.3)
Nausea	38 (33.9)	3 (2.7)
AST	37 (33.0)	12 (10.7)
Headache	31 (27.7)	0
Vomiting	30 (26.8)	1 (>1)

- Majority of TRAEs were low grade (NCI CTCAE Grade 1–2)
- There were 12 patients with DLTs across 400 mg–600 mg total daily doses (QD and BID), with the most common DLTs being Grade 3 ALT and AST elevation
- EGFR-WT associated AEs were low grade and infrequent (<10%)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; DLT, dose limiting toxicity; EGFR, epidermal growth factor receptor; QD, once daily; TRAE, treatment-related adverse event; WT, wild type.
[a]Two patients (1.8%) experienced Grade 5 AE possibly related to BLU-945 as assessed by an investigator: pneumonitis at 300 mg BID and intracranial bleeding at 100 mg BID in a patient with suspected brain metastases.

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BLU-945 + osimertinib combination is well tolerated with limited EGFR WT AEs

TRAEs, (N=55)		
TRAEs, n (%) Safety population	**Any grade**	**Grade ≥3**
Any TRAEs	52 (94.5)	6 (10.9)
EGFR-associated TRAEs		
Diarrhea	16 (29.1)	0
Dry skin	9 (16.4)	0
Dermatitis acneiform	8 (14.5)	1 (1.8)
Paronychia	6 (10.9)	0
TRAEs in ≥10% of patients		
Headache	19 (34.5)	0
Nausea	19 (34.5)	0
Fatigue	12 (21.8)	1 (1.8)
Decreased appetite	7 (12.7)	0
Vomiting	6 (10.9)	0

- Exposure of BLU-945 and osimertinib when coadministered are comparable to PK data from BLU-945 given alone and published osimertinib data[1,2]
- EGFR-WT associated AEs were infrequent, and the majority were Grade 1
- Three patients had DLTs across 200 – 400 mg total daily doses
  - 100 mg BID + 80 mg osi, Grade 3 acute respiratory failure
  - 300 mg QD + 80 mg osi - Grade 4 pneumonitis
  - 400 mg QD + 80 mg osi- Grade 3 dermatitis acneiform
- Two patients (3.6%) discontinued due to TRAEs
- There were no treatment-related deaths
- Dose escalation is on-going with MTD/RP2D yet to be determined

AE, adverse event; BID, twice daily; DLT, dose limiting toxicity; EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; QD, once daily; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event; WT, wild type.

1. Brown K, et al. *Br J Clin Pharmacol.* 2017;83(6):1216-1226. **2.** Planchard D, et al. *Cancer Chemother Pharmacol.* 2016;77: 767-776.

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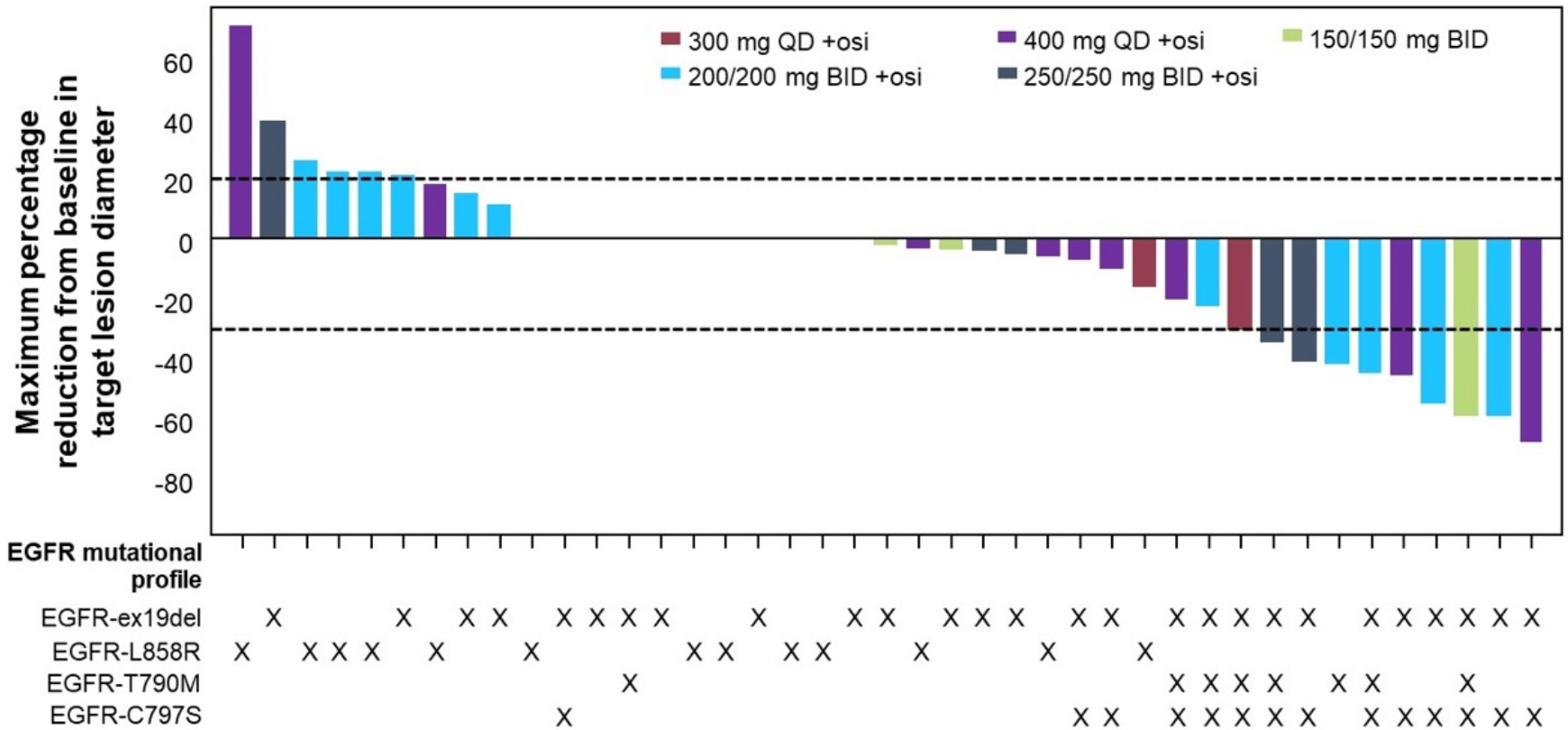
Early BLU-945 + osimertinib antitumor activity[a]



- In the ongoing dose-escalation, tumor shrinkage, including 4 confirmed PRs, was observed in patients who had progressed on osimertinib as the last therapy line

[a]Patients with EGFR-mutant positive NSCLC were enrolled based on local mutation assessment of tumor biopsy or blood ctDNA with a follow-up central ctDNA assessment at C1D1. Patients were counted only once.
BID, twice daily; EGFR, epidermal growth factor receptor.

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Conclusions

- In heavily pretreated EGFR-mutant NSCLC patients, BLU-945 monotherapy was active and well-tolerated; however, due to genomic heterogeneity, responses were not durable
- Emerging BLU-945 + osimertinib combination data demonstrated clinical activity post progression on osimertinib and was well tolerated with infrequent EGFR WT toxicity
- A correspondence between reduction of the resistance mutation alleles by ctDNA and tumor shrinkage was observed in both cohorts
- Phase 1 data support BLU-945 + osimertinib as a differentiated, fully oral, novel combination for treatment of EGFR-mutant NSCLC, warranting further clinical development
    - Combination escalation is ongoing with RP2D/MTD yet to be established

EGFR, epidermal growth factor receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; WT, wild type.

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Predictive biomarkers for treatment with amivantamab plus lazertinib among *EGFR*-mutated advanced NSCLC in the post-osimertinib setting: Analysis of tissue IHC and ctDNA NGS

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CHRYSALIS-2[a] Study Design

Dose Escalation Phase

RP2CD was identified:
Amivantamab 1050 mg (1400 mg if ≥80 kg) IV
plus
Lazertinib 240 mg PO

Dose Expansion Cohorts

Cohort A: *EGFR* ex19del or L858R[b]
Post-osimertinib and platinum-based chemotherapy

Cohort B: *EGFR* ex20ins[b]
Post-standard of care and platinum-based chemotherapy

Cohort C: Uncommon *EGFR* mutations[b]
Treatment naïve or post-1st or 2nd generation EGFR TKI

Cohort D: *EGFR* ex19del or L858R
Post-osimertinib, chemotherapy naïve, biomarker validation

Focus of this presentation

Endpoints

- Objective response rate (primary)
- Duration of response
- Clinical benefit rate[c]
- Progression-free survival
- Overall survival
- Adverse events

- The **objective** of Cohort D was to prospectively validate potential biomarkers (IHC or ctDNA NGS[d])
- Response was assessed by the investigator per RECIST v1.1
- Plasma and tissue[e] were collected at baseline (after osimertinib and prior to treatment on trial)
- **Predefined Bayesian process allowed for biomarker retraining/validation**

[a]ClinicalTrials.gov identifier: NCT04077463.
[b]Cohort A was presented at ASCO 2022 (Shu *J Clin Oncol*; abstract 9006); Cohort B data are pending; Cohort C was presented at ESMO Asia 2022 (Cho *Ann Oncol;* 322MO).
[c]Clinical benefit rate is determined among patients with complete/partial response or stable disease (duration ≥11 weeks).
[d]Analyzed using Guardant360®.
[e]Submission of fresh tumor tissue material or equivalent archival sample after progression on osimertinib was required.

EGFR, epidermal growth factor receptor; ex19del, exon 19 deletions; ex20ins, exon 20 insertion mutations; IHC, immunohistochemistry; IV, intravenous; NGS, next-generation sequencing; PO, per oral; RP2CD, recommended phase 2 combination dose; TKI, tyrosine kinase inhibitor.

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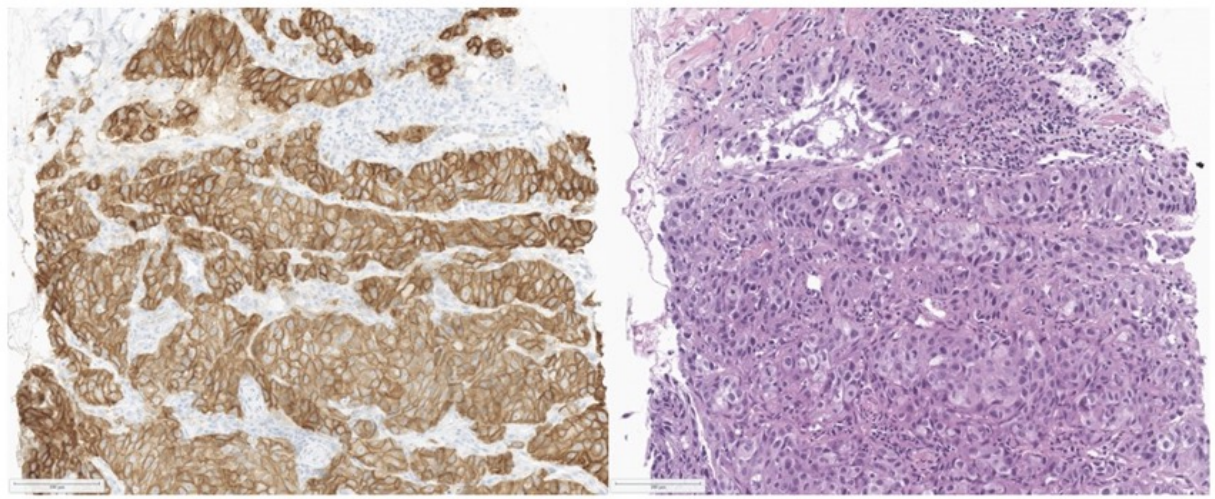
Methodology for Identifying a Predictive IHC Biomarker

Among the 101 response-evaluable patients, 77 had sufficient tissue for MET IHC staining

Note: Submission of fresh tumor tissue material or equivalent archival sample after progression on osimertinib was required

- CHRYSALIS Cohort E suggested MET and EGFR 2+/3+[a] were associated with response[1]
  - After enrolling 50 patients in CHRYSALIS-2 Cohort D, this signature was not predictive
- A retrained signature[b] of **MET 3+ staining[c] on ≥25% of tumor cells** (MET+) was identified as predictive of response
- The new signature was confirmed among 27 new patients in the validation set

MET+ IHC[c] **Corresponding H&E**



[a]Combined MET+EGFR H score ≥400.
[b]Protocol allowed for predefined Bayesian biomarker retraining/validation.
[c]MET IHC was performed by Roche Ventana (Tucson, AZ) using the SP44 antibody.

EGFR, epidermal growth factor receptor; H&E, hematoxylin and eosin staining; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition factor.

1. Bauml et al. Presented at: ASCO; June 4-8, 2021. 9006 (oral).

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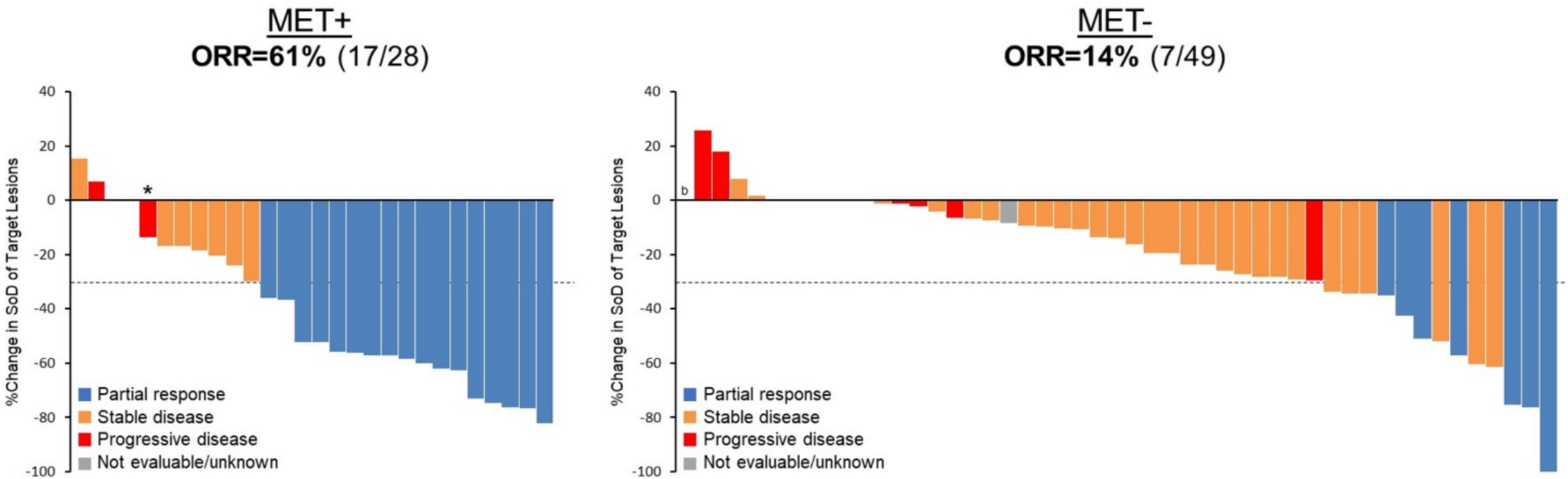
MET+ by IHC Enriched Response to Amivantamab Plus Lazertinib

- A total of 28 of 77 (36%) patients[a] had MET 3+ staining on ≥25% of tumor cells (MET+)
- *MET* amplification was detected by NGS of ctDNA in 1 patient (see asterisk)



[a]Submission of fresh tumor tissue material or equivalent archival sample after progression on osimertinib was required.
[b]One patient did not have any evaluable target lesion measurements in any post-baseline disease assessment.

ctDNA, circulating tumor DNA; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition factor; NGS, next-generation sequencing; ORR, objective response rate; SoD, sum of diameters.

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Conclusions

Treatment Benefit

- Consistent with prior reports, amivantamab plus lazertinib demonstrated activity in patients with *EGFR*-mutated advanced NSCLC whose disease progressed on or after osimertinib
- Based on rebiopsy after osimertinib resistance, **MET 3+ staining on ≥25% of tumor cells** by IHC (MET+) demonstrated:
  - ORR of 61% vs 14% in MET-
  - Longer PFS of 12.2 months in MET+ vs 4.2 months in MET-
- MET+ IHC was predictive of response regardless of molecular resistance mechanism

Safety

- Safety profile was consistent with prior reports

Key Takeaway & Next Step

- MET+ by IHC may be a predictive biomarker for response to amivantamab plus lazertinib in the post-osimertinib, chemotherapy-naïve setting
- This biomarker will be prospectively validated in CHRYSALIS-2 (NCT04077463)

EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; MET, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival.

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Sunvozertinib for the Treatment of NSCLC with *EGFR* Exon20 Insertion Mutations: the First Pivotal Study Results

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WU-KONG6 Study Design

Key inclusion criteria:

- Locally advanced or metastatic NSCLC
- Confirmed EGFR exon20ins in tumor tissues
- Received 1 – 3 lines of prior systemic therapies
- Disease progressed on or after platinum-based chemotherapy

DZD9008

300 mg, QD

Primary endpoint:

- IRC assessed† ORR

Secondary end point:

- IRC assessed† DoR
- ORR (investigator assessed), PFS, DCR, tumor size changes
- OS
- Safety and tolerability
- Pharmacokinetics

† According to RECIST 1.1. Tumor assessment every 6 weeks

IRC, independent review committee; ORR, objective response rate; DoR, duration of response; PFS, progression free survival; DCR, disease control rate; OS, overall survival.

Data cut-off for analysis: October 17, 2022

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Anti-tumor Efficacy of Sunvozertinib by IRC Assessment

Anti-tumor Efficacy	N = 97
Tumor Response, n (%)	
Partial response (confirmed)	59 (60.8)
Stable disease	26 (26.8)
Progression disease	6 (6.2)
Not evaluable	6 (6.2)
Objective Response Rate (ORR), n (%)	59 (60.8)
(95% CI)	(50.4, 70.6)
P value	< 0.0001
Disease Control Rate (DCR), n (%)	85 (87.6)
(95% CI)	(79.4%, 93.4%)

- The IRC assessed ORR (primary endpoint) was 60.8%, which met its pre-defined target with statistical significance.

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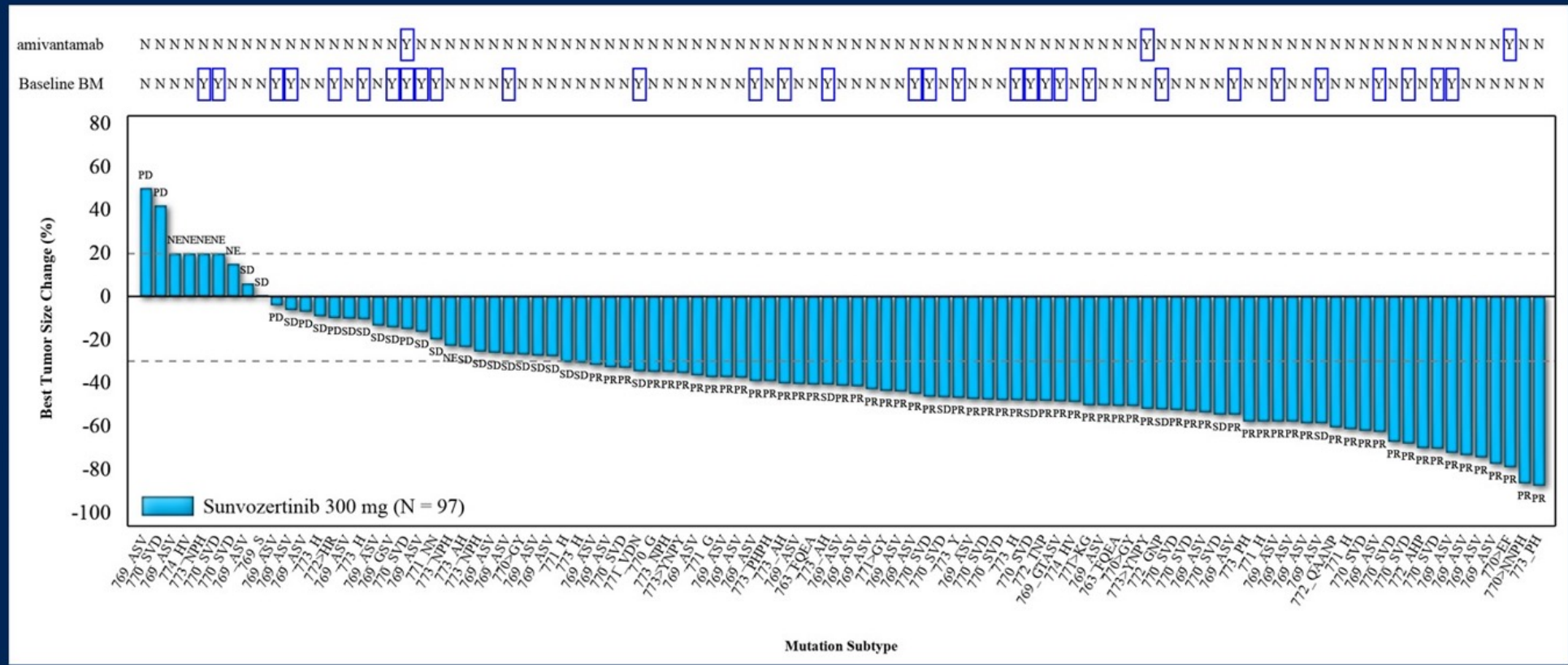
Target Tumor Size Change per IRC Assessment



BM, brain metastasis

- Tumor shrinkage was observed in > 90% of subjects with sunvozertinib treatment.
- Tumor response was observed in patients with baseline brain metastasis or post amivantamab treatment.

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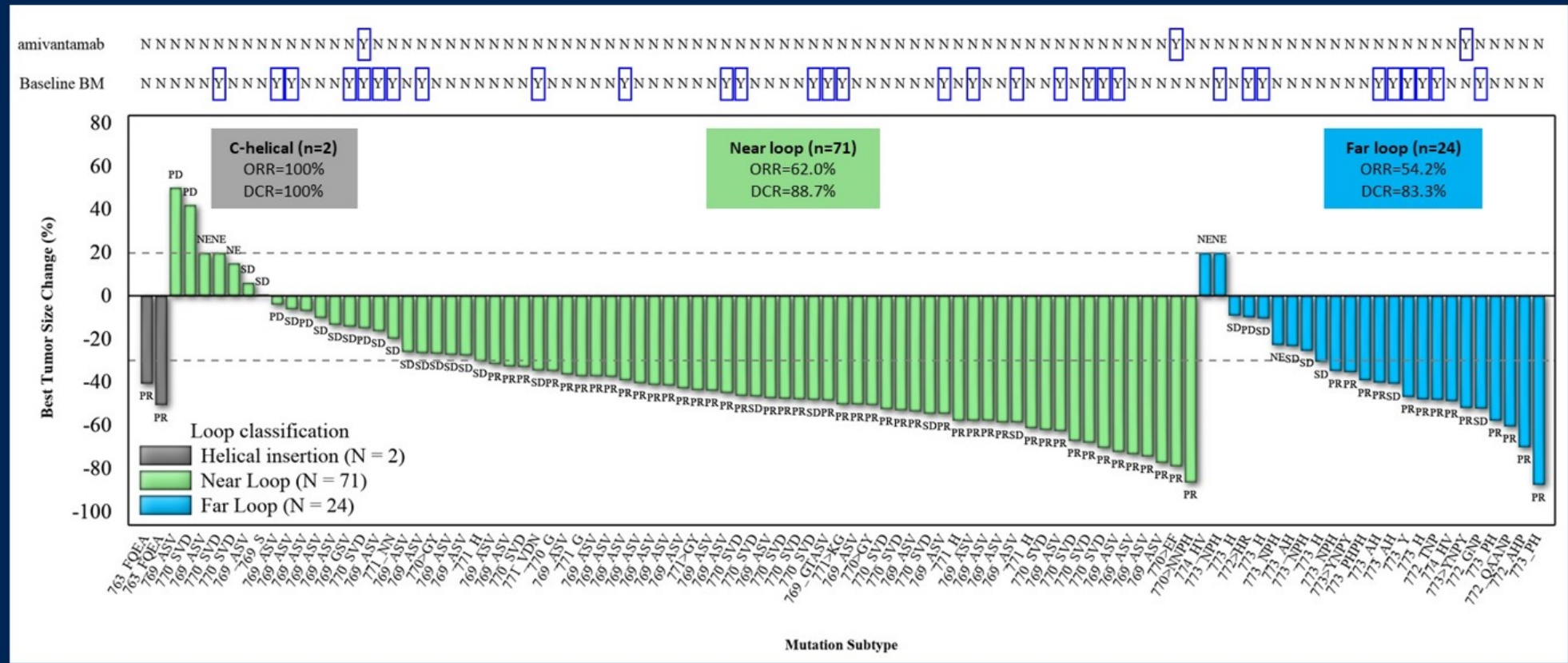
Anti-tumor Efficacy in Different EGFR Exon20ins Subtypes



- A total of 30 different subtypes of EGFR exon20ins were enrolled. Anti-tumor efficacy was observed regardless of mutation subtypes and insertion locations.

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Safety Profile of Sunvozertinib

Common TEAE by PT	N = 104 All Grade	N = 104 ≥ Grade 3
Diarrhea	70（67.3）	8（7.7）
Blood CPK increase	60（57.7）	18（17.3）
Rash	56（53.8）	1（1.0）
Anemia	51（49.0）	6（5.8）
Blood creatinine increase	39（37.5）	0（0.0）
Paronychia	34（32.7）	2（1.9）
Body weight decrease	30（28.8）	1（1.0）
White blood cell decrease	27（26.0）	0（0.0）
Lipase increase	27（26.0）	2（1.9）
Vomiting	25（24.0）	1（1.0）
Decreased appetite	25（24.0）	2（1.9）
Mouth ulceration	24（23.1）	0（0.0）

- Safety profile of sunvozertinib was similar to other EGFR TKIs. Majorities of the AEs were grade 1 or 2.

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Conclusion

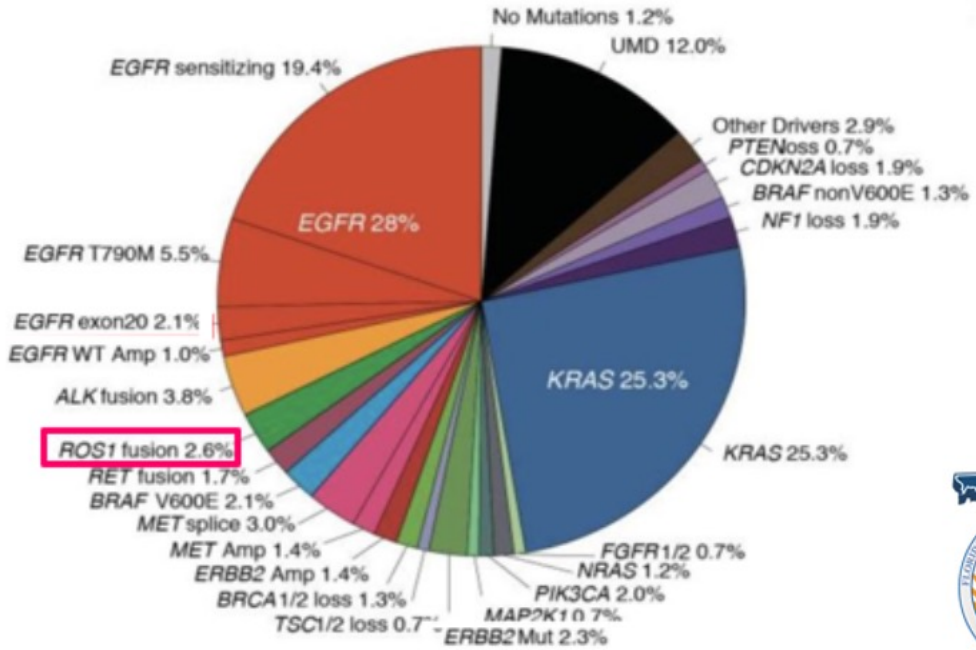
- In WU-KONG6 pivotal study, sunvozertinib demonstrated significant anti-tumor efficacy and well-tolerated safety profile in platinum-based chemotherapy pretreated NSCLC with EGFR exon20ins.
  - The confirmed ORR at 300 mg QD was 60.8% assessed by IRC.
  - Anti-tumor efficacy was observed across a variety of EGFR exon20ins subtypes and regardless of insertion locations.
  - Anti-tumor efficacy was observed in patients with baseline brain metastasis and who failed amivantamab treatment.
  - Sunvozertinib demonstrated comparable safety profile to other EGFR TKIs.

Sunvozertinib can be a potential treatment option for NSCLC with EGFR exon20ins.

A phase III, randomized, multinational study (WU-KONG28, NCT05668988) is ongoing to assess sunvozertinib versus platinum-based chemotherapy in the 1st line EGFR exon20ins NSCLC.

Mengzhao Wang et al. 2023 ASCO Annual Meeting.

ROS1Pathway



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Intracranial and systemic efficacy of repotrectinib in advanced *ROS1* fusion-positive non-small cell lung cancer and central nervous system metastases in the phase 1/2 TRIDENT-1 trial

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Abstract number 9017

Jessica Lin et al. 2023 ASCO Annual Meeting.

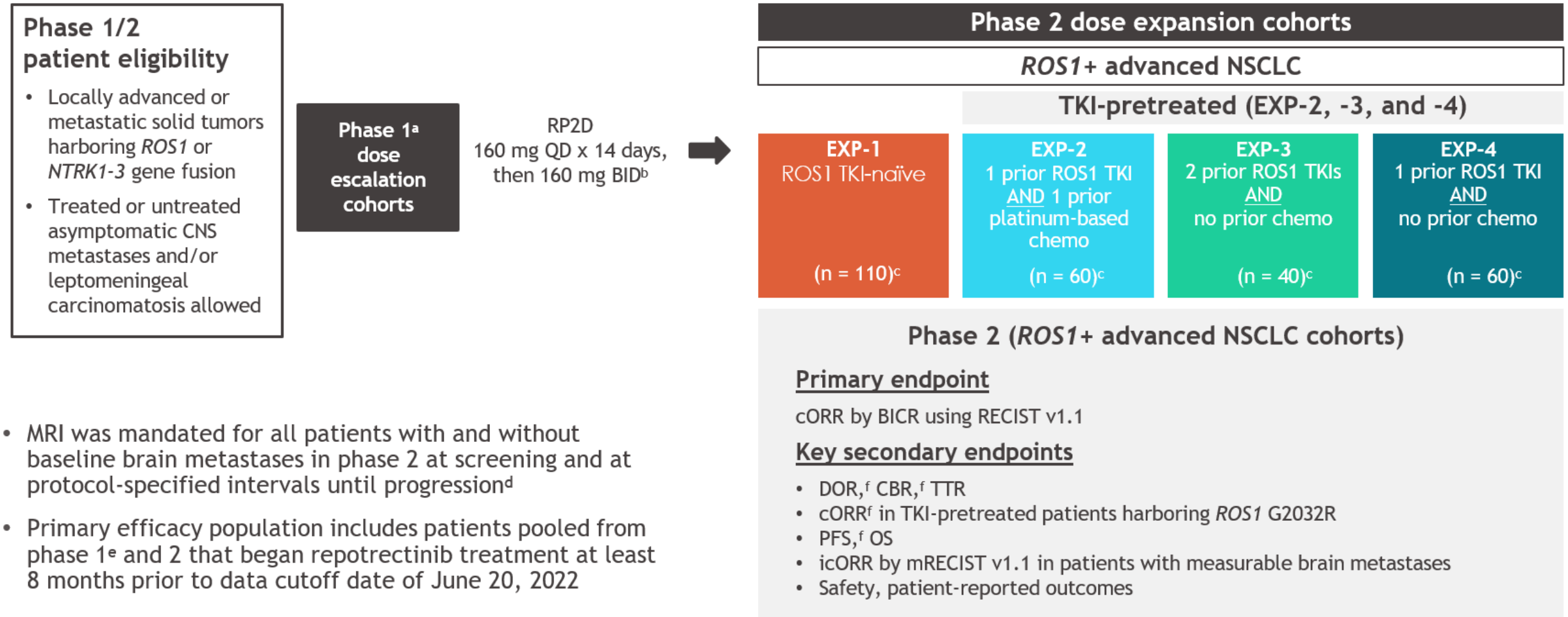
Background

- Oncogenic driver gene fusions involving *ROS1* have been identified in up to 2% of non-small cell lung cancer (NSCLC),[1] and ROS1 tyrosine kinase inhibitor (TKI) therapy is the current standard of care[2,3]; response rates with currently approved therapies (crizotinib and entrectinib) range from 66%–74% but achieving durable benefit remains a challenge[4-8]

- CNS metastases have been detected in up to 36% of patients at the time of diagnosis and up to 56% of TKI-pretreated patients[8-10]; CNS was the first and only site of progression in ≈50% of patients pretreated with crizotinib[10]

- Repotrectinib is a next-generation ROS1 and TRK TKI with a compact macrocyclic structure that is designed to improve durability of benefit by decreasing the potential for developing resistance mutations (TKI-naïve and -pretreated patients) and circumventing known resistance mutations (TKI-pretreated patients), and has favorable CNS drug-like properties for human brain penetration[11]

Figure 1. Efficacy analysis of the phase 1/2 TRIDENT-1 study design



- MRI was mandated for all patients with and without baseline brain metastases in phase 2 at screening and at protocol-specified intervals until progression[d]
- Primary efficacy population includes patients pooled from phase 1[e] and 2 that began repotrectinib treatment at least 8 months prior to data cutoff date of June 20, 2022

Data cutoff date: June 20, 2022.

[a]Phase 1 primary endpoints: DLT, MTD, RP2D. [b]Based on tolerability. [c]N's for expansion cohorts indicate enrollment targets. [d]MRI brain scans performed at Cycle 3 day 1 (± 7 days), every 2 cycles (± 7 days) up to Cycle 19 and then every 3 cycles (± 7 days) up to Cycle 37 and then every 4 cycles (± 7 days); brain CT was acceptable if brain MRI was contraindicated. [e]Patients from phase 1 received 40 mg QD to 160 mg QD and 160 mg BID. [f]By RECIST v1.1. BICR, blinded independent central review; BID, twice daily; CBR, clinical benefit rate; chemo, chemotherapy; cORR, confirmed objective response rate; CT, computed tomography; DLT, dose-limiting toxicity; DOR, duration of response; icORR, intracranial objective response rate; mRECIST, modified Response Evaluation Criteria in Solid Tumors; MRI, magnetic resonance imaging; MTD, maximum-tolerated dose; OS, overall survival; PFS, progression-free survival; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TTR, time to response.

Results

Efficacy

Confirmed ORR, DOR, and PFS in patients with or without baseline CNS metastases

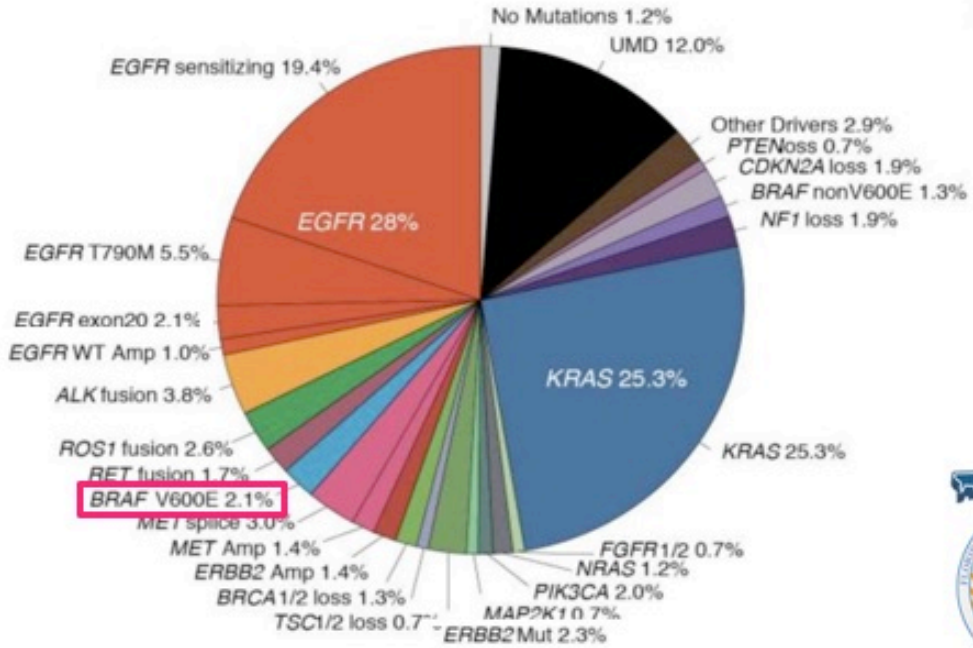
- At data cutoff, median follow-up was 18.1 months in the TKI-naïve cohort (n = 71) and 15.5 months in the 1 prior TKI and no chemo cohort (n = 56)
- In TKI-naïve patients with and without CNS metastases, respectively, cORR was 89% (95% CI, 65-99) and 75% (62-86), with responses ongoing at 12 months in 93% and 84% of responders (**Table 2**)
- cORR, DOR, and PFS results for TKI-pretreated cohorts are shown in **Table 2**

Table 2. Systemic efficacy in patients with *ROS1*+ NSCLC with baseline CNS metastases per BICR

	ROS1 TKI-naïve (n = 71)	1 prior ROS1 TKI AND no prior chemo (n = 56)	1 prior ROS1 TKI AND 1 prior platinum-based chemo (n = 26)	2 prior ROS1 TKIs AND no prior chemo (n = 18)
Median follow-up, months	18.1	15.5	21.3	14.1
Patients with CNS mets,[a] n (%)	18 (25)	24 (43)	10 (38)	8 (44)
cORR,[b] % (95% CI)	89 (65-99)	33 (16-55)	40 (12-74)	12 (0.3-53)
CR, n (%)	1 (6)	0 (0)	0 (0)	1 (12)
PR, n (%)	15 (83)	8 (33)	4 (40)	0 (0)
SD,[b] n (%)	1 (6)	11 (46)	3 (30)	1 (12)
DOR,[c] % (95% CI)				
≥ 6 months	100 (100-100)	62 (29-96)	50 (1-99)	100 (100-100)
≥ 12 months[d]	93 (79-100)	—	—	—
PFS,[c] % (95% CI)				
≥ 6 months	94 (83-100)	57 (35-78)	40 (10-70)	12 (0-35)
≥ 12 months[d]	87 (71-100)	—	—	—
Patients without CNS mets, n (%)	53 (75)	32 (57)	16 (62)	10 (56)
cORR,[b] % (95% CI)	75 (62-86)	41 (24-59)	44 (20-70)	40 (12-74)
CR, n (%)	3 (6)	3 (9)	1 (6)	0 (0)
PR, n (%)	37 (70)	10 (31)	6 (38)	4 (40)
SD,[b] n (%)	10 (19)	14 (44)	5 (31)	2 (20)
DOR,[c] % (95% CI)				
≥ 6 months	87 (77-98)	92 (76-100)	71 (38-100)	50 (1-99)
≥ 12 months[d]	84 (72-96)	—	—	—
PFS,[c] % (95% CI)				
≥ 6 months	90 (81-98)	75 (59-91)	38 (12-63)	30 (2-58)
≥ 12 months[d]	77 (65-89)	—	—	—

[a]Including patients with measurable and non-measurable lesions. [b]By RECIST v1.1. [c]DOR and PFS were calculated by Kaplan-Meier estimates. [d]Not reported for TKI-pretreated cohorts due to small number of patients at risk. CR, complete response; mets, metastases; PR, partial response; SD, stable disease.

BRAF^{V600E} Pathway



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Abstract 9018

Efficacy and safety of encorafenib plus binimetinib in patients with metastatic *BRAF* V600E-mutant (*BRAF*^{V600E}) non-small cell lung cancer (NSCLC) from the phase 2 PHAROS study

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Encorafenib plus binimetinib in patients with metastatic BRAF V600E NSCLC

- The combination of encorafenib (BRAF inhibitor) plus binimetinib (MEK inhibitor) has demonstrated clinical efficacy with an acceptable safety profile in patients with metastatic BRAF V600E/K–mutant melanoma[1]
- For patients with metastatic BRAF V600E–mutant NSCLC the combination of dabrafenib and trametinib was approved by the US FDA and is a current standard of care [2]
  - This approval was based on the results of a single-arm, phase 2 study that showed meaningful antitumor activity and a manageable safety profile[3,4]
    - In treatment-naïve and previously treated patients, the ORR by IRR was 64% and 63%, respectively
    - The median DOR by IRR was 15.2 months and 9.0 months, respectively
- Given the observed efficacy and safety profile of encorafenib plus binimetinib in patients with BRAF V600E/K–mutant metastatic melanoma, this combination therapy was assessed in patients with metastatic BRAF V600E–mutant NSCLC

PHAROS (NCT03915951):
A single-arm, open-label, multicenter, phase 2 study

Key eligibility criteria

- Metastatic BRAF V600E–mutant NSCLC
- ECOG performance status 0 or 1
- No *EGFR* mutation, *ALK* fusion, or *ROS1* rearrangement
- No more than 1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases

***BRAF* mutation testing**

- Determined locally by PCR- or NGS-based assay; sent to central laboratory[a]
- Pleural fluid, fresh and archived tissue, and fine needle aspiration were acceptable

Patients enrolled

- Treatment naïve n=59
- Previously treated n=39

Encorafenib: 450 mg QD
Binimetinib: 45 mg BID
28-day cycles
Treat until progression or unacceptable toxicity

Primary endpoint
- ORR[b] by IRR

Secondary endpoints
- ORR by investigator
- DOR, DCR, PFS, and TTR (all by IRR and investigator)
- OS
- Safety

Exploratory endpoints
- Biomarker and pharmacokinetic analyses

BID, twice daily; **DCR**, disease control rate; **DOR**, duration of response; **ECOG**, Eastern Cooperative Oncology Group; **IRR**, independent radiology review; **ORR**, objective response rate; **NGS**, next-generation sequencing; **OS**, overall survival; **PCR**, polymerase chain reaction; **PFS**, progression-free survival; **QD**, once daily; **TTR**, time to response.
[a]BRAF V600 mutations were retrospectively confirmed by FoundationOne CDx (Foundation Medicine, Cambridge, MA). [b]According to RECIST 1.1.

1. Dummer R, et al. *Lancet Oncol*. 2018;19(5):603-615. 2. Dabrafenib prescribing information. June 2022. 3. Planchard D, et al. *Lancet Oncol*. 2016;17(7):984-993. 4. Planchard D, et al. *Lancet Oncol*. 2017;18(10):1307-1316.

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Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC

Antitumor activity endpoints by IRR

	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)

IRR, independent radiology review; **NE**, not estimable.
[a]Response of 3 patients were not evaluable in the treatment-naïve group, and 5 were not evaluable in the previously treated group.

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Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Conclusions

- The combination of encorafenib plus binimetinib showed a meaningful clinical benefit with an acceptable safety profile in patients with BRAF V600E–mutant metastatic NSCLC in the phase 2 PHAROS study
  - Efficacy was observed in both cohorts:
    - ORRs by IRR were 75% (95% CI: 62-85%) in treatment –naïve patients and 46% (95% CI: 30-63%), in previously treated patients
    - Median DORs by IRR were NE (95% CI, 23.1 months, NE) and 16.7 months (95% CI, 7.4 months, NE), respectively
  - The safety profile was consistent with that observed in the approved indication in melanoma
- Encorafenib plus binimetinib represents a potential new treatment option for patients with BRAF V600E–mutant metastatic NSCLC

IRR, independent radiology review; **NE**, not estimable; **ORR**, objective response rate.

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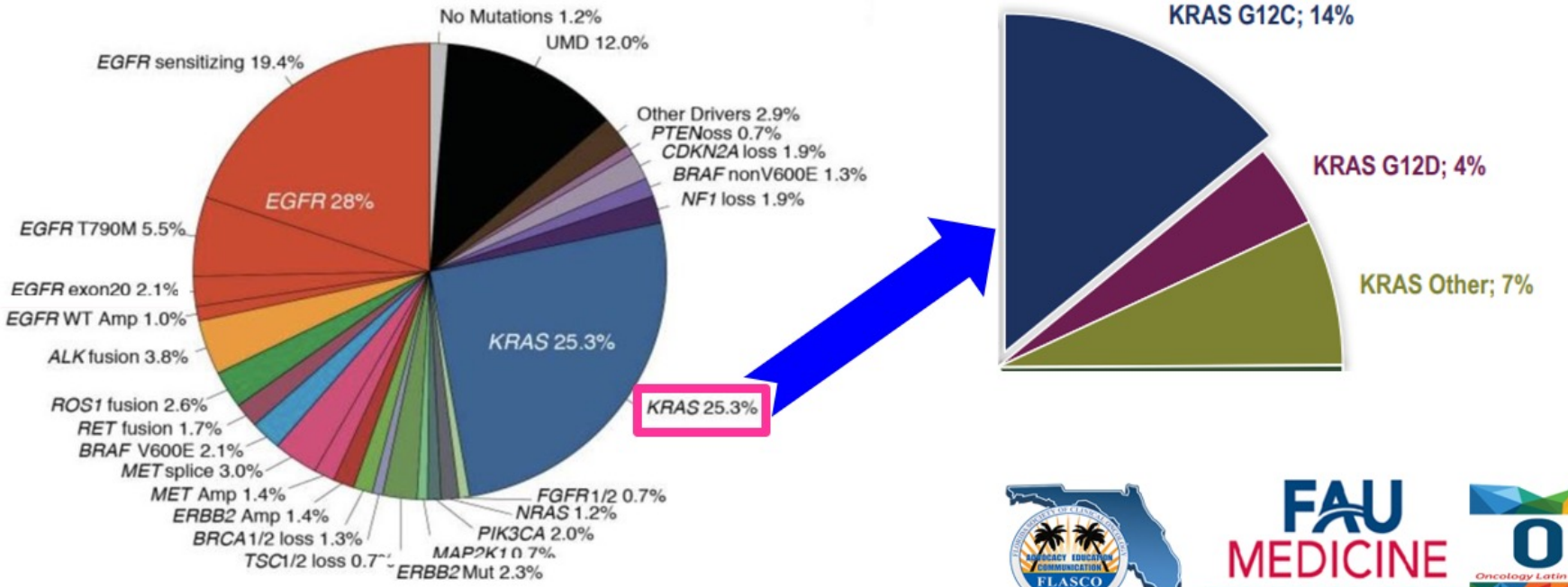
KRAS^{G12C} Pathway



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Biomarker subgroup analyses of CodeBreaK 200, a phase 3 trial of sotorasib versus docetaxel in patients with pretreated *KRAS* G12C-mutated advanced non-small cell lung cancer (NSCLC)

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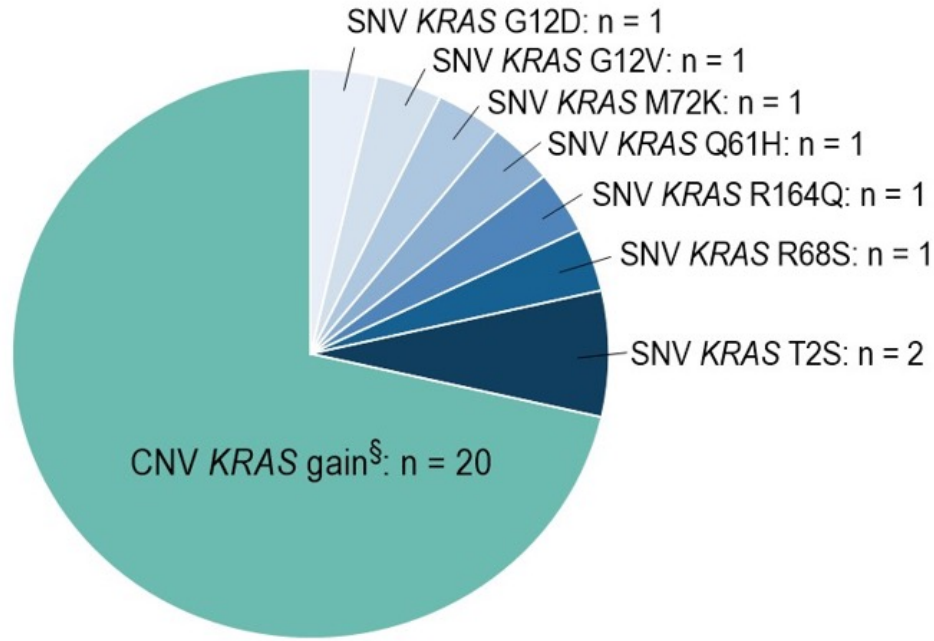
KRAS Co-alterations Were Potentially Associated with Primary Resistance Irrespective of Treatment

	Sotorasib (n = 164)	Docetaxel (n = 154)	Treatment Difference (*P*-value)
***KRAS* co-alteration*, n (%)**	**9 (5)**	**17 (11)**	
ORR†, n (%)	0	0	–
Median PFS (95% CI)†	1.8 (0.8, 3.0)	2.5 (1.4, 3.1)	0.016‡
HR (95% CI)‡	1.74 (0.84, 3.58)		



- **No response observed in patients with additional *KRAS* co-alterations in either treatment arm**
- **Outcomes align with preclinical data suggesting some non-G12C *KRAS* alterations mediate sotorasib resistance[8]**

*Excluding G12C.
†Medians were estimated using the Kaplan-Meier method. 95% CIs were estimated using the method by Klein and Moeschberger with log-log transformation.
‡Hazard ratios, 95% CIs, and *P*-values were estimated using a stratified Cox proportional hazards model with treatment, stratification factors, and co-alterations as covariates and treatment by co-alteration interaction. A hazard ratio <1.0 indicates a lower average event rate and a longer PFS for sotorasib versus docetaxel.
§Limit of detection for CNV was >2, all *KRAS* CNV were copy number gains.

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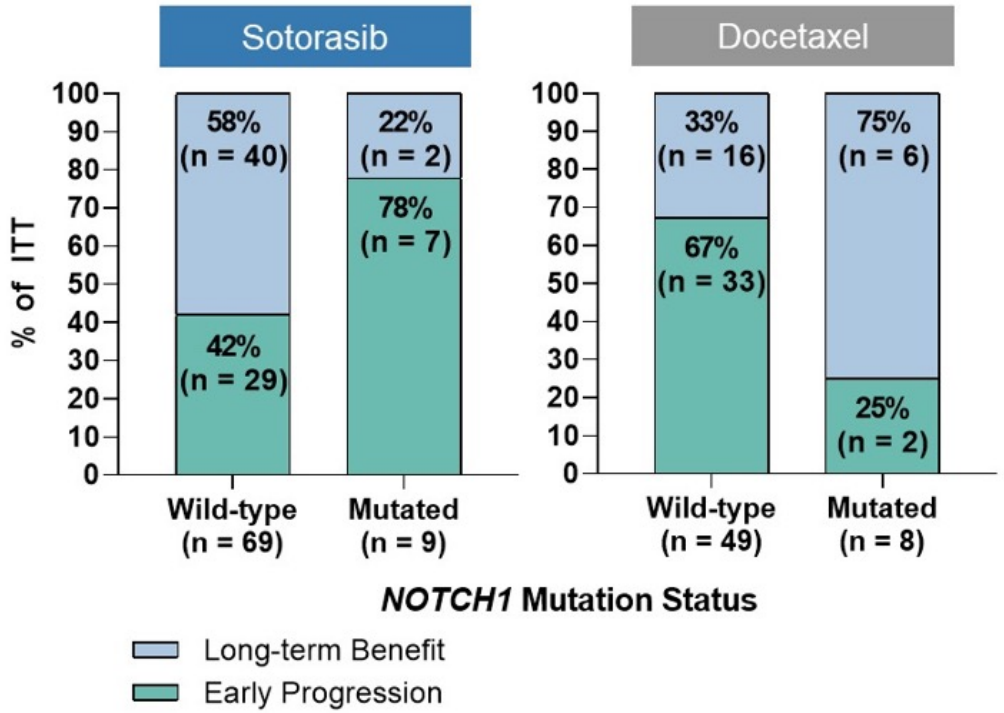
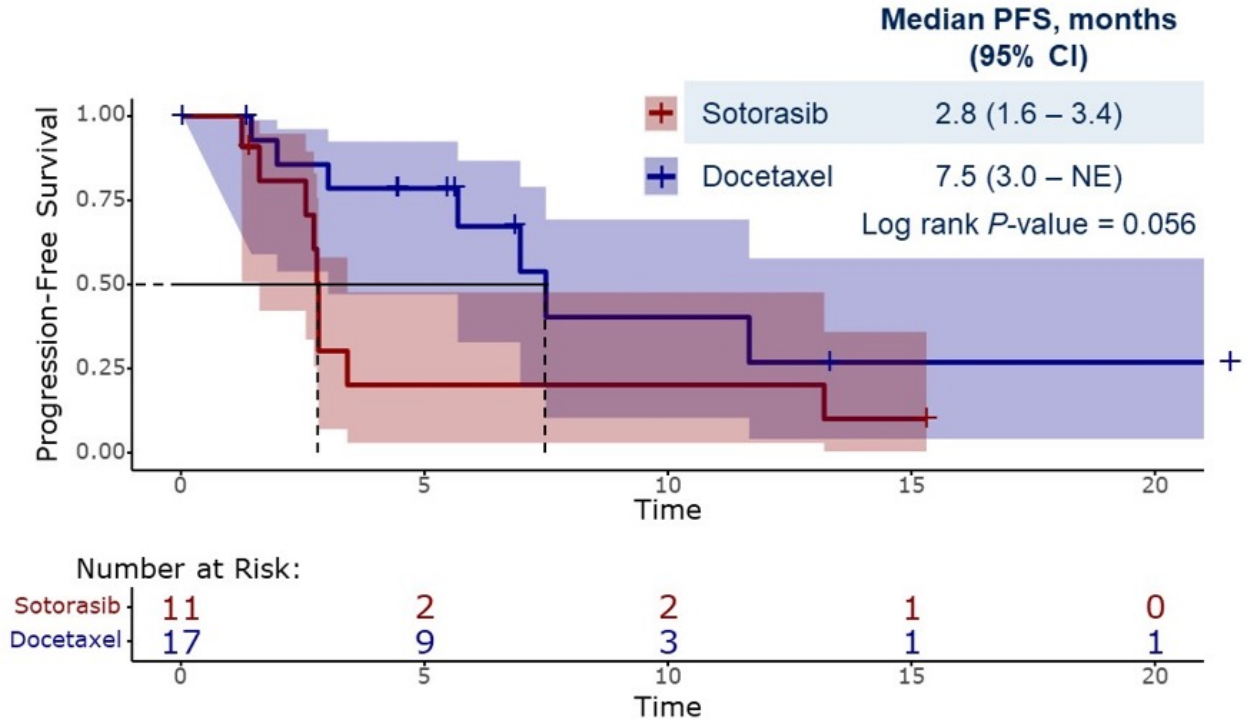
In a Limited Data Set, *NOTCH1m* Had an Early Progression Signal With Sotorasib That Warrants Further Exploration





Long-term benefit defined as ≥ 6 months PFS; early progression defined as < 3 months PFS with no clinical responders (no complete/partial responders).
Left-hand figure includes patients with *NOTCH1* mutation or wild-type who were classified as having early progression or long-term benefit. Right-hand figure includes all biomarker-evaluable patients with *NOTCH1* mutation.

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Conclusions

- In the first randomized, molecularly-defined analysis of a KRAS^{G12C} inhibitor versus docetaxel,
  - Sotorasib demonstrated consistent clinical benefit vs docetaxel in prespecified key co-alteration subgroups (eg, *STK11*, *KEAP1*, *TP53*)
  - Sotorasib improved PFS over docetaxel, regardless of PD-L1 expression
- Novel hypothesis-generating findings were observed
  - Patients with additional *KRAS* co-alterations were more refractory to either treatment
  - In a small subset of patients with *NOTCH1* mutations, sotorasib was associated with worse outcomes
- Additional studies will explore and validate the roles of non-G12C *KRAS* and *NOTCH1* co-alterations as potential biomarkers to sotorasib treatment

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KontRASt-01 update: Safety and efficacy of JDQ443 in *KRAS G12C*-mutated solid tumors including non-small cell lung cancer (NSCLC)

Philippe A Cassier,[1] Christophe Dooms,[2] Anas Gazzah,[3] Enriqueta Felip,[4] Neeltje Steeghs,[5] Kristoffer Staal Rohrberg,[6] Filippo De Braud,[7] Benjamin Solomon,[8] Martin Schuler,[9] Daniel SW Tan,[10] Noboru Yamamoto,[11] Herbert HF Loong,[12] Byoung Chul Cho,[13] Jürgen Wolf,[14] Chia-Chi Lin,[15] Marcelo V Negrao,[16] Lillian Werner,[17] Xiaoming Cui,[18] Anna F Farago,[17] **María de Miguel**[19]

1. Centre Léon Bérard, Lyon, France; 2. University Hospitals Leuven, Leuven, Belgium; 3. Gustave Roussy, Villejuif, France; 4. Vall d'Hebron University Hospital, Barcelona, Spain; 5. The Netherlands Cancer Institute, Amsterdam, the Netherlands; 6. Department of Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, Denmark; 7. Fondazione IRCCS Istituto Nazionale dei Tumori and University of Milan, Milan, Italy; 8. Peter MacCallum Cancer Centre, Melbourne, Australia; 9. West German Cancer Center, University Hospital Essen, Essen, Germany; 10. National Cancer Centre Singapore, Singapore; 11. National Cancer Center Hospital, Tokyo, Japan; 12. Department of Clinical Oncology, The Chinese University of Hong Kong, Hong Kong; 13. Yonsei University College of Medicine, Seoul, Republic of Korea; 14. Department I of Internal Medicine, Center for Integrated Oncology, University Hospital Cologne, Cologne, Germany; 15. National Taiwan University Hospital, Taipei, Taiwan; 16. MD Anderson Cancer Center, Houston, TX, USA; 17. Novartis Institutes for BioMedical Research, Cambridge, MA, USA; 18. Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; 19. START-CIOCC Hospital Universitario HM Sanchinarro, Madrid, Spain.

Dr. María de Miguel

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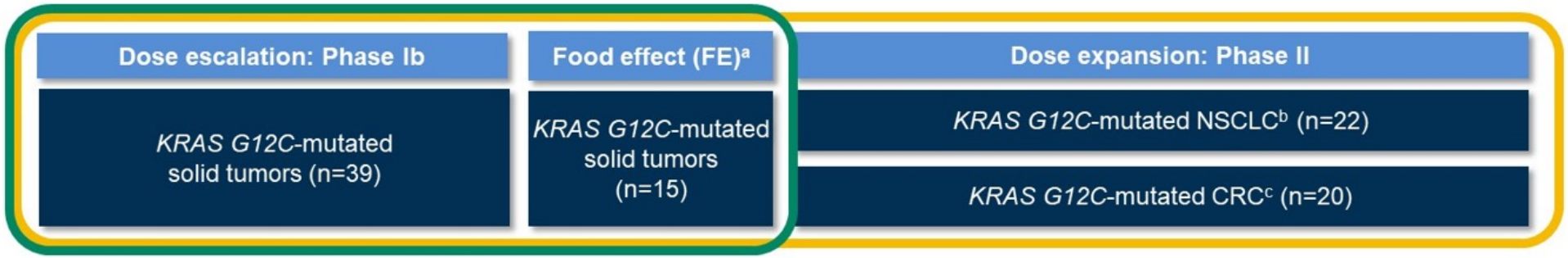
KontRASt-01: JDQ443 monotherapy



Safety data set: All patients (N=96) across dose escalation, FE and dose expansion cohorts

Efficacy data set: Patients with NSCLC (N=27) from dose escalation and FE cohorts

Pre-planned analyses in the Phase II NSCLC expansion group will be the subject of future presentations.

Key objectives for dose escalation	Key objectives for dose expansion
Primary: Assess the safety and tolerability of JDQ443 and identify the MTD and/or RD and regimen for future studies **Secondary:** Evaluate the antitumor activity and characterize the PK of JDQ443	**Primary:** Evaluate the antitumor activity of JDQ443 monotherapy **Secondary:** Assess the safety and tolerability and characterize the PK of JDQ443
Key eligibility criteria	
Patients with advanced, *KRAS G12C*-mutated solid tumors who have received standard-of-care therapy or who are intolerant of or ineligible for approved therapies; ECOG PS 0–1; no prior treatment with a $KRAS^{G12C}$ inhibitor	

Data presented are from a cut-off date of February 1, 2023. [a]Patients in the FE cohort received treatment on an empty stomach, at least 1 hour before and 2 hours after a meal, from Day 1 to Day 7. Following a washout period with no treatment on Day 8, patients commenced standard treatment cycles at the same dose and schedule, receiving JDQ443 with food. For dose escalation and dose expansion, JDQ443 was dosed with food at all time points; [b]All patients with NSCLC must have been previously treated with a platinum-based chemotherapy regimen and an immune checkpoint inhibitor, either in combination or in sequence, unless ineligible to receive such therapy; [c]Patients with CRC must have previously received standard-of-care therapy, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, unless ineligible to receive such therapy.
BID, twice daily; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; FE, food effect; KRAS, Kirsten rat sarcoma viral oncogene homolog; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; PS, performance status; QD, once daily; RD, recommended dose.

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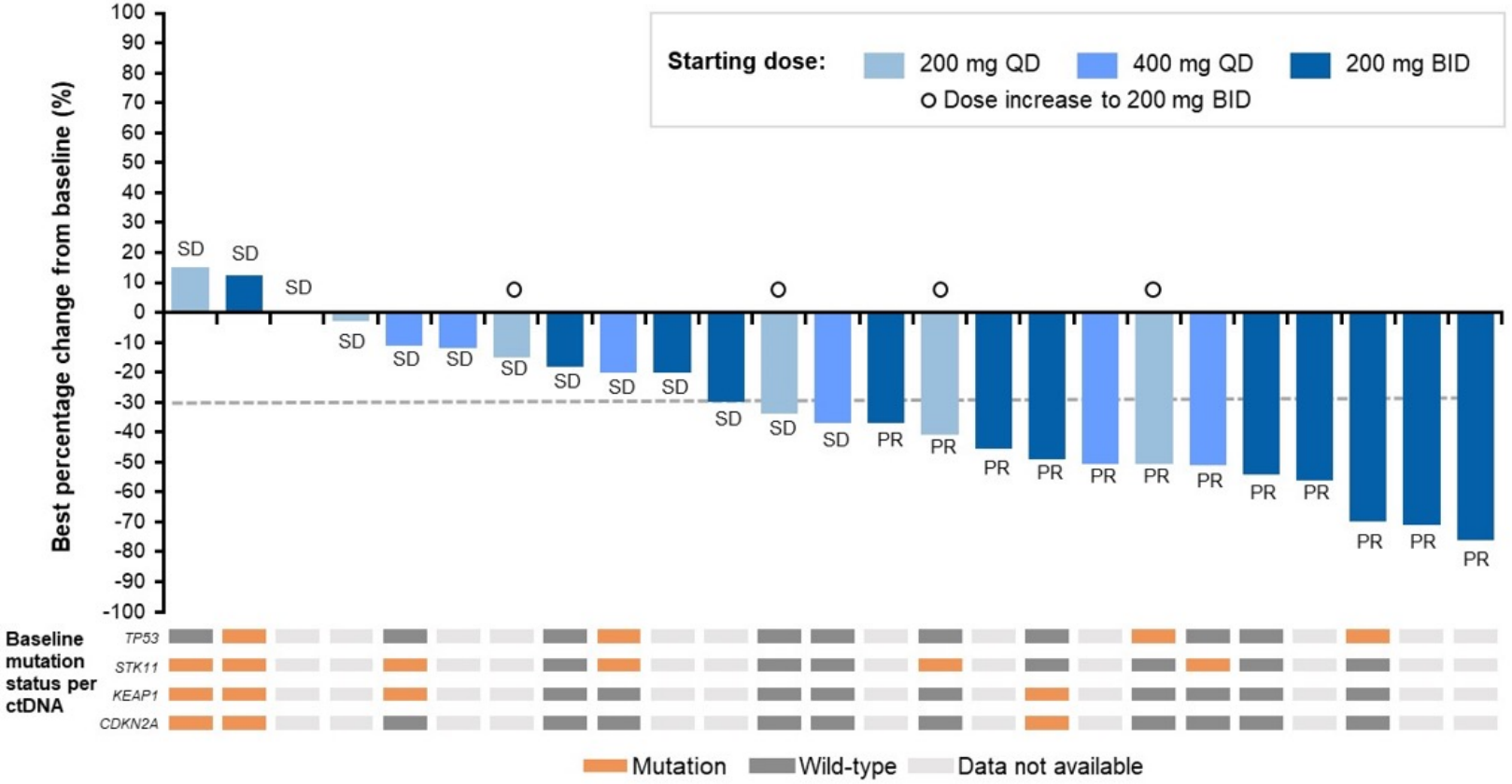
NSCLC: Best overall response



	JDQ443 200 mg BID (n=14)	JDQ443 All dose levels, pooled (n=27)
Confirmed ORR	**57.1%**	44.4%
DCR	**92.9%**	92.6%
BOR[a], n (%)		
PR	8 (57.1)	12 (44.4)
SD	5 (35.7)	13 (48.1)
PD	0	0
Unknown	1 (7.1)	2 (7.4)

Data presented with a cut-off date of February 1, 2023. Waterfall plot: 25 (92.6%) patients with NSCLC with available change from baseline tumor assessments; data are plotted out of n=27 patients with NSCLC who received JDQ443 single-agent. Patients were enrolled in dose escalation and food effect cohorts. [a]Best overall response per RECIST 1.1 based on investigator's assessment. Intra-patient dose escalation, per protocol, occurred in four patients from 200 mg QD to 200 mg BID. Mutation detection: plasma ctDNA at baseline; assay validated to 0.5% allele frequency. 95% CI for ORR: 28.9–82.3 for 200 mg BID; 25.5–64.7 for all dose levels.
BID, twice daily; CI, confidence interval; ctDNA, circulating tumor DNA; DCR, disease control rate; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD, progressive disease; PR, partial response; QD, once daily; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

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Summary

- JDQ443 is a structurally unique KRAS^{G12C} inhibitor that exhibits antitumor activity in NSCLC
  - Preliminary ORR: 57.1% (8/14) at recommended dose for expansion of 200 mg BID
- JDQ443 is well tolerated and has an acceptable safety profile
  - TRAEs were low-frequency, low-grade events
    - No Grade 4–5 TRAEs
    - No nausea, vomiting, or diarrhea higher than Grade 2
    - ALT/AST Grade 2–3 elevation events were rare and of limited duration
  - Safety/tolerability profile supports potential for combination strategies
- Actively enrolling: JDQ443 doublet combinations in KontRASt-01 have completed dose escalation and are now in Phase II dose expansion
  - JDQ443 + tislelizumab (anti–PD-1)
  - JDQ443 + TNO155 (SHP2 inhibitor)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; KRAS, Kirsten rat sarcoma viral oncogene homolog; NSCLC, non-small cell lung cancer; ORR, overall response rate; PD-1, programmed cell death protein-1; SHP2, Src homology-2 domain–containing protein tyrosine phosphatase-2; TRAE, treatment-related adverse event.

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2023 ASCO ANNUAL MEETING

The primary endpoint analysis of SCARLET study:

A single-arm, phase II study of Sotorasib plus CARbopLatin-pemETrexed in advanced non-squamous, non-small cell lung cancer patients with KRAS G12C mutation: WJOG14821L

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FLASCO ADVOCACY EDUCATION COMMUNICATION

FAU MEDICINE FLORIDA ATLANTIC UNIVERSITY

OLA Oncology Latin American Association

Background

- Molecular-targeted drugs have a critical role in advanced non-squamous, non-small cell lung cancer (non-Sq, NSCLC) patients with oncogenic driver alterations
- In EGFR-mutated tumor, phase III trials showed the benefit of adding cytotoxic chemotherapy on gefitinib

Hosomi Y, JCO 2019. Miyauchi E, JCO 2022. Noronha V, JCO 2020. Hou X, JAMA Network Open 2023.

Umbrella-type, phase II studies @ WJOG
for advanced non-Sq, NSCLC patients with rare driver oncogenes

ALK-rearranged	KRAS G12C (SCARLET)	MET ex14 skipping	.....
ALK-TKI +/- platinum-doublet	Sotorasib + CBDCA / PEM	MET-TKI +/- platinum-doublet	

Wakuda K, BMC Cancer 2023

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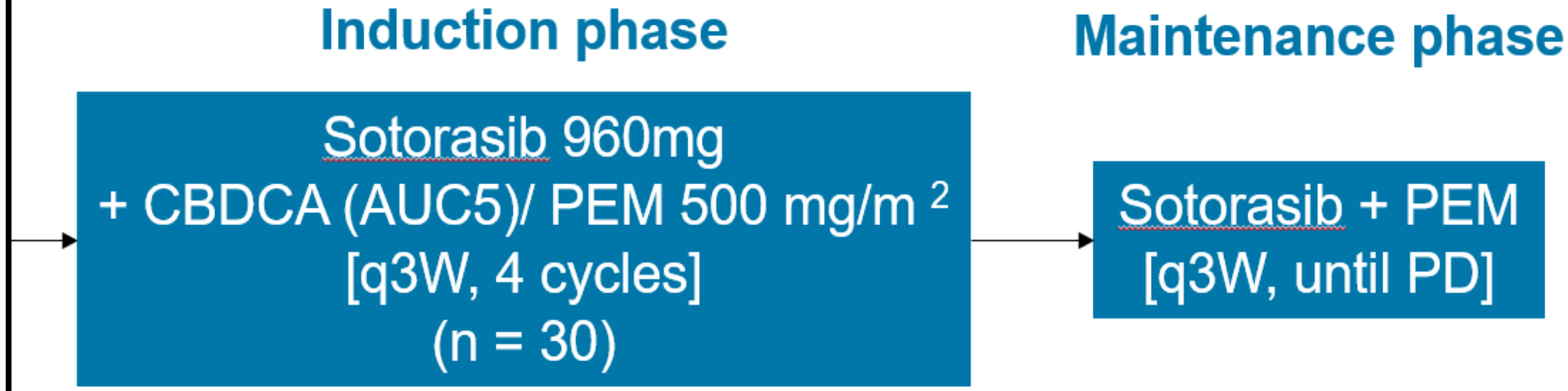
SCARLET: study schema

Key inclusion criteria

- Advanced non-Sq, NSCLC
- With KRAS G12C
- Naïve for Cytotoxic chemotherapy and KRAS inhibitor
- With measurable lesion
- ECOG PS 0-1
- Asymptomatic CNS mets allowed



- Primary endpoint; ORR by blinded independent central review (BICR)
- Secondary endpoints; DCR, PFS, DOR, OS and AEs
- Translational research; NGS analysis (tissue and plasma [at baseline, 3 wks, and PD])

Trial identifier: jRCT2051210086

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Baseline characteristics

	N = 30
Age	
median (range)	70 (49-79)
Sex-no. (%)	
Male / Female	25 / 5
Smoking status-no. (%)	
Never / (ex-) smoker	1 / 29
ECOG performance status-no. (%)	
0 / 1	13 / 17
Histology	
Adenocarcinoma / others	27 / 3
PD-L1 expression (22C3)	
High (≥50%) / Low (1-49%) / Negative	15 / 10 / 5
Clinical stage-no. (%)	
IVA / IVB / Recurrence	9 / 16 / 5
CNS metastasis	
Yes / No	7 / 23
Prior history of ICI	
Yes / No	2* / 28

*Both received ICI (Durva) as a consolidative treatment after CRT

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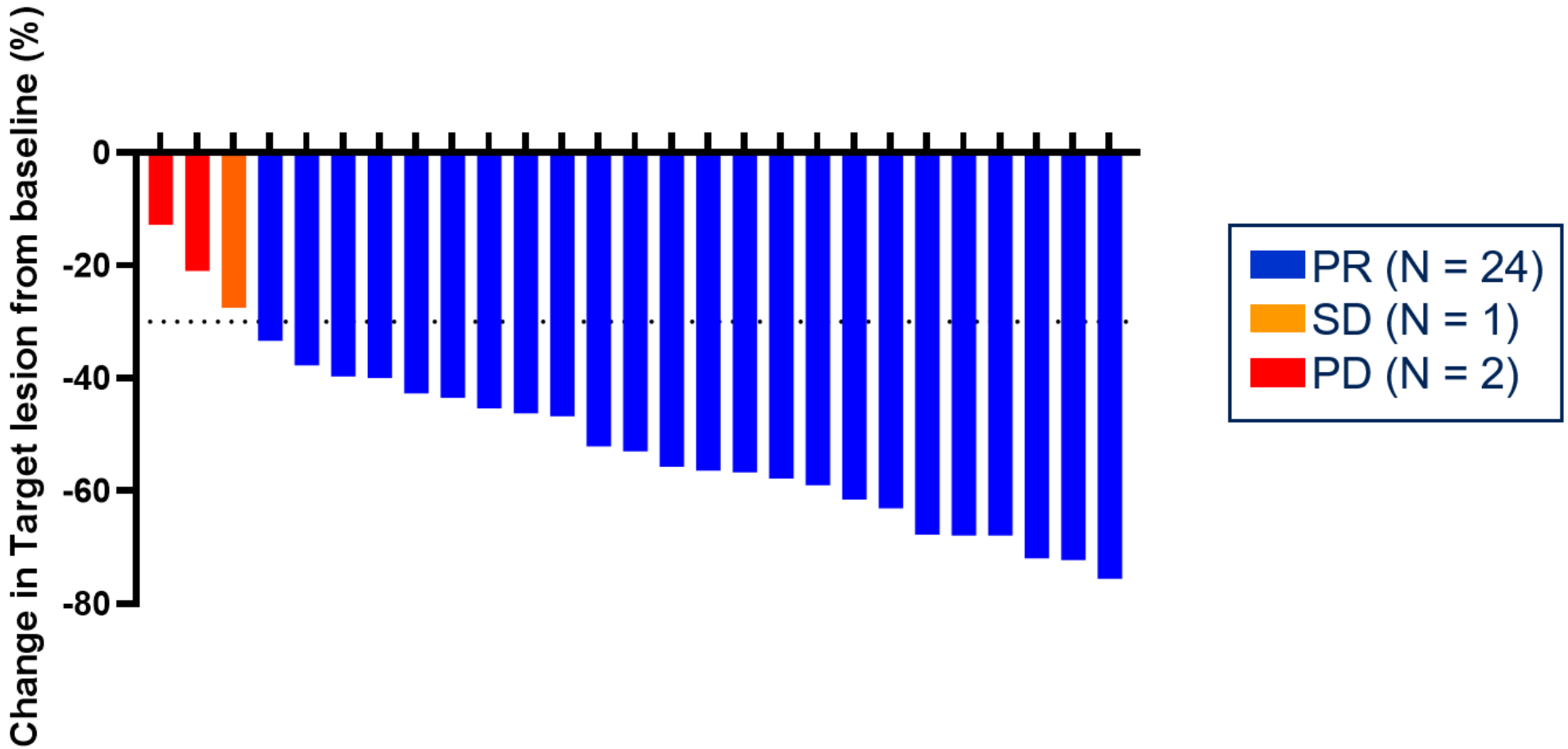
Primary endpoint: ORR by BICR

ORR 88.9% (80%CI 76.9-95.8%, 95%CI 70.8-97.6%)



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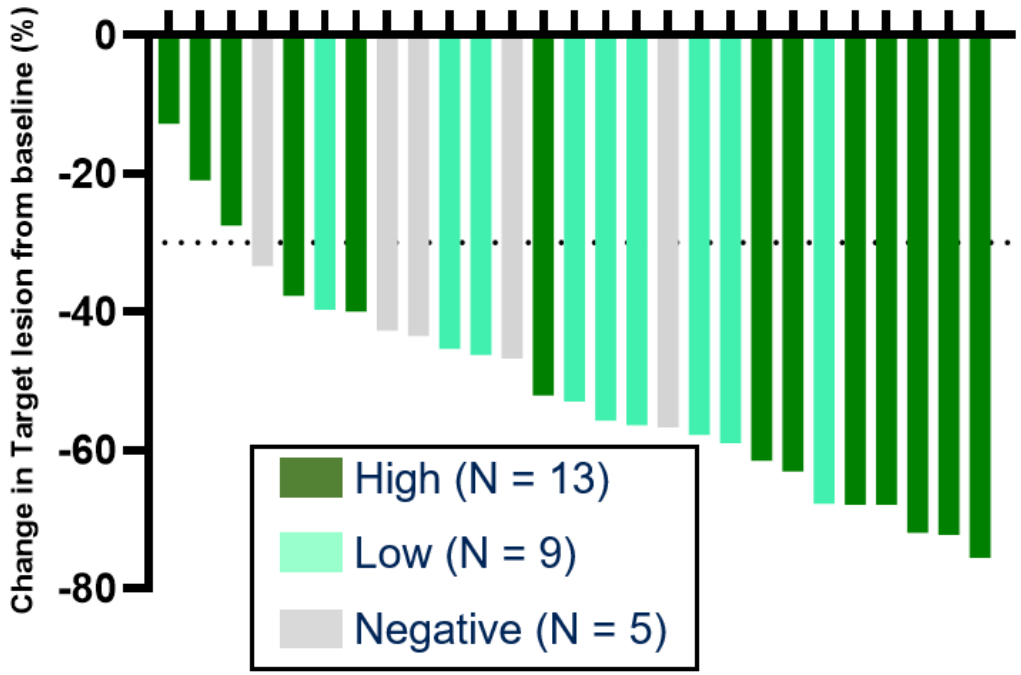
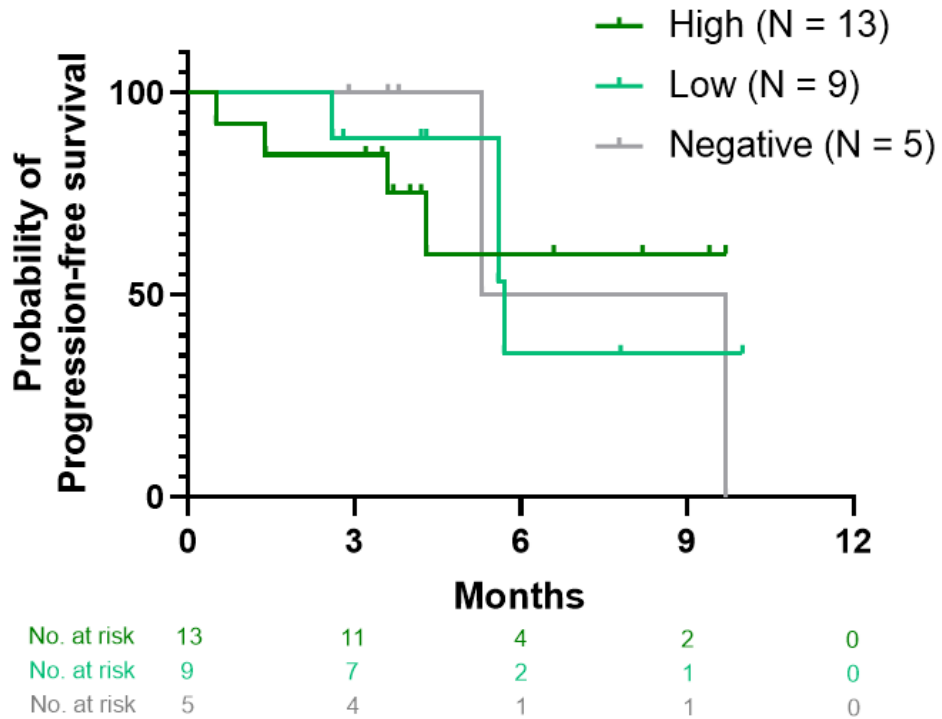
Efficacy by PD-L1 expression level





PD-L1 expression level	N	ORR	Median PFS (mo)
High (≥50%)	13	76.9% (95%CI 46.2-95.0%)	Not reached
Low (1-49%)	9	100% (95%CI 66.4-100%)	5.7
Negative (<1%)	5	100% (95%CI 47.8-100%)	7.5

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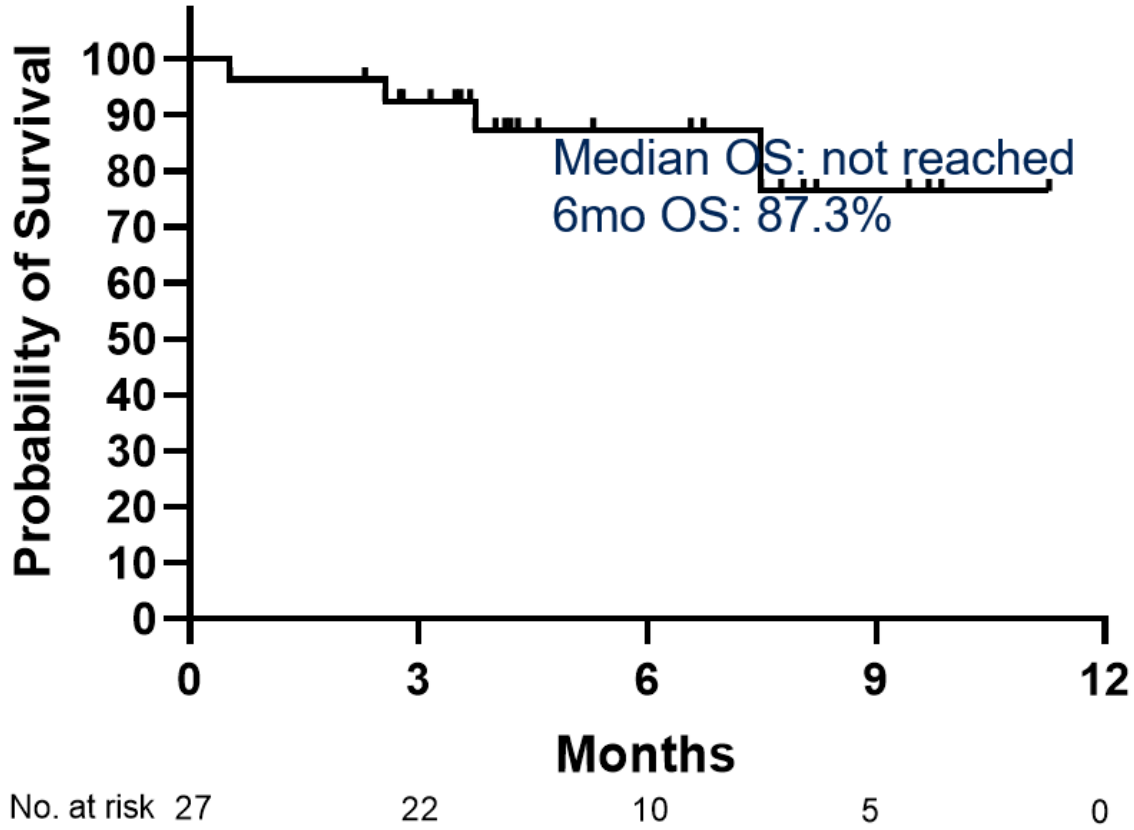
Overall survival



Post-study treatment	
No. of patients who discontinued study Tx	8
Chemotherapy	4
Radiation therapy	3
Lung	1
Bone	2
Surgery	0

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Treatment-related AEs (≥ 15% or any severe cases)

	Any Grade		>=Grade 3		Grade 1		Grade 2		Grade 3		Grade 4		Grade 5	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Any adverse event	29	100.0	21	72.4	1	3.4	7	24.1	14	48.3	6	20.7	1	3.4
Anaemia	21	72.4	11	37.9	2	6.9	8	27.6	10	34.5	1	3.4	0	0.0
PLT decreased	13	44.8	7	24.1	4	13.8	2	6.9	5	17.2	2	6.9	0	0.0
Neutrophil decreased	12	41.4	7	24.1	0	0.0	5	17.2	4	13.8	3	10.3	0	0.0
Decreased appetite	10	34.5	0	0.0	4	13.8	6	20.7	0	0.0	0	0.0	0	0.0
Nausea	10	34.5	0	0.0	3	10.3	7	24.1	0	0.0	0	0.0	0	0.0
WBC decreased	10	34.5	6	20.7	1	3.4	3	10.3	4	13.8	2	6.9	0	0.0
Malaise	8	27.6	0	0.0	5	17.2	3	10.3	0	0.0	0	0.0	0	0.0
Constipation	7	24.1	0	0.0	4	13.8	3	10.3	0	0.0	0	0.0	0	0.0
Diarrhoea	7	24.1	2	6.9	3	10.3	2	6.9	2	6.9	0	0.0	0	0.0
γ-GTP increased	6	20.7	1	3.4	4	13.8	1	3.4	1	3.4	0	0.0	0	0.0
Neutropenia	5	17.2	3	10.3	0	0.0	2	6.9	3	10.3	0	0.0	0	0.0
Hiccups	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
ALT increased	5	17.2	1	3.4	2	6.9	2	6.9	0	0.0	1	3.4	0	0.0
Blood Cre increased	5	17.2	0	0.0	4	13.8	1	3.4	0	0.0	0	0.0	0	0.0
AST increased	4	13.8	2	6.9	2	6.9	0	0.0	2	6.9	0	0.0	0	0.0
Hyperkalaemia	3	10.3	1	3.4	0	0.0	2	6.9	1	3.4	0	0.0	0	0.0
Lymph decreased	3	10.3	1	3.4	1	3.4	1	3.4	1	3.4	0	0.0	0	0.0
Cellulitis	2	6.9	1	3.4	0	0.0	1	3.4	1	3.4	0	0.0	0	0.0
Pneumonia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	0	0.0	1	3.4
Thrombocytopenia	2	6.9	1	3.4	0	0.0	1	3.4	0	0.0	1	3.4	0	0.0
Anaphylactic reaction	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Gastritis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0
Cholecystitis	1	3.4	1	3.4	0	0.0	0	0.0	1	3.4	0	0.0	0	0.0

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Conclusion

- Sotorasib in combination with CBDCA/PEM demonstrated favorable ORR and tolerability in advanced non-Sq, NSCLC patients with KRAS G12C mutation.

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Conclusions

- Broad molecular testing at the time of diagnosis is essential to select the optimal treatment (NGS DNA & RNA in tissue and NGS DNA in blood are what we have right now).
- BLU-945 plus Osimertinib is an emerging combination which has demonstrated clinical activity post-OSI progression, well tolerated and infrequent EGFR WT toxicity.
- MET 3+ staining on > 25% of tumor cells by IHC is a predictive biomarker for Amivantamab plus Lazertinib in post-OSI progression, chemo-naïve setting. (CHRYSALIS-2, Cohort D).
- WU-KUNG6 study revealed ORR 61% for sunvozertinib in patients previously treated with chemotherapy and harboring EGFRex20ins.
- Sunvozertinib shown CNS activity, RR regardless of EGFRex20ins subtypes and location, and good toxicity profile.

Conclusions

- In the phase 1/2 TRIDENT-1 trial, repotrectinib demonstrated durable clinical activity in both ROS1 TKI-naïve and TKI-pretreated patients with *ROS1+* advanced NSCLC with or without baseline CNS metastases.
- Encorafenib and binimetinib showed a meaningful clinical benefit with an acceptable safety profile in $BRAF^{V600E}$-mutant metastatic NSCLC in PHAROS study.
- Patients whose tumors harbor KRAG12C and additional KRAS co-alterations were more refractory to either sotorasib and docetaxel in CodeBreak 200 study.
- JDQ443, a novel $KRAS^{G12C}$ inhibitor showed an ORR of 57.1% and DCR 92.9% at 200 mg BID.
- SCARLET study revealed ORR 88.9% and great tolerability of sotorasib/platinum/ pemetrexed in advanced NSCLC.