Updates in Targeted Therapies for NSCLC

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UCDAVIS COMPREHENSIVE CANCER CENTER

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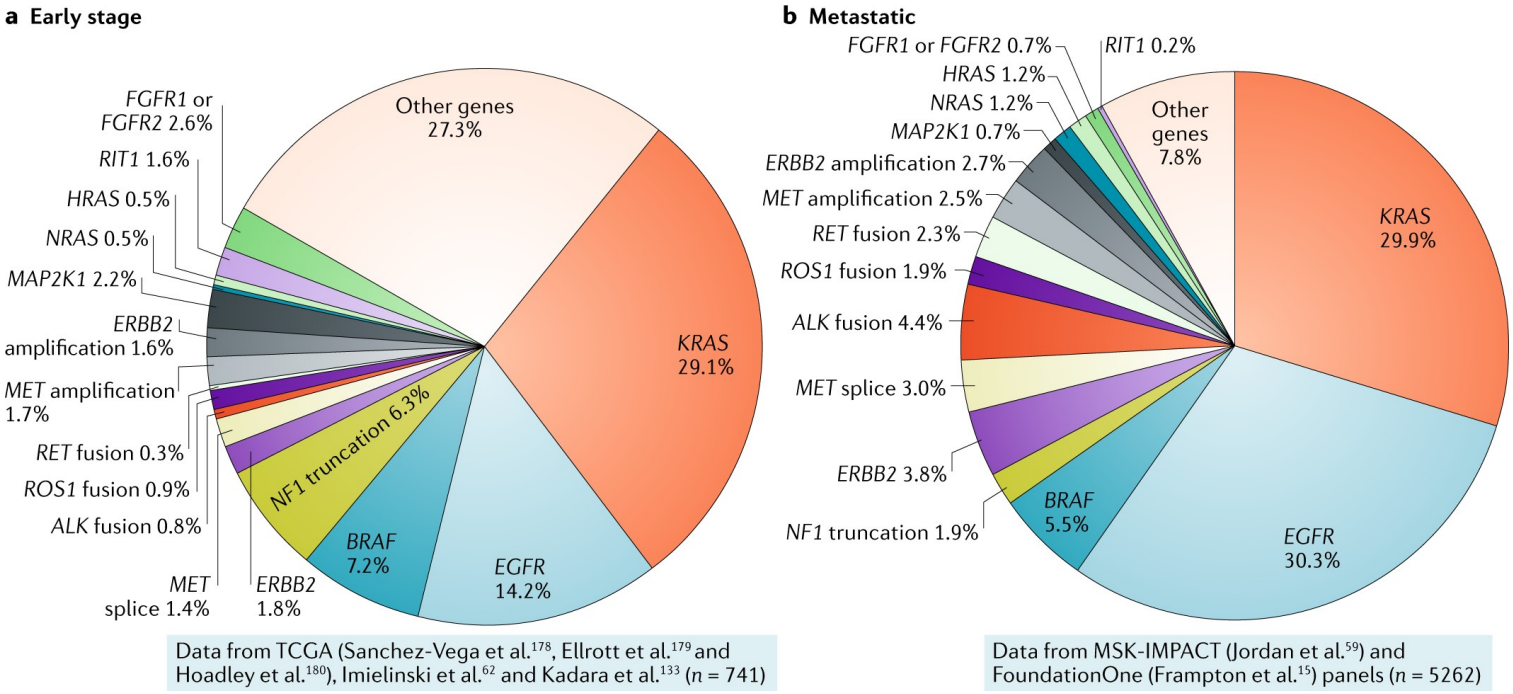
Disclosures

- Grant/Research Support (To Institution): Merck, AstraZeneca, Novartis, Spectrum

- Consultant (Advisory Board): Celgene, Boehringer Ingelheim, Novartis, Blueprint

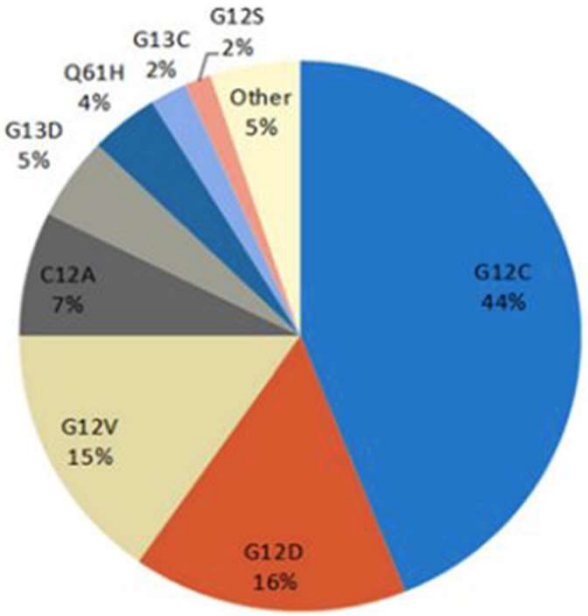
Targetable Alterations

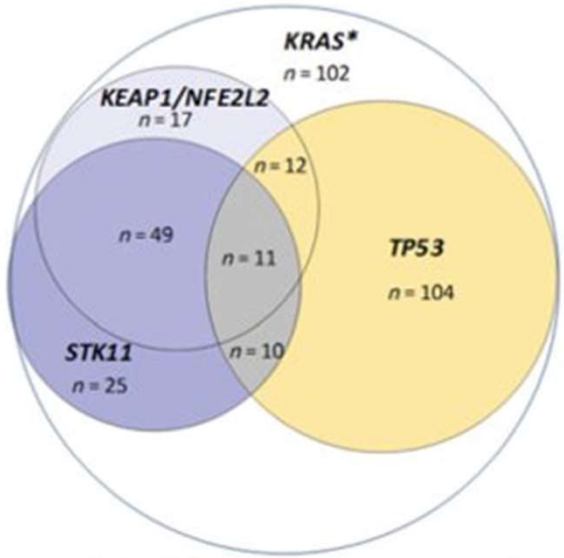


Data from TCGA (Sanchez-Vega et al.[178], Ellrott et al.[179] and Hoadley et al.[180]), Imielinski et al.[62] and Kadara et al.[133] (n = 741)

Data from MSK-IMPACT (Jordan et al.[59]) and FoundationOne (Frampton et al.[15]) panels (n = 5262)

Spectrum of KRAS mutations and Co-Mutations in NSCLC

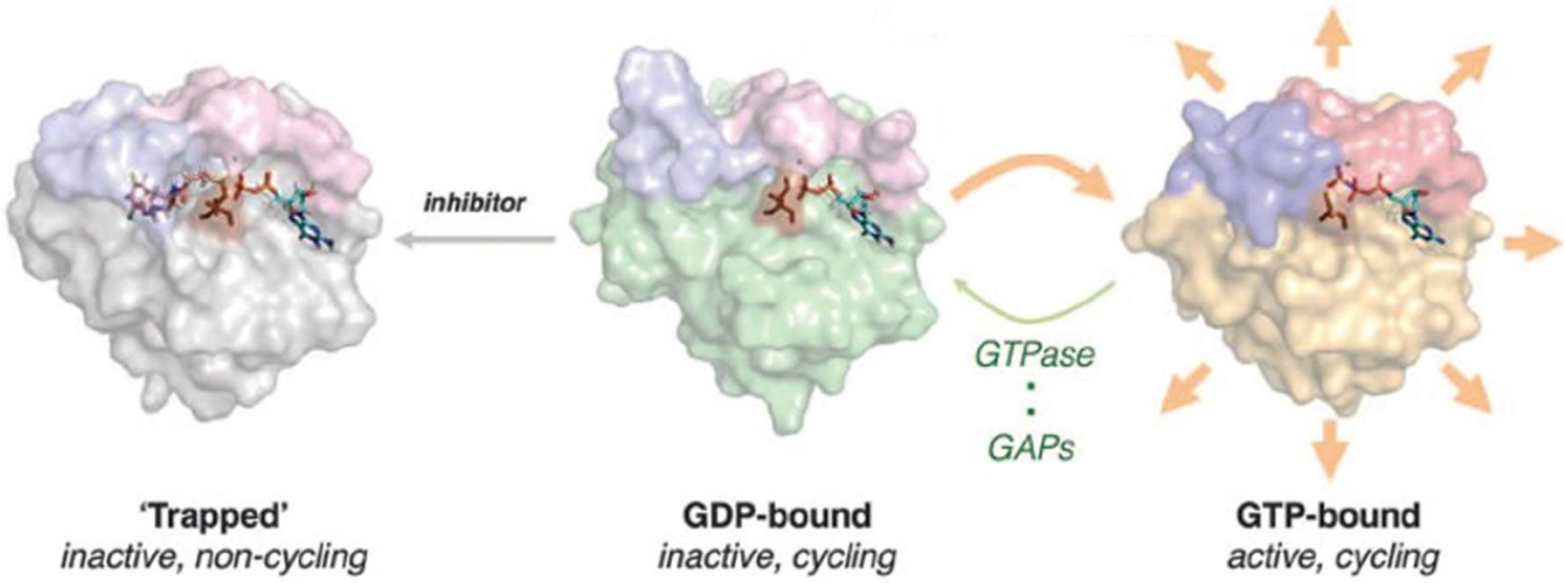




*KRAS (*n* = 102) listed above represents number of patients with *KRAS* mutations but without cooccurring mutations in *TP53*, *STK11*, *KEAP1* or *NFE2L2*

Arbour et al CCR 2018

KRAS G12C Inhibitors Bind, Inactive GDP bound RAS and Trap It In Inactive State

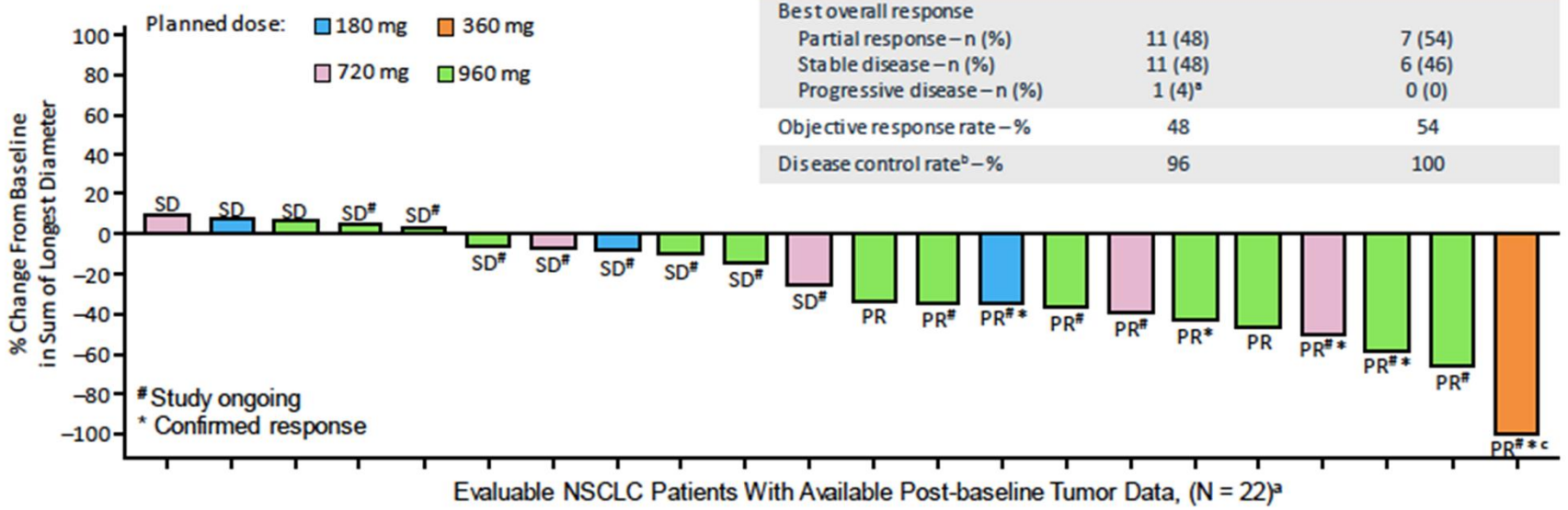


From P. Lito et al. Science 2016

AMG510: Best Response in NSCLC

Efficacy in NSCLC Patients

Efficacy outcomes	All evaluable patients N = 23	Evaluable patients treated with 960mg N = 13
Best overall response		
Partial response – n (%)	11 (48)	7 (54)
Stable disease – n (%)	11 (48)	6 (46)
Progressive disease – n (%)	1 (4)[a]	0 (0)
Objective response rate – %	48	54
Disease control rate[b] – %	96	100



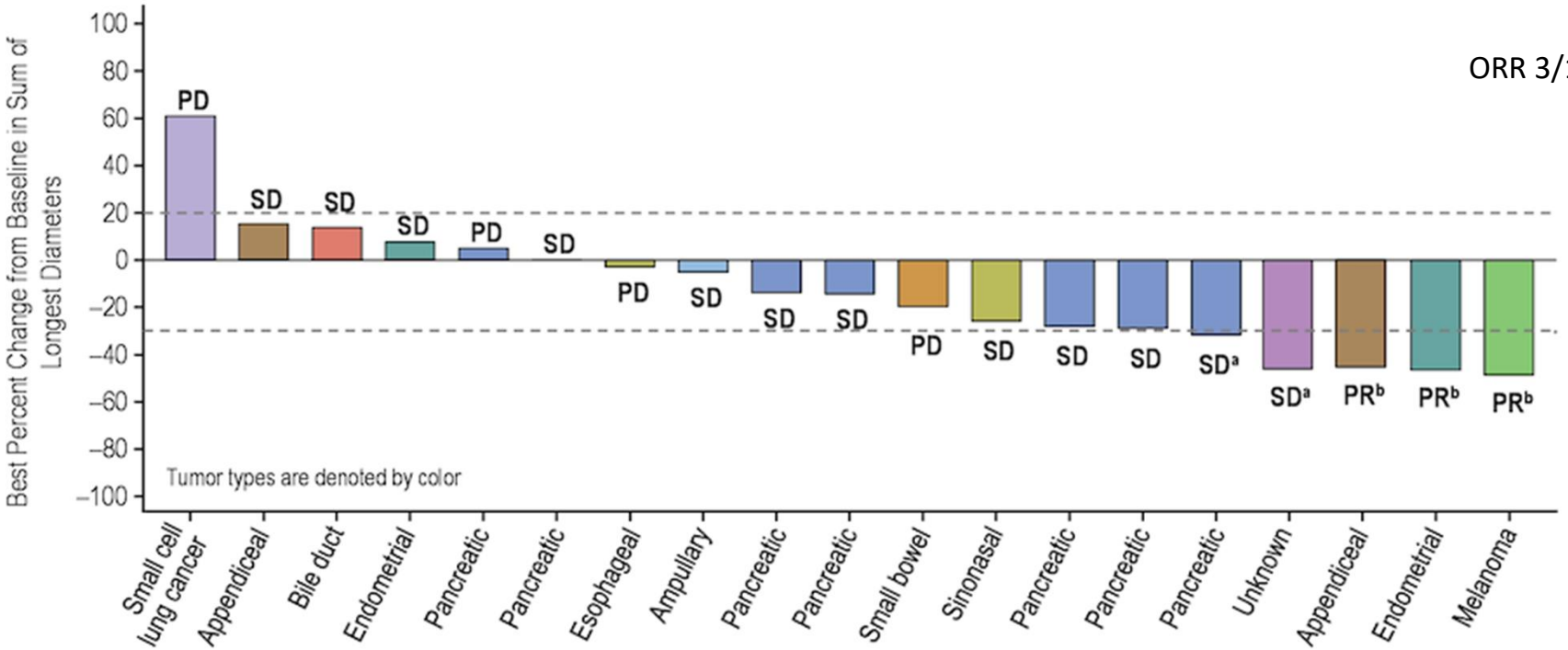
[a]One patient discontinued study due to PD prior to the 1st assessment, and the post-baseline tumor burden data are missing. [b]PR or SD at week 6. [c]Patient had complete response to the target lesions. Evaluable patients: patients who had the first 6-week scan or early PD

Govindan R. et al. WCLC 2019. Abstract PR02.02.

Govindan R. et al. WCLC 2019; Abstract PR02.02

AMG510: Best Response in Other KRAS G12C mutant Cancers

ORR 3/19

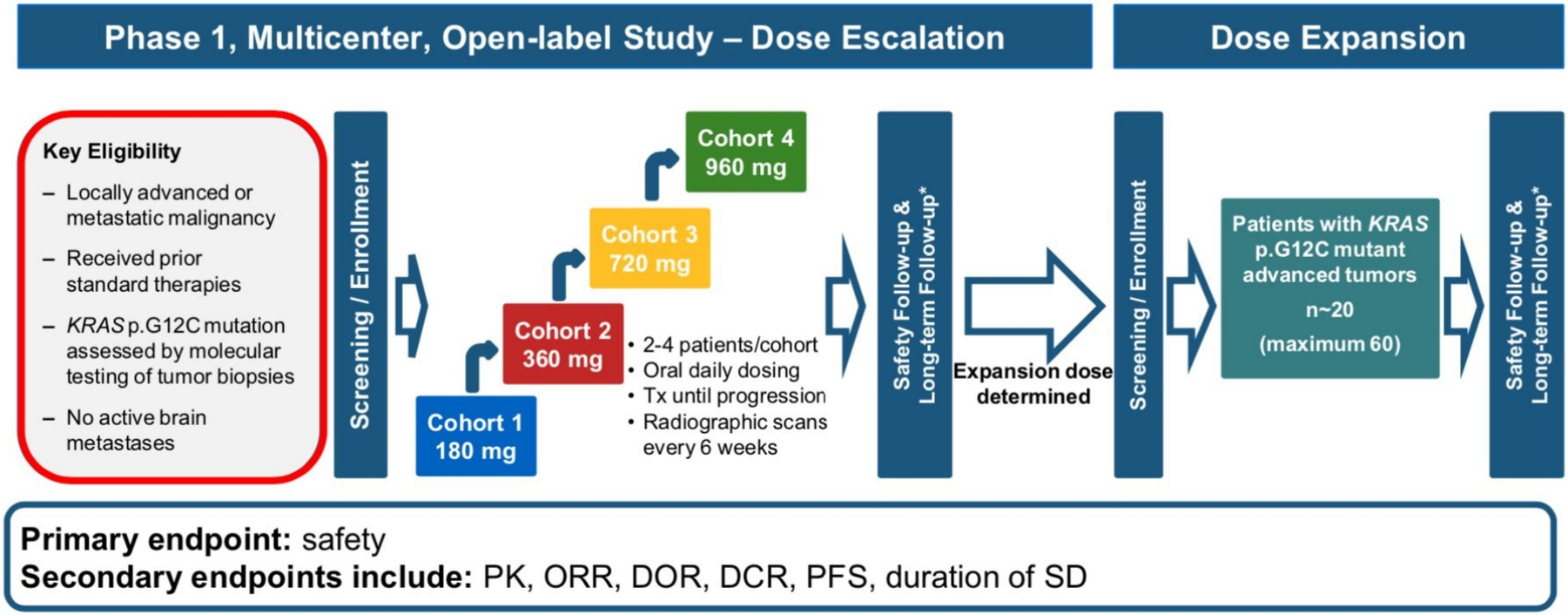


Three patients are not included due to missing postbaseline tumor data: 2 patients with appendiceal cancer (1 PD, 1 SD) and 1 with pancreatic cancer (PD)
[a]Patients had unconfirmed PR; [b]Of 3 patients with confirmed PR, 1 with appendiceal cancer received 720 mg and the other 2 received 960 mg.

Hong et al. ASCO 2020

VIRTUAL 2020 ESMO congress

Phase 1 study design (CodeBreaK100: NCT03600883)



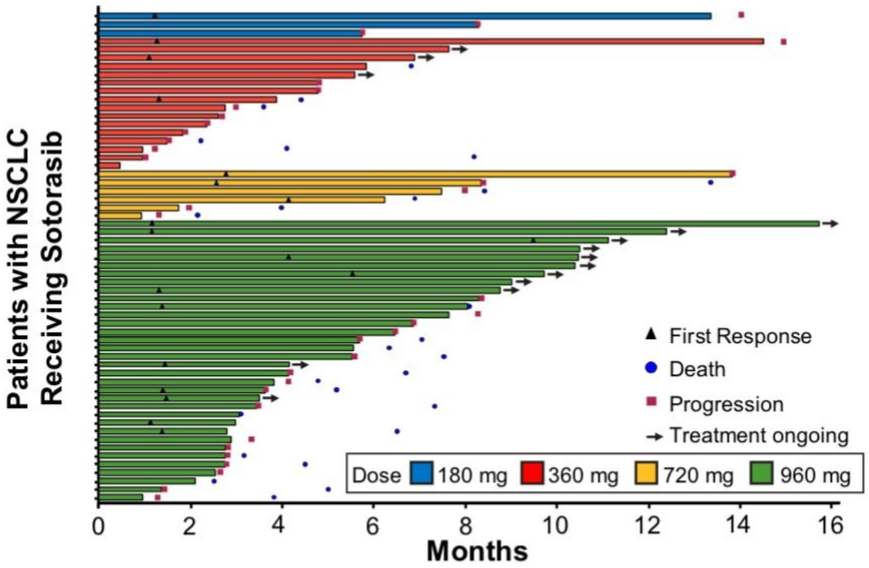
Primary endpoint: safety
Secondary endpoints include: PK, ORR, DOR, DCR, PFS, duration of SD

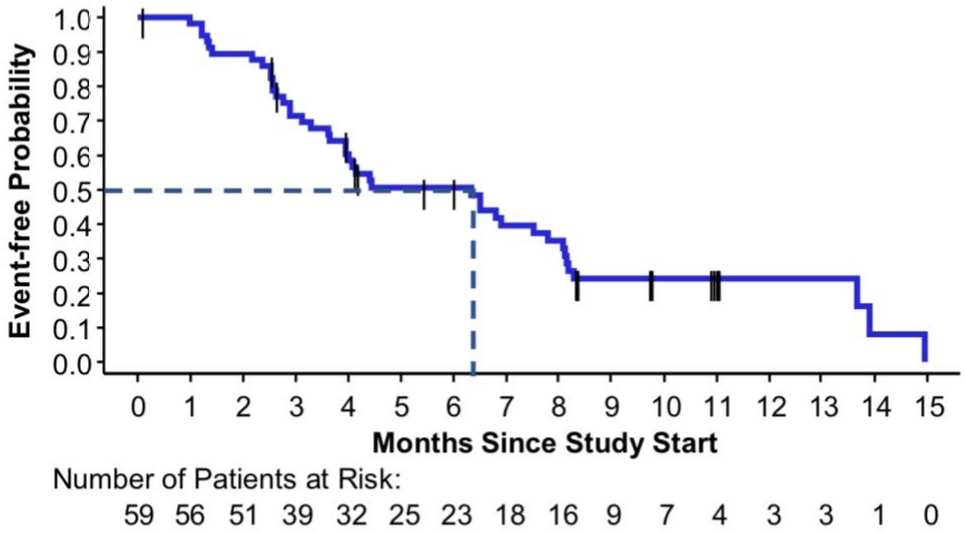
*30 (+7) days after end of treatment for safety follow-up; every 12 weeks for long-term follow-up.

DCR, disease control rate; **DLT,** dose-limiting toxicity; **DOR,** duration of response; **KRAS,** Kirsten rat sarcoma viral oncogene homolog; **ORR,** objective response rate; **PFS,** progression-free survival; **PK,** pharmacokinetic; **RP2D,** recommended phase 2 dose; **SD,** stable disease; **Tx**, treatment.

VIRTUAL ESMO congress 2020

Durability of clinical benefit and progression-free survival





Confirmed PR, n = 19

Duration of response*
Median of 10.9 (1.1+ to 13.6) months
10/19 responders still in response†

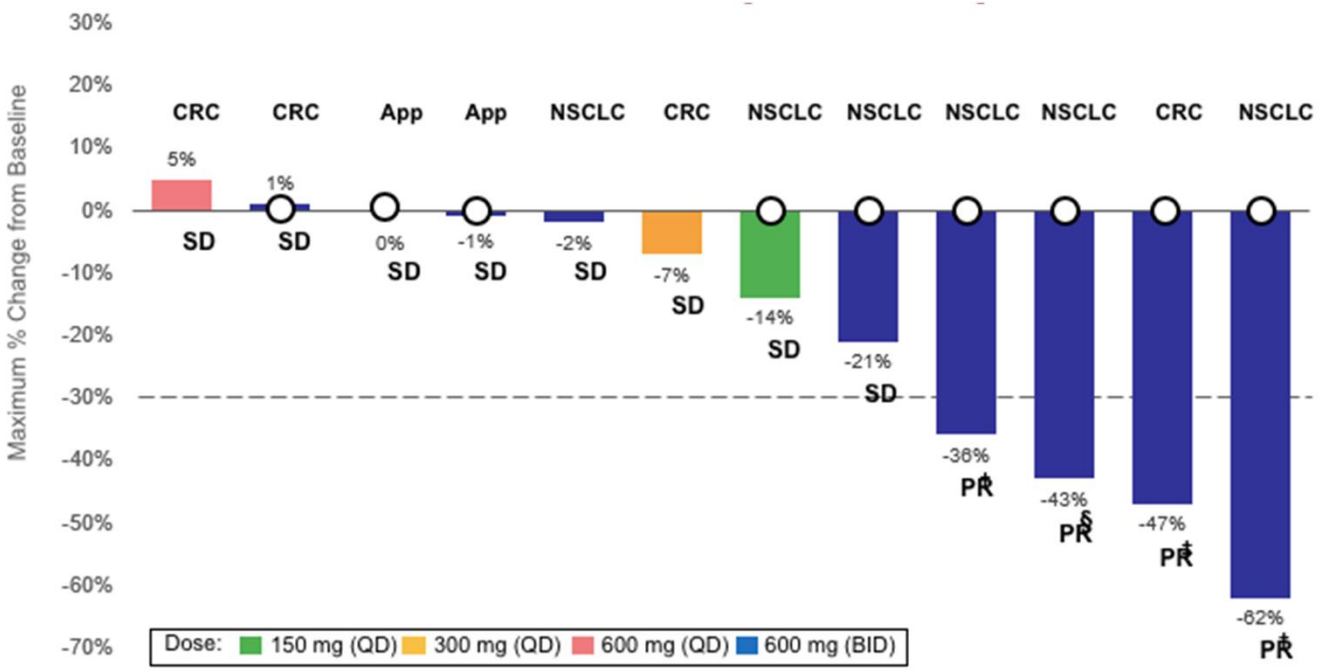
Patients with SD, n = 33

Duration of stable disease‡
Median of 4.0 (1.4 to 10.9+) months

Median PFS: 6.3 (range 0.0+ to 14.9) months

*Duration of response was measured from first evidence of PR/CR to disease progression or death due to any cause, whichever was earlier. ‡Duration of SD was measured from the start of the treatment until the criteria for disease progression were met or death, whichever was earlier. †At data cutoff of June 1, 2020; + Indicates censored value; median follow-up time was 11.7 (range 4.8-21.2) months.
NSCLC, non-small cell lung cancer; **PR,** partial response; **SD,** stable disease. **PFS**, progression-free survival

MTRX849: Best Tumor Response



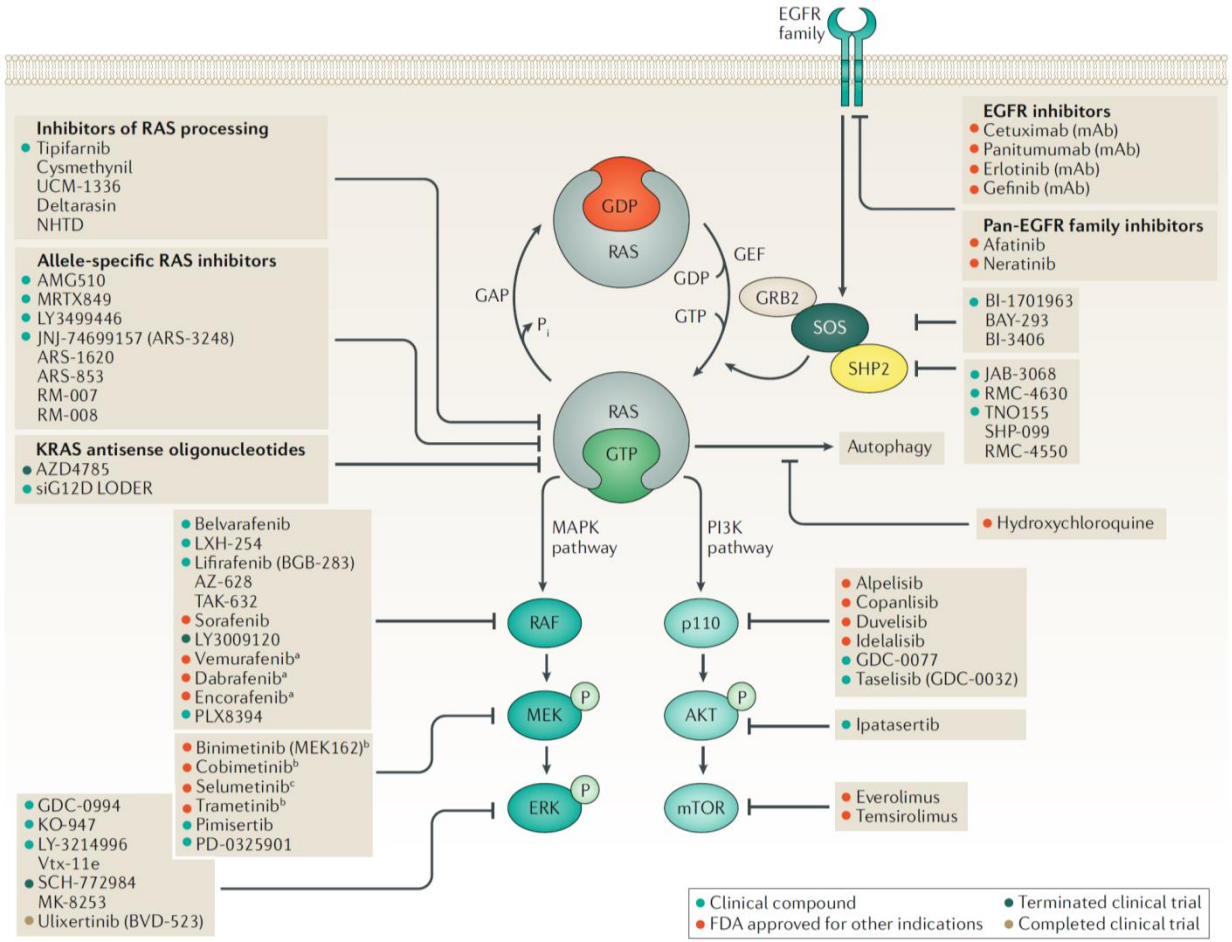
Evaluable Patients at All Doses	
NSCLC	ORR: 3/6 DCR: 6/6
CRC	ORR: 1/4 DCR: 3/4
Append	ORR: 0/2 DCR: 2/2

DCR: Disease Control Rate
(SD+PR at 6 weeks)

* Based on local radiographic scans every 6 weeks using RECIST 1.1 criteria
‡ Confirmed response (1st scan: -37%, 2nd scan: -47%); † Response yet to be confirmed (on study but only 1 scan)
§ Patient had confirmed PR post data cut-off (1st scan: -33%, 2nd scan: -43%)
O Patient on study (off study patients: 1 progressive disease, 1 global deterioration of health, 1 patient withdrawal of consent)

Data cut-off date: 11-Oct-2019

Targeting Kras mutations

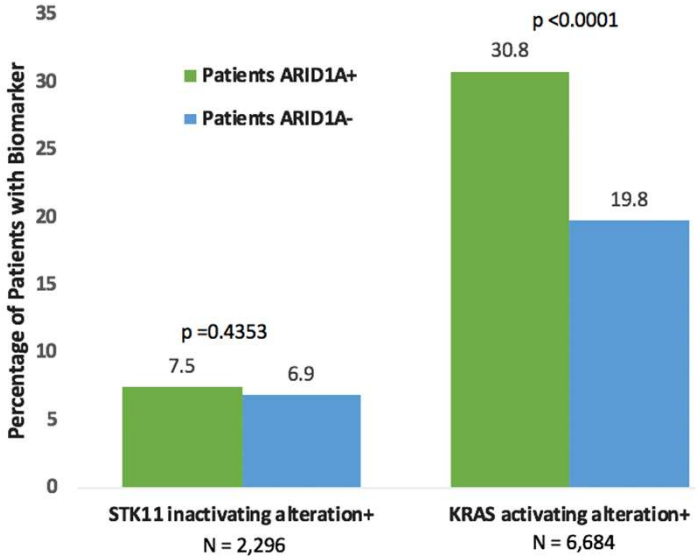


Direct G12Ci
JNJ-74699157
MTRX849
AMG510
LY4399446

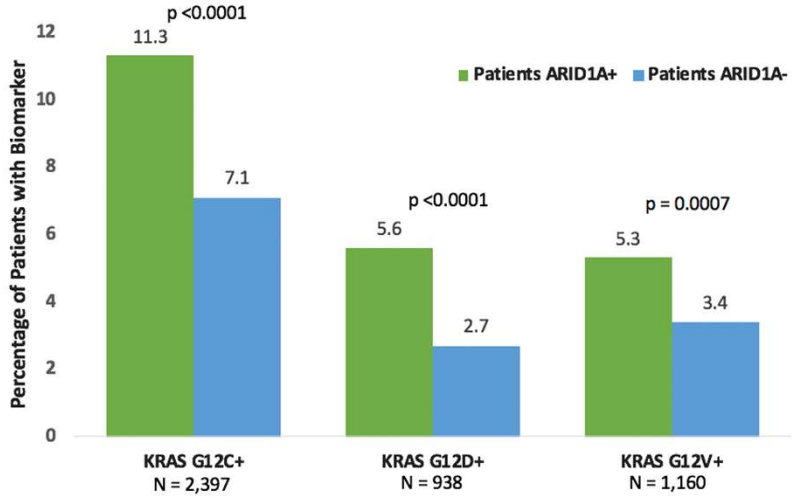
Moore, et al Nature Reviews, Drug Discovery 2020

Mechanism of Action	Drug
PD-1	Pembrolizumab
EGFR-TKI	Afatinib
EGFR moAb	Cetuximab (CRC)
CDK4/6i	Palbociclib

Activating *KRAS* mutations were significantly more frequent in patients with f*ARID1A* mutations

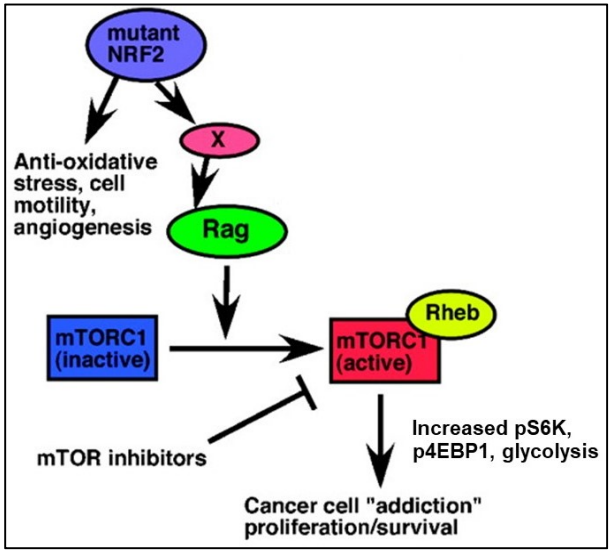


KRAS mutations associated with smoking (G12C/V) and non- smoking (G12D) were significantly more frequent in patients with f*ARID1A* mutations

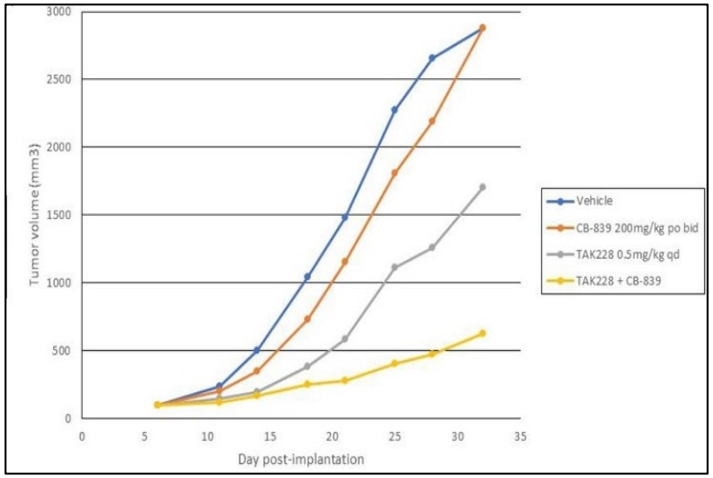


References: Herbst R, et al. ESMO Immuno-Oncology Congress, 2019; Aggarwal C, et al. *Clin Canc Res*, 2020; Skoulidis F, et al. *Cancer Discovery,* 2018; Skoulidis F, et al. World Conference on Lung Cancer, 2018

NRF2 upregulation (~25% KRAS-mut NSCLC via KEAP1 mutation) increases glycolysis and inhibition of glutaminolysis with CB-839 exhibits synergistic anti-tumor activity



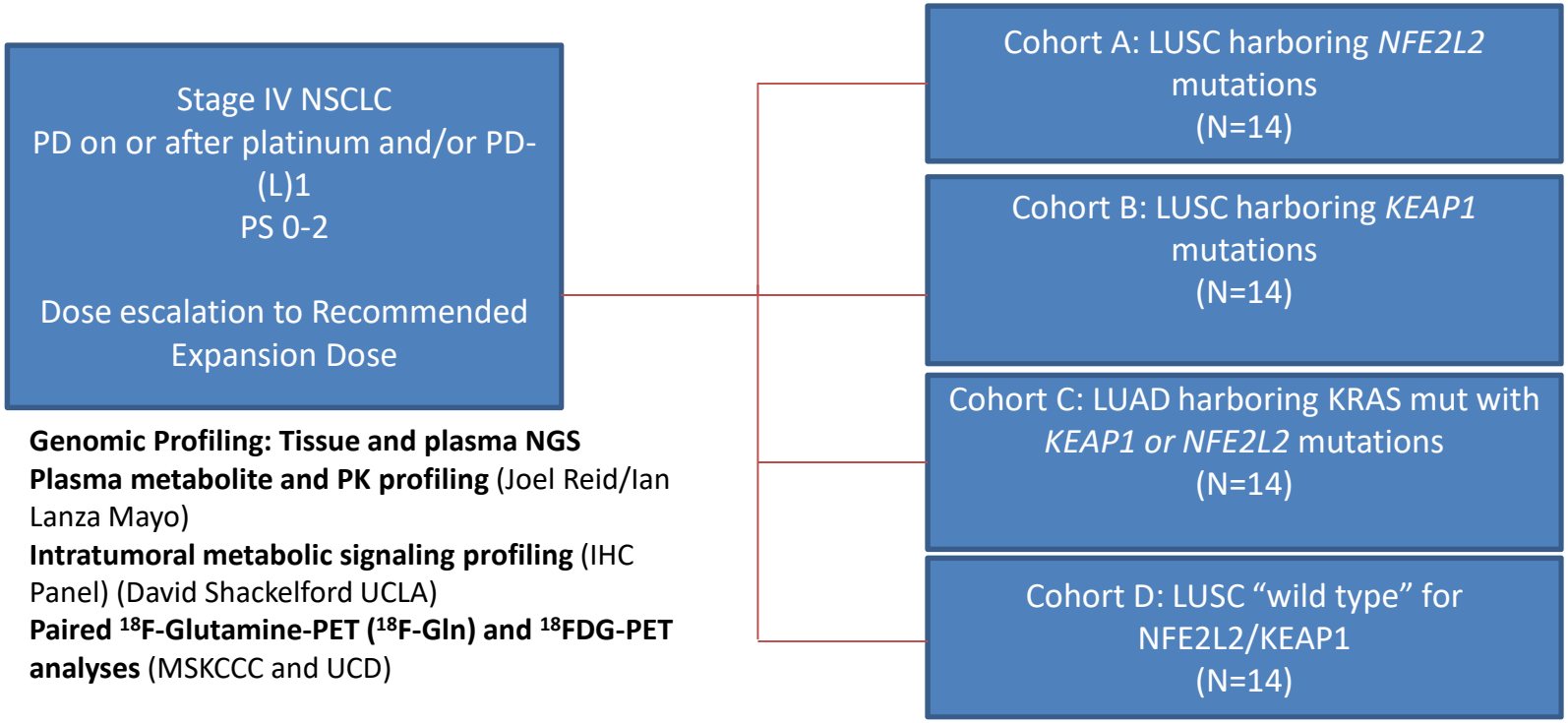
NRF2 upregulation activated TORC1 with increase in pS6K, p4EBP1, glycolysis, and proliferation/survival (adapted from Shibata et al. CCR 2010)



TAK228 and CB-839 exhibit synergistic anti-tumor activity in A549 *KRAS/KEAP1* co-mutant xenograft. Mice were treated with vehicle, CB-839, TAK228, or the combination of TAK228 + CB-389. **Courtesty of P. Paik et al.**

Keap1 loss promotes dependence on glutaminolysis in KRAS mut NSCLC (Romero et al Nat Med 2017)

A Phase 1 Trial of TAK-228 (Sapanisertib) and CB-839 in Advanced NSCLC (NCI 10327; PHI-II3)



- **Genomic Profiling: Tissue and plasma NGS**
- **Plasma metabolite and PK profiling** (Joel Reid/Ian Lanza Mayo)
- **Intratumoral metabolic signaling profiling** (IHC Panel) (David Shackelford UCLA)
- **Paired ^{18}F-Glutamine-PET (^{18}F-Gln) and ^{18}FDG-PET analyses** (MSKCCC and UCD)

co-PIs: JW Riess, P. Paik

EGFR Updates

FLAURA: Osimertinib vs Gefitinib/Erlotinib in EGFR-mutated NSCLC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- **≥18 years***
- **WHO performance status 0 / 1**
- **Exon 19 deletion / L858R (enrolment by local# or central‡ EGFR testing)**
- **No prior systemic anti-cancer / EGFR-TKI therapy**
- **Stable CNS metastases allowed**

Stratification by **mutation status** (Exon 19 deletion / L858R) and **race** (Asian / non-Asian)

Osimertinib (80 mg p.o. qd) (n=279)

Randomised 1:1

EGFR-TKI SoC§; **Gefitinib** (250 mg p.o. qd) or **Erlotinib** (150 mg p.o. qd) (n=277)

RECIST 1.1 assessment every 6 weeks¶ until objective progressive disease

Crossover was allowed for patients in the **SoC** arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

Endpoints
- **Primary endpoint: PFS** based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

FLAURA data cut-off: 12 June 2017; NCT02296125

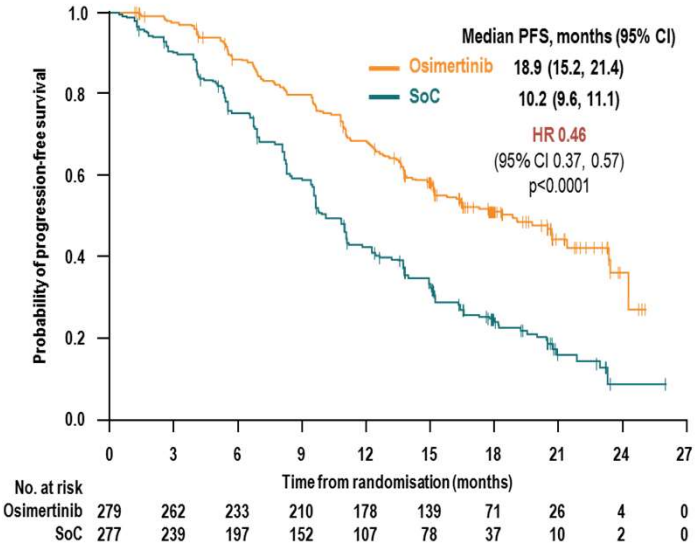
*≥20 years in Japan; #With central laboratory assessment performed for sensitivity; ‡cobas EGFR Mutation Test (Roche Molecular Systems); §Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; ¶Every 12 weeks after 18 months

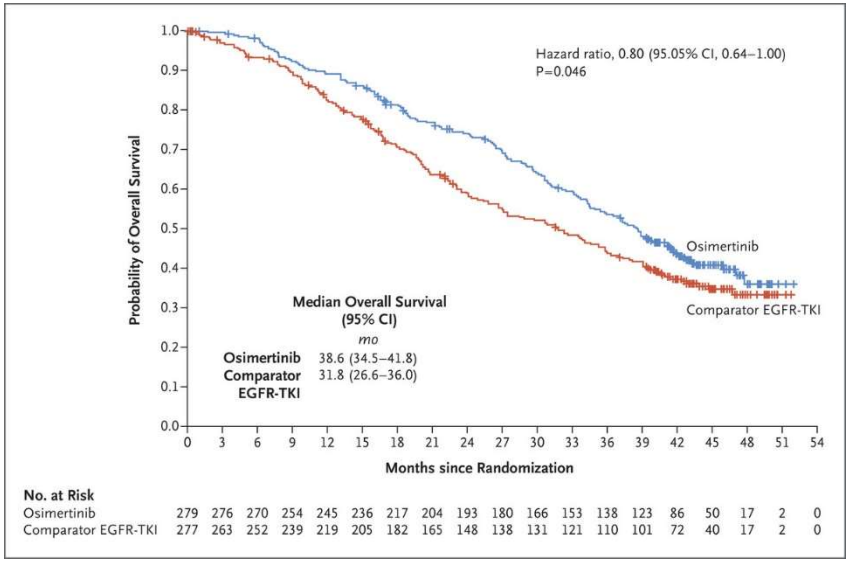
CNS, central nervous system; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; p.o., orally; RECIST 1.1, Response Evaluation Criteria In Solid Tumors version 1.1; qd, once daily; SoC, standard-of-care;

TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Ramalingam S, et al. ESMO 2017. Abstract LBA2_PR

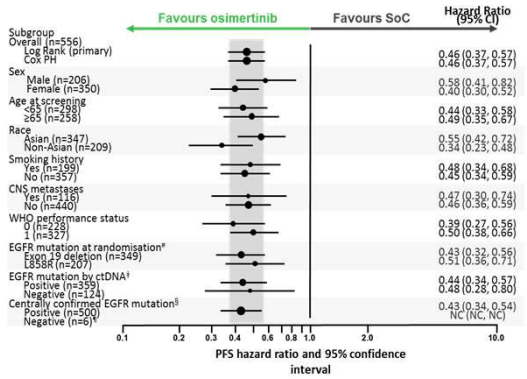
PFS and OS from FLAURA





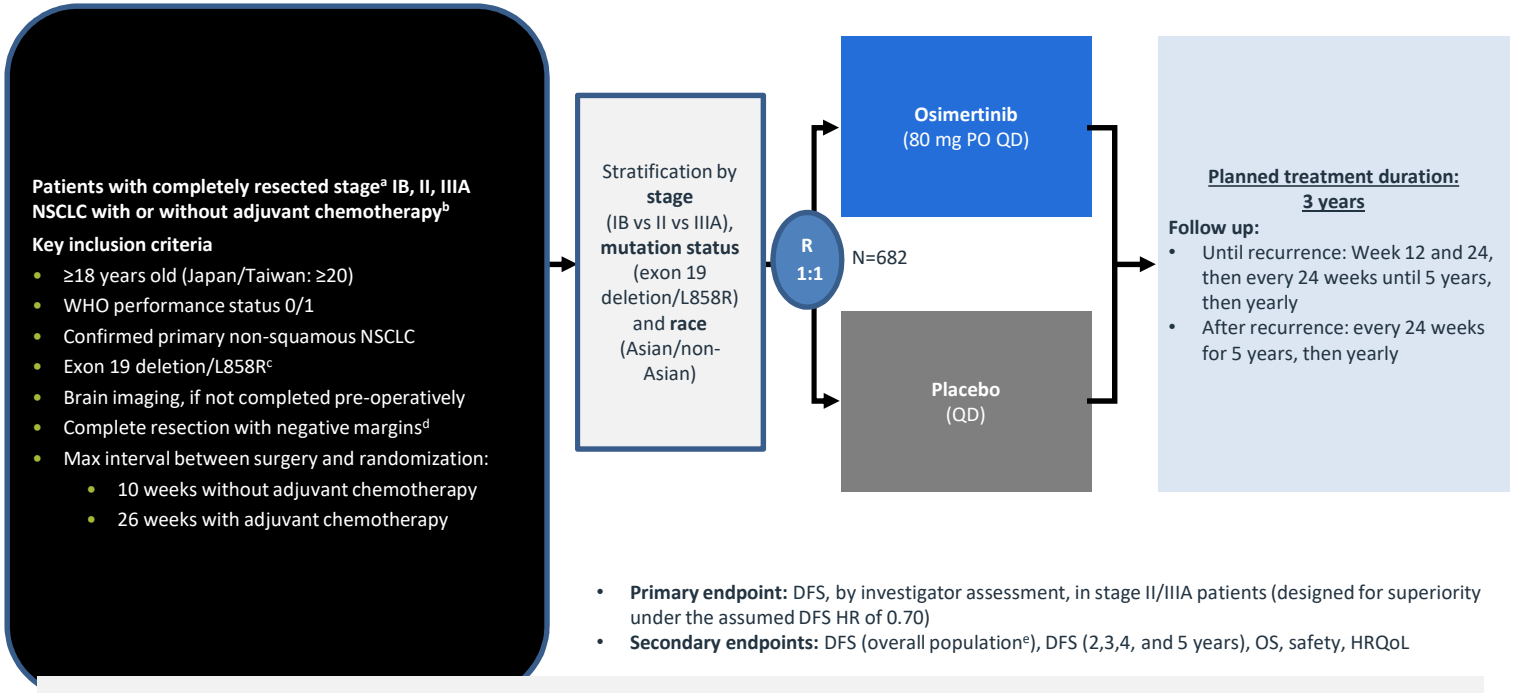
PFS in patients with brain mets (n=116)
HR=0.47
PFS in patients without brain mets (n=440)
HR=0.46

mOS 38.6 vs. 31.8 months



Ramalingam et al. ESMO 2017, NEJM 2020.

ADAURA: Osimertinib as adjuvant therapy in patients with stage IB–IIIA *EGFR*m NSCLC after surgical resection



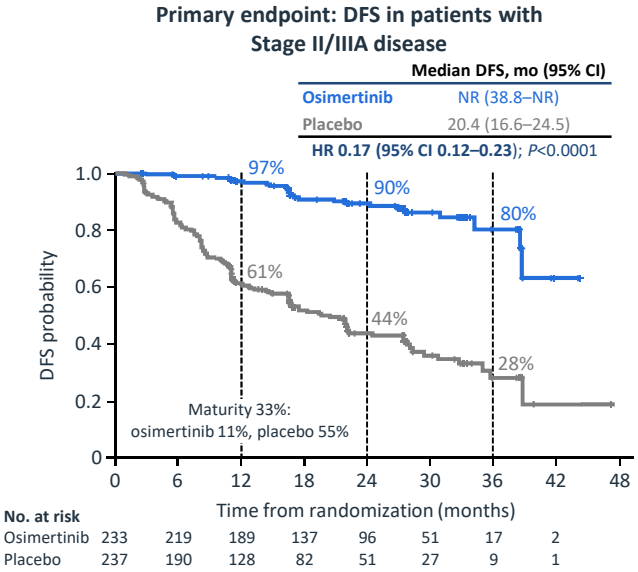
- **Primary endpoint:** DFS, by investigator assessment, in stage II/IIIA patients (designed for superiority under the assumed DFS HR of 0.70)
- **Secondary endpoints:** DFS (overall population[e]), DFS (2,3,4, and 5 years), OS, safety, HRQoL

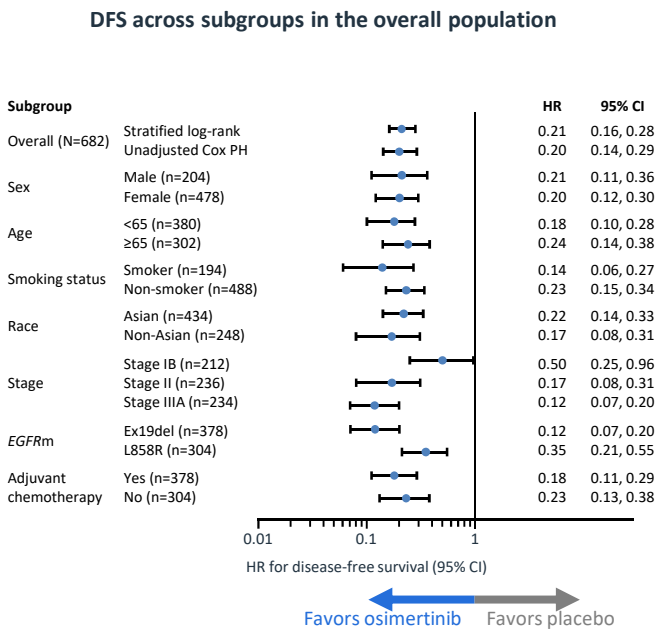
- **Following data monitoring committee recommendation, the study was unblinded early due to efficacy; reported here is an unplanned interim analysis**
- **At the time of unblinding, the study had completed enrollment and all patients were followed up for ≥1 year**

[a]AJCC 7th edition; [b]Prior, post, or planned radiotherapy was not allowed; [c]Centrally confirmed in tissue; [d]Patients received a CT scan after resection and within 28 days prior to treatment; [e]Stage IB, II, IIIA.

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

ADAURA: Disease-free survival (DFS)

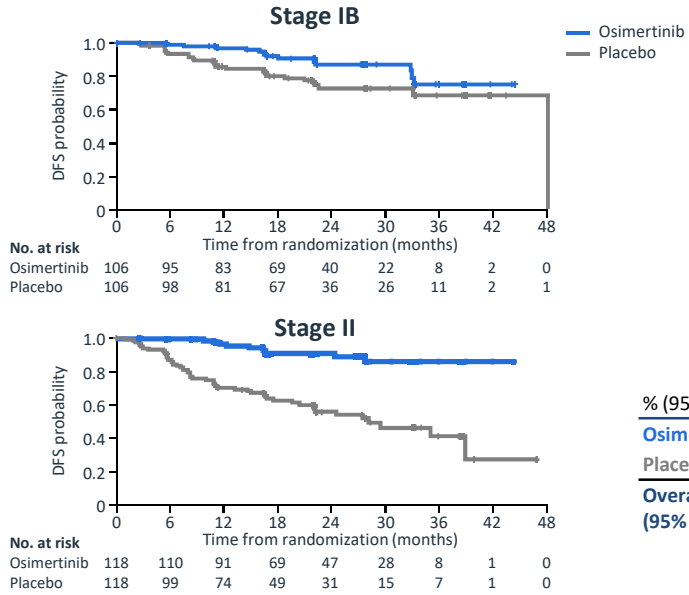


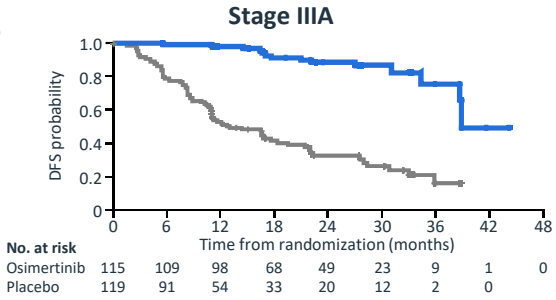


Data cutoff: January 17, 2020. NR, not reached

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

ADAURA: Disease-free survival by stage





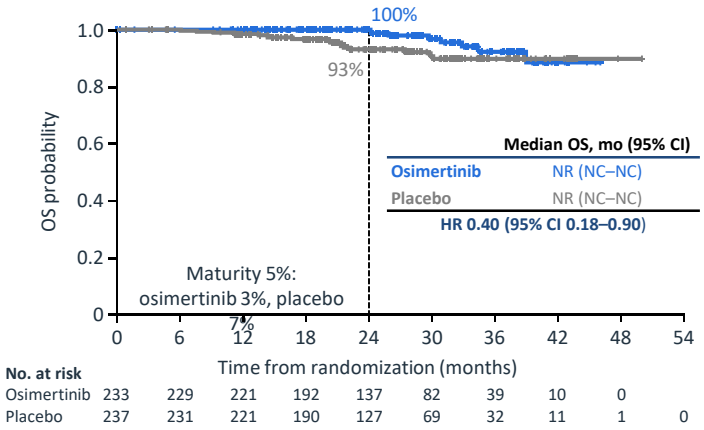
2 Year DFS rate

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

Data cutoff: January 17, 2020.

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

ADAURA: Overall survival in patients with Stage II/IIIA disease



Data cutoff: January 17, 2020.

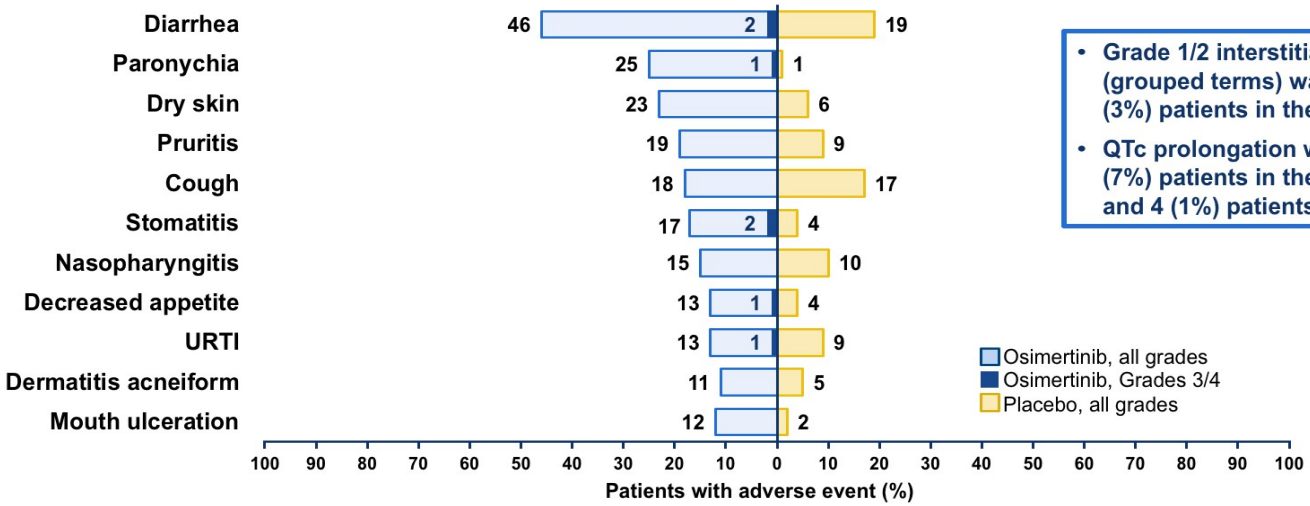
Herbst RS, et al. ASCO 2020. Abstract LBA5.

- ADAURA met its primary endpoint of improved DFS in Stage II/IIIA disease (HR 0.17)
- The trial was closed early by the safety and monitoring committee, and OS estimates are immature
- It is unique in delivery of adjuvant EGFR TKI for 3 years (compared to 2)
- Not yet FDA approved
- Lots of debate about whether to utilize osimertinib or not in this setting

ADAURA: AE's

All causality adverse events (≥10% of patients)

Median duration of exposure: osimertinib: 22.3 months (range 0 to 43), placebo: 18.4 months (range 0 to 48)

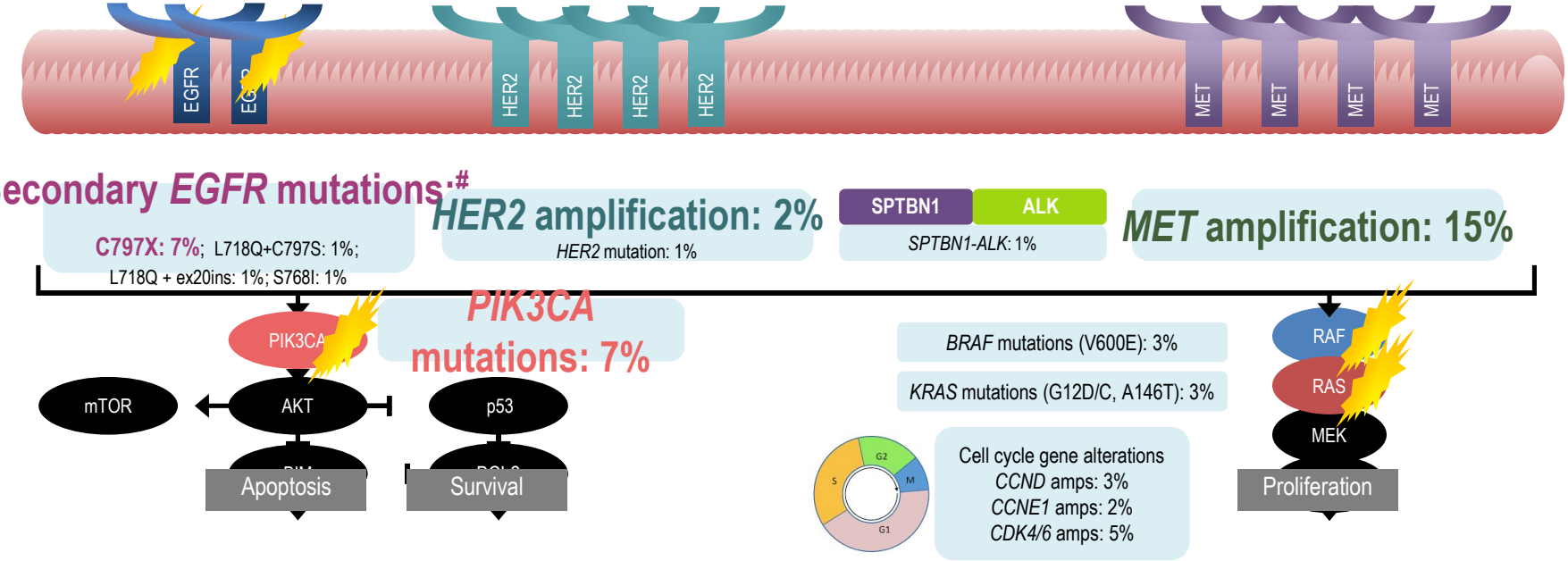


- **Grade 1/2 interstitial lung disease (grouped terms) was reported in 10 (3%) patients in the osimertinib arm***
- **QTc prolongation was reported in 22 (7%) patients in the osimertinib arm and 4 (1%) patients in the placebo arm†**

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

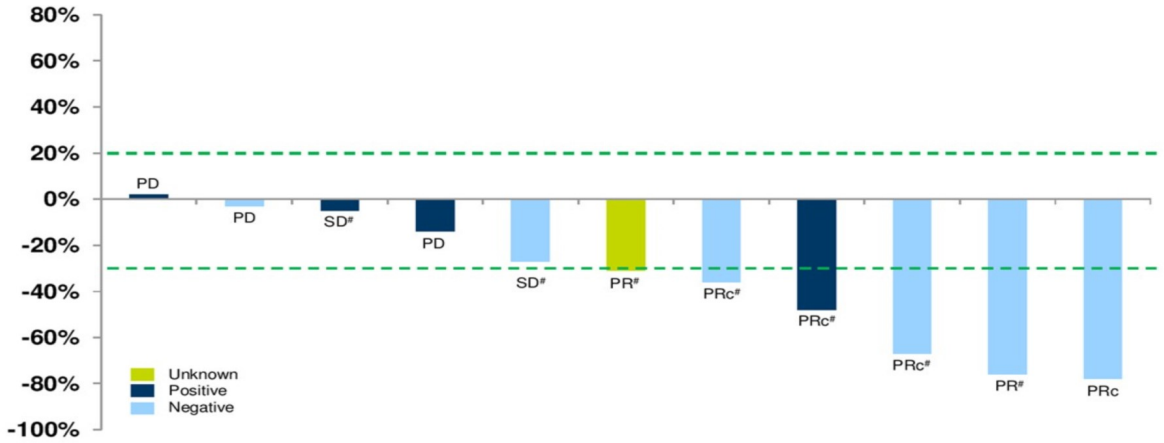
RESULTS of CURRENT STUDY: CANDIDATE ACQUIRED RESISTANCE MECHANISMS WITH OSIMERTINIB (n=91)*

- **No evidence of acquired EGFR T790M**
- **The most common resistance mechanisms were *MET* amplification and *EGFR* C797S mutation**
  - **Other mechanisms included *HER2* amplification, *PIK3CA* and *RAS* mutations**

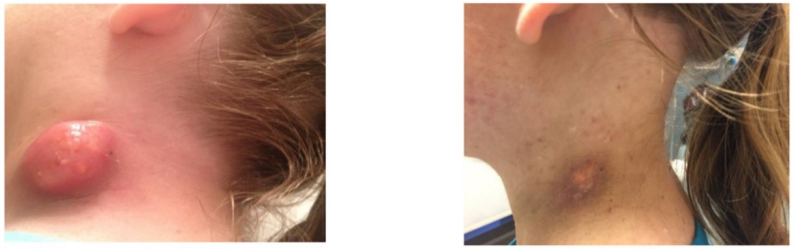


*Resistance mechanism reported may overlap with another; #Two patients had *de novo* T790M mutations at baseline of whom one acquired C797S at progression

Osimertinib and Savolitinib in *EGFR*+ NSCLC



*Population: all patients dosed who had a baseline and 6-week RECIST assessment
#Patients ongoing treatment at data cut-off
PD, progressive disease; PR, partial response; PRc,· confirmed partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease

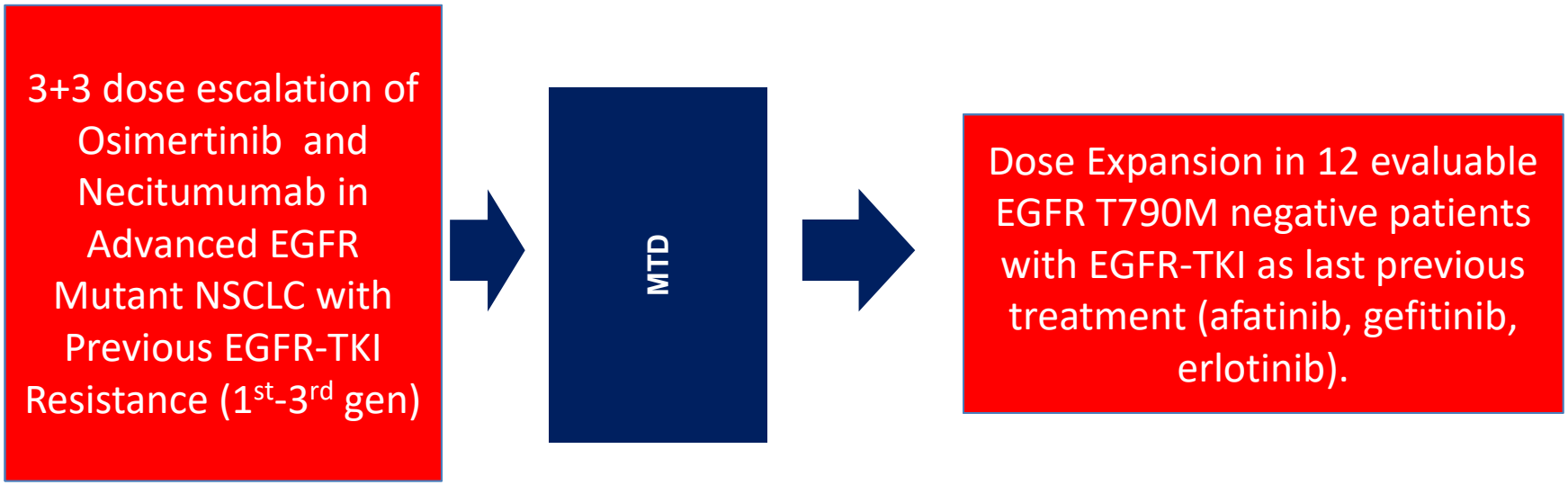


Pre-treatment **4 weeks**

32-year-old female with a tumor harboring exon 19 deletion and high MET amplification responds to AZD9291/savolitinib 800 mg.

Oxnard et al J Clin Oncol 2015; abstract 2509

A Phase I Trial of Osimertinib and Necitumumab in EGFR Mutant NSCLC with Previous EGFR-TKI Resistance (PHI-77)



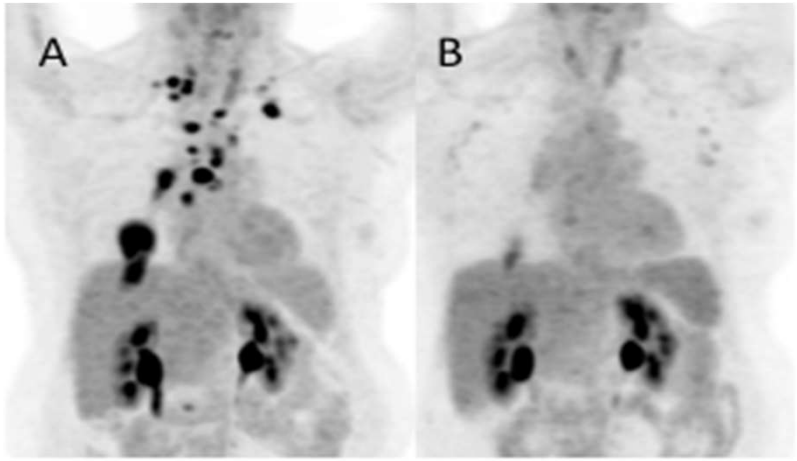
Primary Endpoint: Safety and Tolerability
Main Secondary Endpoint:
ORR is T790M negative population (3≥12 responses)

Molecular Studies
Biopsy – Pre-treatment and post progression for EGFR T790M, EGFR FISH and NGS
Plasma cfDNA for EGFR-TKI resistance mechanisms
Creation of EGFR-TKI resistant PDX
Single Cell NGS for Intratumoral Heterogeneity

Clinical and Radiographic Responses in Unmet EGFR-mutant Patient Populations: EGFR T790M negative after erlotinib and in C797S positive lung cancer after osimertinib

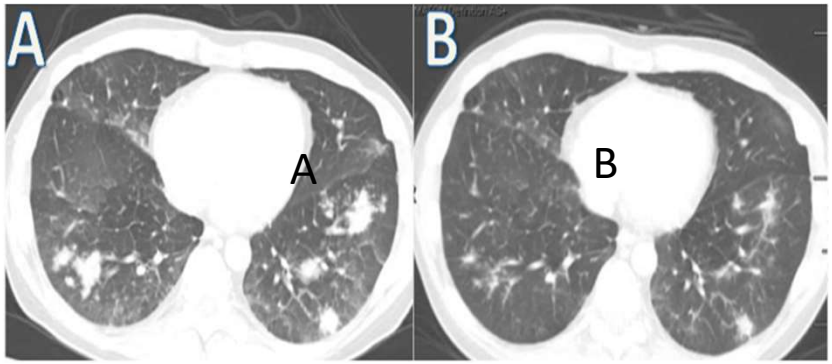
E19del/T790M^{neg}

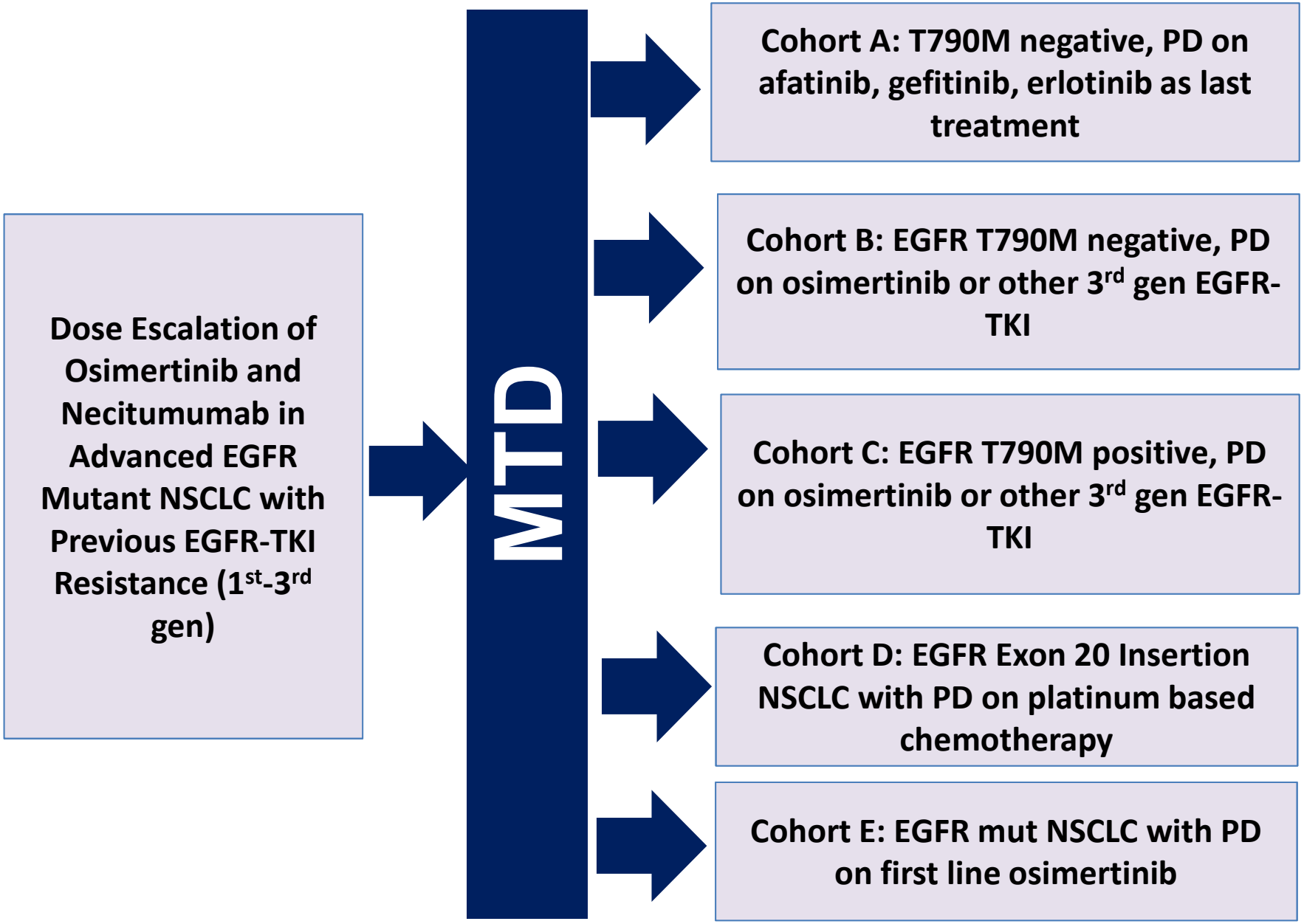
PD on erlotinib



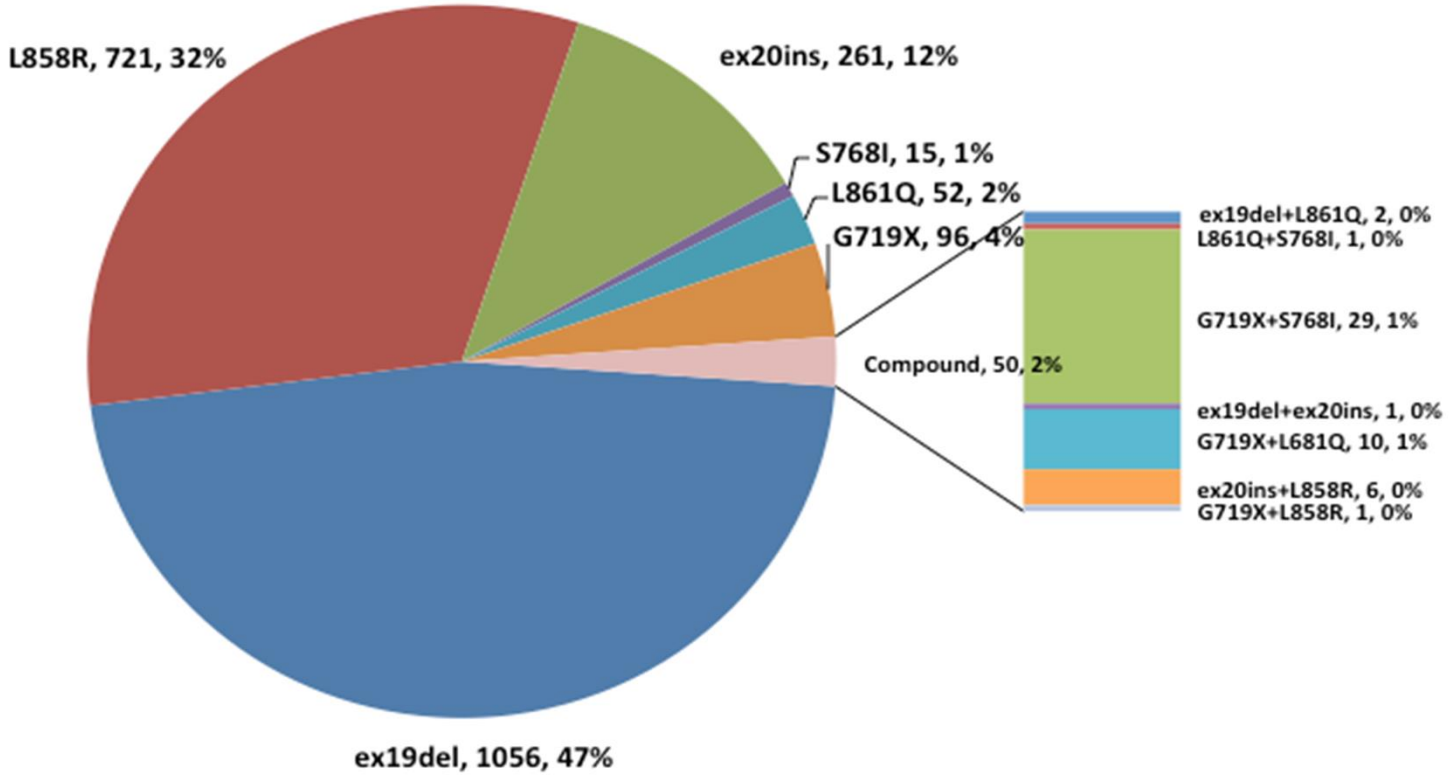
E19del/T790M^{pos}/C797S^{pos}

PD on osimertinib



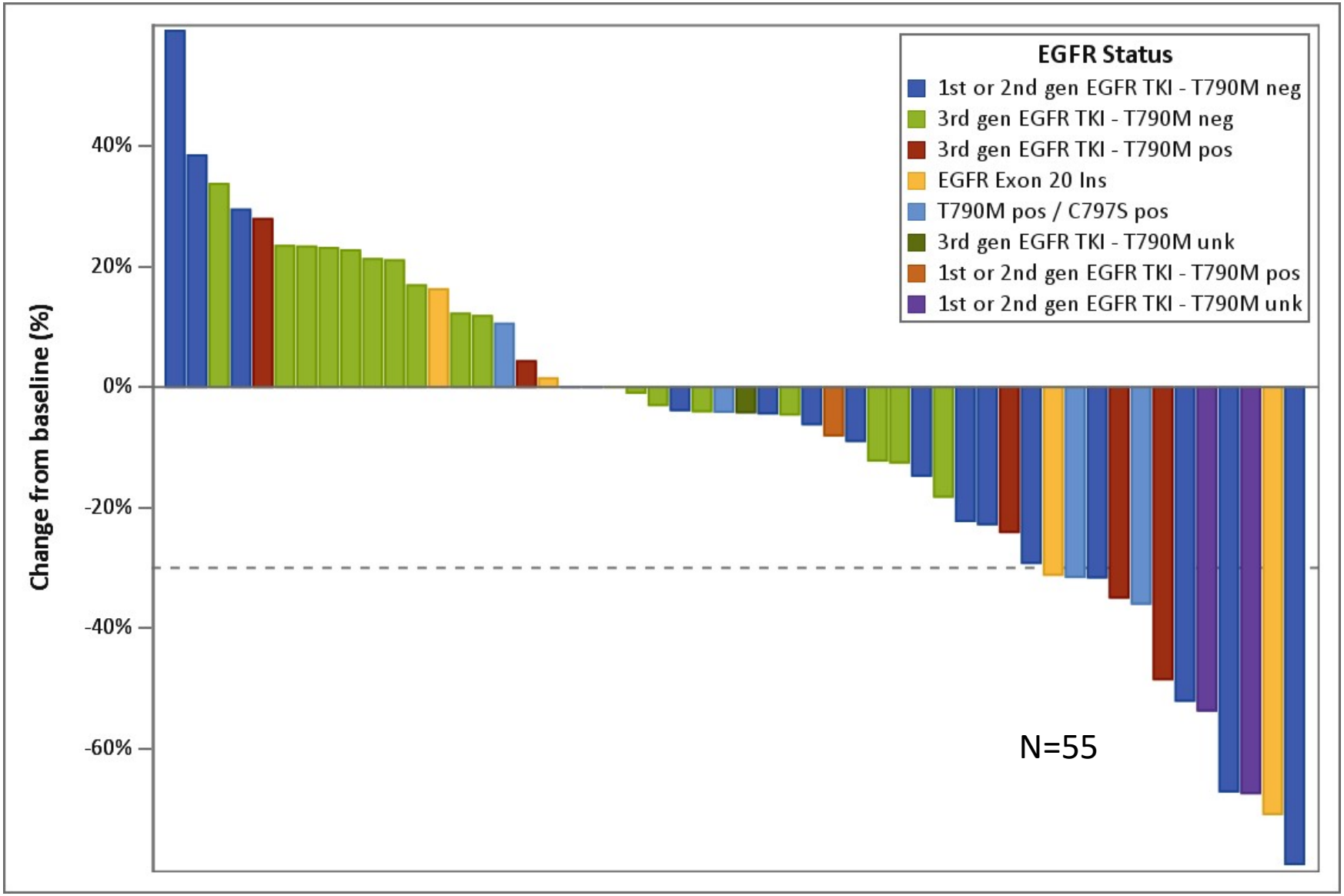

Dose Escalation of Osimertinib and Necitumumab in Advanced EGFR Mutant NSCLC with Previous EGFR-TKI Resistance (1st-3rd gen)
MTD
Cohort A: T790M negative, PD on afatinib, gefitinib, erlotinib as last treatment
Cohort B: EGFR T790M negative, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort C: EGFR T790M positive, PD on osimertinib or other 3rd gen EGFR-TKI
Cohort D: EGFR Exon 20 Insertion NSCLC with PD on platinum based chemotherapy
Cohort E: EGFR mut NSCLC with PD on first line osimertinib

Frequency and Distribution of 2,251 *EGFR* mutations in NSCLC Detected by Broad Genomic Profiling.



JW Riess et al. Journal of Thoracic Oncology 2018.

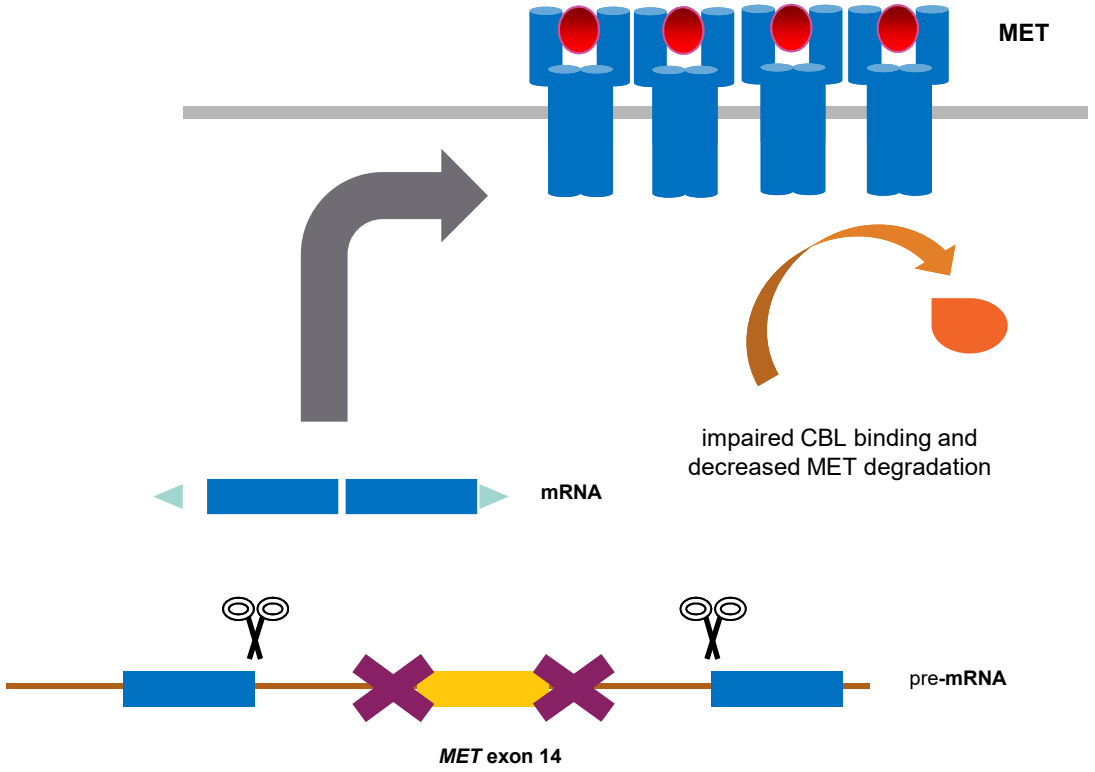
Waterfall Plot of Best Response by Molecular Status



JW Riess et al. ASCO 2019

MET ex14 alterations in NSCLC

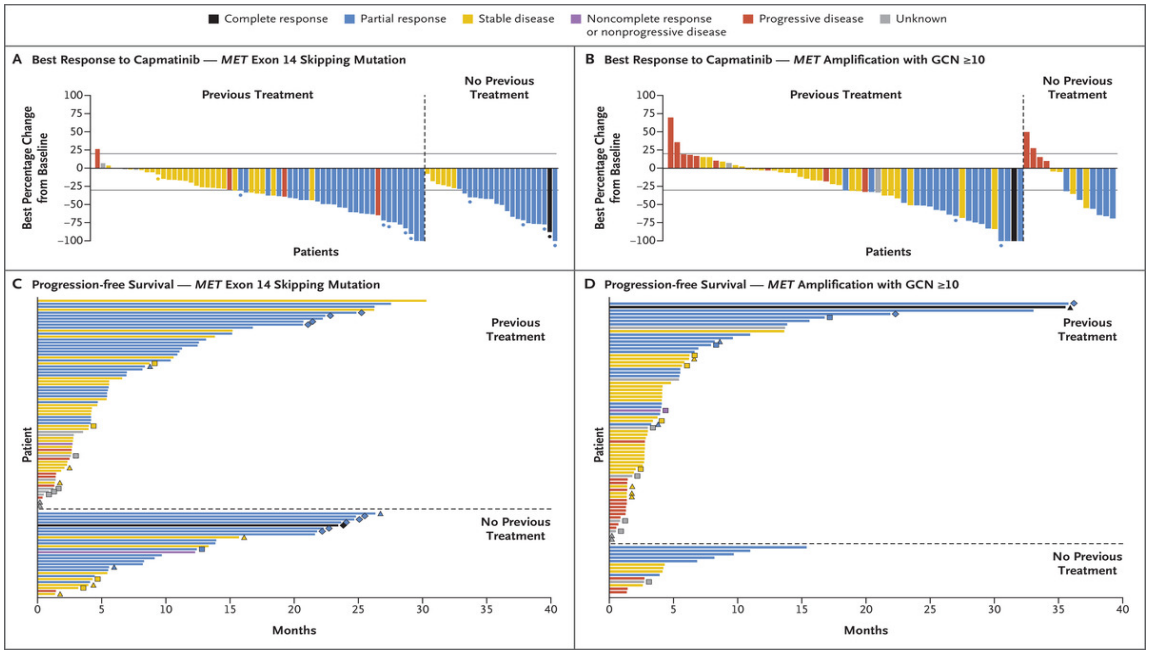
- *MET* mutations can lead to decreased MET degradation
  - – deletions, insertions, or base substitutions
  - – disrupt splice sites flanking *MET* exon 14 → exon 14 skipping
  - – absence of JM domain, Cbl ubiquitination process inhibited
  - – increased MET receptor on the tumor cell surface



Adapted from Drilon et al J Thorac Oncol 2016

Drilon et al Clin Cancer Res 2016; Kong-Beltran M et al. Cancer Res 2006;66. Ma et al. Cancer Res 2003;63. Frampton GM et al. Cancer Discov 2015; Drilon et al J Thorac Oncol 2016.

Capmatinib in MET Exon 14 Skipping Mutation/MET Amplification



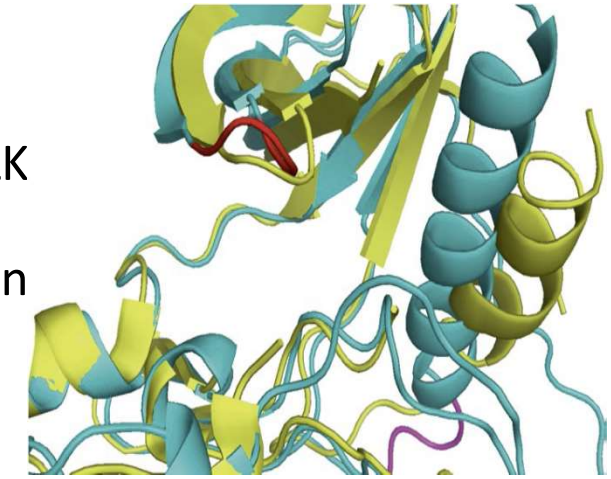
	Met Ex14		MET Amp (CNG 10)	
	ORR	PFS	ORR	
Pretreated	**41%**	**5.4**	**29%**	**4.1**
Untreated	**68%**	**12.4**	**40%**	**4.2**

Tepotinib also with excellent clinical data
In MET Exon 14 skipping mutations.
ORR = 48% in pretreated patients.

P. Paik et al NEJM 2020.

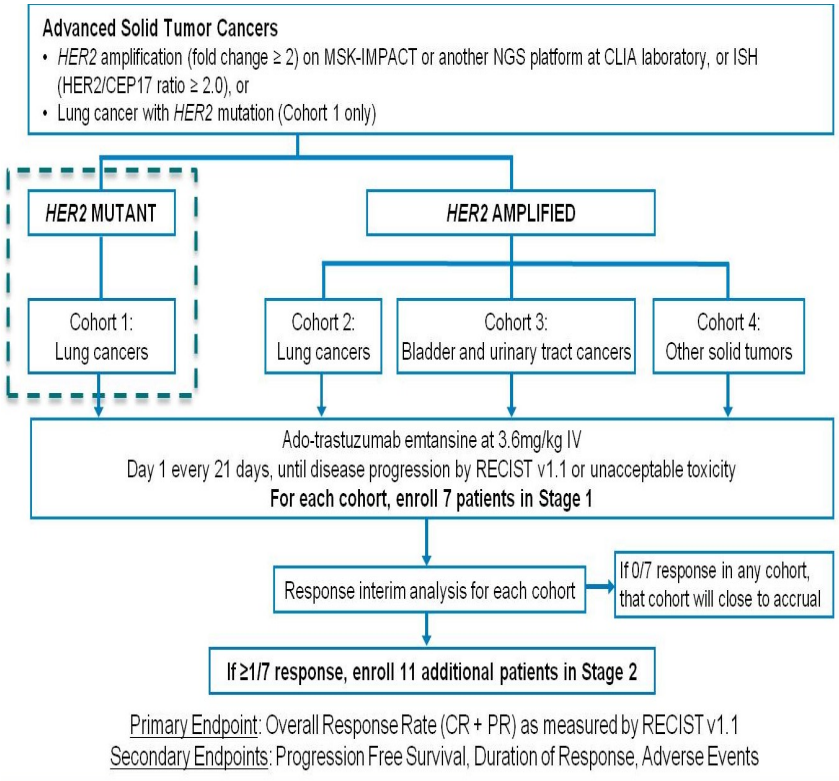
HER2 (ERBB2, *neu*) in NSCLC

- HER2 mutations are seen in 2-4% NSCLC patients, usually mutually exclusive with EGFR, KRAS, and ALK gene alterations
- HER2 mutation incidence up to 6% in EGFR/KRAS/ALK negative pts
- HER2 mutations usually seen with adenocarcinoma in never smokers and women
- HER2 mutations occur in exons 18 to 21 of the tyrosine kinase domain, altering the ATP-binding pocket of the HER2 receptor
- 90% HER2 mutations are exon 20 mutations



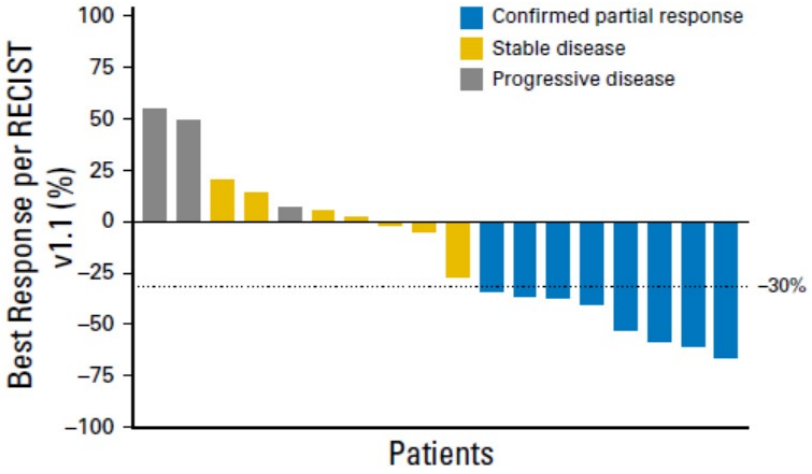
Ado-trastuzumab emtansine (T-DM1)

- Phase II basket trial in 18 HER2-mutant NSCLC patients
- N=18, mostly women (72%) and nonsmokers
- RR 44%
- Median PFS 5 months
- Minor toxicities (grade 1-2) included infusion reactions, thrombocytopenia, transaminitis

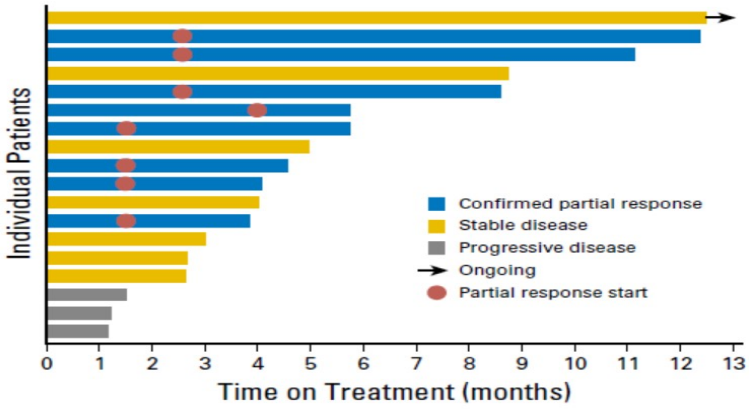


Li BT, et al. JCO. 2018;36:2532–7.

Activity of ado-trastuzumab emtansine (T-DM1) in *HER2*-mutant lung cancers



ORR 44% (95% CI: 22-69%)
Median PFS 5 months



Li et al. *J Clin Oncol*. 2018

Trastuzumab Deruxtecan (T-DXd; DS-8201) in Patients With HER2-Mutated Metastatic Non-Small Cell Lung Cancer: Interim Results of DESTINY-Lung01

Egbert F. Smit, Kazuhiko Nakagawa, Misako Nagasaka, Enriqueta Felip, Yasushi Goto, Bob T. Li, Jose M. Pacheco, Haruyasu Murakami, Fabrice Barlesi, Andreas Saltos, Maurice Perol, Hibiki Udagawa, Kapil Saxena, Ryota Shiga, Ferdinand Guevara, Suddhasatta Acharyya, Javad Shahidi, David Planchard, Pasi A. Jänne

On behalf of the DESTINY-Lung01 investigators

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

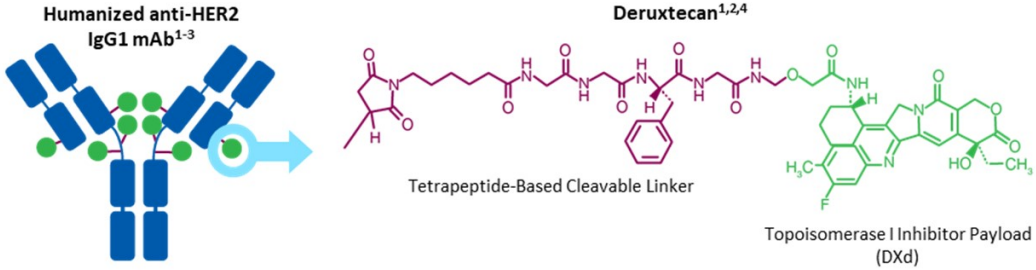
PRESENTED BY: Prof Egbert F. Smit; Netherlands Cancer Institute; e.smit@nki.nl

Presented By Egbert Smit at TBD

T-DXd is a Novel ADC Designed to Deliver an Optimal Antitumor Effect

T-DXd is an ADC with 3 components:

- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



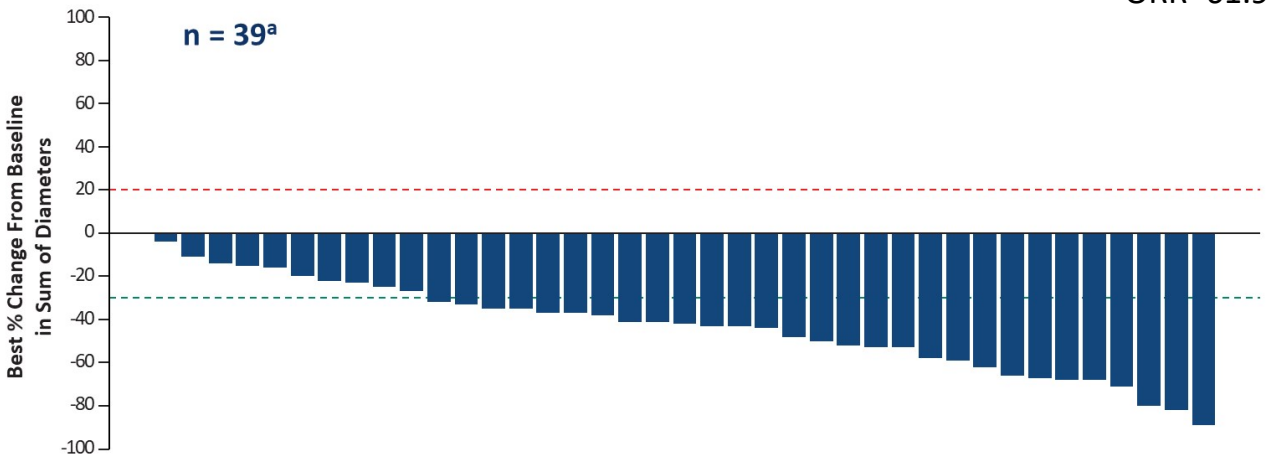
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

The clinical relevance of these features is under investigation.
ADC, antibody-drug conjugate.
1. Nakada T, et al. *Chem Pharm Bull* (Tokyo). 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

PRESENTED BY: Prof Salvatore Siena; Università degli Studi di Milano, Milan, Italy; salvatore.siena@unimi.it

Best Change in Tumor Size

ORR=61.9%



Based on independent central review. Baseline is last measurement taken before enrollment. Shown is best (minimum) percent change from baseline in the sum of diameters for all target lesions.

[a] One patient was missing a baseline assessment and 2 additional patients were missing post-baseline assessments.

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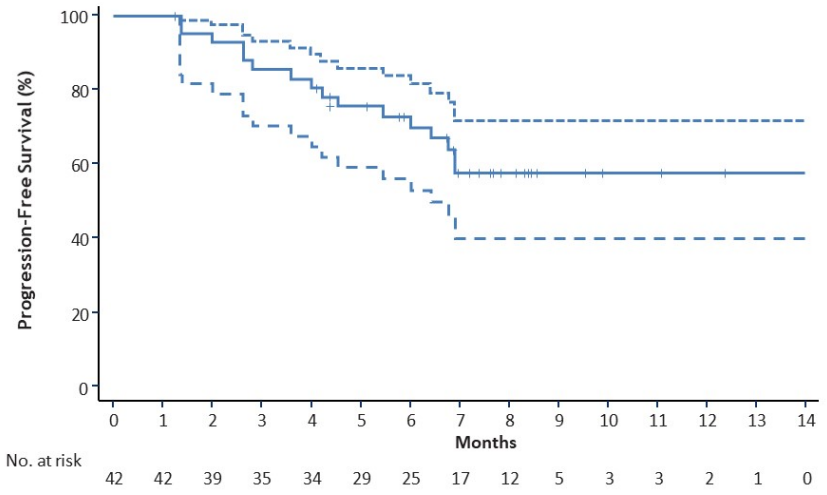
Progression-Free and Overall Survival

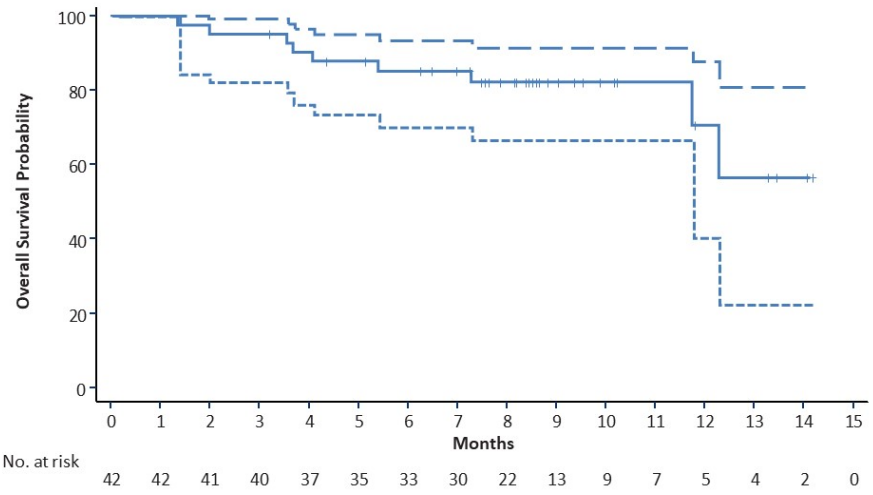
Progression-Free Survival (N = 42)[a]

Median: 14.0 months (95% CI, 6.4-14.0)



Overall Survival (N = 42)

Median: Not reached (95% CI, 11.8-NE)



[a] Patients were censored if they discontinued treatment; the median is estimated by Kaplan-Meier analysis. Median follow-up, 8.0 months (range, 1.4-14.2 months). Dashed lines indicate upper and lower 95% CI.

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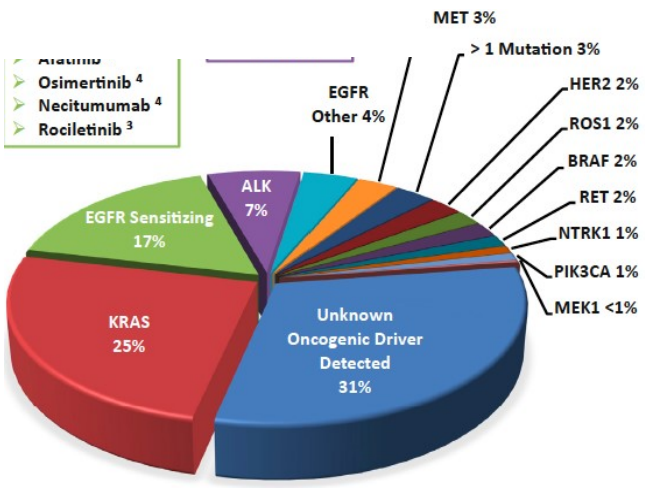
Progress in Targeted Therapy for NSCLC-Adenocarcinoma



EGFR:
gefitinib, afatinib, erlotinib, osimertinib, dacomitinib

ALK:
Crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, ensartinib, entrectinib

ROS1:
Crizotinib, cabozatinib, ceritinib, brigatinib, lorlatinib, entrectinib, ropotrectinib

BRAF:
Dabrafenib/trametinib, vemurafenib, dabrafenib

MET:
Crizotinib, cabozatinib, capmatinib, tepotinib, savolitinib, merestinib, glesatinib

FDA

KRAS G12C
MTRX-849, AMG 510

PI3K
LY3023414, PQR-309

MEK
Trametinib, selumetinib, cobimetinib

EGFR exon 20 insertions
TAK-788, poziotinib, JNJ 372

HER2:
Transtuzumab emtansine, afatinib, dacomitinib, poziotinib, neratinib-temsirolimus, XMT-1522, TAK-788, DS-8201a

RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib, lenvatinib, apatinib, selpercatinib, BLU-667, RXDX-105

NTRK:
Larotrectinib, entrectinib, LOXO-195, DS-6051b, ropotrectinib

FDA

Adapted by L Bazhenova from Tsao AS, et al. J Thorac Oncol. 2016;11:613-638.