New Therapeutic Directions in Non-Small Cell Lung Cancer

Jonathan W. Riess, M.D. M.S.
Associate Professor of Medicine
University of California Davis School of Medicine
UC Davis Comprehensive Cancer Center

UCDAVIS COMPREHENSIVE CANCER CENTER

NCI CCC
A Comprehensive Cancer Center Designated by the National Cancer Institute

Disclosures

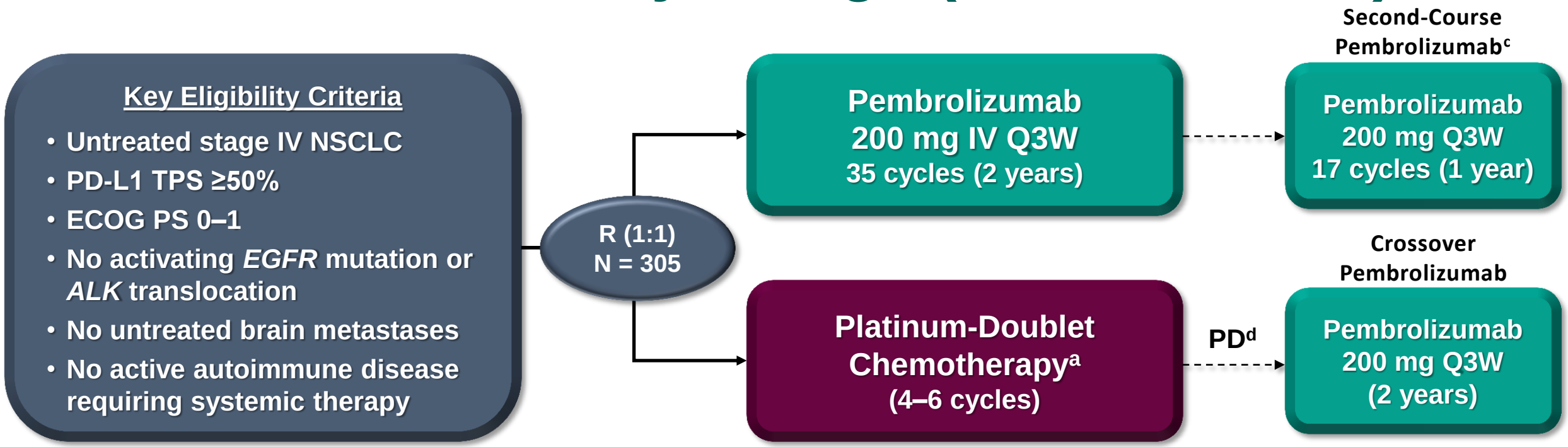
- Honoraria/Consulting: Novartis, Roche/Genentech, Blueprint Medicine
- Research Funding (To Institution): Merck, Novartis, Spectrum, AstraZeneca, Revolution Medicines

KEYNOTE-024 5-Year OS Update: First-Line Pembrolizumab vs Platinum-Based Chemotherapy in Patients with Metastatic Non–Small-Cell Lung Cancer and PD-L1 Tumor Proportion Score ≥50%

Julie R. Brahmer,[1] Delvys Rodríguez-Abreu,[2] Andrew G. Robinson,[3] Rina Hui,[4] Tibor Csőszi,[5] Andrea Fülöp,[6] Maya Gottfried,[7] Nir Peled,[8] Ali Tafreshi,[9] Sinead Cuffe,[10] Mary O'Brien,[11] Suman Rao,[12] Katsuyuki Hotta,[13] Ticiana A. Leal,[14] Jonathan W. Riess,[15] Erin Jensen,[16] Bin Zhao,[16] M. Catherine Pietanza,[16] Martin Reck[17]

[1]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA; [2]Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; [3]Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; [4]Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [5]Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; [6]Országos Korányi Pulmonológiai Intézet, Budapest, Hungary; [7]Meir Medical Center, Kfar-Saba, Israel; [8]Soroka Cancer Center, Ben Gurion University, Beer Sheva, Israel; [9]Wollongong Private Hospital and University of Wollongong, Wollongong, NSW, Australia; [10]St. James's Hospital and Cancer Trials Ireland (formerly ICORG – All Ireland Cooperative Oncology Research Group), Dublin, Ireland; [11]The Royal Marsden Hospital, Sutton, Surrey, UK; [12]MedStar Franklin Square Hospital, Baltimore, MD, USA; [13]Okayama University Hospital, Okayama, Japan; [14]Carbone Cancer Center, University of Wisconsin, Madison, WI, USA ; [15]UC Davis Comprehensive Cancer Center, Sacramento, CA, USA; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]Lung Clinic Grosshansdorf, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshansdorf, Germany

KEYNOTE-024 Study Design (NCT02142738)

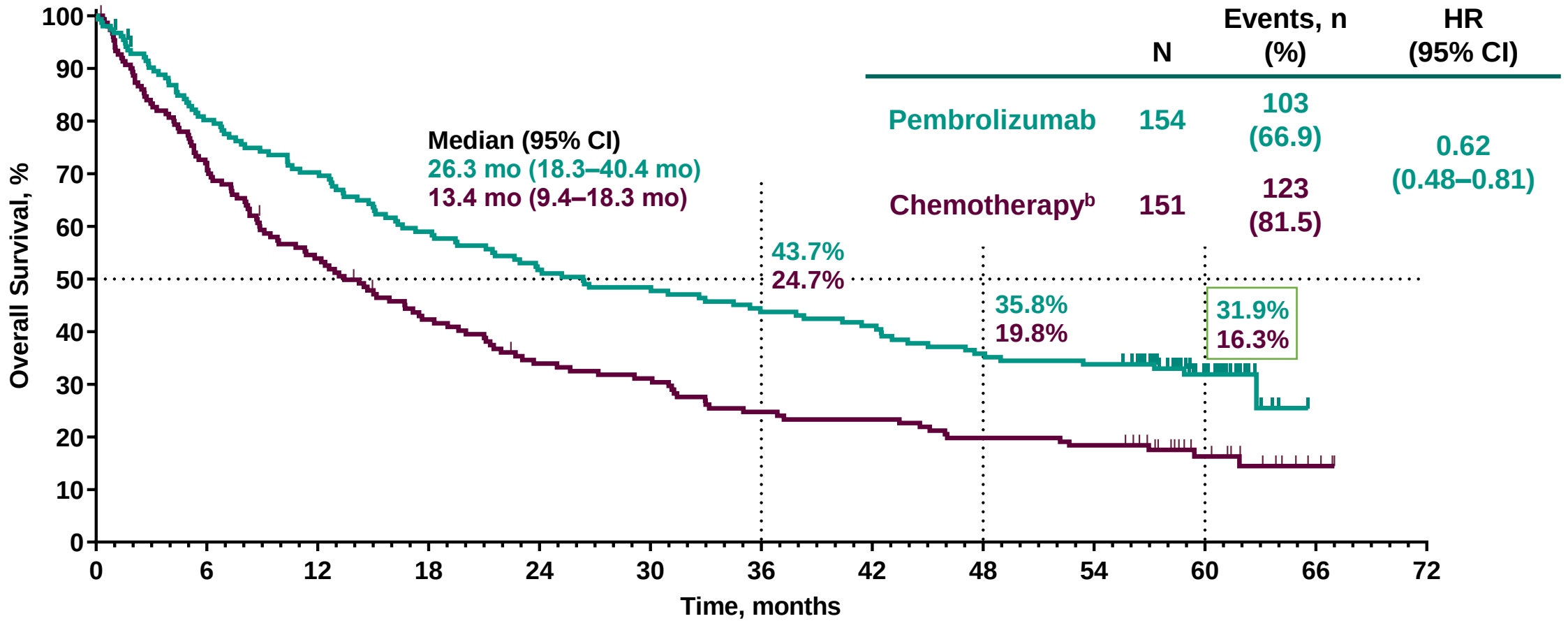


End Points

Primary:	PFS (RECIST v1.1 per blinded, independent, central review)
Key secondary:	OS
Secondary:	ORR, safety, PFS (RECIST v1.1 per investigator review)
Exploratory:	DOR

[a]Optional pemetrexed maintenance therapy for nonsquamous disease. [b]Permitted for nonsquamous disease only. [c]Patients randomized to pembrolizumab who completed 2 years of therapy or who stopped pembrolizumab after achieving CR and then had PD were eligible for a second course of pembrolizumb monotherapy. [d]Before the DMC recommendation and amendment 8, which permitted those in the chemotherapy arm to be offered pembrolizumab (based on interim analysis 2 data), patients were eligible for crossover when PD was confirmed by blinded, independent, central radiology review.

Overall Survival[a]

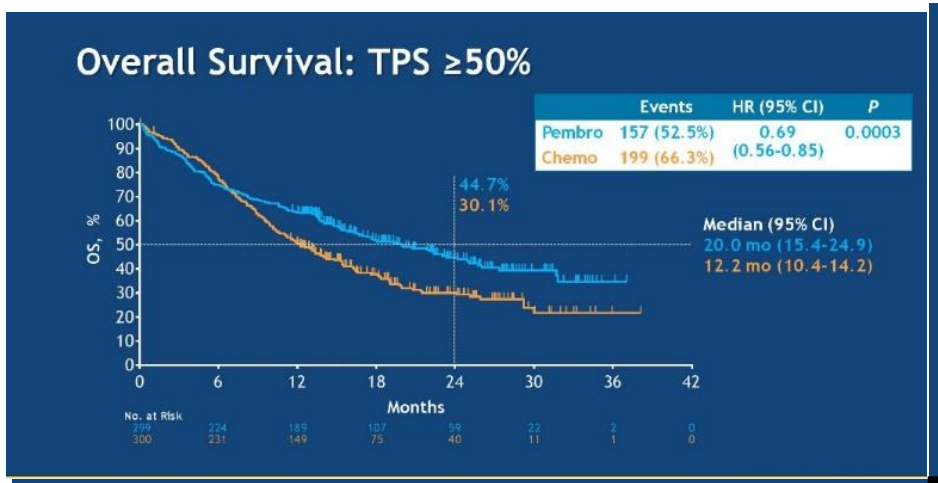


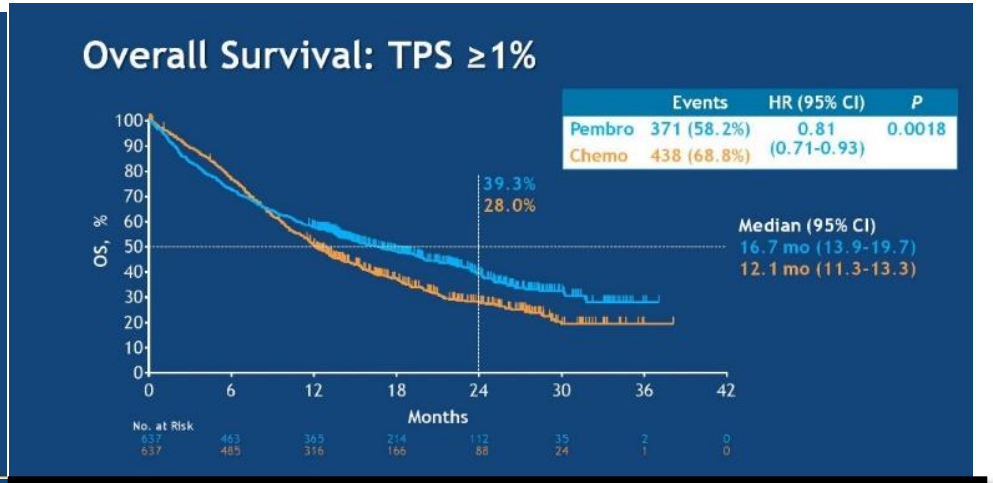
No. at risk												
Pembrolizumab	154	121	106	89	78	73	66	62	54	51	20	0	0
Chemotherapy	151	108	80	61	48	44	35	33	28	26	13	3	0

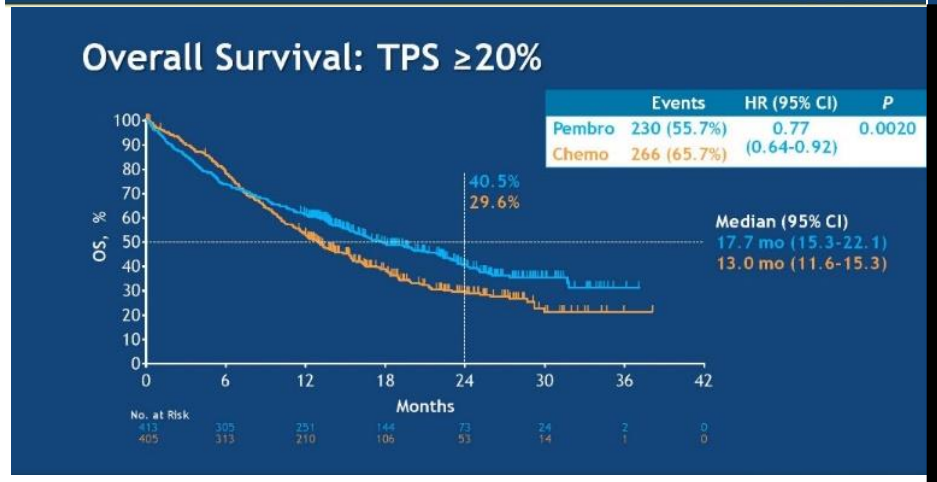
[a]ITT population.
[b]Effective crossover rate from chemotherapy to anti–PD-L1 therapy, 66.0% (99 patients in total crossed over to anti–PD-[L]1 therapy: 83 patients crossed over to pembrolizumab during the study, and 16 patients received subsequent anti–PD-L1 therapy outside of crossover; patients may have received >1 subsequent anti–PD-L1 therapy). Data cutoff: June 1, 2020.

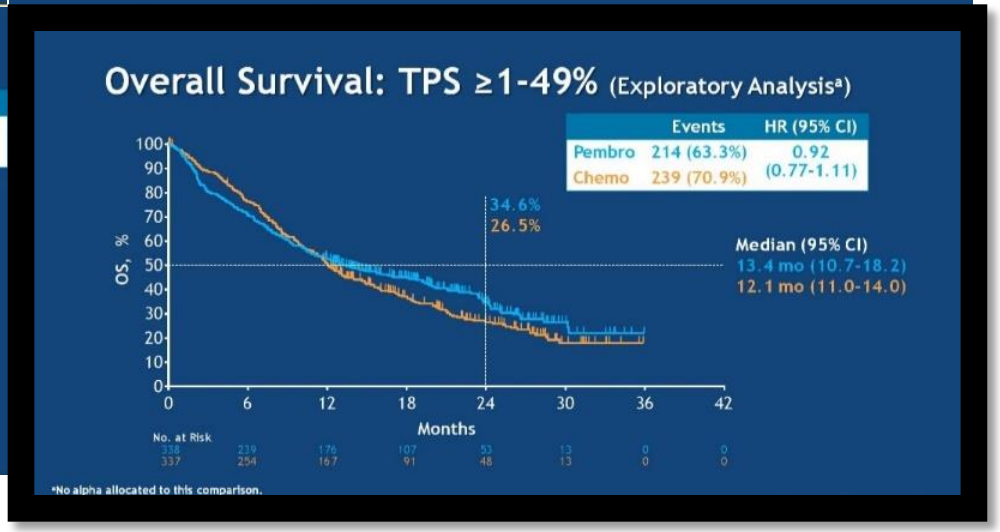
Is 1L Pembrolizumab good enough in **PD-L1 1-49%**?

PH III KEYNOTE-042 Study





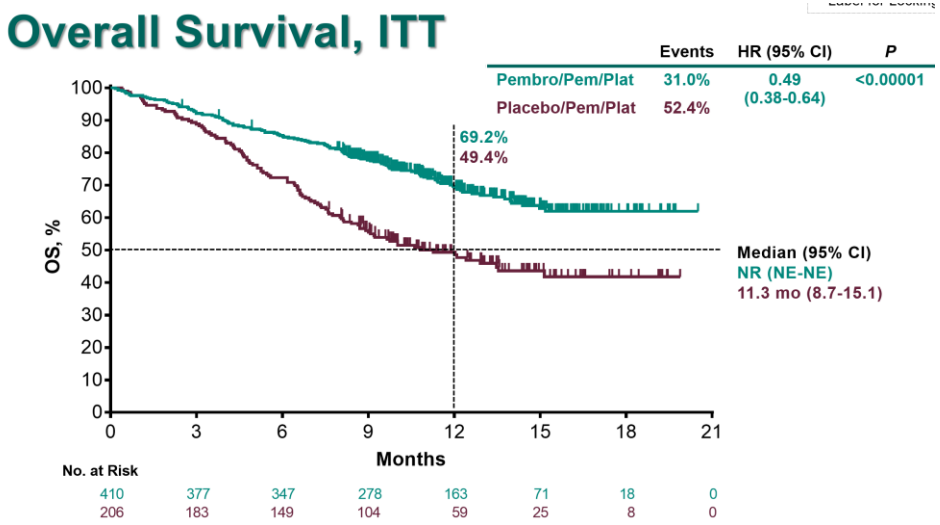




Mok. Lancet. 2019 May 4;393(10183):1819-1830.

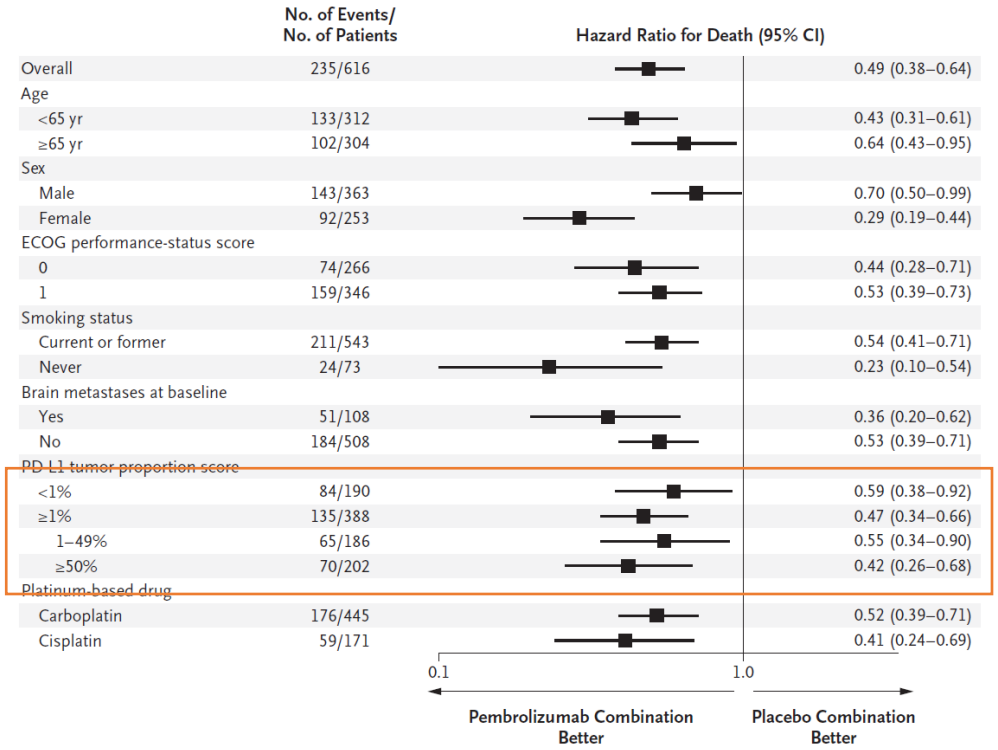
1L Platinum-pemetrexed +/- Pembrolizumab

KN189 Non-squamous NSCLC 1L (PD-L1 unselected)



- **OS HR 0.49***; P<0.00001
- PFS HR 0.52; P<0.001
- ORR 47.6% vs. 18.9%

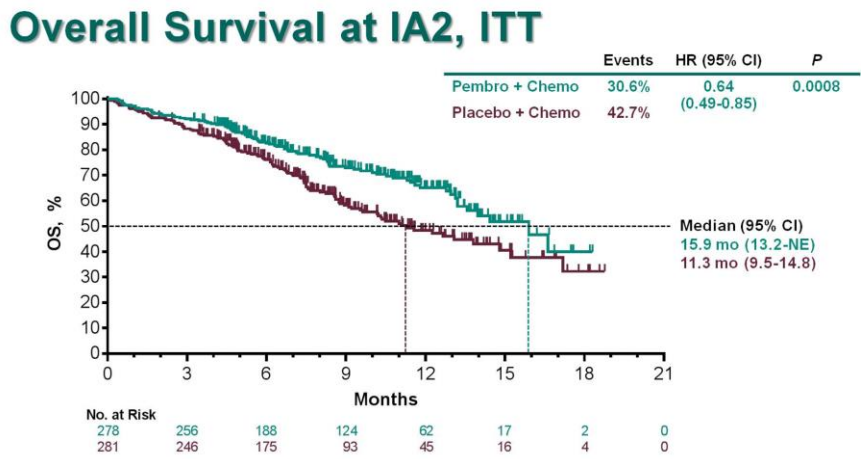
*median follow-up of 10.5 months; 1/3 cross-over



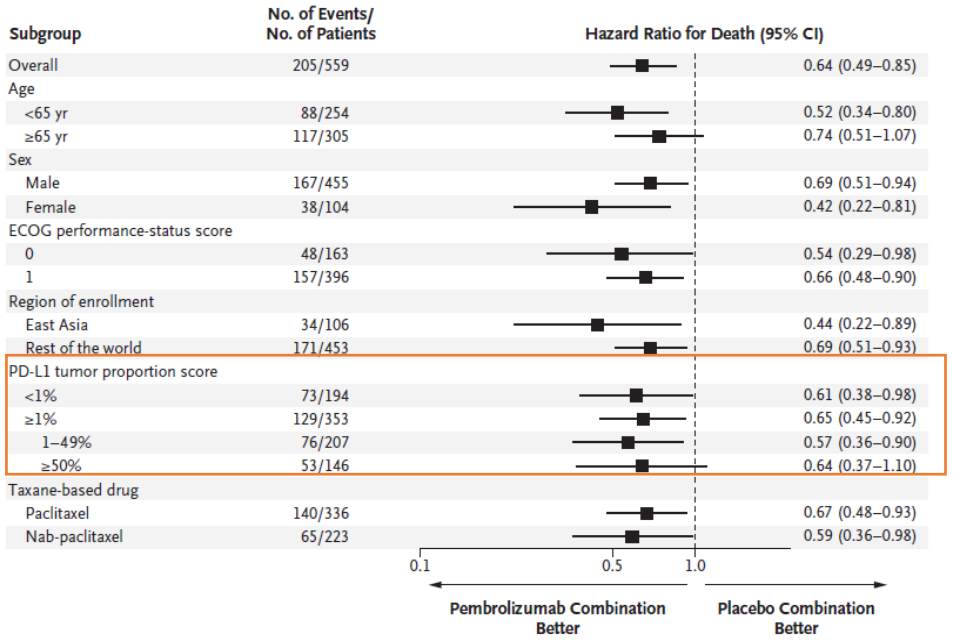
Gandhi L et al. N Engl J Med. 2018 May 31;378(22):2078-2092.

1L Carboplatin/taxane (pac/nab-pac) +/- Pembrolizumab

KN407 Squamous NSCLC 1L (PD-L1 unselected)



- **OS HR 0.64***; p=0.0008
- PFS HR 0.56; p<0.0001
- ORR 58% vs. 38%

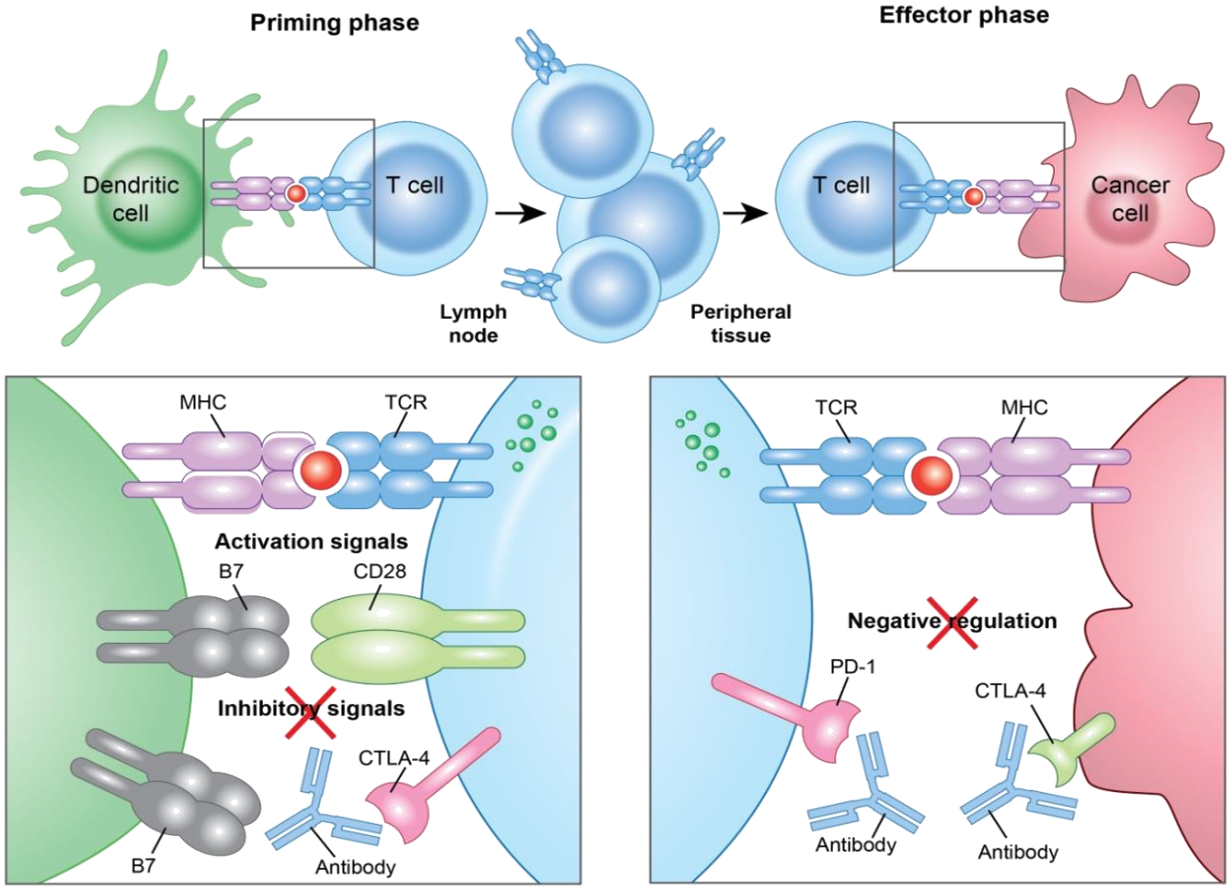


*median f/u 7.8 months; 27% crossover

Paz-Ares et al. N Engl J Med. 2018 Nov 22;379(21):2040-2051.

Combination Immune Checkpoint Blockade

- PD-1 acts as an “off-switch” for T cells when interacting with PD-L1
- Tumor PD-L1 expression allowing cancer cells to evade immune attack
- Antibodies against PD-1 and PD-L1 boost the immune response against cancer cells
- CTLA-4 acts as an “off-switch” for T cells when interacting with B7
- Combination strategies combine both CTLA-4 and PD-1/PD-L1 blockade



Ribas A, NEJM, 2012

2020 ASCO ANNUAL MEETING
UNITE AND CONQUER: ACCELERATING PROGRESS TOGETHER

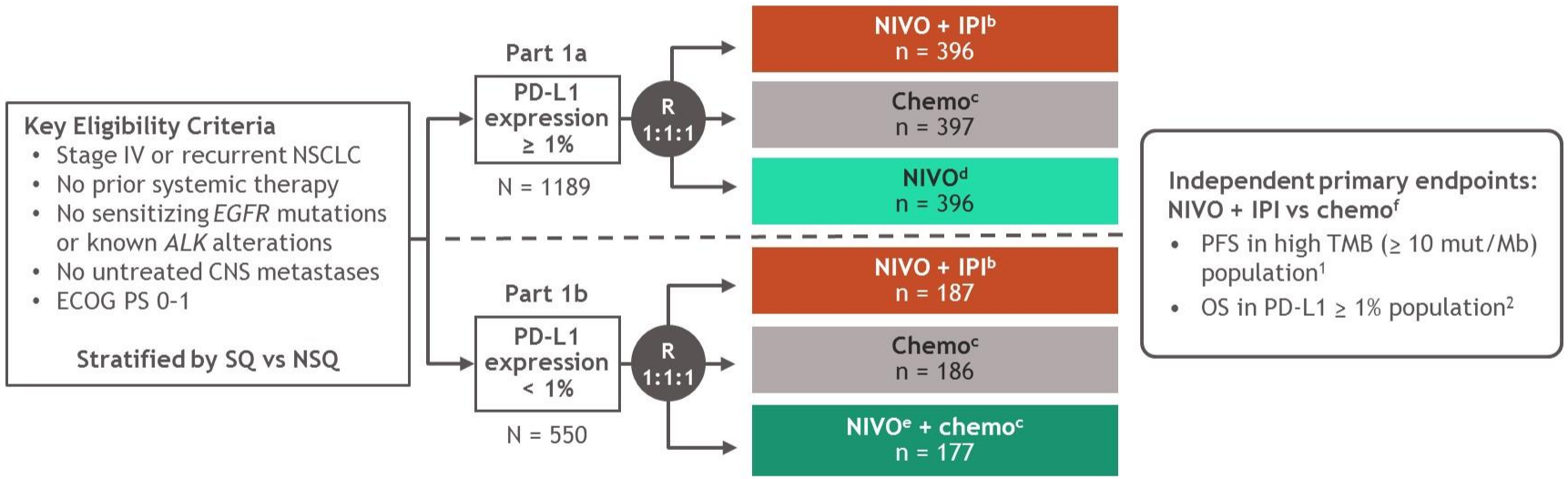
Nivolumab + ipilimumab versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1

Suresh S. Ramalingam,[1] Tudor-Eliade Ciuleanu,[2] Adam Pluzanski,[3] Jong-Seok Lee,[4] Michael Schenker,[5] Reyes Bernabe Caro,[6] Ki Hyeong Lee,[7] Bogdan Zurawski,[8] Clarisse Audigier-Valette,[9] Mariano Provencio,[10] Helena Linardou,[11] Sang-We Kim,[12] Hossein Borghaei,[13] Matthew David Hellmann,[14] Kenneth John O'Byrne,[15] Luis G. Paz-Ares,[16] Martin Reck,[17] Faith E. Nathan,[18] Julie R. Brahmer[19]

[1]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [2]Institutul oncologic Prof Dr Ion Chiricuta and UNF Iulia Hatieganu, Cluj Napoca, România; [3]Maria Sklodowska-Curie National Research Institute of Oncology, Warsaw, Poland; [4]Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [5]SF. Nectarie Oncology Center, Craiova, Romania; [6]Hospital Universitario Virgen Del Rocio, Instituto de Biomedicina de Sevilla, Sevilla, Spain; [7]Chungbuk National University Hospital, Cheongju, Republic of Korea; [8]Ambulatorium Chemioterapii, Bydgoszcz, Poland; [9]Hôpital Sainte Musse, Toulon, France; [10]Hosp. Univ. Puerta De Hierro, Madrid, Spain; [11]Metropolitan Hospital, Neo Faliro, Greece; [12]Asan Medical Center, Seoul, Republic of Korea; [13]Fox Chase Cancer Center, Philadelphia, PA, USA; [14]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [15]Princess Alexandra Hospital, Brisbane, Queensland, Australia; [16]Hospital Universitario 12 de Octubre, CNIO, Universidad Complutense & CiberOnc, Madrid, Spain; [17]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany; [18]Bristol-Myers Squibb Company, Princeton, NJ, USA; [19]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Abstract Number 9500

CheckMate 227[a] Part 1 study design

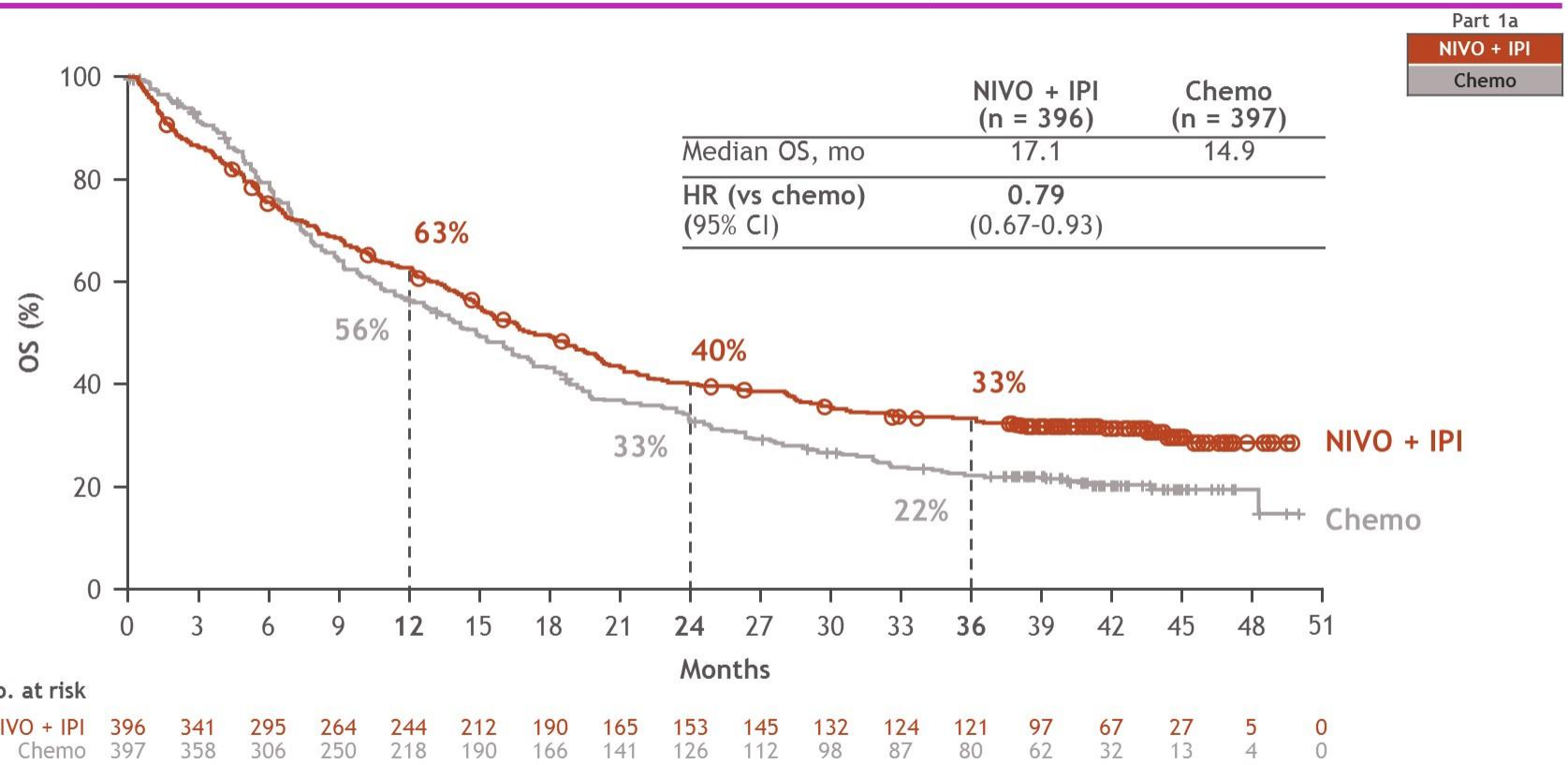


Database lock: February 28, 2020; minimum / median follow-up for OS: 37.7 months / 43.1 months.

Treatment was continued until disease progression, unacceptable toxicity, or for 2 years for immunotherapy; [a]NCT02477826; [b]NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W); [c]**NSQ:** pemetrexed + cisplatin or carboplatin, Q3W for ≤ 4 cycles, with optional pemetrexed maintenance following chemo or NIVO + pemetrexed maintenance following NIVO + chemo; **SQ:** gemcitabine + cisplatin, or gemcitabine + carboplatin, Q3W for ≤ 4 cycles; [d]NIVO (240 mg Q2W); [e]NIVO (360 mg Q3W); [f]Both endpoints were met; results were previously reported.

1. Hellmann MD, et al. *N Engl J Med* 2018;378(22):2093-2104; 2. Hellmann MD, et al. *N Engl J Med* 2019;381(21):2020-2031.

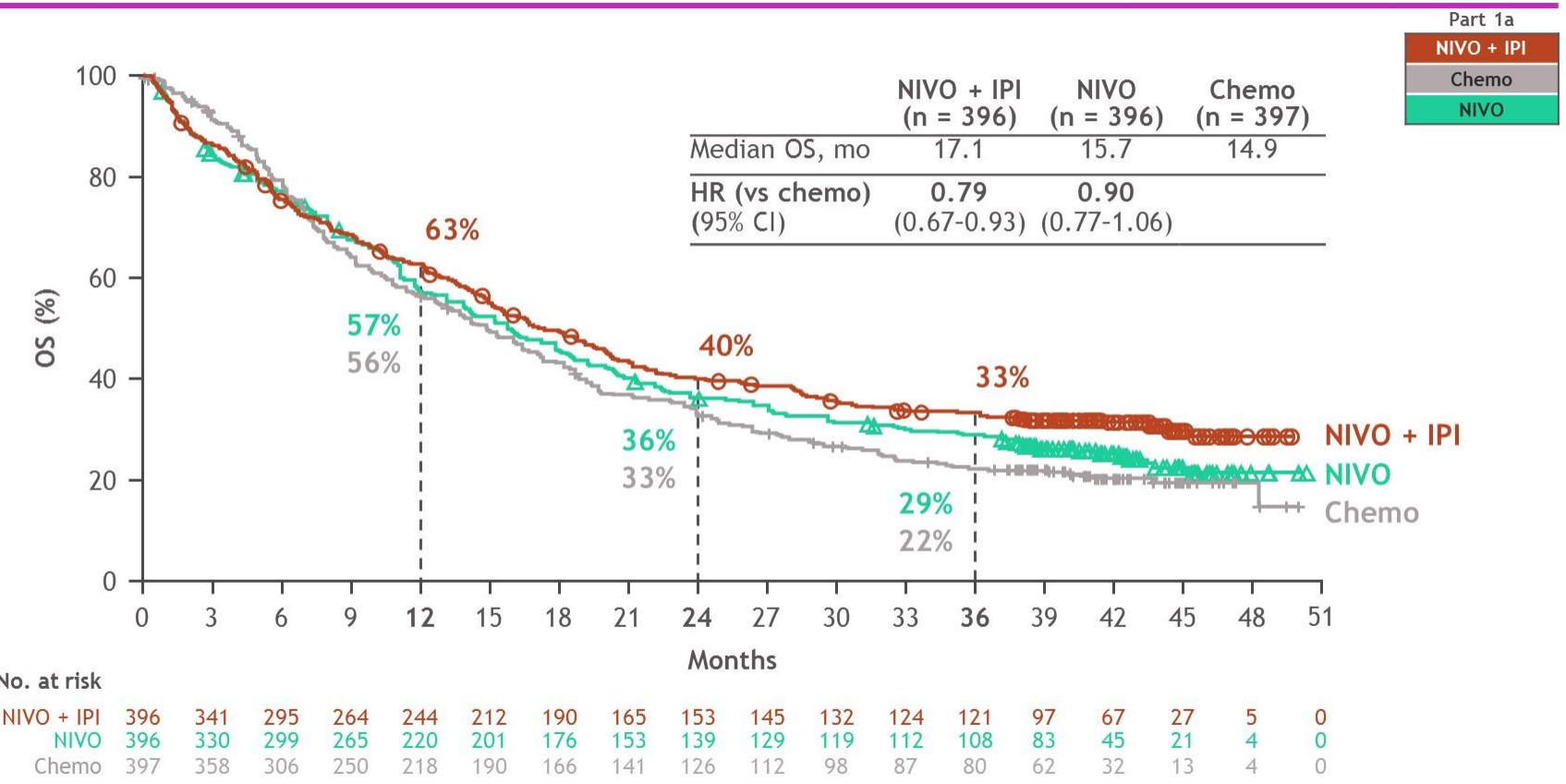
3-year update: OS with NIVO + IPI vs chemo (PD-L1 ≥ 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W). Among patients who were alive at 3 years, subsequent systemic therapy was received by 35% in the NIVO + IPI arm and 76% in the chemo arm; subsequent immunotherapies were received by 13% and 71%, respectively, and subsequent chemotherapy was received by 28% and 30%, respectively.

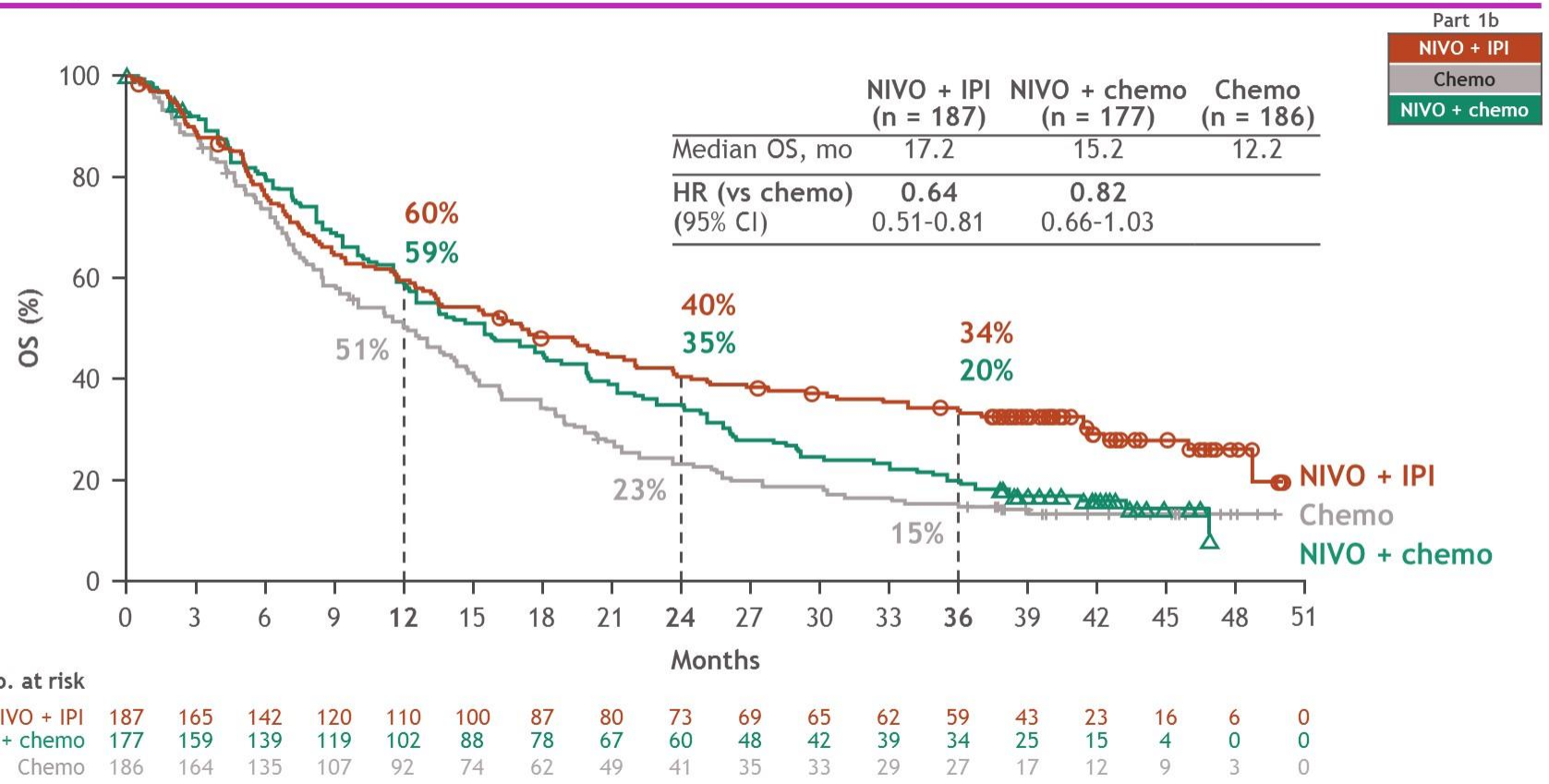
3-year update: OS with NIVO + IPI vs chemo vs NIVO (PD-L1 ≥ 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W) and NIVO (240 mg Q2W). Among patients who were alive at 3 years, subsequent systemic therapy was received by 35% in the NIVO + IPI arm, 45% in the NIVO arm, and 76% in the chemo arm; subsequent immunotherapies were received by 13%, 21%, and 71%; and subsequent chemotherapy was received by 28%, 33% and 30%, respectively.

3-year update: OS with NIVO + IPI vs Chemo vs NIVO + Chemo (PD-L1 < 1%)



Database lock: February 28, 2020; minimum follow-up for OS: 37.7 months.

Dosages were NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), and NIVO (360 mg Q3W) plus chemo. Among patients who were alive at 3 years, subsequent systemic therapy was received by 49% in the NIVO + IPI arm, 38% in the NIVO + chemo arm, and 78% in the chemo arm; subsequent immunotherapies were received by 12%, 12%, and 74%; and subsequent chemotherapy was received by 46%, 35% and 33%, respectively.

2020 ASCO ANNUAL MEETING
UNITE AND CONQUER: ACCELERATING PROGRESS TOGETHER

Nivolumab + ipilimumab + 2 cycles of platinum-doublet chemotherapy vs 4 cycles chemotherapy as first-line treatment for stage IV/recurrent NSCLC: CheckMate 9LA

Martin Reck,[1] Tudor-Eliade Ciuleanu,[2] Manuel Cobo,[3] Michael Schenker,[4] Bogdan Zurawski,[5] Juliana Menezes,[6] Eduardo Richardet,[7] Jaafar Bennouna,[8] Enriqueta Felip,[9] Oscar Juan-Vidal,[10] Aurelia Alexandru,[11] Hiroshi Sakai,[12] Arnaud Scherpereel,[13] Shun Lu,[14] Thomas John,[15] David P. Carbone,[16] Stephanie Meadows-Shropshire,[17] Jinchun Yan,[17] Luis G. Paz-Ares[18]

[1]Department of Thoracic Oncology, Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany; [2]Institutul Oncologic Prof. Dr. Ion Chiricuta and UMF Iuliu Hatieganu, Cluj-Napoca, Romania; [3]Unidad de Gestión Clínica Intercentros de Oncología Médica, Hospitales Universitarios Regional y Virgen de la Victoria, IBIMA, Málaga, Spain; [4]SF. Nectarie Oncology Center, Craiova, Romania; [5]Ambulatorium Chemioterapii, Bydgoszcz, Poland; [6]Hospital Nossa Senhora Da Conceição, Porto Alegre, Brazil; [7]Instituto Oncológico De Córdoba, Córdoba, Argentina; [8]Thoracic Oncology Unit, University Hospital of Nantes, Nantes, France; [9]Vall d'Hebron University Hospital, Barcelona, Spain; [10]Hospital Universitario La Fe, Valencia, Spain; [11]Institute of Oncology "Prof. Dr. Alexandru Trestioreanu" Bucha, Bucharest, Romania; [12]Saitama Cancer Center, Saitama, Japan; [13]Regional University Hospital Center of Lille, Hospital Calmette, Lille, France; [14]Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China; [15]Austin Hospital, Heidelberg, Australia; [16]The Ohio State University Comprehensive Cancer Center, Columbus, Ohio, USA; [17]Bristol-Myers Squibb, Princeton, NJ, USA; [18]Hospital Universitario 12 de Octubre, CNIO, Universidad Complutense & CiberOnc, Madrid, Spain

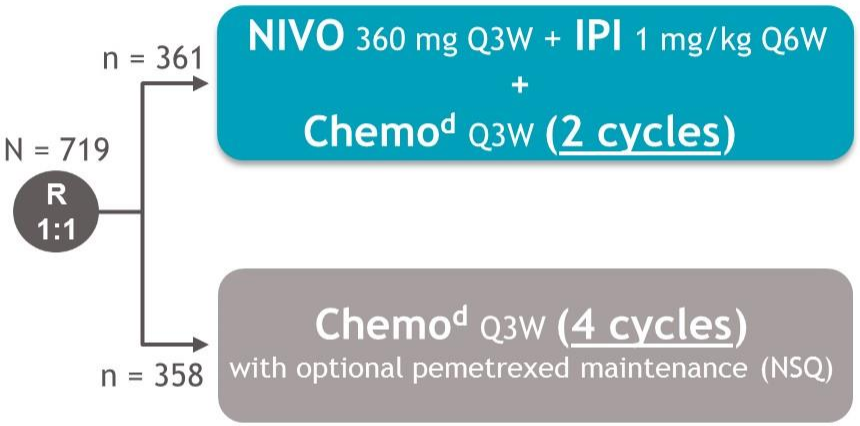
Abstract Number 9501

CheckMate 9LA study design[a]

Key Eligibility Criteria

- Stage IV or recurrent NSCLC
- No prior systemic therapy
- No sensitizing *EGFR* mutations or known *ALK* alterations
- ECOG PS 0-1

Stratified by PD-L1[b] (< 1%[c] vs ≥ 1%), sex, and histology (SQ vs NSQ)



Until disease progression, unacceptable toxicity, *or* for 2 years for immunotherapy

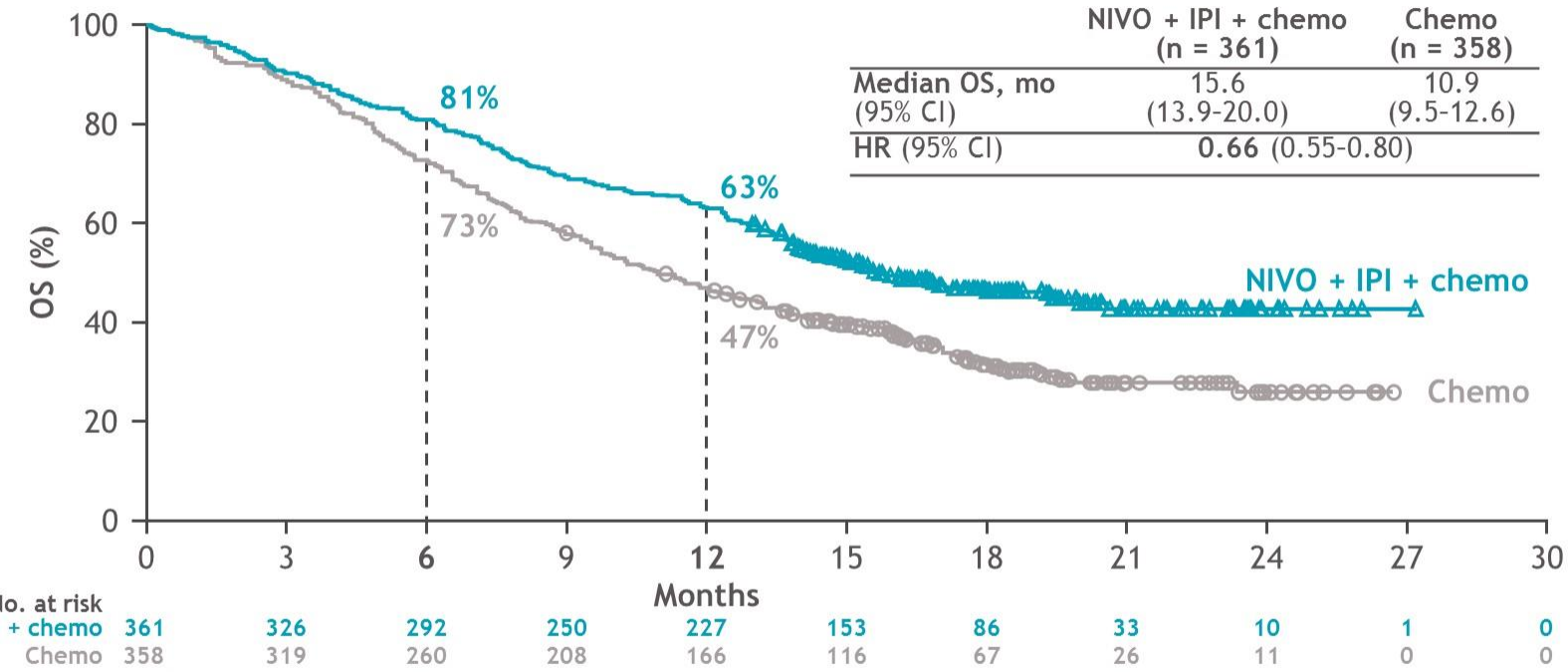
Primary endpoint
- OS

Secondary endpoints
- PFS by BICR[e]
- ORR by BICR[e]
- Efficacy by tumor PD-L1 expression

Interim database lock: October 3, 2019; minimum follow-up: 8.1 months for OS and 6.5 months for all other endpoints.
Updated database lock: March 9, 2020; minimum follow-up: 12.7 months for OS and 12.2 months for all other endpoints.

[a]NCT03215706; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Patients unevaluable for PD-L1 were stratified to PD-L1 < 1% and capped to 10% of all randomized patients; [d]**NSQ**: pemetrexed + cisplatin or carboplatin; SQ: paclitaxel + carboplatin; [e]Hierarchically statistically tested.

Primary endpoint (updated): Overall survival[a]

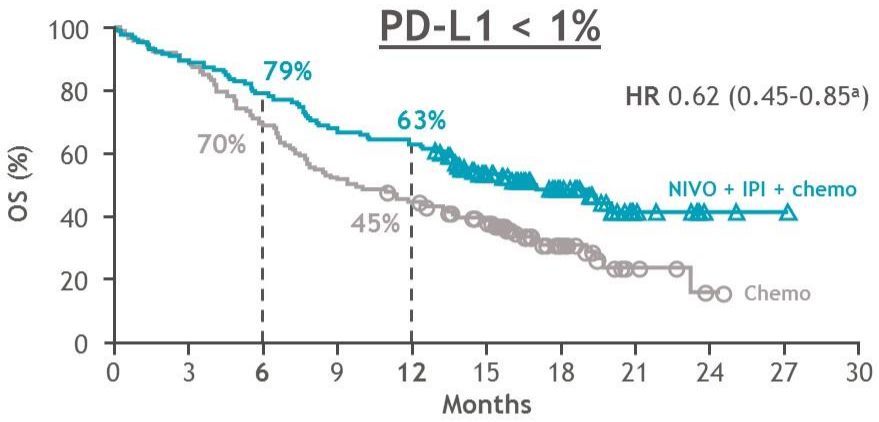


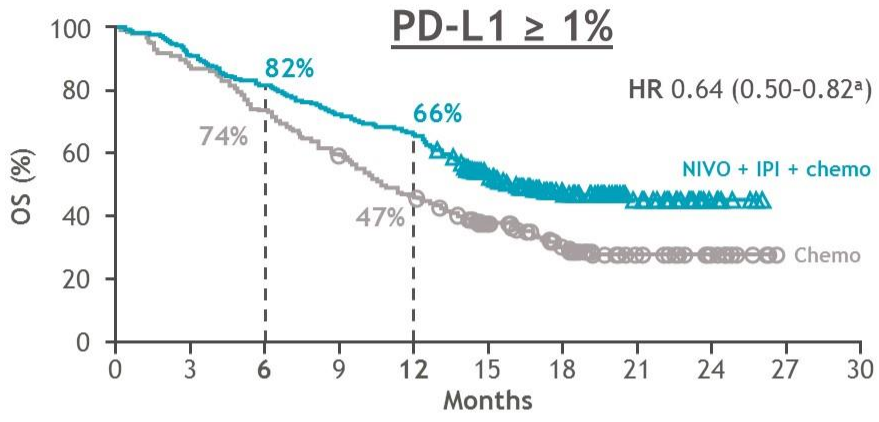
	NIVO + IPI + chemo (n = 361)	Chemo (n = 358)
Median OS, mo (95% CI)	15.6 (13.9-20.0)	10.9 (9.5-12.6)
HR (95% CI)	**0.66** (0.55-0.80)	

Minimum follow-up: 12.7 months.

[a]Patients remaining in follow-up were censored on the last date they were known to be alive; 47% of patients in the NIVO + IPI + chemo arm and 32% of patients in the chemo arm were censored. Subsequent systemic therapy was received by 31% of patients in the NIVO + IPI + chemo arm and 40% in the chemo arm; subsequent immunotherapy was received by 5% and 30%, and subsequent chemotherapy by 29% and 22%, respectively. Among patients with BICR-confirmed disease progression on study, subsequent systemic therapy was received by 40% in the NIVO + IPI + chemo arm and 44% in the chemo arm; subsequent immunotherapy was received by 7% and 34%, and subsequent chemotherapy by 38% and 24%, respectively

Overall survival by PD-L1 expression level

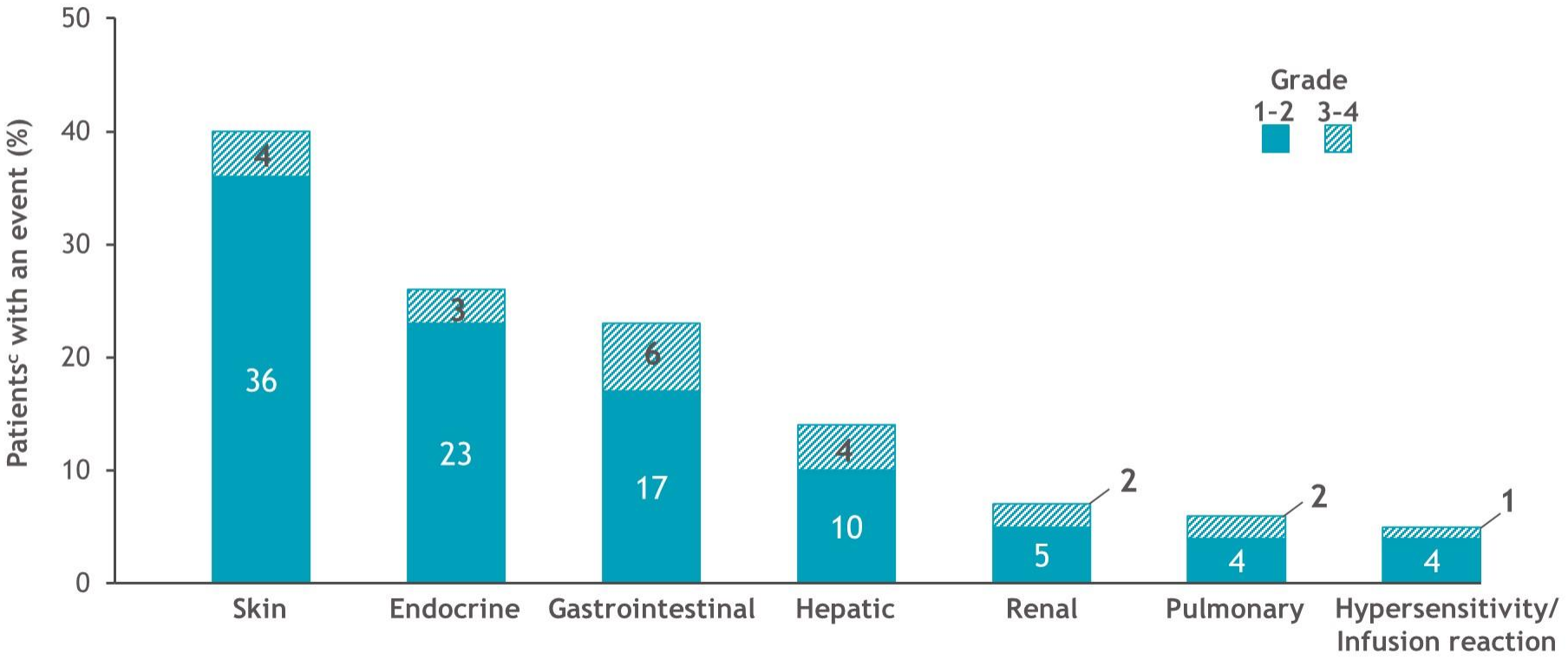




Minimum follow-up: 12.7 months.

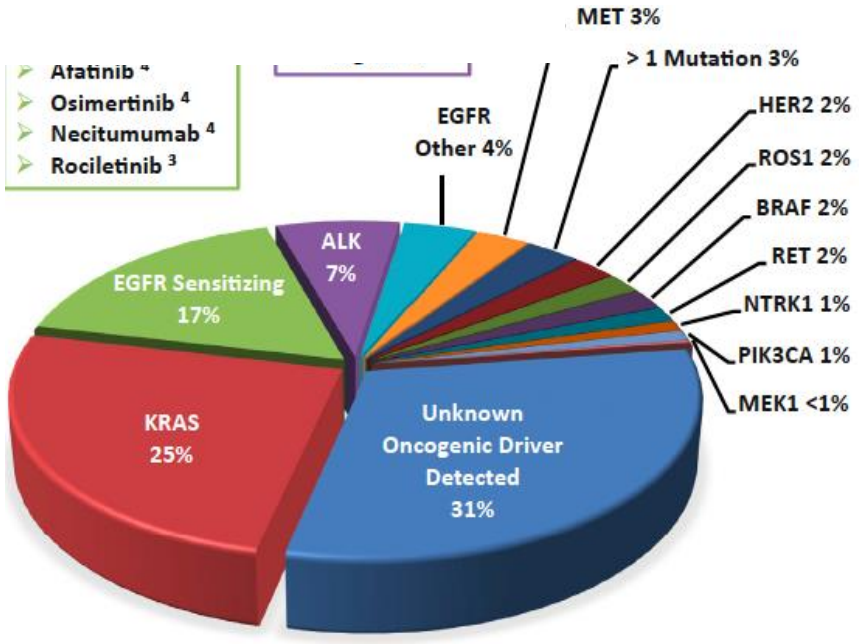
[a]95% CI.

Treatment-related select AEs with NIVO + IPI + chemo[a,b]



[a]Treatment-related select AEs are those with potential immunologic etiology that require frequent monitoring/intervention; [b]Includes events reported between first dose and 30 days after last dose of study drug; [c]The total number of patients treated with NIVO + IPI + chemo was 358.

Progress in Targeted Therapy for NSCLC-Adenocarcinoma



KRAS G12C
MTRX-849, AMG 510

PI3K
LY3023414, PQR-309

MEK
Trametinib, selumetinib, cobimetinib

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

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

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

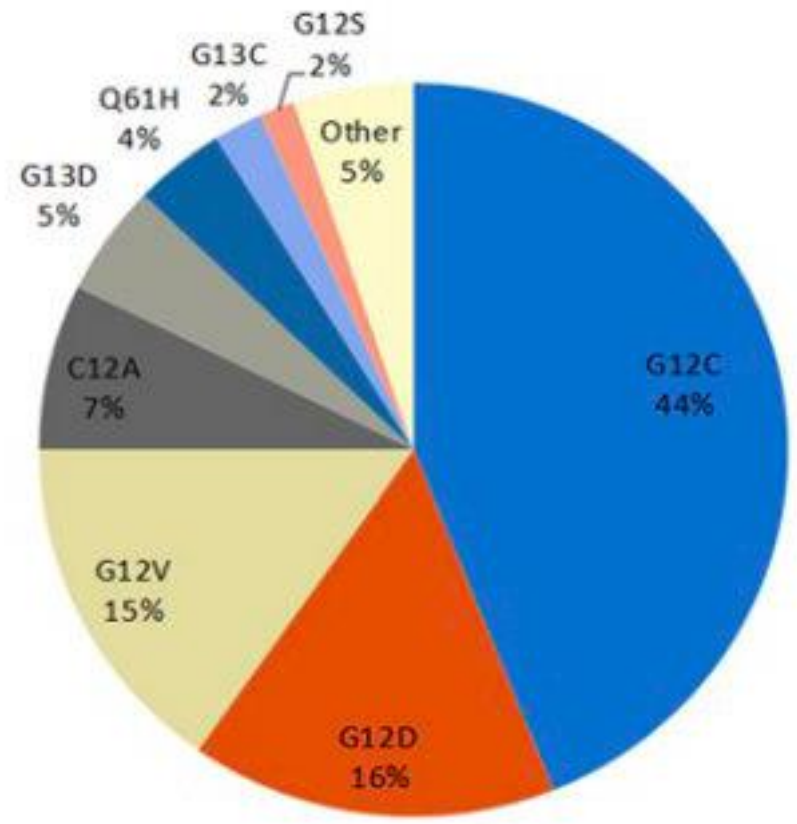
RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib, lenvatinib, apatinib, selpercatinib, BLU-667, RXDX-105

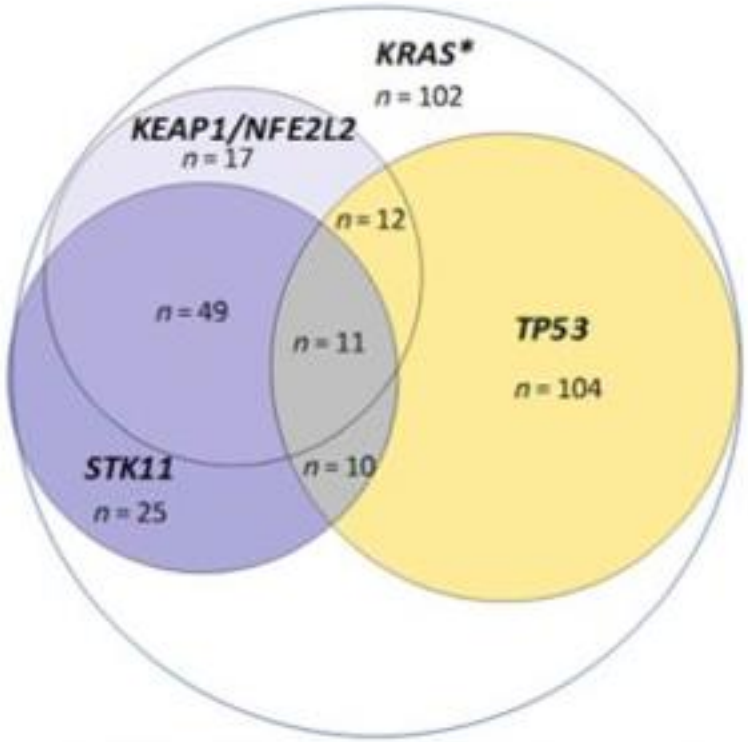
NTRK:
Larotrectinib, entrectinib, LOXO-195, DS-6051b, ropotrectinib

FDA

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

Spectrum of KRAS mutations and Co-Mutations in NSCLC

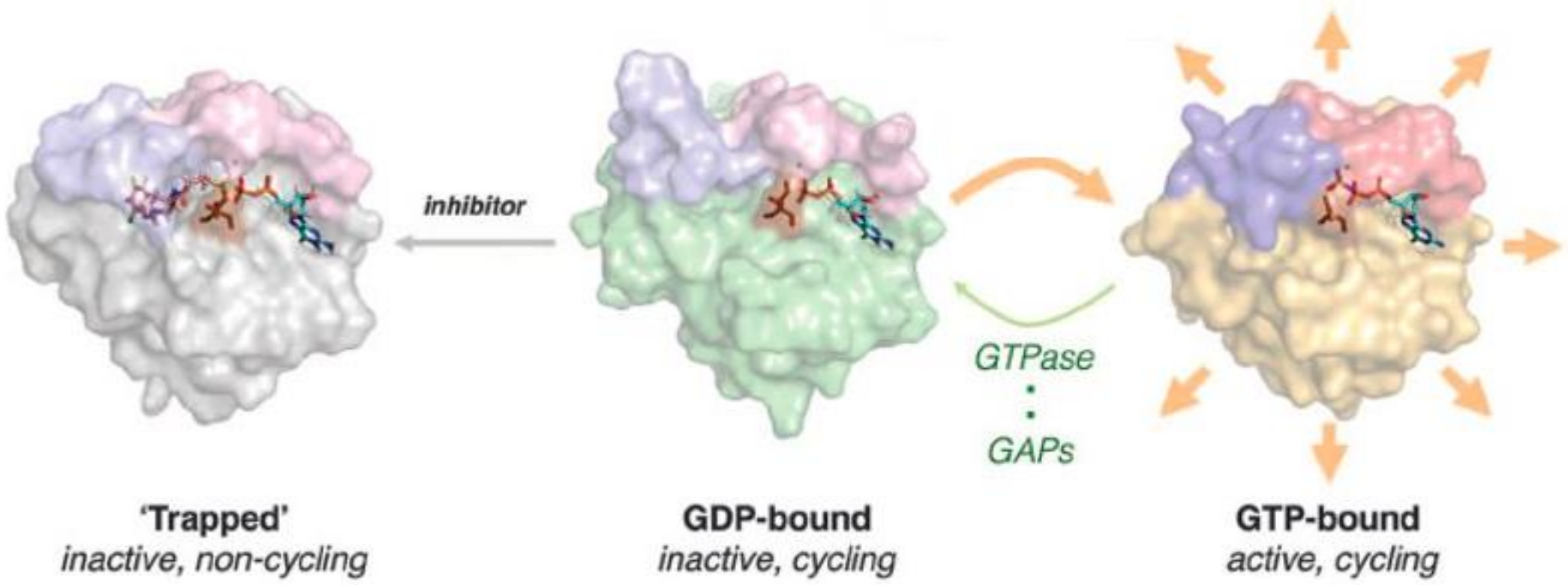




*KRAS (*n* = 102) listed above represents number of patients with *KRAS* mutations but without cooccurring mutations in *TP53*, *STK11*, *KEAP1* or *NFE2L2*

Arbour et al CCR 2018

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

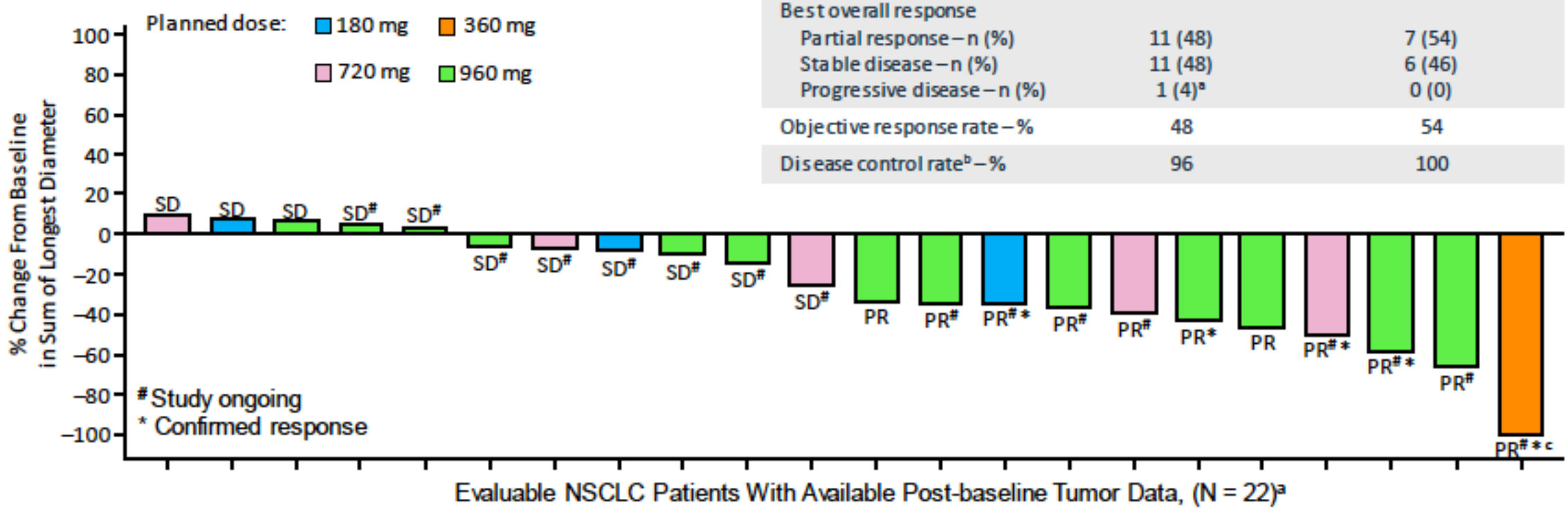


From P. Lito et al. Science 2016

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



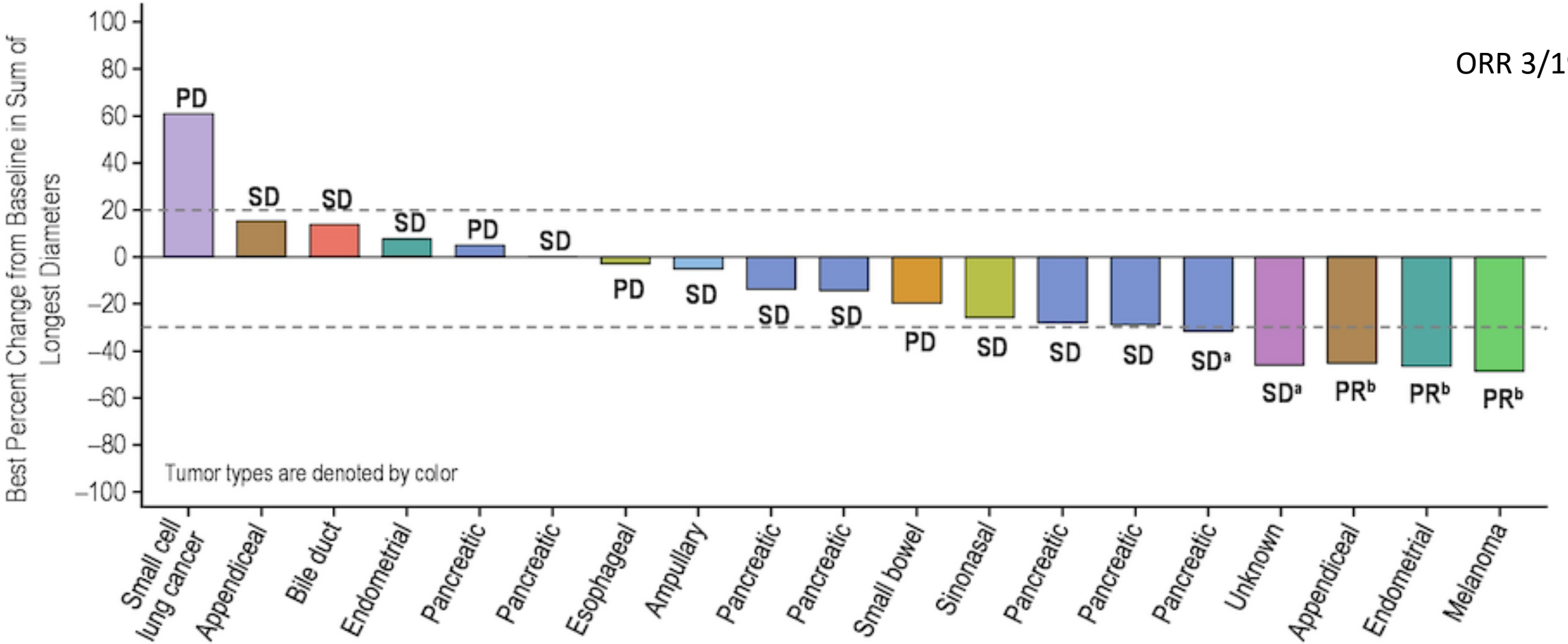
[a]One patient discontinued study due to PD prior to the 1st assessment, and the post-baseline tumor burden data are missing. [b]PR or SD at week 6. [c]Patient had complete response to the target lesions. Evaluable patients: patients who had the first 6-week scan or early PD

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

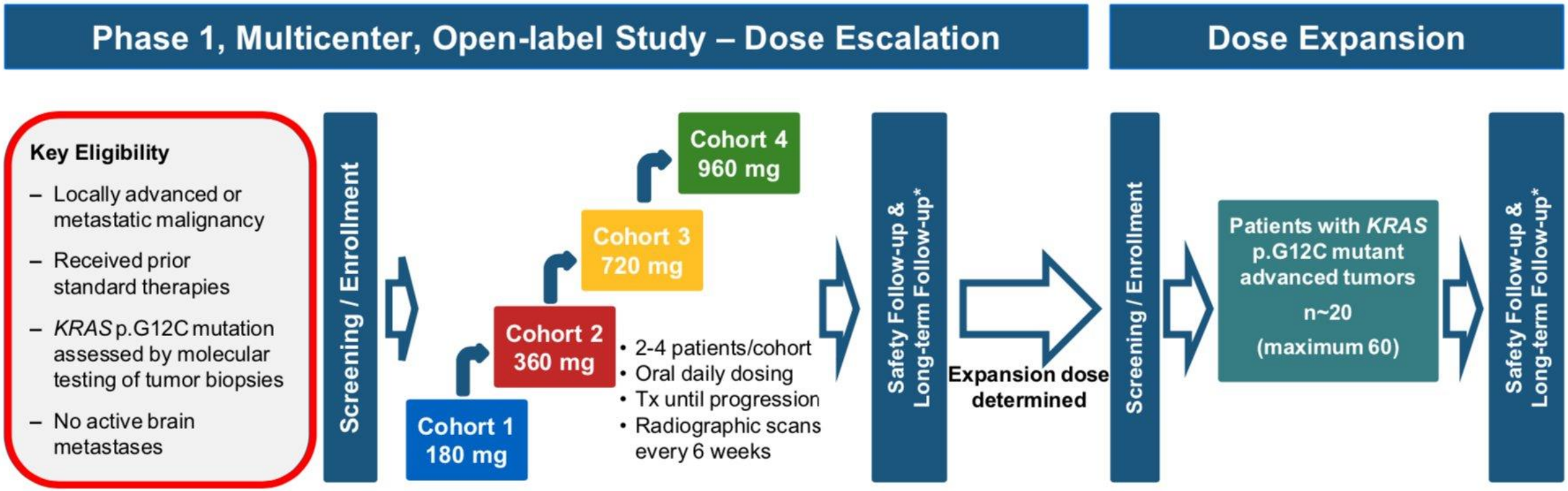
ORR 3/19



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

Phase 1 study design (CodeBreaK100: NCT03600883)

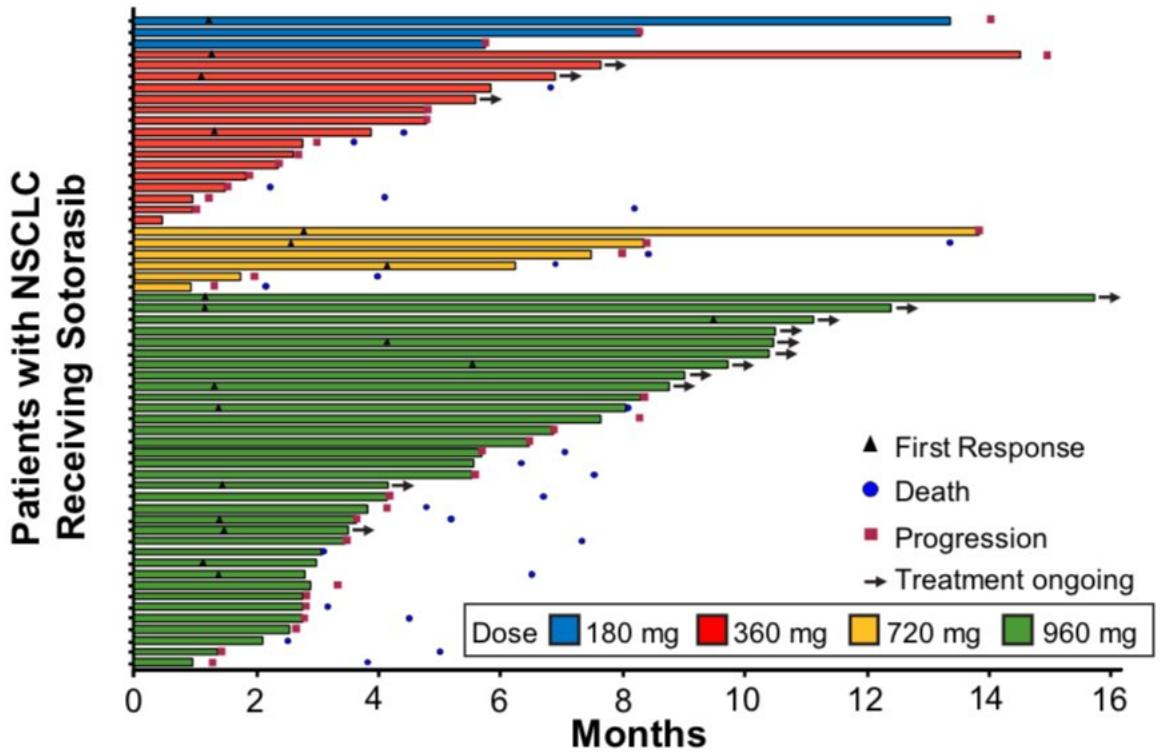


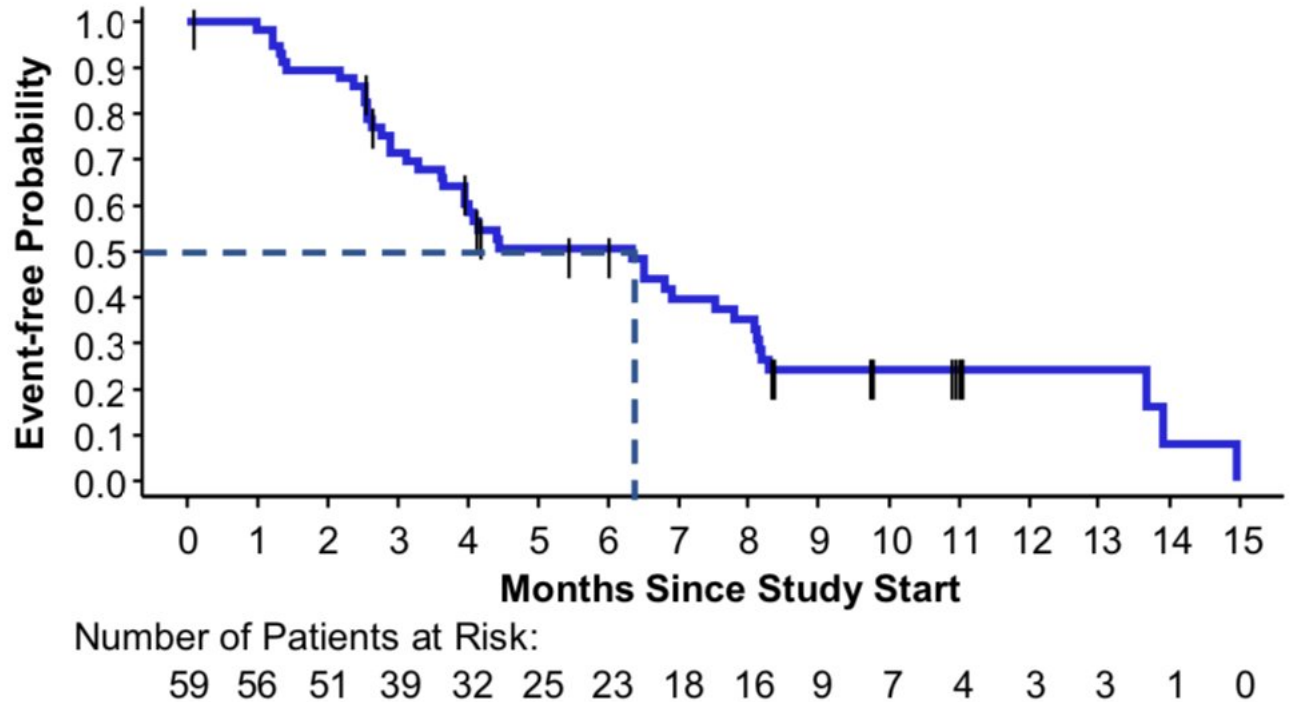
Primary endpoint: safety
Secondary endpoints include: PK, ORR, DOR, DCR, PFS, duration of SD

*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.

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

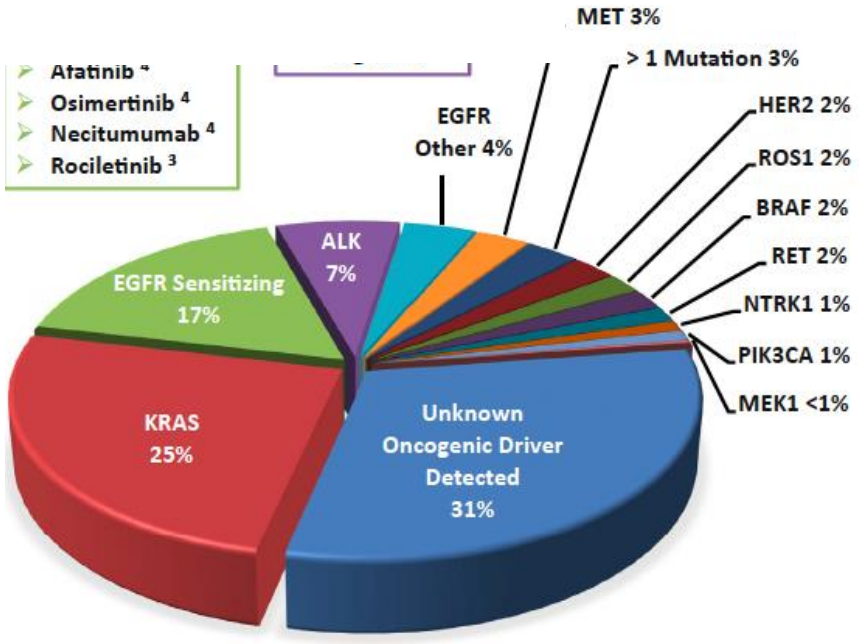
*Duration of response was measured from first evidence of PR/CR to disease progression or death due to any cause, whichever was earlier. ‡Duration of SD was measured from the start of the treatment until the criteria for disease progression were met or death, whichever was earlier. †At data cutoff of 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

Direct G12C inhibitors in Development and Rational Combination Strategies

Direct G12Ci
JNJ-74699157
MTRX849
AMG510
LY4399446

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

Progress in Targeted Therapy for NSCLC-Adenocarcinoma



KRAS G12C
MTRX-849, AMG 510

PI3K
LY3023414, PQR-309

MEK
Trametinib, selumetinib, cobimetinib

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

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

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

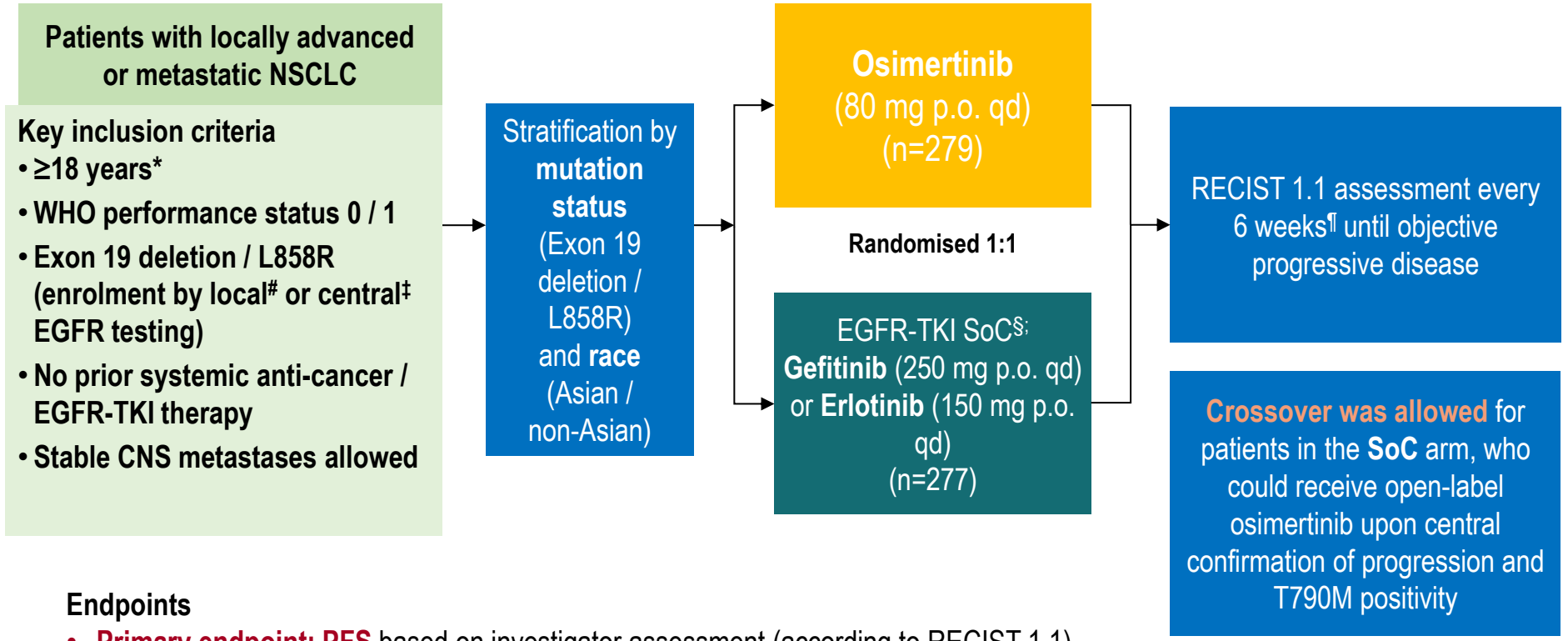
RET:
Cabozatinib, alectinib, vandetanib, sunitinib, ponatinib, lenvatinib, apatinib, selpercatinib, BLU-667, RXDX-105

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.

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



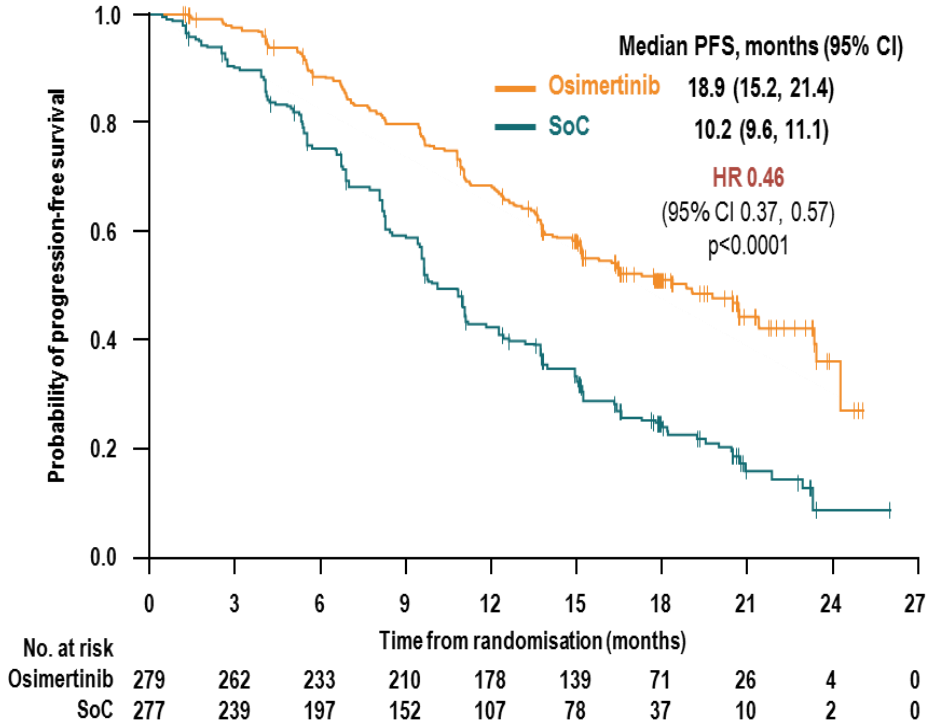
Endpoints

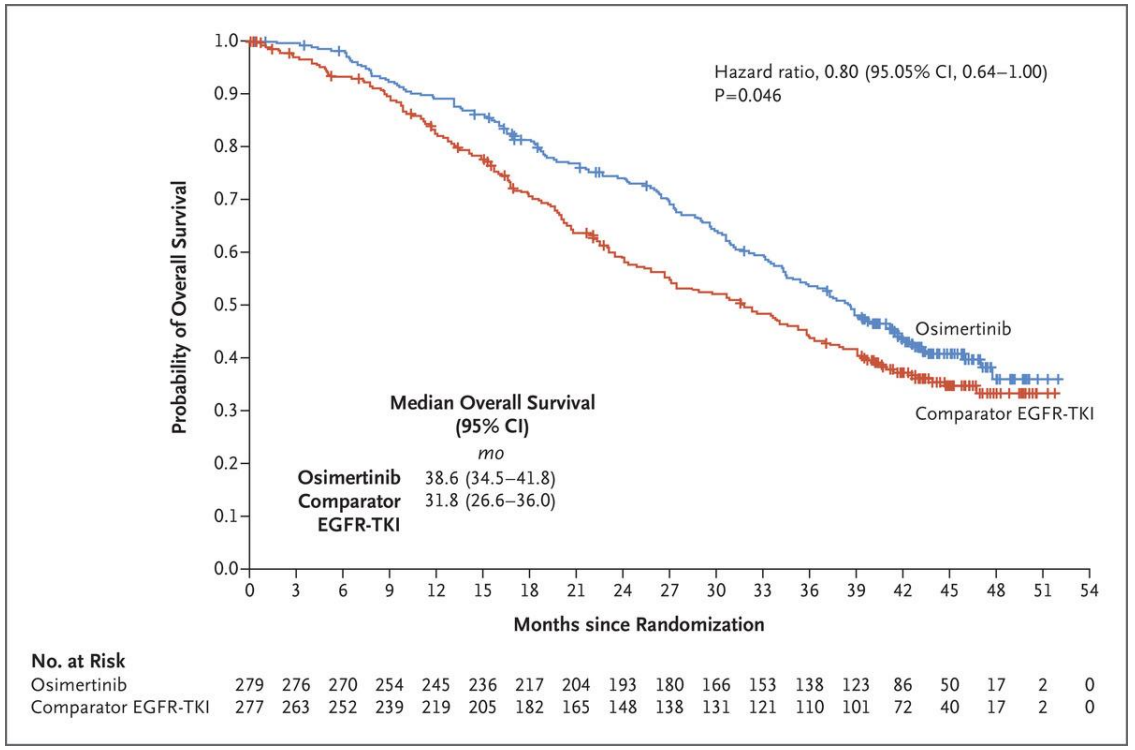
- **Primary endpoint: PFS** based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing a 29% improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** objective response 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

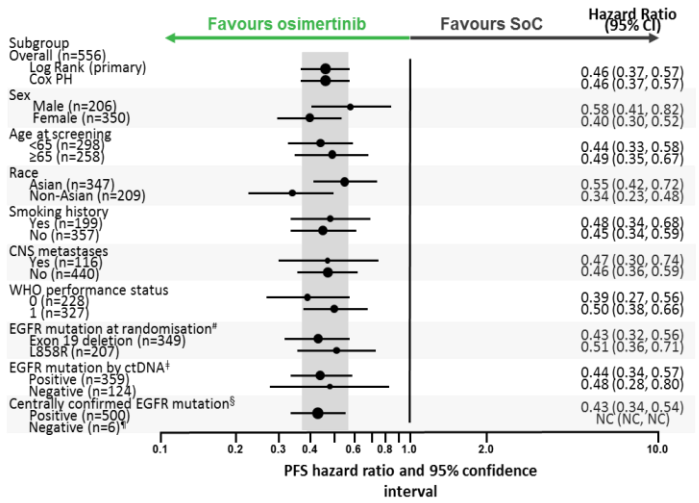
PFS and OS from FLAURA





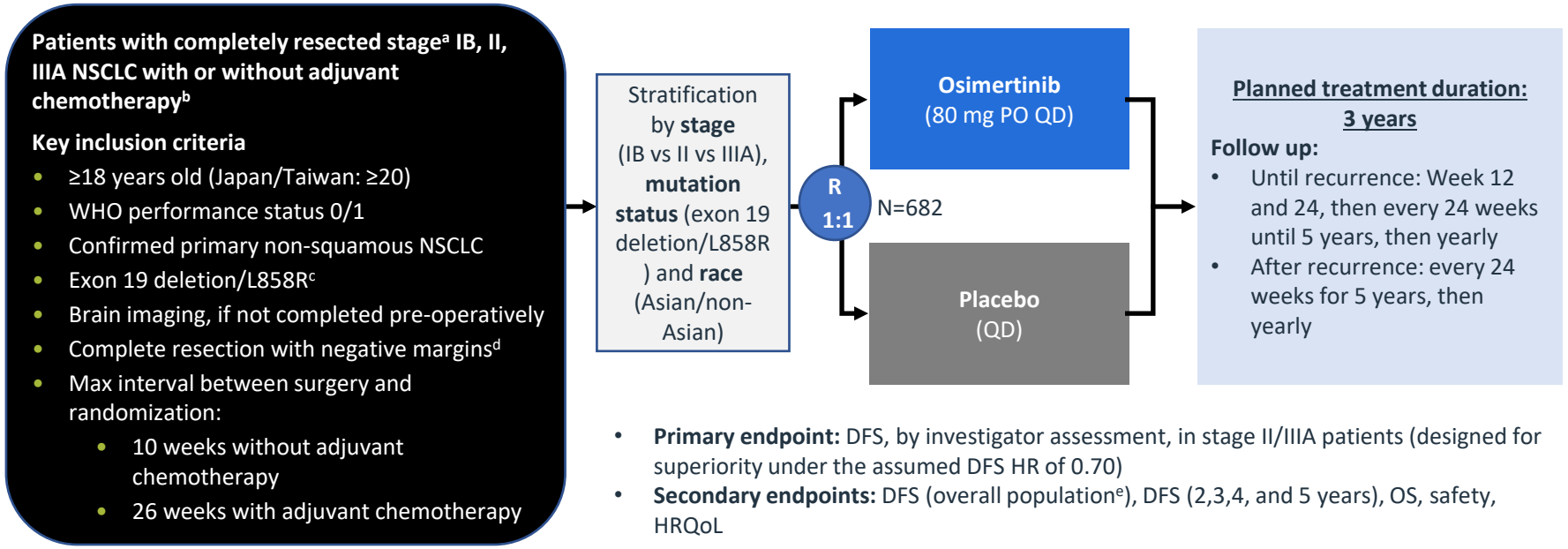
PFS in patients with brain mets (n=116) HR=0.47
PFS in patients without brain mets (n=440)
HR=0.46

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

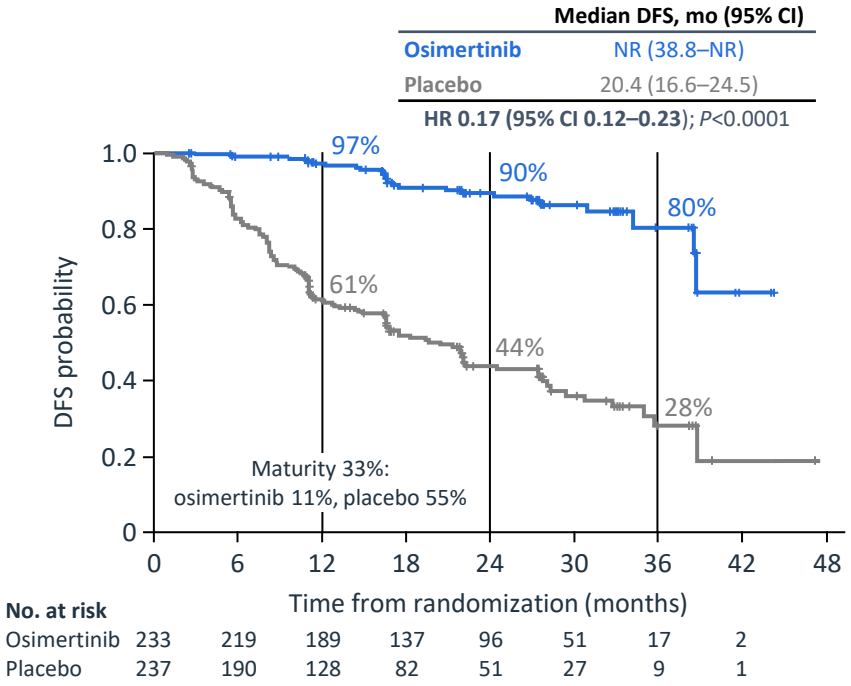
- **Following data monitoring committee recommendation, the study was unblinded early due to efficacy; reported here is an unplanned interim analysis**
- **At the time of unblinding, the study had completed enrollment and all patients were followed up for ≥1 year**

[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.

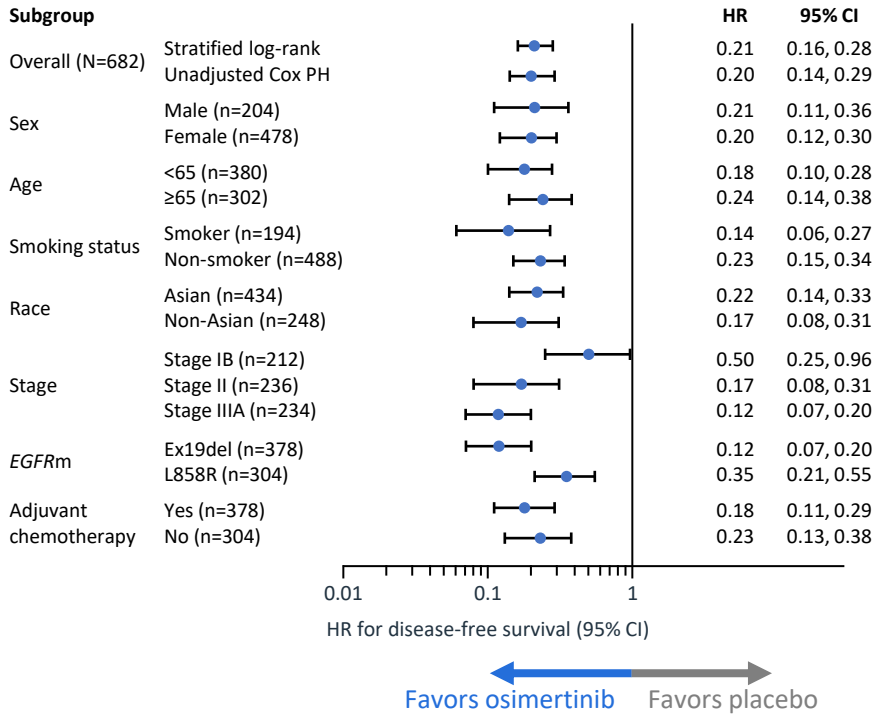
Herbst RS, et al. ASCO 2020. Abstract LBA5.

ADAURA: Disease-free survival (DFS)

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



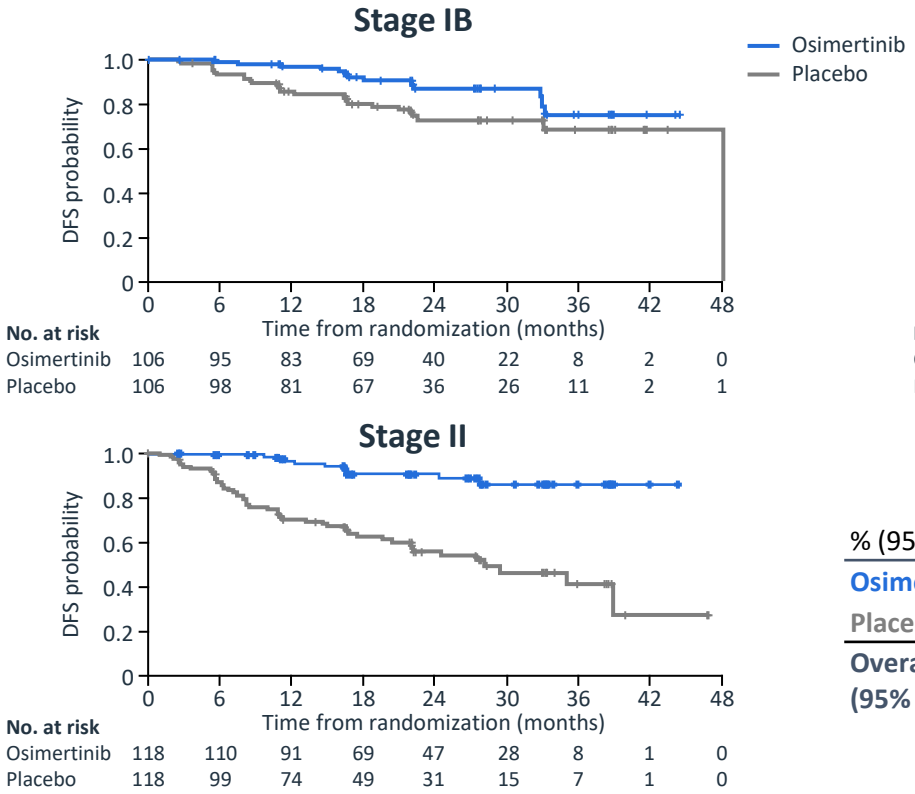
DFS across subgroups in the overall population

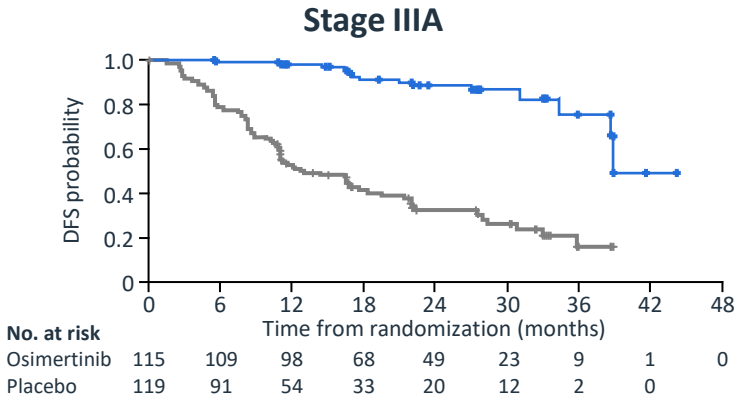


Data cutoff: January 17, 2020. NR, not reached

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

ADAURA: Disease-free survival by stage





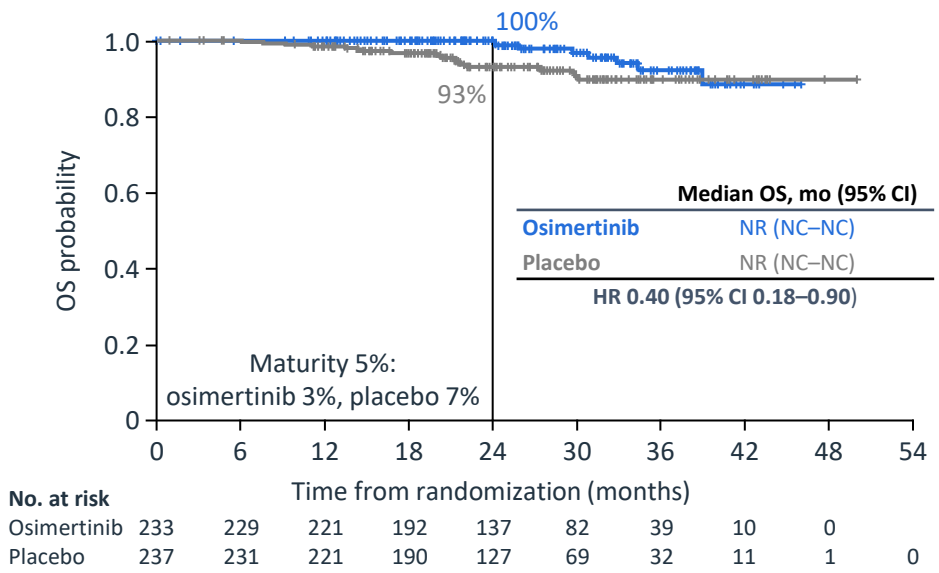
2 Year DFS rate

% (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



- 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

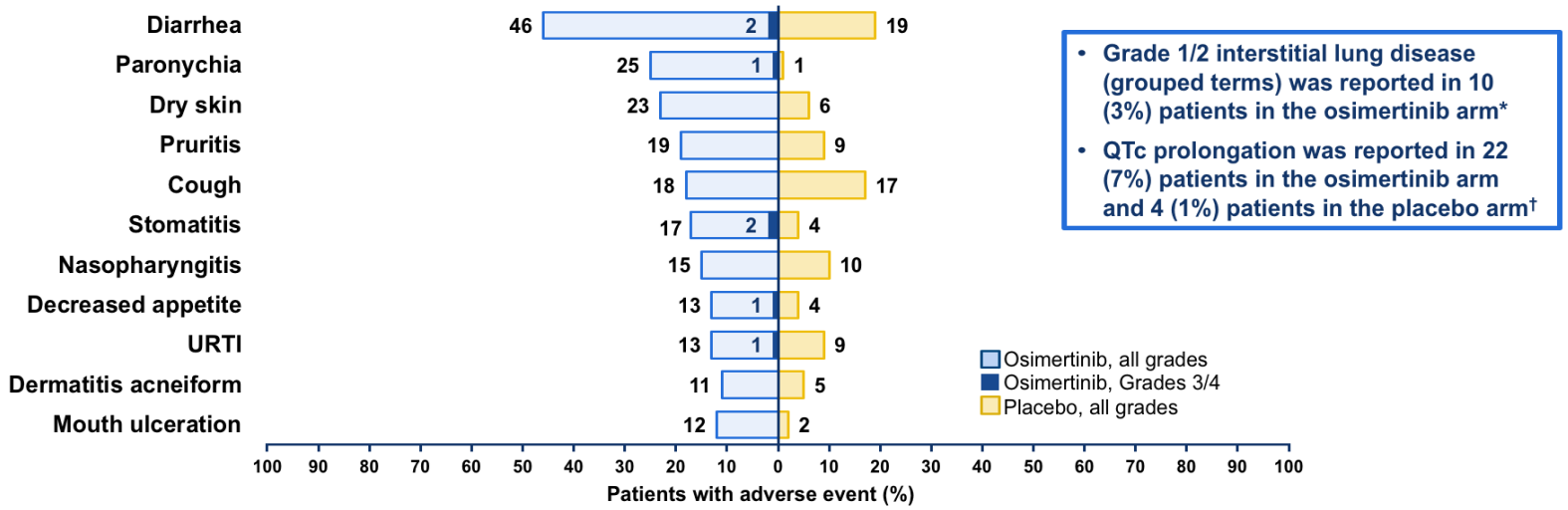
Data cutoff: January 17, 2020.

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

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)

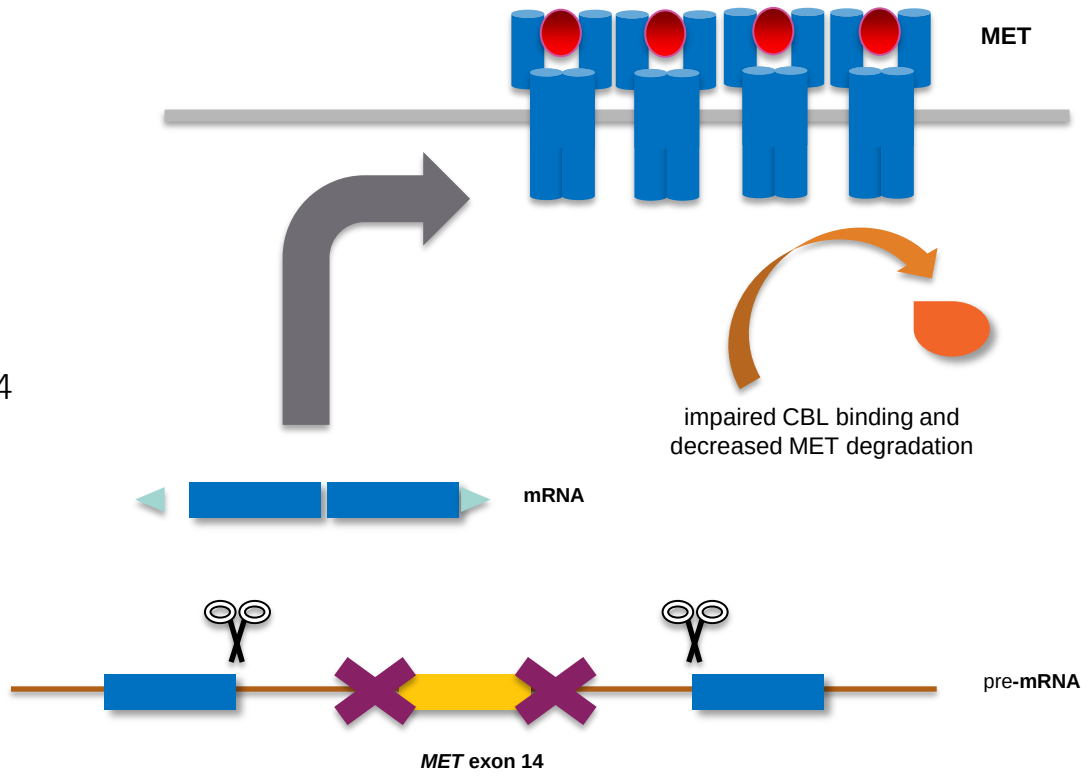


- **Grade 1/2 interstitial lung disease (grouped terms) was reported in 10 (3%) patients in the osimertinib arm***
- **QTc prolongation was reported in 22 (7%) patients in the osimertinib arm and 4 (1%) patients in the placebo arm†**

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

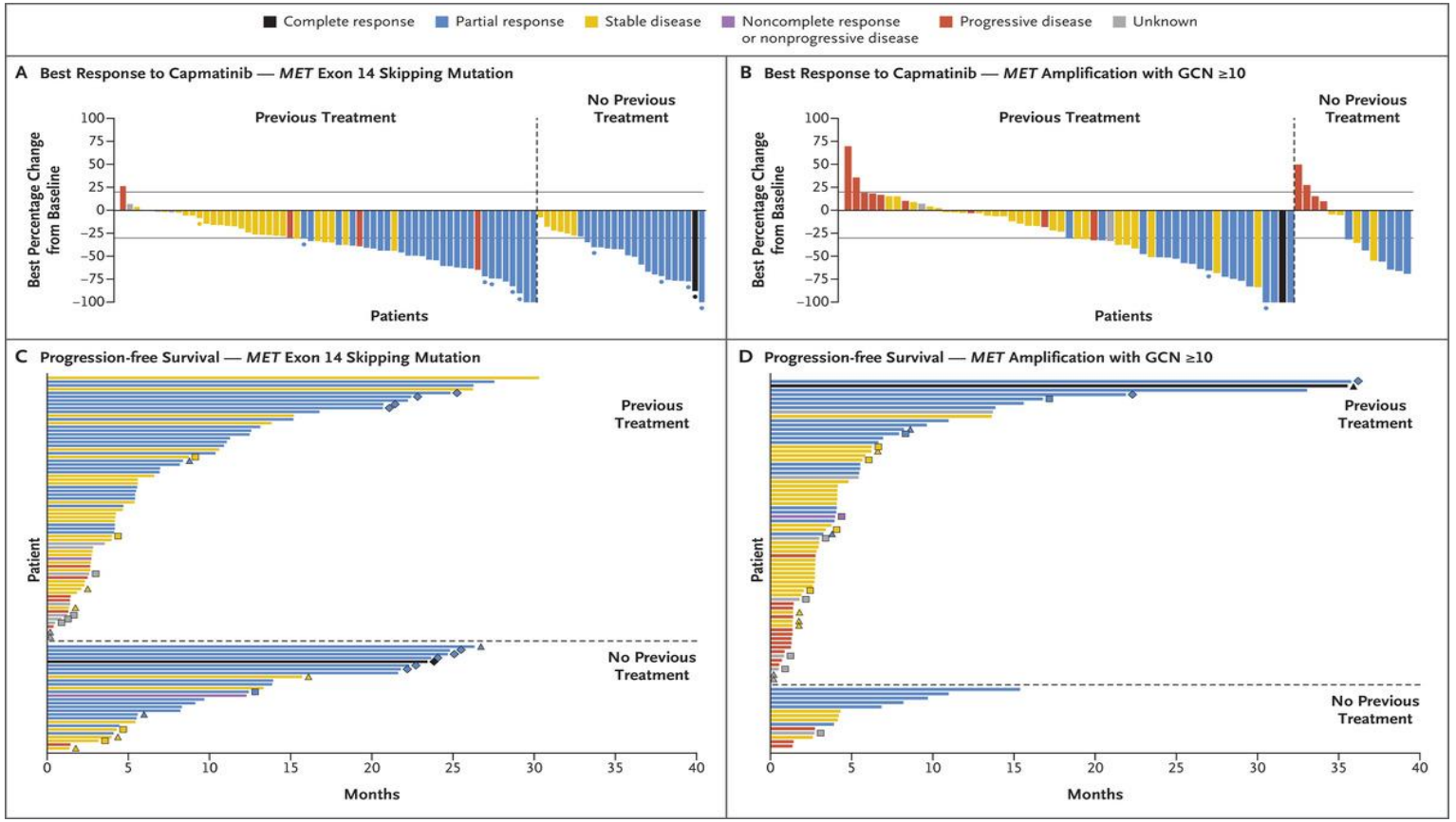
MET Exon 14 Alterations

- *MET* mutations that lead to decreased MET degradation (~2-4% NSCLC)
  - deletions, insertions, or base substitutions
  - many disrupt splice sites flanking *MET* exon 14 → exon 14 skipping
  - increased MET receptor on the tumor cell surface



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;5. Drilon A. Clin Cancer Res 2016.

Capmatinib in MET Exon 14 Skipping Mutation/MET Amplification



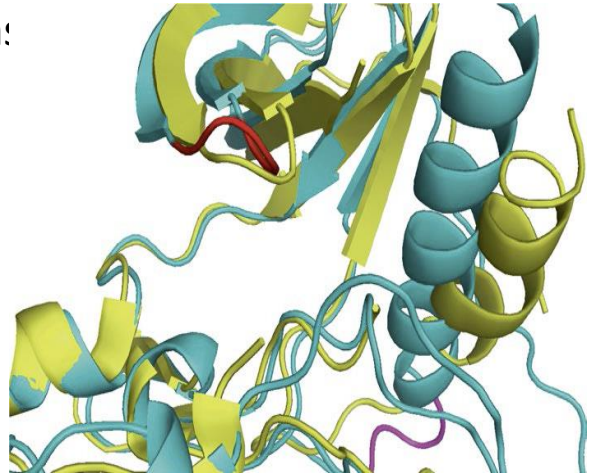
	Met Ex14		MET Amp (CNG 10)	
	ORR	PFS	ORR	
Pretreated	**41%**	**5.4**	**29%**	**4.1**
Untreated	**68%**	**12.4**	**40%**	**4.2**

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



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

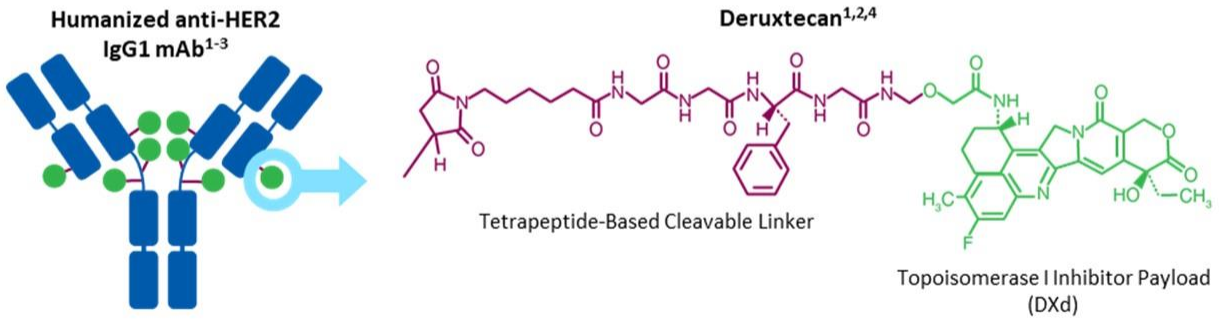
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

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

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



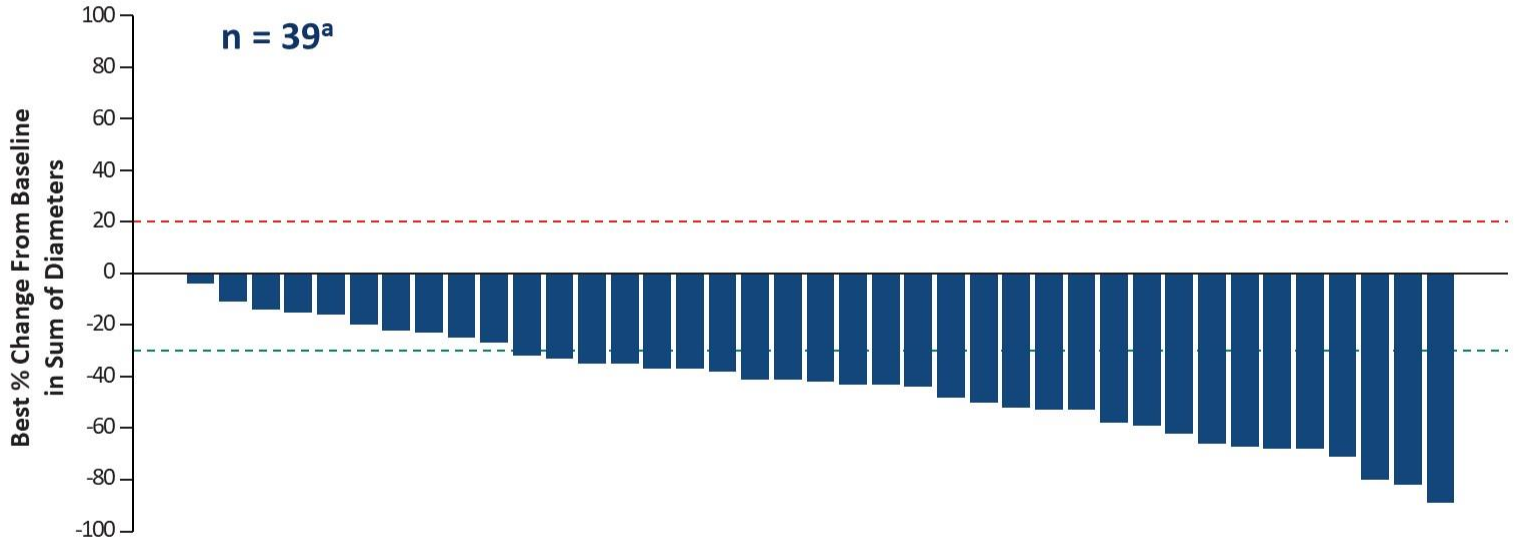
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug to antibody ratio ≈ 8
Payload with short systemic half-life
Stable linker-payload
Tumor-selective cleavable linker
Membrane-permeable payload

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.

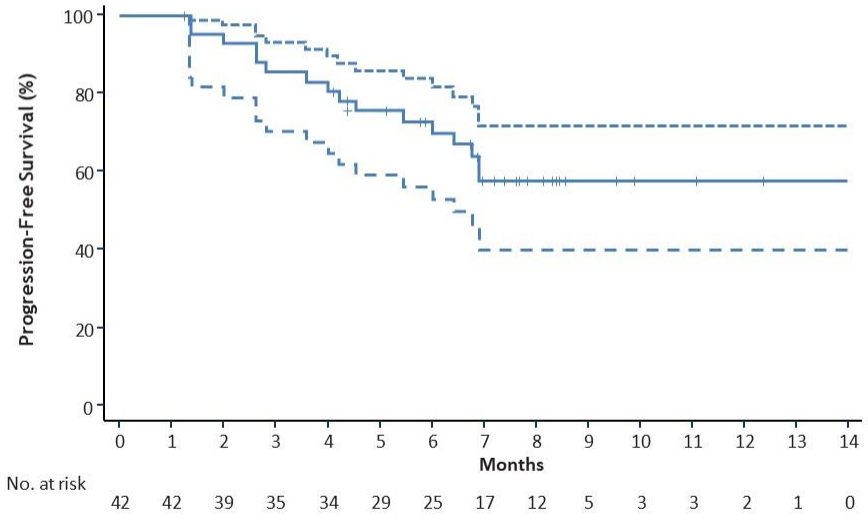
[a] One patient was missing a baseline assessment and 2 additional patients were missing post-baseline assessments.

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

Progression-Free and Overall Survival

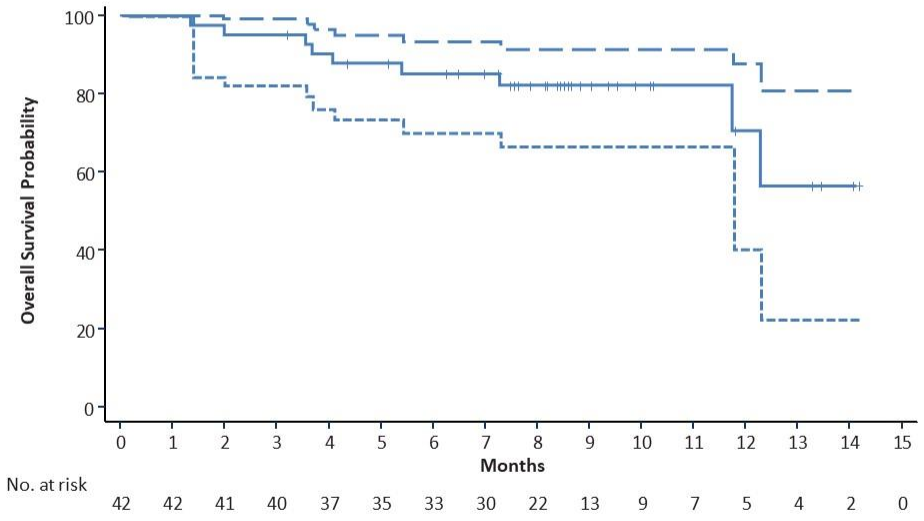
Progression-Free Survival (N = 42)[a]

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



Overall Survival (N = 42)

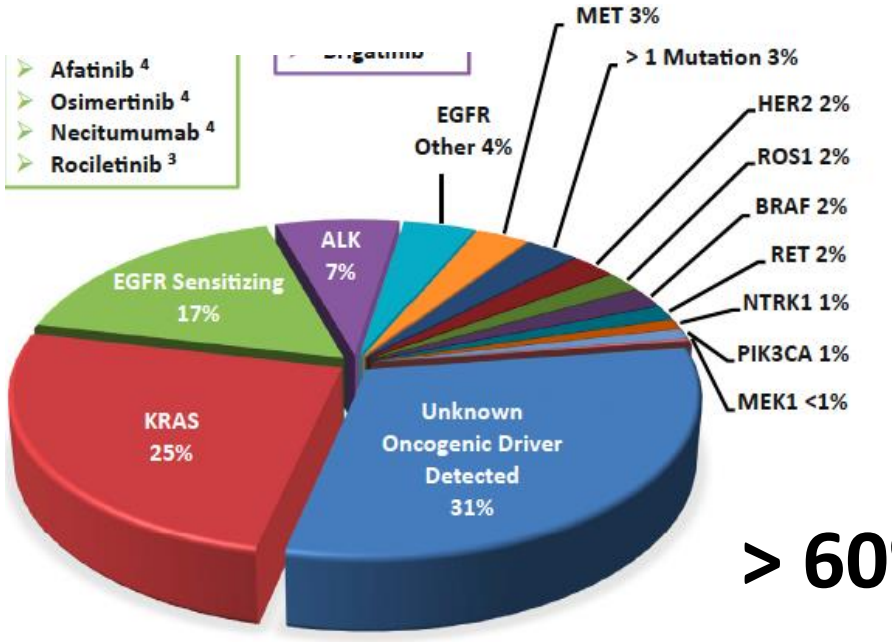
Median: Not reached (95% CI, 11.8-NE)



[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.

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

Summary – More and Better Pieces of Pie

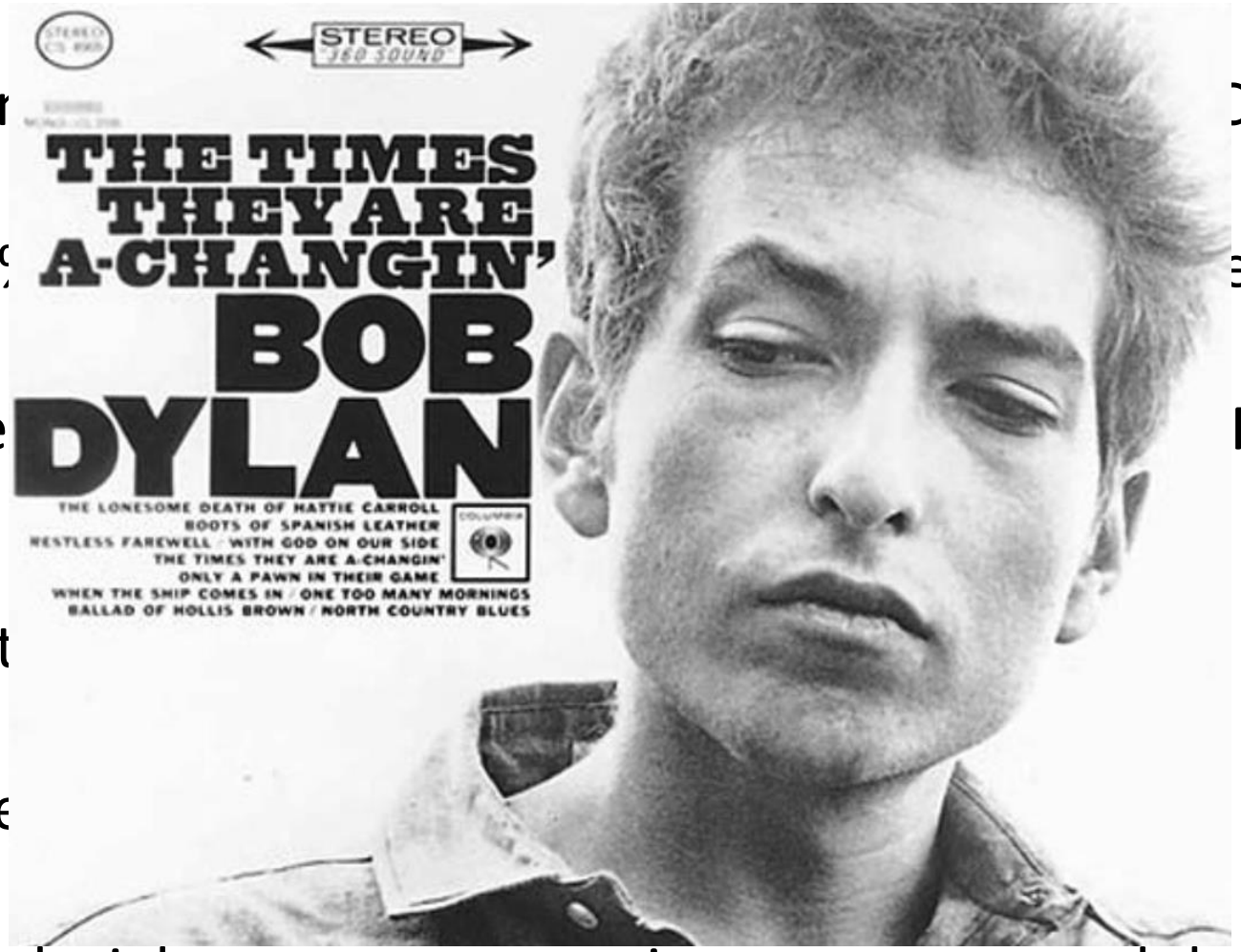


FDA Approvals

EGFR-mut – Osimertinib
ALK Fusion – Alectinib/Brigatinib/Lorlatinib
BRAF V600E – Dabrafenib and Trametinib
ROS1 Fusion – Entrectinib and Crizotinib
MET Exon 14 mut – Capmatinib
RET Fusion – Selpercatinib, Pralsetinib
NTRK Fusion - Larotrectinib

> 60%

Take Home Points



- Multiple Firstli CLC
- PD-L1 high (50 ear survival
- New oncogene R2, RET, KRAS G12C)
- Can now target
- Adjuvant osime
- UC Davis Clinical trials to overcome resistance to targeted therapies and immunotherapy