MaTOS™
Masters in Thoracic Oncology Summit
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Improving Targeted Therapies for Patients with Lung Cancers
Where are the gaps and ways to fill them

Mark G Kris
Attending Physician and Member
Memorial Sloan Kettering Cancer Center
Professor of Medicine
Weill Cornell Medical college

Filling the Gaps with Lung Cancer Targeted Therapies

Introduction

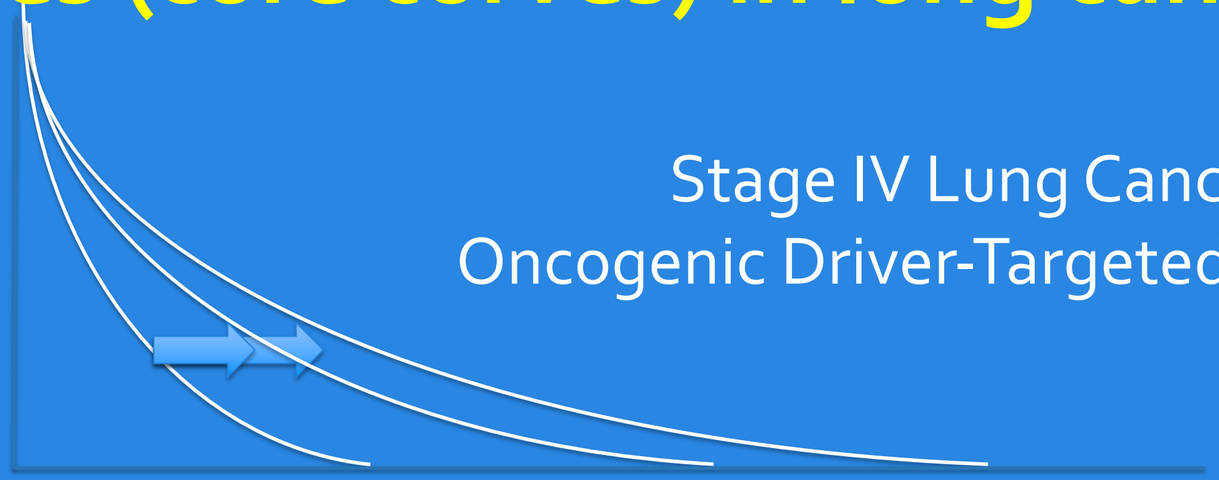
Targets

Gaps

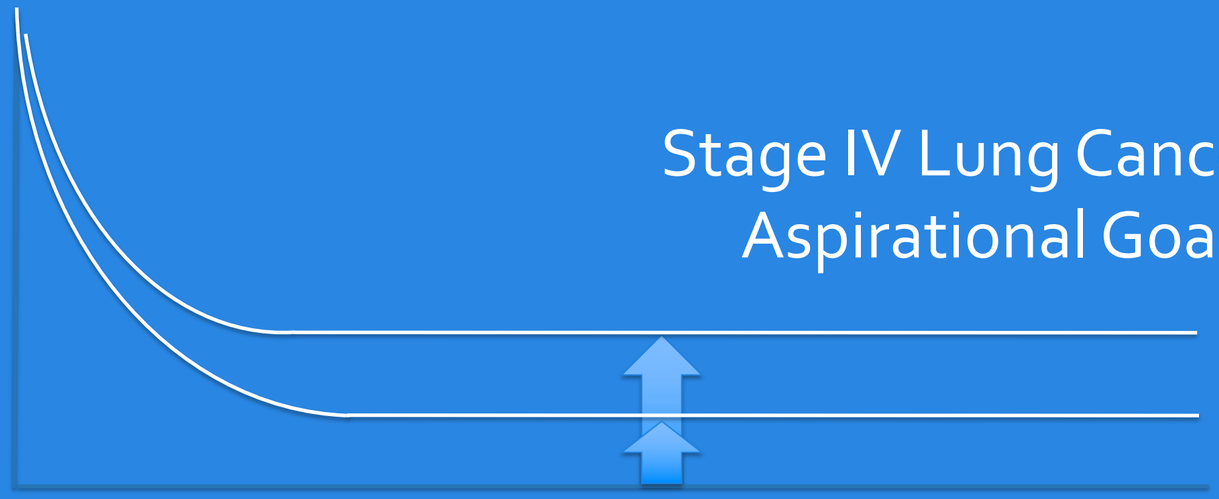
Ways Forward

- Short Term
- Long Term

Bending the disease free and progression free survival curves (cure curves) in lung cancers



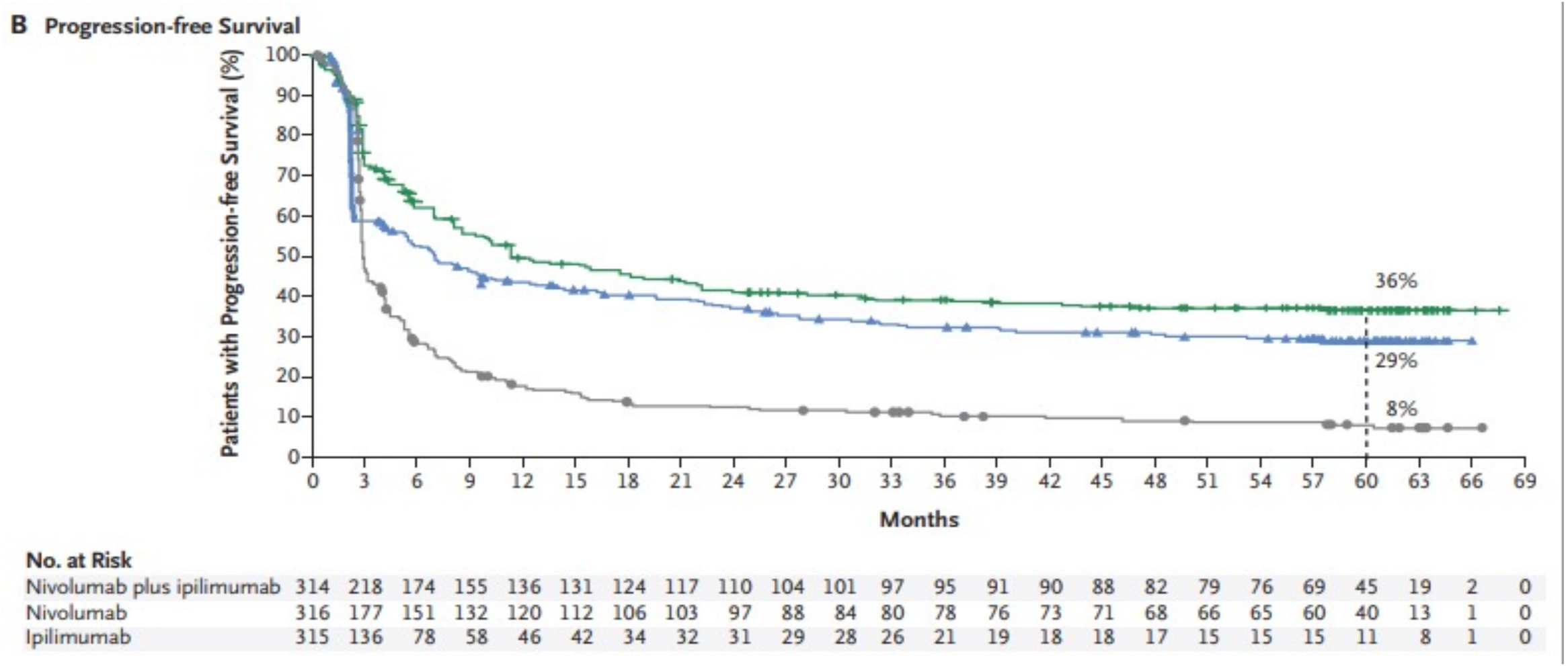
Stage IV Lung Cancers
Oncogenic Driver-Targeted Therapies



Stage IV Lung Cancers
Aspirational Goal

Hellmann JAMA Oncology 2015

Stage IV melanoma: 5 yr progression free survival (cure?) Nivolumab vs Ipimumab vs Nivo+Ipi Combination



No. at Risk																								
Nivolumab plus ipilimumab	314	218	174	155	136	131	124	117	110	104	101	97	95	91	90	88	82	79	76	69	45	19	2	0
Nivolumab	316	177	151	132	120	112	106	103	97	88	84	80	78	76	73	71	68	66	65	60	40	13	1	0
Ipilimumab	315	136	78	58	46	42	34	32	31	29	28	26	21	19	18	18	17	15	15	15	11	8	1	0

Wolchock NEJM 2022

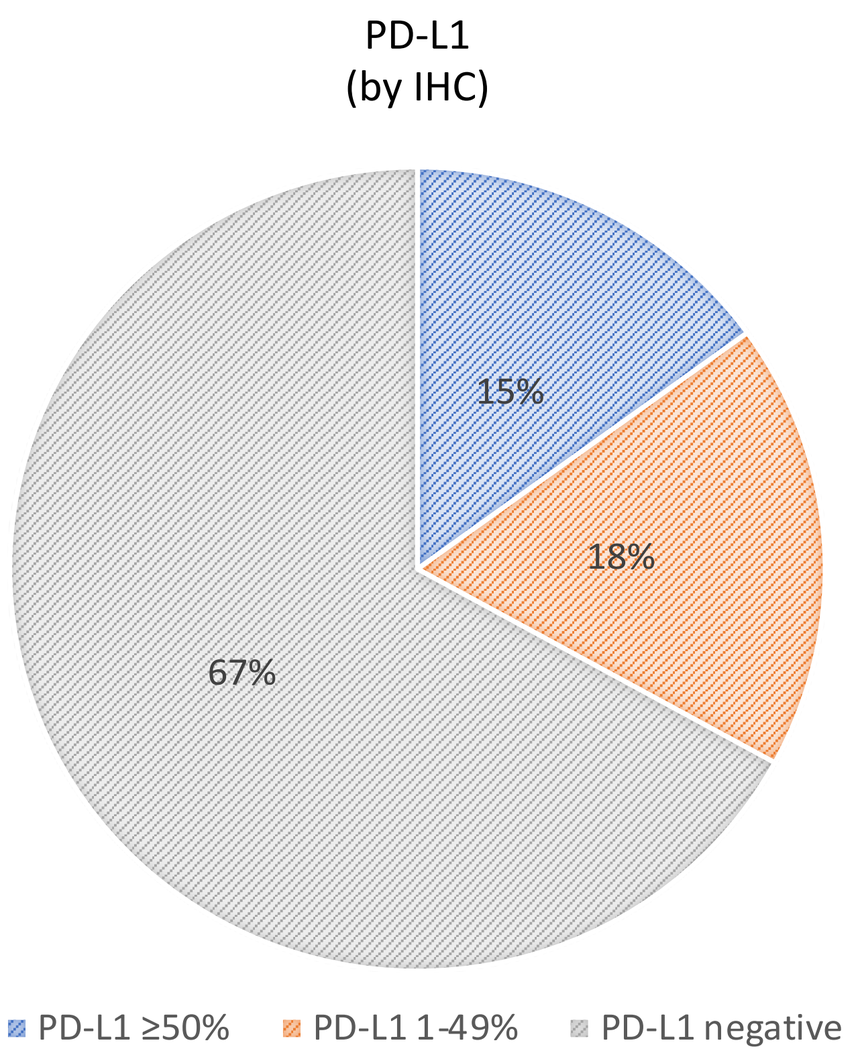
Human impact of recurrence/progression
One patient's perspective

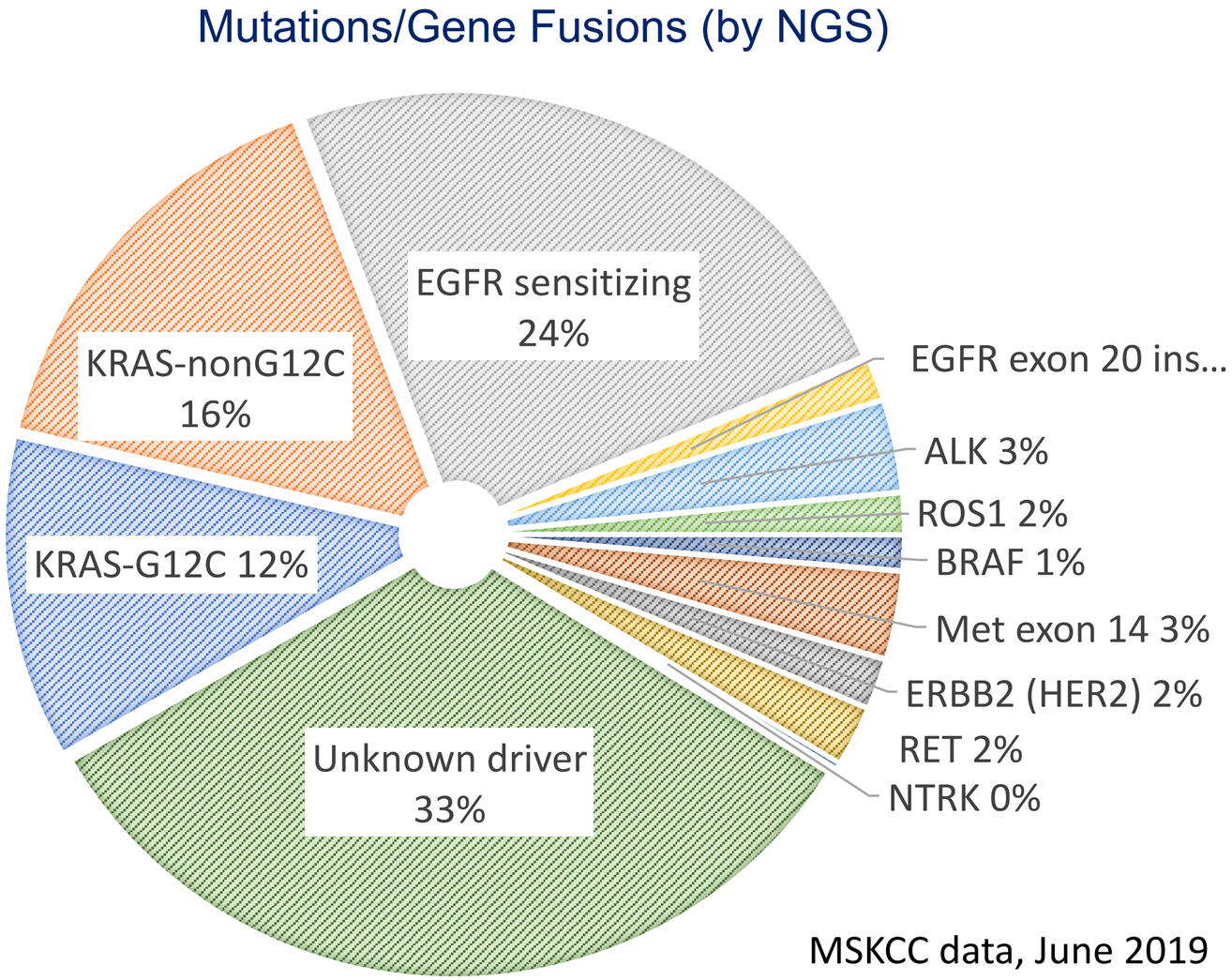
"Time for me is double-edged: Every day brings me further from the low of my last cancer relapse, but every day also brings me closer to the next cancer recurrence --- and eventually, death."

Paul Kalanithi, MD'07 Author of "*When Breath Becomes Air*"

Neurosurgeon, Writer, Patient with stage IV *EGFR* mutant lung cancer

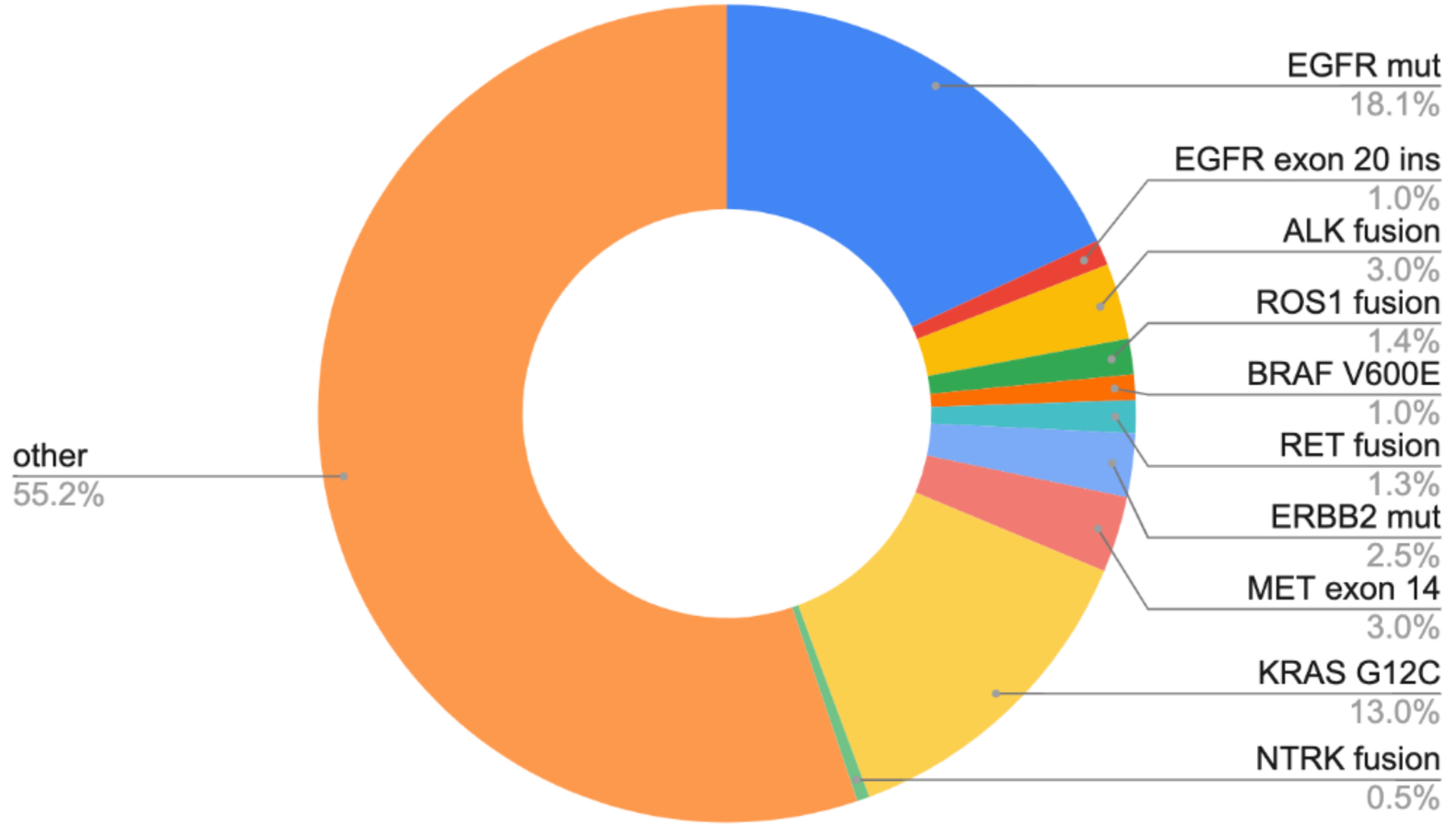
Classification of lung carcinomas by targets





MSKCC data, June 2019

Lung cancer molecular subtypes with FDA-approved agents



AACR GENIE BPC lung, Data available at https://genie.cbioportal.org/

Filling the Gaps with Lung Cancer Targeted Therapies

Targets With Drugs in Lung Cancers 2023

ADCs {HER2, HER3, TROP-2, B7:H4, CEACAM1) Are they really targets?

ALK Fusions

BRAF (V600E, type II and III mutations, fusions)

EGFR Mutations (sensitizing and “atypical”)

EGFR Exon 20 insertions

HER2 Mutations and Amplification

KRAS G12C Mutations

KRAS G12X Mutations

MET Exon 14 Mutations and *MET* Amplification

NTRK Fusions

NRG1 fusions

PD-L1/Tumor Mutational Burden

RET Fusions

ROS1 Fusions

Filling the Gaps with Lung Cancer Targeted Therapies

Gaps – Common to All Small Molecule Targeted Therapies for Lung Cancers

1. No Single Agent Cures

2. No Single Agent Cures

3. Long term side effects (even grade 1 rash, diarrhea, edema a problem when it happens daily for years, weight gain)

4. Acute severe side effects (pneumonitis, hepatotoxicity)

5. With some exceptions (KRAS), no immunotherapies for patients with tumors with targets

6. Interactions with radiation and immunotherapies

Ways to fill the gaps in targeted therapies

- **Short-Term**
  1. Combinations with cytotoxic chemotherapies
  2. Combinations with anti-angiogenesis agents
  3. Combinations with additional targeted treatments
  4. Use with local therapies : surgery, radiation, and ablation
- **Long Term**
  1. Agents
     A. More effective
     B. Better targeted
     C. New Targets
  2. Degraders
  3. Vaccines
  4. Targeting Persisting cells

Ways to fill the gaps in targeted therapies

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Inconvenient Truth: Chemo with Targeted Drugs Better
FLAURA2 Phase III study design

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

Randomization 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m^2 + carboplatin AUC5 or cisplatin 75 mg/m^2 (Q3W for 4 cycles for platinum-based treatments)

Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†

Osimertinib 80 mg (QD)

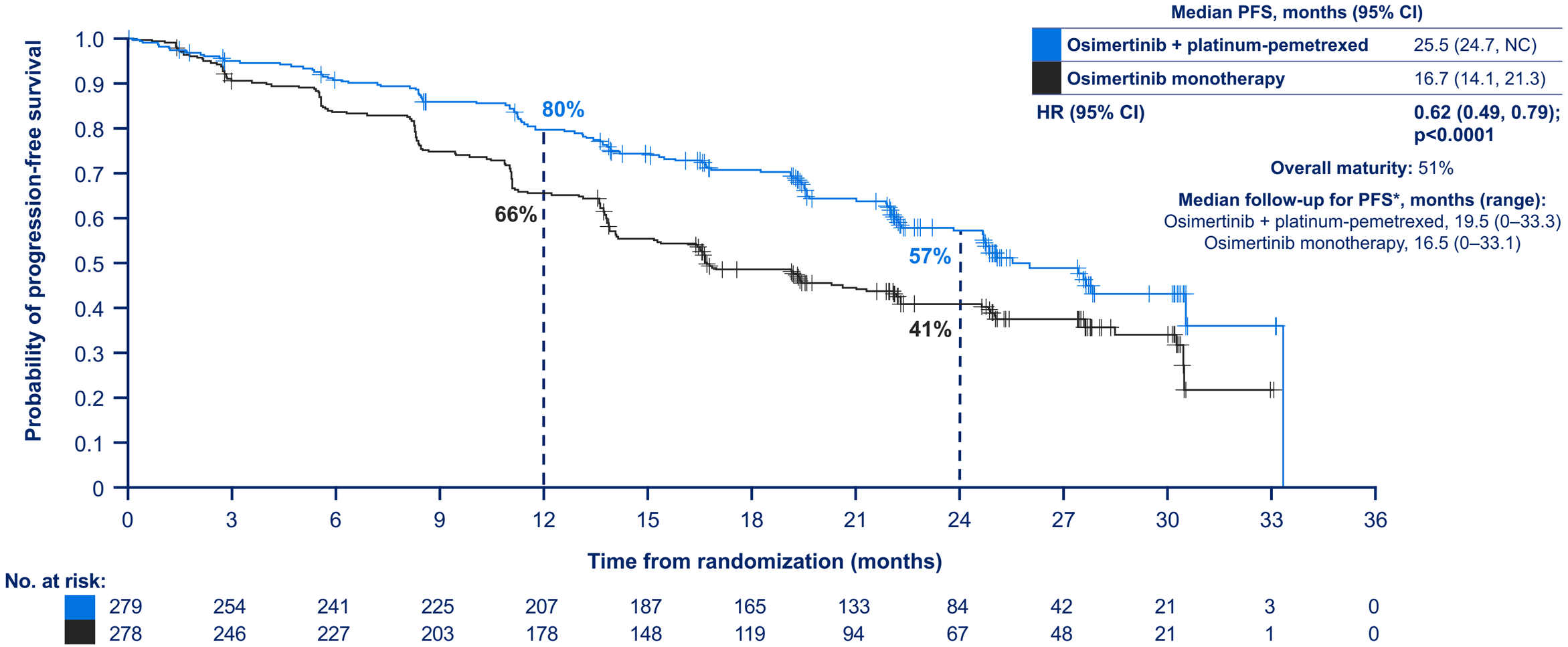
Follow-up:

- RECIST 1.1 assessment at 6 and 12 weeks, then every 12 weeks until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints:** OS, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5) and PFS2‡

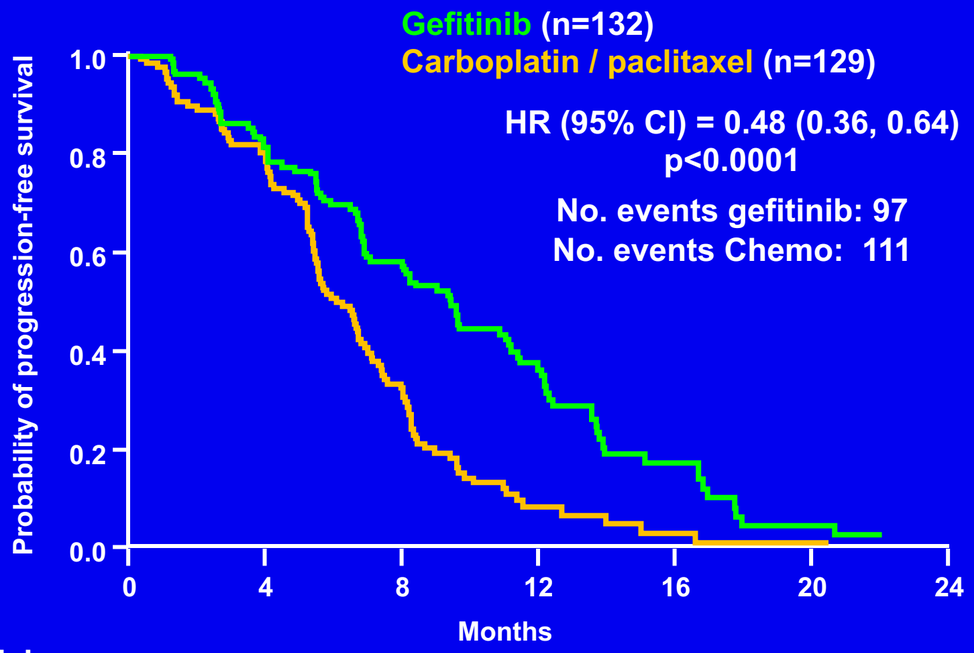
Osimertinib+Cemotherapy vs Osimertinib
9 month improvement in progression-free survival with chemotherapy

- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy



Chemotherapy work better in patients with *EGFR* mutations: Remember IPASS?

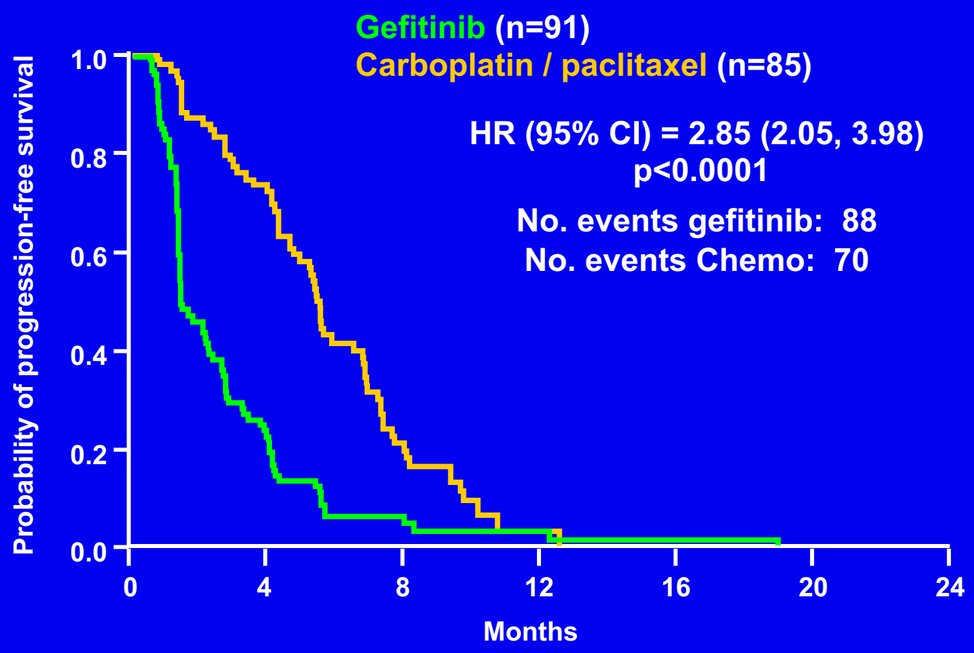
EGFR mutation positive



At risk :							
Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

Gefitinib CR/PR Rate 71%
CBP/PTX CR/PR Rate 47%

EGFR mutation negative



	91	21	4	2	1	0	0
	85	58	14	1	0	0	0

Gefitinib CR/PR Rate 1%
CBP/PTX CR/PR Rate 24%

Mok NEJM 2009

Targeted Drugs Better with Chemotherapy
Amivantinab+Chemotherapy vs Chemotherapy

Key Eligibility Criteria

- Treatment-naïve,[a] locally advanced or metastatic NSCLC
- Documented *EGFR* Exon 20 insertion mutations
- ECOG PS 0 or 1

Stratification Factors

- ECOG PS
- History of brain metastases[b]
- Prior EGFR TKI use[a]

1:1 Randomization (N=308)

Amivantamab-Chemotherapy (n=153)

Chemotherapy (n=155)

Dosing (in 21-day cycles)

Amivantamab: 1400 mg (1750 mg if ≥80 kg) for the first 4 weeks, then 1750 mg (2100 mg if ≥80 kg) every 3 weeks starting at week 7 (first day of cycle 3)

Chemotherapy on the first day of each cycle:

- **Carboplatin:** AUC5 for the first 4 cycles
- **Pemetrexed:** 500 mg/m^2 until disease progression

Primary endpoint: Progression-free survival (PFS) by BICR according to RECIST v1.1[c]

Secondary endpoints:

- Objective response rate (ORR)[c]
- Duration of response (DoR)
- Overall survival (OS)[c]
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS[d]
- Time to subsequent therapy[d]
- Safety

Optional crossover to 2nd-line amivantamab monotherapy[e]

PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

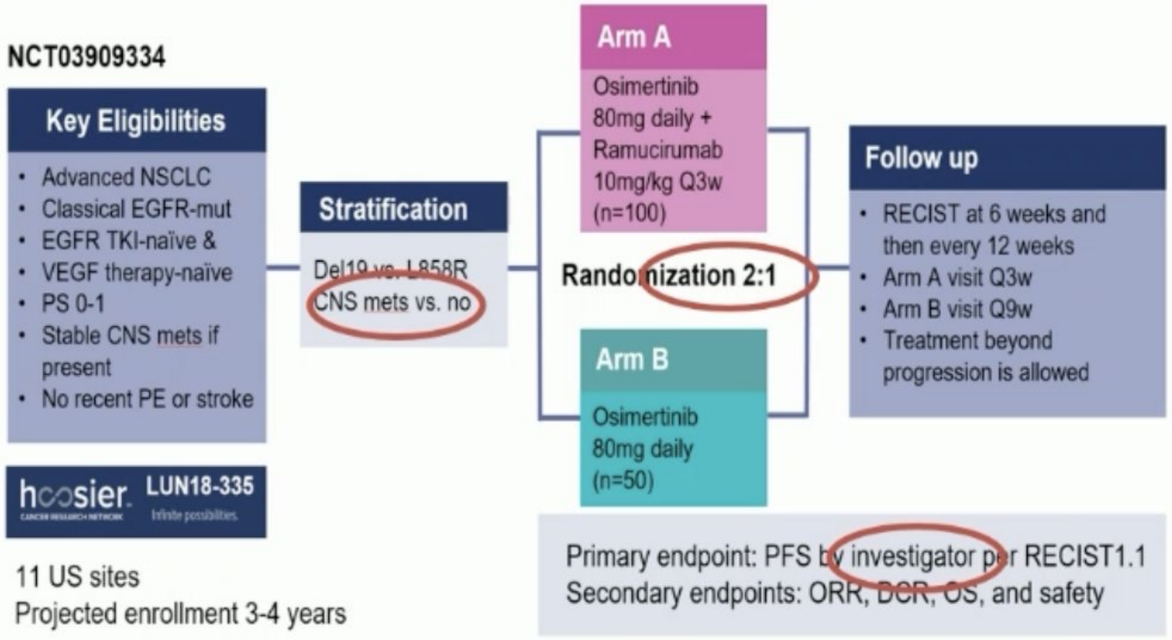
[a]Removed as stratification factor since only 4 patients had prior EGFR TKI use (brief monotherapy with common EGFR TKIs was allowed if lack of response was documented).
[b]Patients with brain metastases were eligible if they received definitive treatment and were asymptomatic, clinically stable, and off corticosteroid treatment for ≥2 weeks prior to randomization.
[c]Key statistical assumption: 300 patients with 200 events needed for 90% power to detect an HR of 0.625 (estimated PFS of 8 vs 5 months). PFS, ORR, and then OS were included in hierarchical testing.
[d]These secondary endpoints (time to subsequent therapy and symptomatic progression-free survival) will be presented at a future congress.
[e]Crossover was only allowed after BICR confirmation of disease progression; amivantamab monotherapy on Q3W dosing per main study.

AUC, area under the curve; BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.

MADRID 2023 ESMO congress

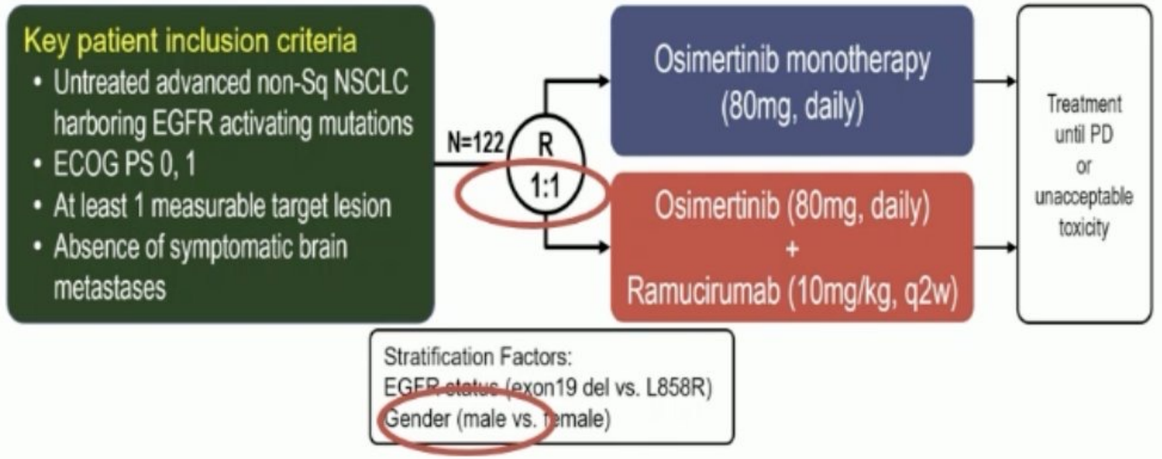
Combinations with Anti-Angiogenesis Agents
Osimertinib+Ramucirumab vs Osimertinib

RAMOSE Phase 2 Study Design



MADRID 2023 ESMO congress Xiuning Le MD PhD MDACC USA

OSIRAM-1 (TORG1833) : Study Design



Primary Endpoint: PFS assessed by the BICRs

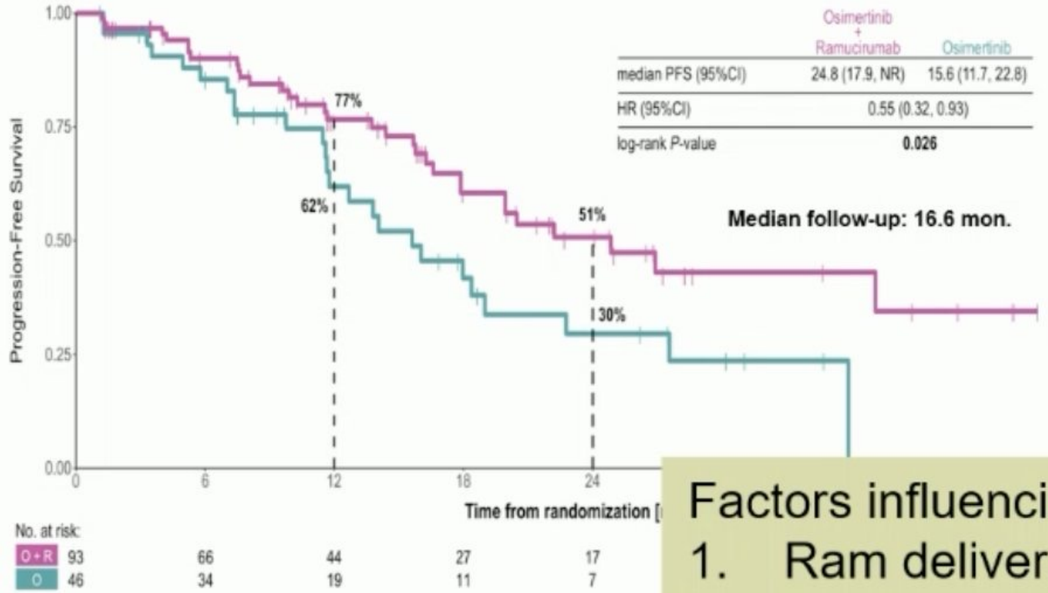
Secondly Endpoints: PFS assessed by investigators, ORR, DCR, OS and Safety

MADRID 2023 ESMO congress Yoshiro Nakahara, MD PhD, LBA70 OSIRAM-1/TORG1833

Osimertinib+Ramucirumab vs Osimertinib

LBA71: RAMOSE

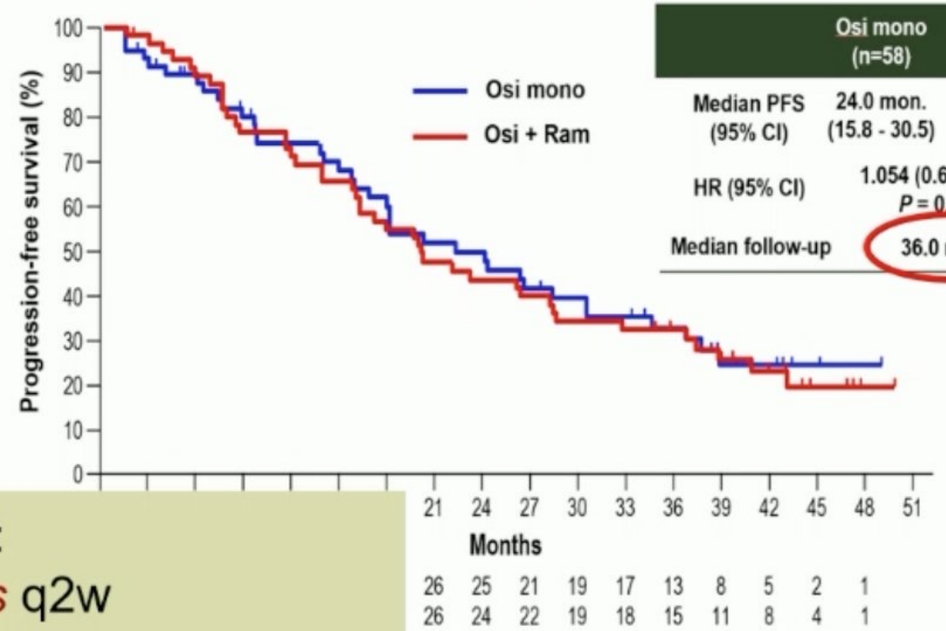
Progression-free survival by investigator (primary endpoint)



	Osimertinib + Ramucirumab	Osimertinib
median PFS (95%CI)	24.8 (17.9, NR)	15.6 (11.7, 22.8)
HR (95%CI)	0.55 (0.32, 0.93)	
log-rank *P*-value	**0.026**	

LBA70: OSIRAM-1

Progression-Free Survival, assessed by BICRs (Primary Endpoint)



	Osi mono (n=58)	Osi + Ram (n=57)
Median PFS (95% CI)	24.0 mon. (15.8 - 30.5)	20.0 mon. (15.9 - 28.3)
HR (95% CI)	1.054 (0.674-1.648) *P* = 0.4621	
Median follow-up	36.0 mon.	

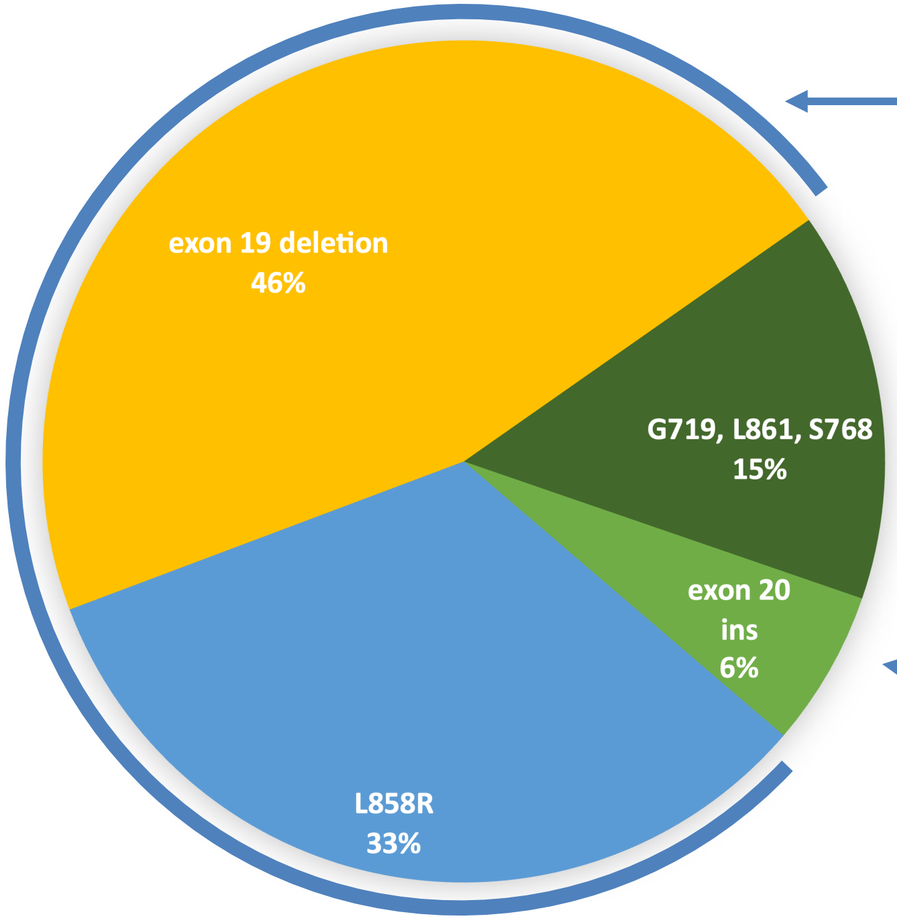
Factors influencing PFS:

1. Ram deliver: q3w *vs* q2w
2. Follow-up visit: q3-9w *vs* q2w
3. PFS by Invest. *vs* PFS by BIRC
4. Exon19: 69% *vs* 61%
5. **Exposure to Ram: 14.4 *vs* 4.7 m**

Yi-Long Wu, Guangdong Lu

More Targets – More Precise Targets?
EGFR has Become More Complicated

Among patients with EGFR mutant NSCLC…



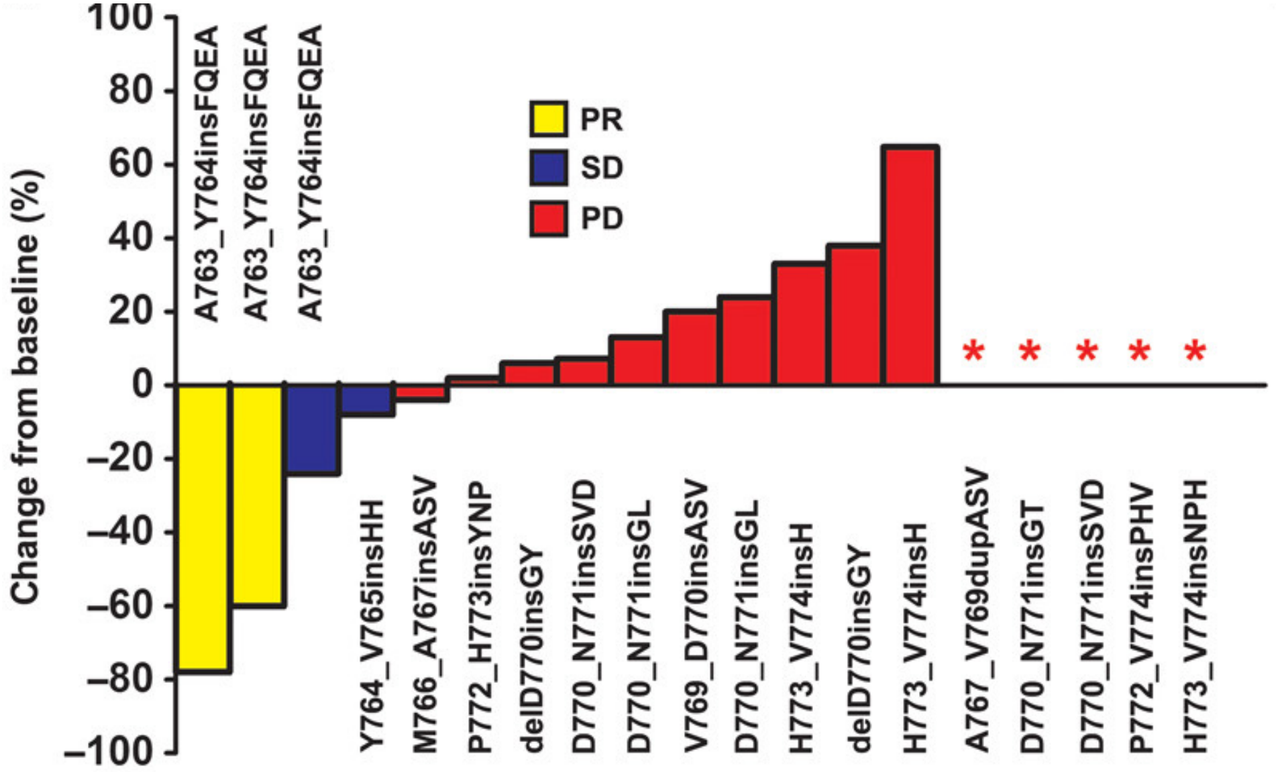
79% of patient have classically sensitizing EGFR mutations (exon 19 deletion and L858R)

15% of patient have “atypical” EGFR mutations

6% of patient have EGFR exon 20 insertions

From AACR GENIE v 11 public, Data available at https://genie.cbioportal.org/

Gefitinib and Erlotinib generally not active against EGFR exon 20 insertions (except FQEA!)



	Best response to reversible EGFR TKI				
***EGFR* mutation**	**Drug**	**PR**	**SD**	**PD**	**RR [%]**
A763_Y764insFQEA	Erlotinib	2	1	—	66.6
Y764_V765insHH	Gefitinib	—	1	—	0
M766_A767insASV	Erlotinib	—	—	1	0
A767_V769dupASV	Gefitinib	—	—	1	0
V769_D770insASV	Erlotinib	—	—	1	0
D770_N771insGL	Erlotinib	—	—	2	0
D770_N771insGT	Erlotinib	—	—	1	0
D770_N771insSVD	Erlotinib	—	1	1	0
delD770insGY	Erlotinib	—	—	2	0
P772_H773insYNP	Gefitinib	—	—	1	0
P772_V774insPHV	Erlotinib	—	—	1	0
H773_V774insH	Gefitinib/ erlotinib	—	—	2	0
H773_V774insNPH	Erlotinib	—	—	1	0

Costa Science Translational Medicine 2013

New Target: BRAF fusions

97,024 samples from 69,337 patients with NGS testing

298 *BRAF* fusions

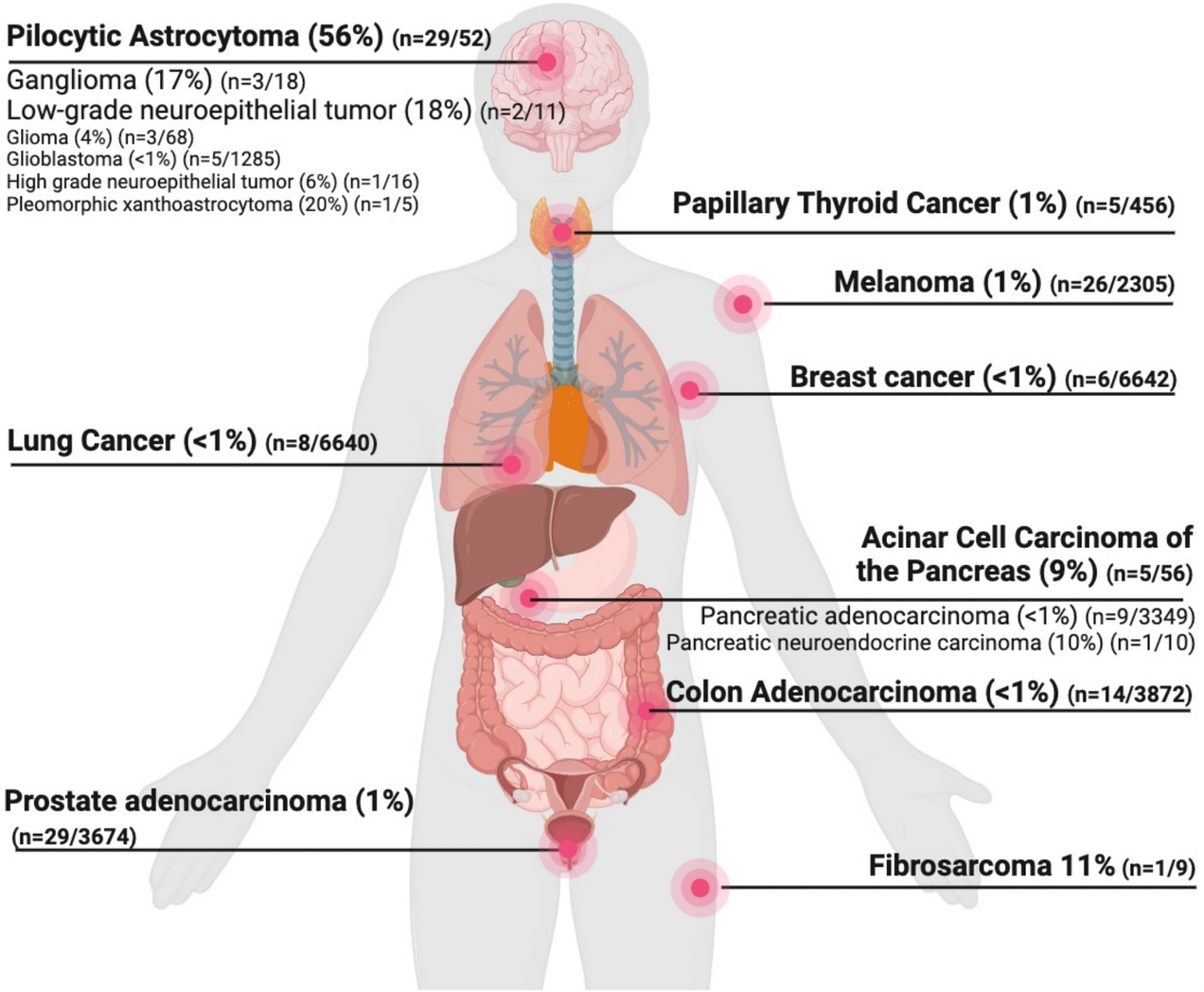
1. In-frame
2. Intact BRAF KD
3. Non-*BRAF* partner

210 oncogenic *BRAF* fusions

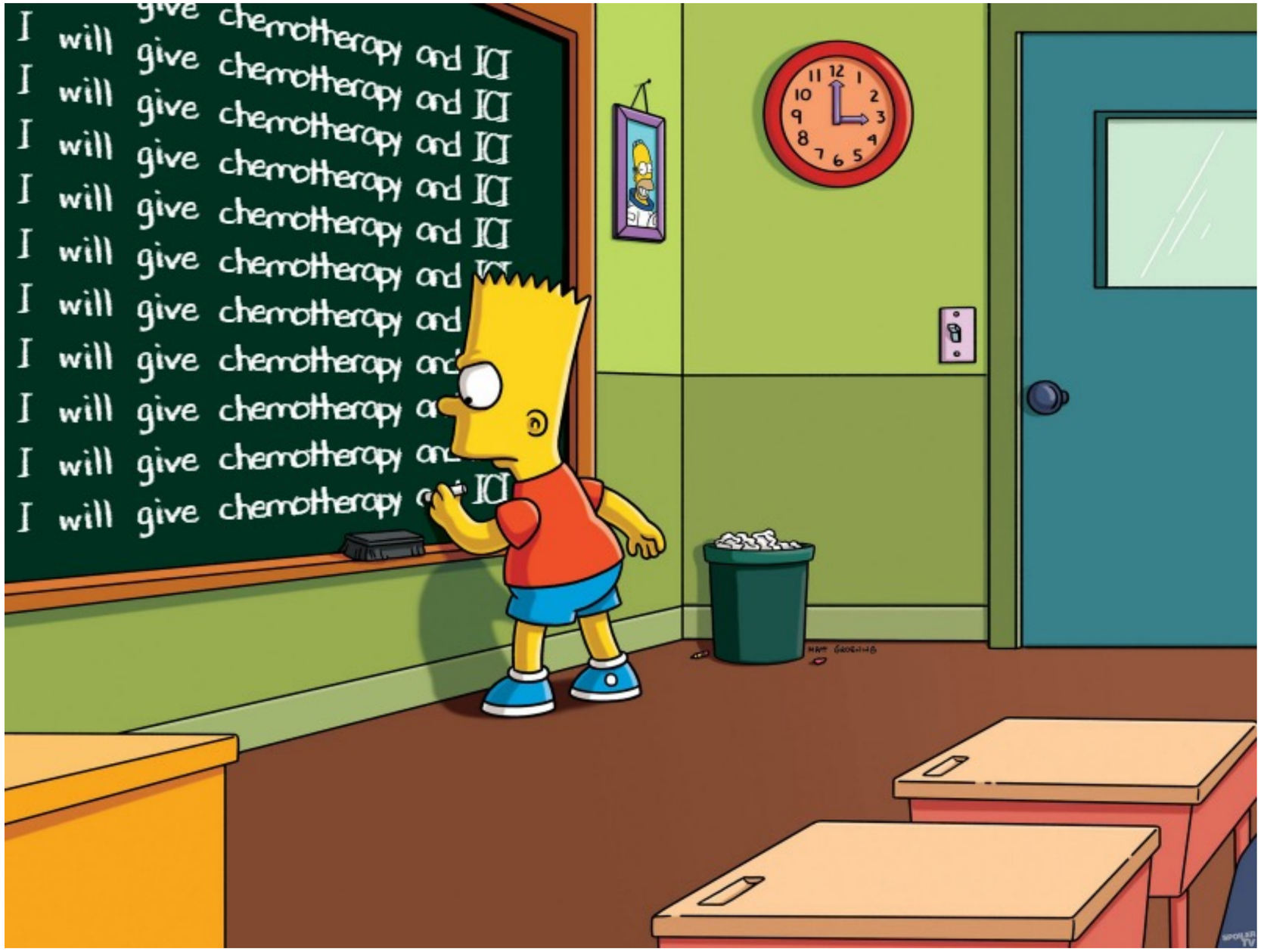
195 de novo *BRAF* fusions

15 acquired *BRAF* fusions detected post targeted therapy

Frequency of de novo *BRAF* Fusions



Chen, MF … Offin M, Murciano YG manuscript in preparation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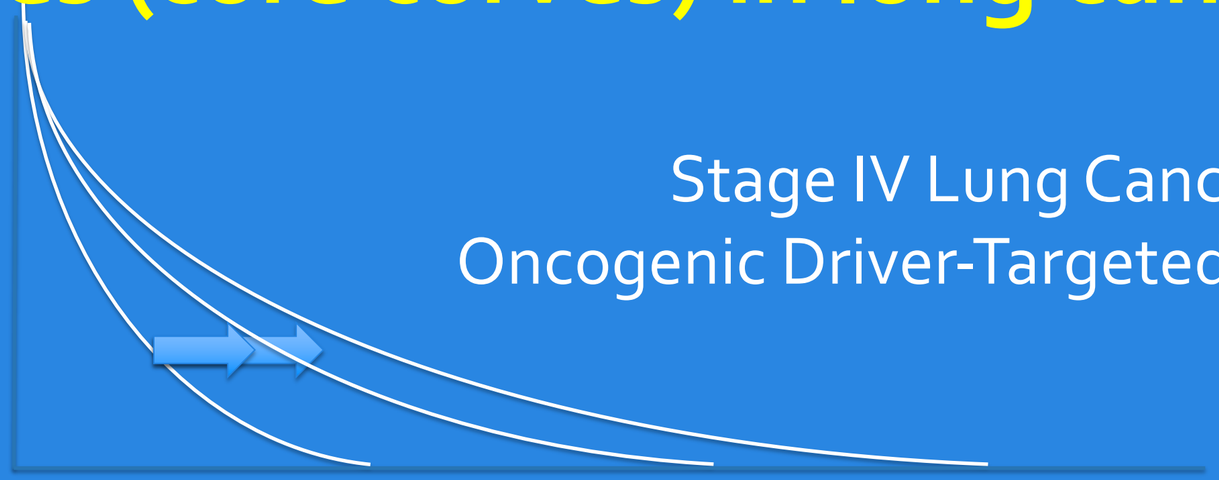
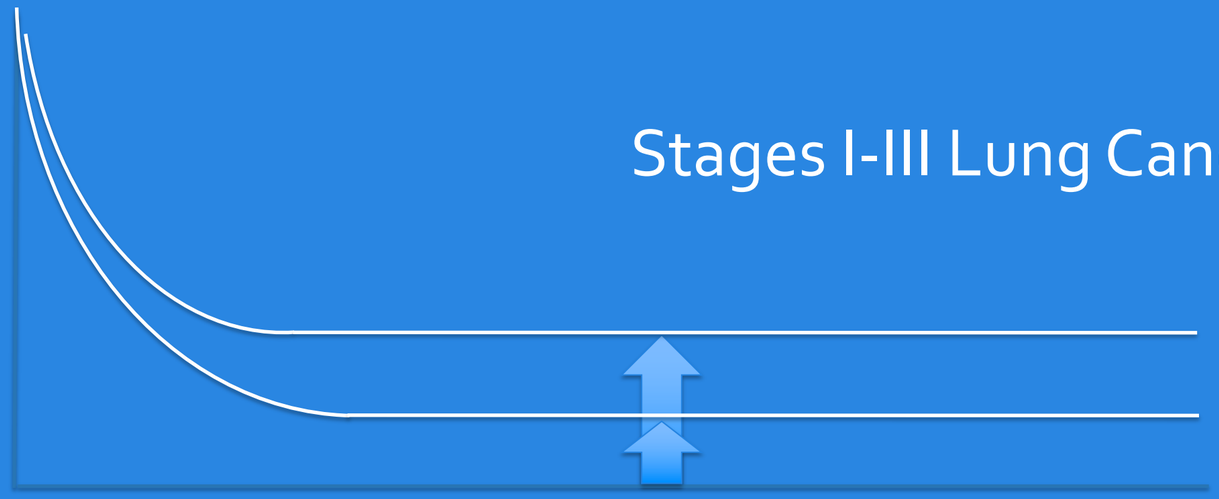
Bending the disease free and progression free survival curves (cure curves) in lung cancers



Stage IV Lung Cancers
Oncogenic Driver-Targeted Therapies



Stages I-III Lung Cancers

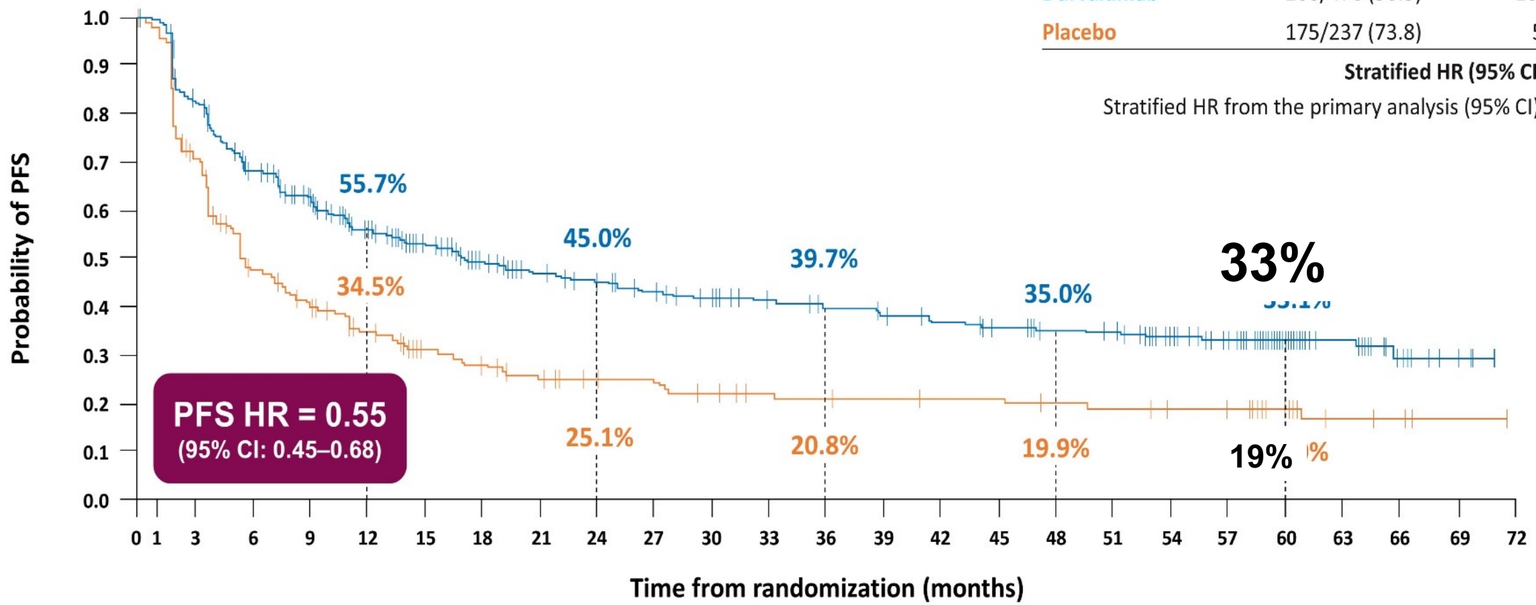
Hellmann JAMA Oncology 2015

PACIFIC: 14% Improvement in 5 Year Progression Free Survival with Durvalumab

	No. of events/ total no. of patients (%)	Median PFS (95% CI), months
Durvalumab	268/476 (56.3)	16.9 (13.0–23.9)
Placebo	175/237 (73.8)	5.6 (4.8–7.7)

Stratified HR (95% CI): 0.55 (0.45–0.68)

Stratified HR from the primary analysis (95% CI):[1] 0.52 (0.42–0.65)



No. at risk

Durvalumab	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

1. Antonia SJ, et al. New Engl J Med 2017;377:1919–29

ADAURA: Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:

≥18 years (Japan / Taiwan: ≥20)

WHO performance status 0 / 1

Confirmed primary non-squamous NSCLC Ex19del / L858R‡

MRI or CT scan of the brain prior to surgery or randomisation

Complete resection with negative margins§

Max. interval between surgery and randomisation:

- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Osimertinib 80 mg, once daily

Randomisation 1:1 (N=682)

Placebo, once daily

Planned treatment duration: 3 years

Treatment continued until:

- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Assessments:

- For recurrence: Weeks 12 and 24, then every 24 weeks to 5 years, then yearly (brain scans not mandated)
- All sites of NSCLC and post-relapse cancer treatments were recorded at recurrence
- Patients received regular CT scans,# with additional imaging as indicated by signs and symptoms

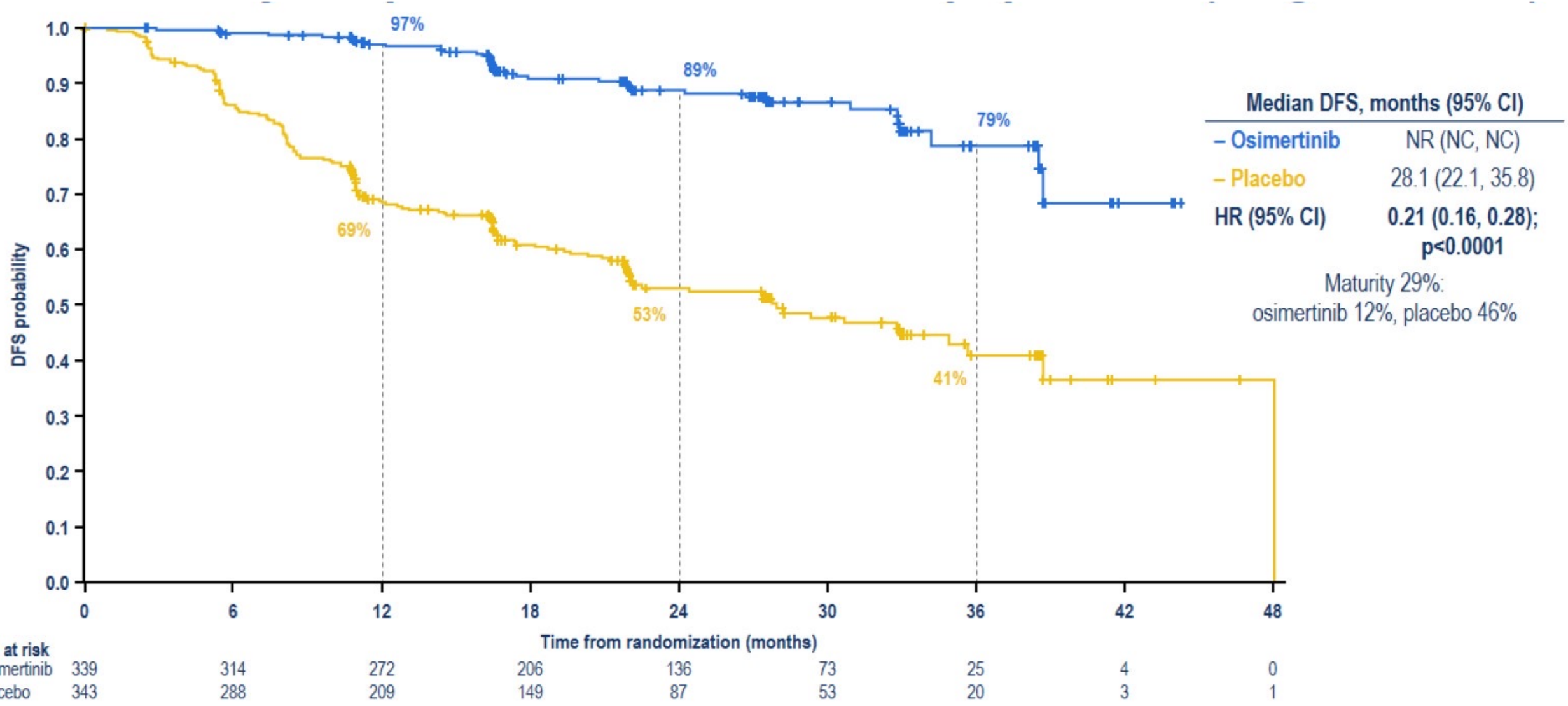
- The primary and key secondary endpoints of DFS¶ in stage II/IIIA patients and the overall population, respectively, have been reported previously[1]
- **Here we report results from a pre-specified exploratory analysis of disease recurrence patterns in ADAURA, including CNS**

CT, computed tomography; MRI, magnetic resonance imaging; WHO, World Health Organization; ex19del, exon 19 deletion; *AJCC 7th edition; †Prior, post, or planned radiotherapy was not allowed; ‡Centrally confirmed in tissue; §Patients received a CT scan after resection and within 28 days prior to treatment; ¶By investigator assessment; #CT scans of the chest and abdomen, including liver and adrenal glands.

1. Herbst et al. J Clin Oncol 2020;38:18_suppl.LBA5.

ADAURA data cut-off: 17 January, 2020

Disease Free Survival with Osimertinib: 36% Improvement at 2 Years



ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 22.1, placebo: 16.6 months;
DFS by investigator assessment; Tick marks indicate censored data.

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

N=257

Alectinib 600 mg BID 2 years → **Recurrence**

Platinum-based chemotherapy† Q3W; 4 cycles → **Recurrence**

Further treatments at investigator's choice and survival follow-up

Primary endpoint
- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

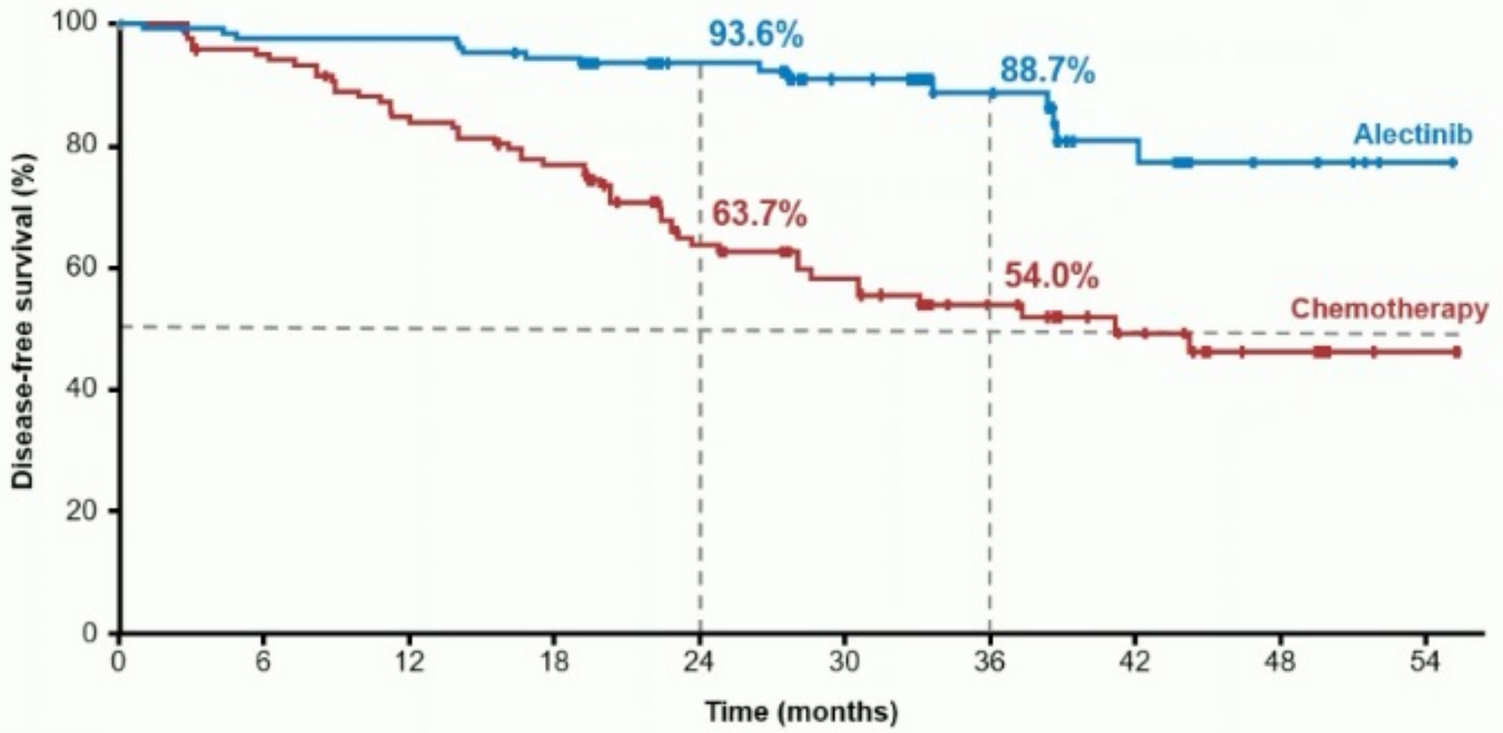
Other endpoints
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

MADRID 2023 ESMO congress

Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

Disease-free survival: ITT (stage IB–IIIA)*

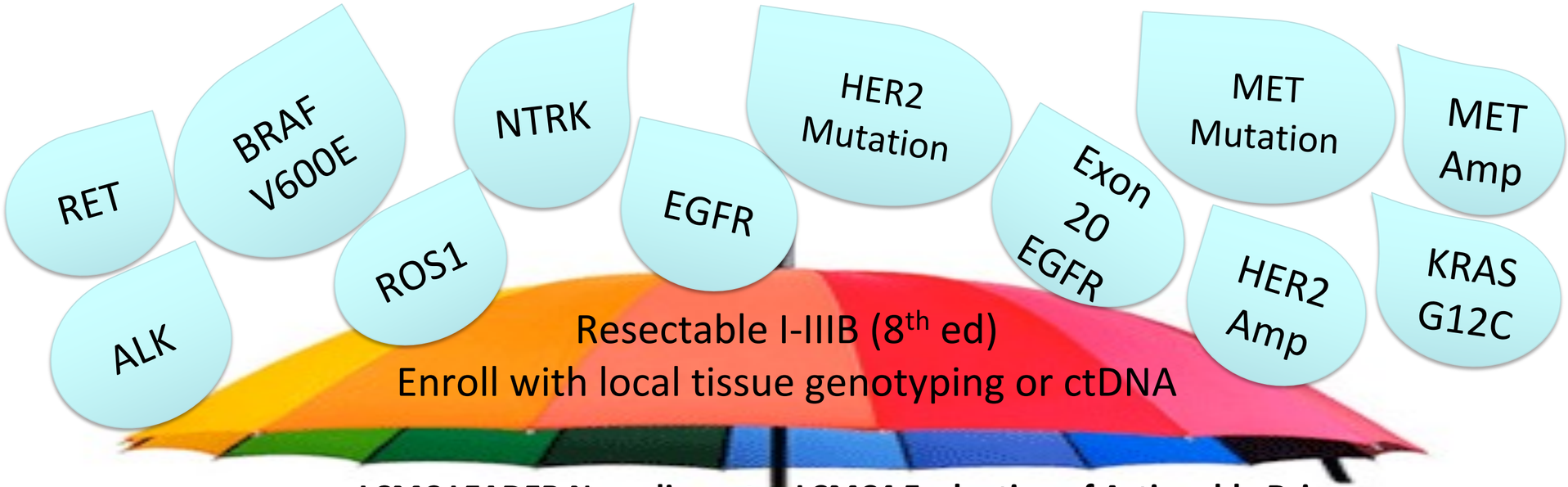


No. at risk

Alectinib	130	123	123	118	74	55	39	22	10	3
Chemo	127	112	98	89	55	41	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p†<0.0001	

Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months



LCMC LEADER Neoadjuvant Screening Trial: NCT

ALK/BRAF/NTRK/ROS1/RET/KRASG12C
Alectinib/Vemurafinib+Cobimetinib/Entrectinib/Pralsetinib/Divarasib
NAUTIKA1 - NCT04302025

LCMC4 Evaluation of Actionable Drivers in Early Stage Lung Cancers 04712877

EGFR
Osimertinib + Chemotherapy
NeoADAURA - NCT04351555

MSKCC-Isbell	MDACC	JHMI	(TBA)
HER2 Mutation Trastuzumab Deruxtecan	KRAS G12C Sotorasib NCT05118854	KRAS G12C Adagrasib NCT05472623	Exon 20 EGFR

LUNG CANCER MUTATION CONSORTIUM
Matching Patients with the Best Possible Therapies

LUNG CANCER RESEARCH FOUNDATION
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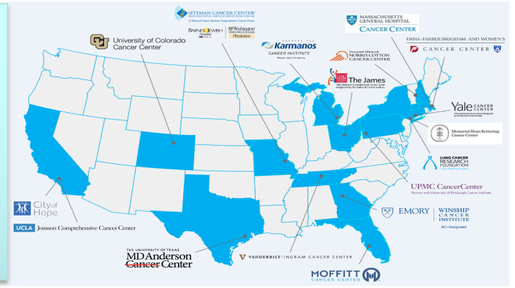
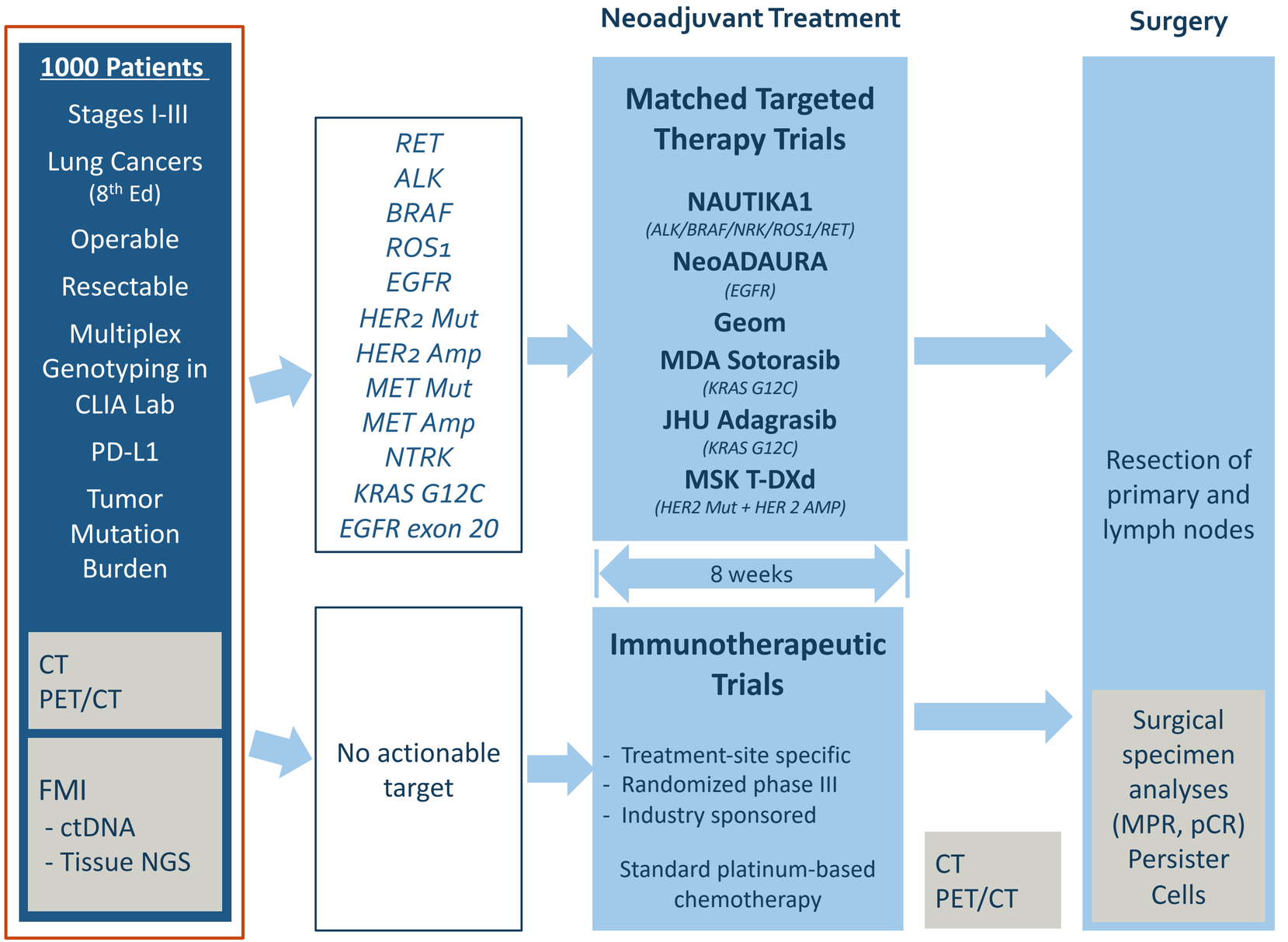
- Complete and major pathologic response assessment
- Percent viable cells in resection specimen
- Correlates in persister cells
- Adjuvant therapy – per protocol or investigator's choice



LCMC LEADER Neoadjuvant Screening Trial: LCMC4 Evaluation of Actionable Drivers in Early Stage Lung Cancers (Scott Swanson PI, ClinicalTrials.gov – NCT0471287)



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LCMC4 LEADER October 2023 Data – 100 patients enrolled
Clinical Stage I to III lung adenocarcinomas

Oncogenic Drivers	
BRAF V600E	1
EGFR	5
EGFR exon 20	4
HER2 mutation	0
KRAS G12C	9
MET exon 14	1
ALK	0
NTRK	1
RET	1
ROS1	1
HER2 Amplification	0
MET Amplification	0

Actionable target detected in blood
14%

Actionable target detected in tissue
49%

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Ways to fill the gaps in targeted therapies

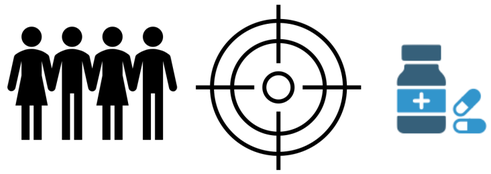
- **Short-Term**
  1. Combinations with cytotoxic chemotherapies
  2. Combinations with anti-angiogenesis agents
  3. Combinations with additional targeted treatments
  4. Use with local therapies : surgery, radiation, and ablation
- **Long Term**
  1. Drugs
     A. More effective
     B. Better targeted
     C. New Targets
  2. Degraders
  3. Vaccines
  4. Targeting Persisting cells

Essential Steps from Target to Treatment

Find and Validate a Target Driver

Create a Drug that Inhibits the Target

Identify Patients with the Target

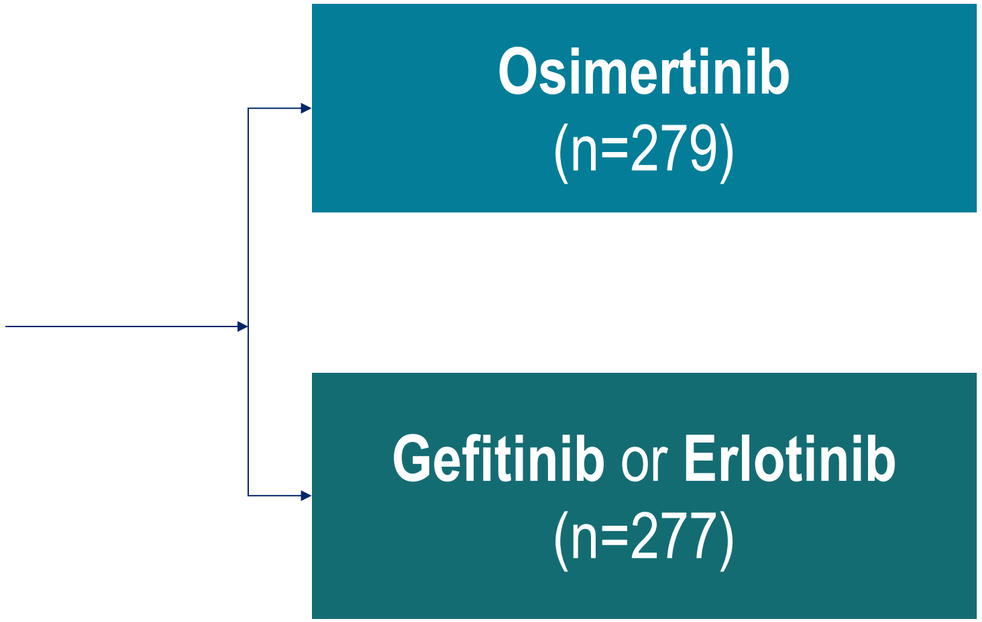


Hit the Target in the Patient at the Right Time … Safely

After Neal Rosen and Brian Druker

Osimertinib vs gefitinib or erlotinib
Proof osimertinib a better drug

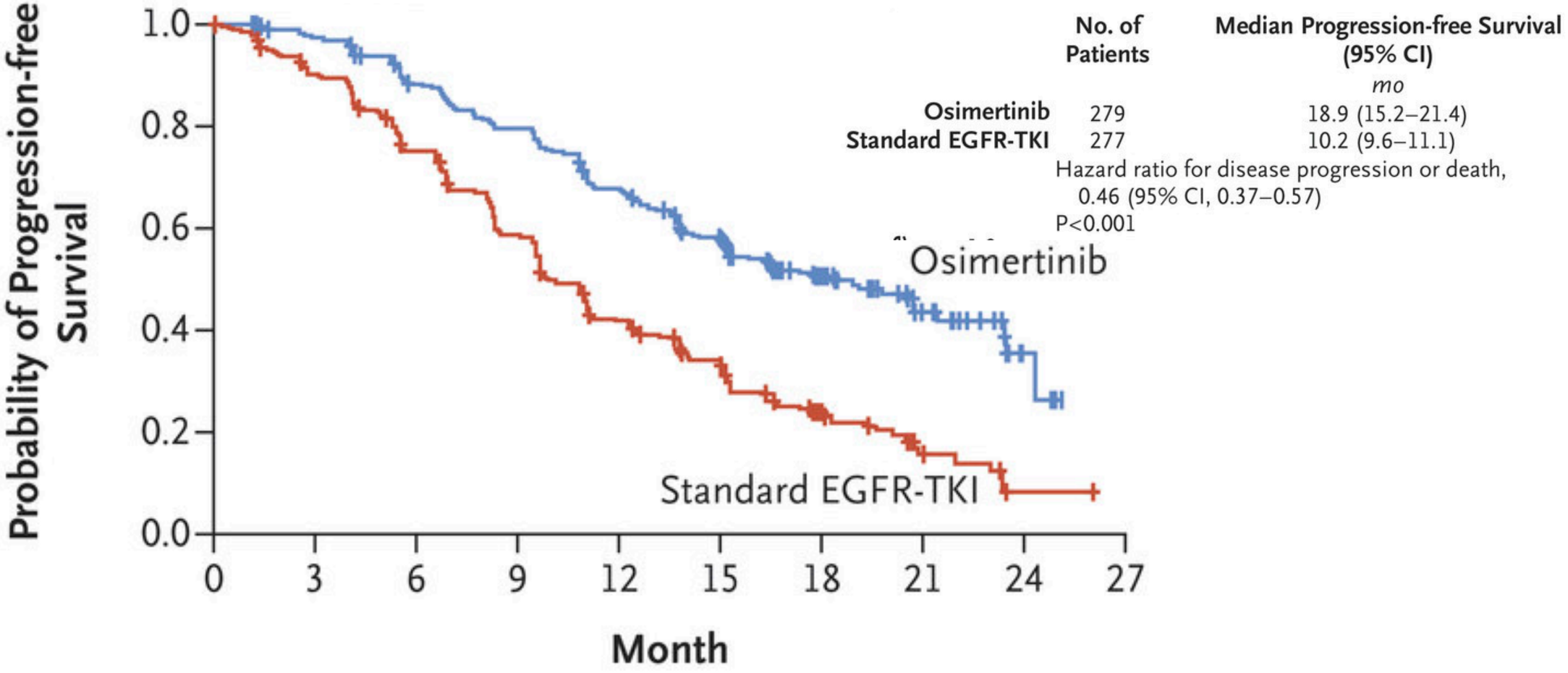
- **Metastatic NSCLC**
- **EGFR mutation**
- **No prior therapy**
- **Stable CNS metastases allowed**
- **Performance status 0 / 1**



- **Primary endpoint:** PFS
- **Secondary endpoints:** response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

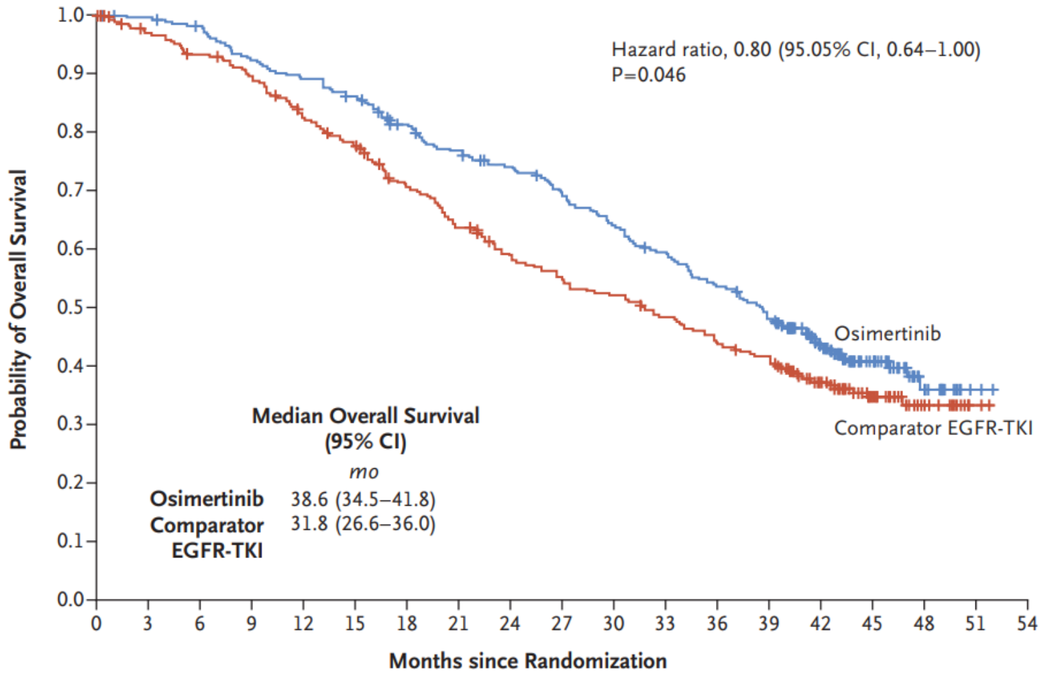
Soria et al, NEJM 2017

Osimertinib vs Gefitinib or Erlotinib as initial treatment for EGFR-mutant lung adenocarcinoma - Progression-Free Survival



Soria et al, NEJM 2017

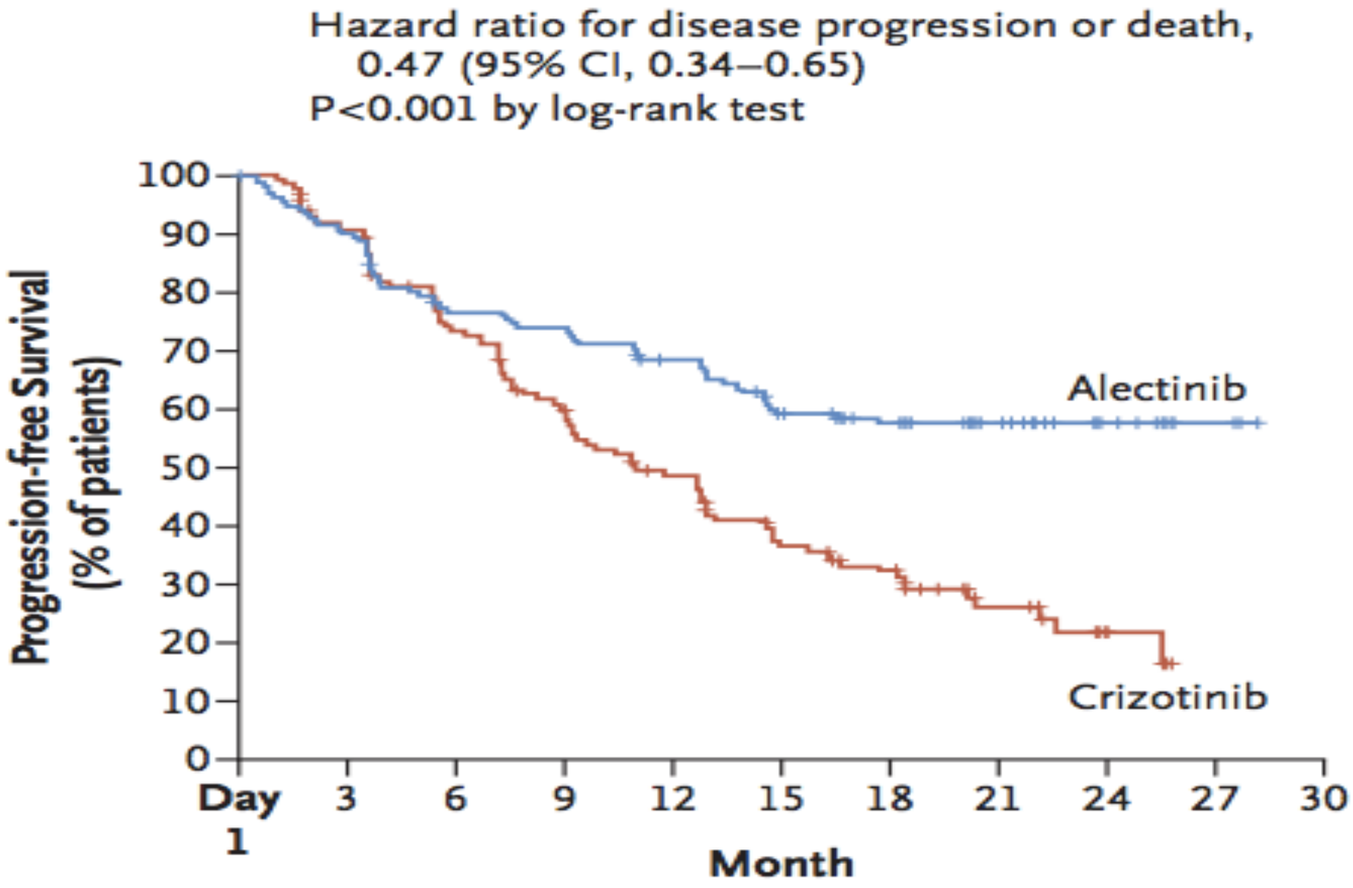
Osimertinib vs Gefitinib or Erlotinib as initial treatment for EGFR-mutant lung adenocarcinoma - Overall Survival



Ramalingam et al, NEJM 2020

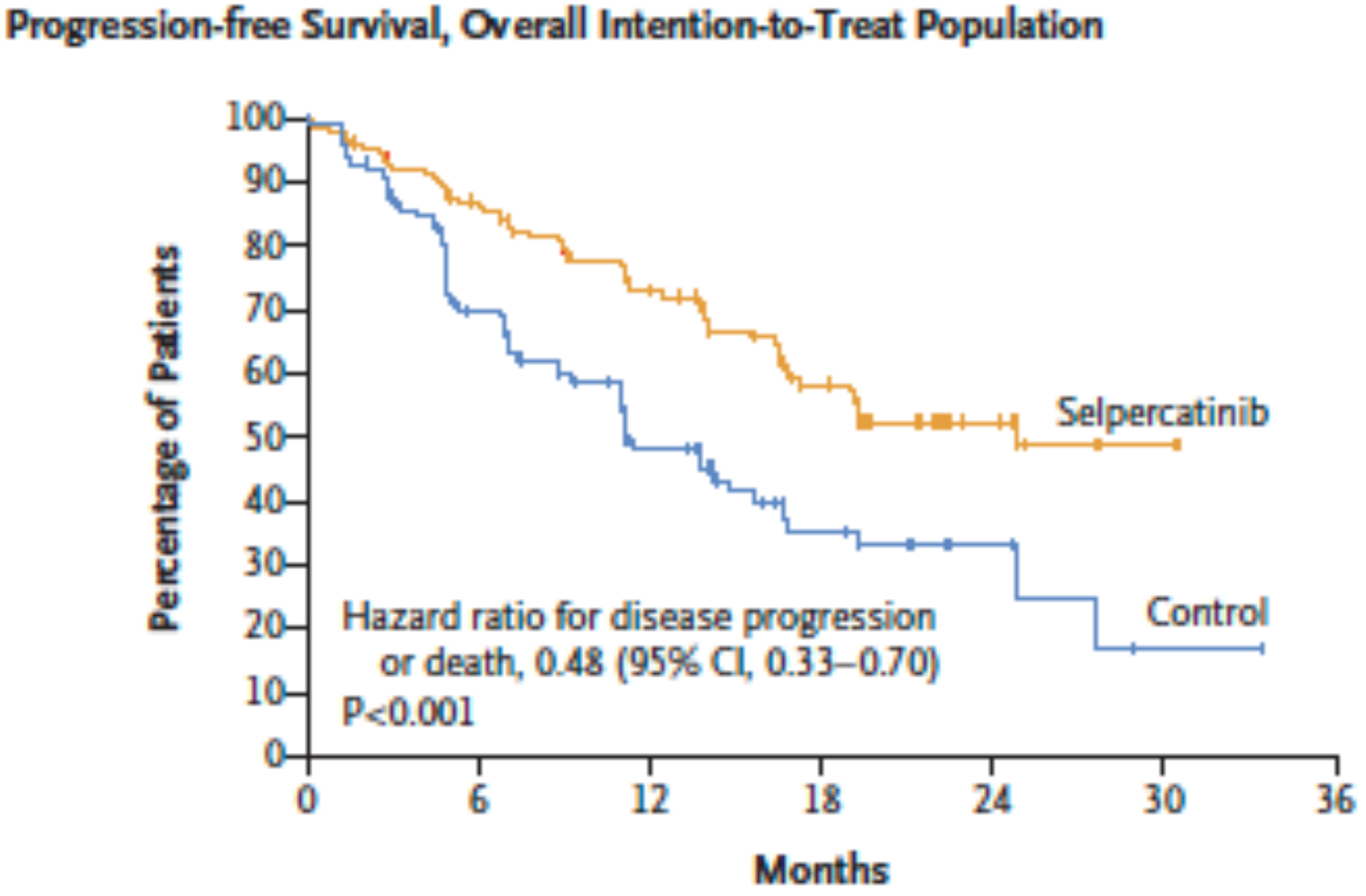
Alectinib vs Crizotinib as Initial Therapy for ALK+ NSCLC

Improved PFS with alectinib



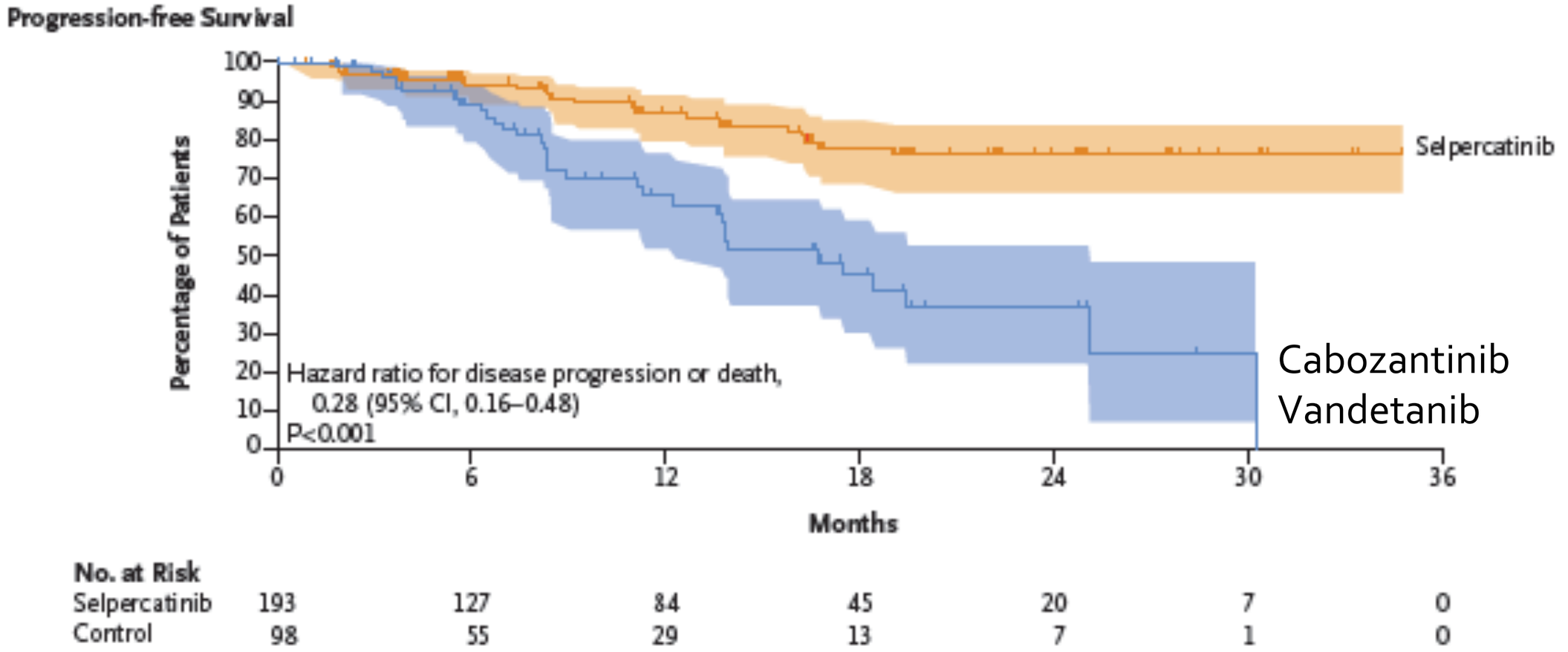
Peters et al, NEJM 2017

Progression-free survival: Selpercatinib vs Chemotherapy RET-positive Lung Cancers



Zhou *NEJM* 2023

Progression-free survival: Selpercatinib vs Cabozantinib or Vandetanib RET-mutant Medullary Thyroid Cancers

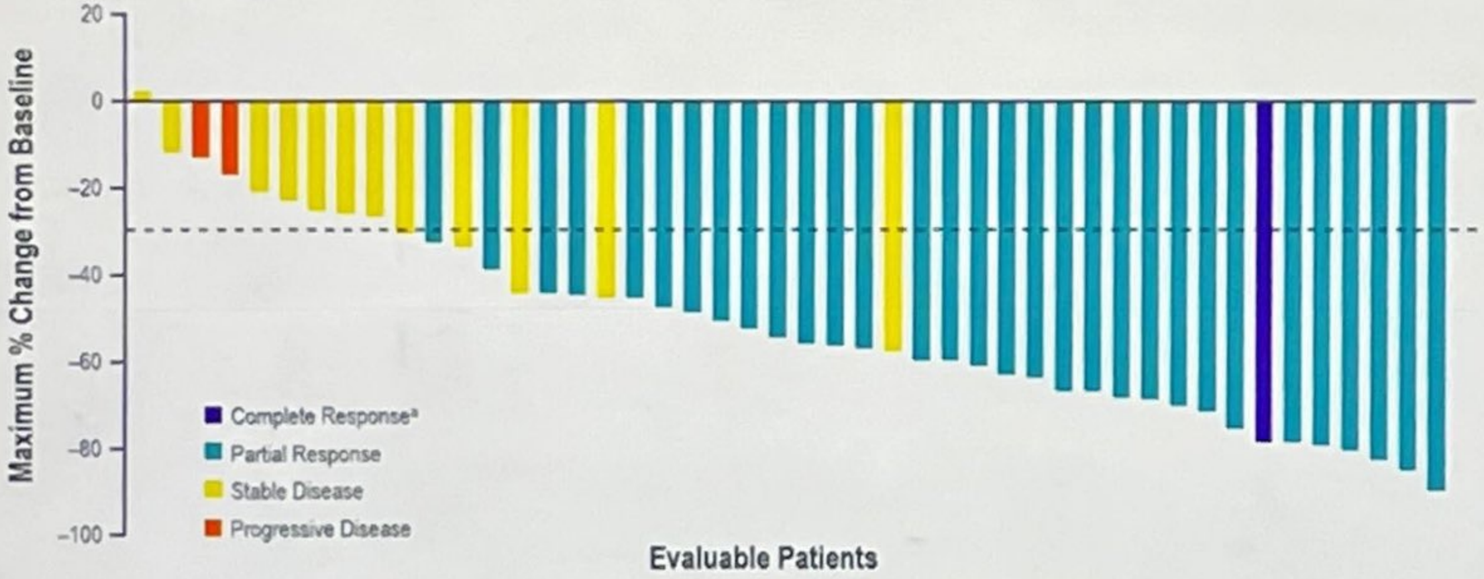


Hadoux N Engl J Med 2023

Adagrasib + Pembrolizumab

KRYSTAL-7: Adagrasib + Pembrolizumab in 1L Advanced/Metastatic KRAS^{G12C} NSCLC

ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS ≥50%



- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)

Response per investigator assessment (n=51, modified full analysis set). Waterfall plot excludes three patients without post-baseline measurement and one patient without confirmatory scan (only one assessment of PR on day 28, but minimum duration requirement for SD is 42 days). [a]One patient had CR without −100% change from baseline due to lymph node as target lesion. [b]Includes AST increase, ALT increase, mixed liver injury and liver function test increase; no grade 4 hepatotoxicity was observed in patients with PD-L1 TPS ≥50%. Data as of 19 June 2023. Median follow-up 10.1 months.

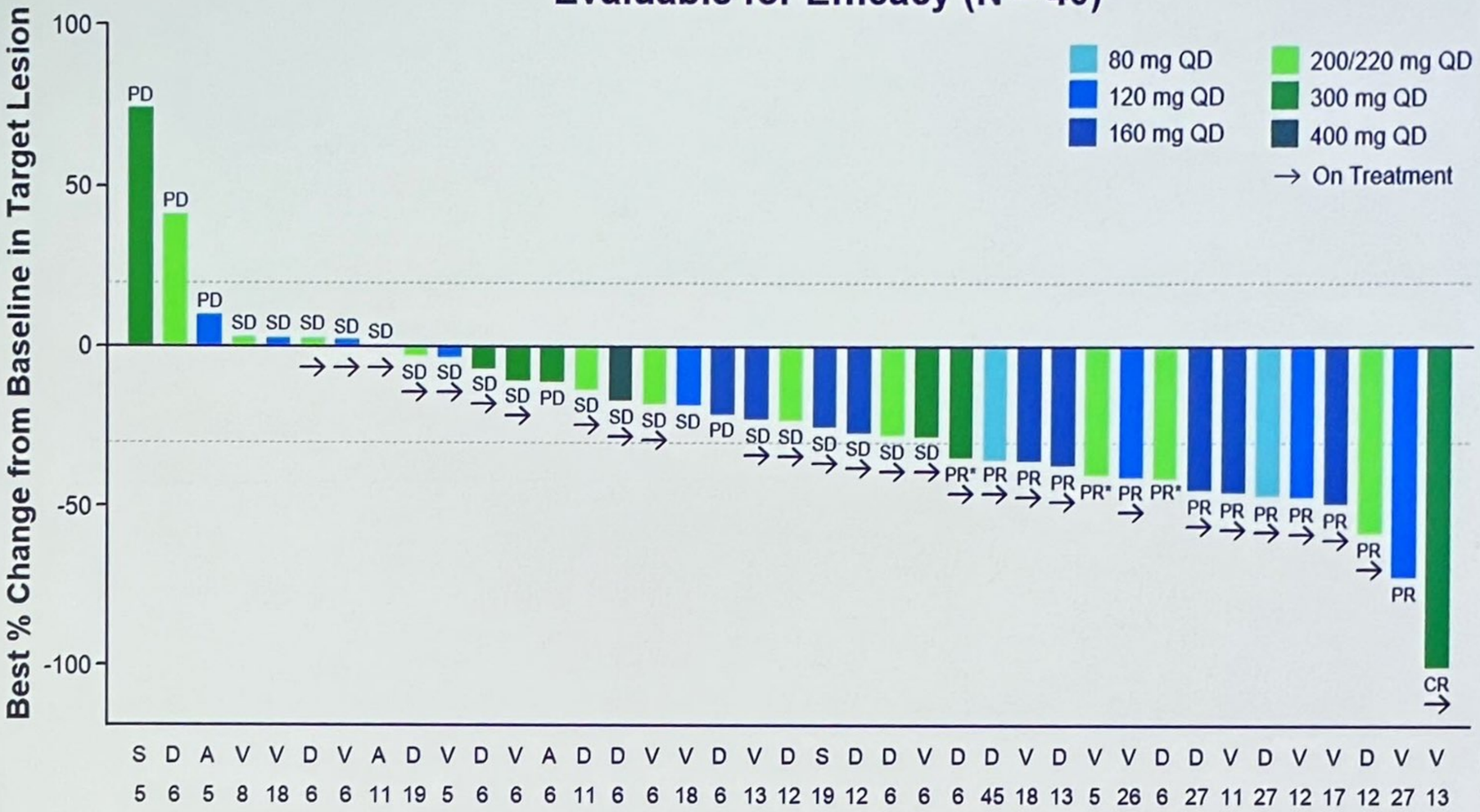
Marina Garassino

KRYSTAL-7: Efficacy and safety of adagrasib with pembrolizumab in patients with treatment-naïve, advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation

KRAS^{G12X} NSCLC

RMC-6236

Evaluable for Efficacy (N = 40)[a]



Tumor Response (per RECIST 1.1)	
Best overall response, n (%)	
CR	1 (3)
PR	14 (35)
SD	19 (48)
PD	5 (13)
NE[b]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)

*Unconfirmed PR per RECIST 1.1.

[a]Patients who received first dose of RMC-6236 at least 8 weeks prior to data extract date.

[b]One subject withdrew from study without post-baseline scans.

CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

MADRID 2023 ESMO congress

Kathryn C. Arbour, MD

Data Extracted 12 Oct 2023.

Clinical Trials of Targeted Therapies at MSK 2023
New Agents Against Mutated Proteins/Kinases

Target	Drug	MSK Trial Number	NCT Trial Number
ALK	NVL-655	22-396	05384626
FGFR2	RLY-4008	20-523	04526106
FGFR3	LOXO-435	23-005	05614739
KRAS G12C	LY3537982	21-389	04956640
KRAS G12D	MRTX1133	23-161	05737706
RET	LOXO-260	22-249	05241834
ROS1	NVL-520	21-499	05118789

Clinical Trials of Targeted Therapies at MSK 2023
New Targets, Mechanisms, Combinations, and Constructs

Target	Mechanism	MSK Trial Number	NCT Trial Number
BRAF	CFT1946- BiDAC degrader	23-091	NCT05668585
BRAF	BGB-3245- RAF dimer inhibitor	20-279	NCT04249843
BRAF	PF-07799933 (BRAF inhibitor) +/- cetuximab + binimetinib	22-410	NCT05355701
HER2	HER2 immune stimulating antibody conjugate +/- Pembrolizumab	20-430	NCT04278144
KRAS G12C	Sotorasib + MEK or SHP2 inhibitor	20-183	NCT04185883
MET	REGN5093-M114- MET x MET ADC	21-395	NCT04982224
NRG1 fusion	MCLA-128- Anti-HER2/anti-HER3	19-378	NCT02912949
SMARCA4	PRT3789- SMARCA2 degrader	23-090	NCT05639751

nature cancer

Article

https://doi.org/10.1038/s43018-023-00591-2

ALK peptide vaccination restores the immunogenicity of *ALK*-rearranged non-small cell lung cancer

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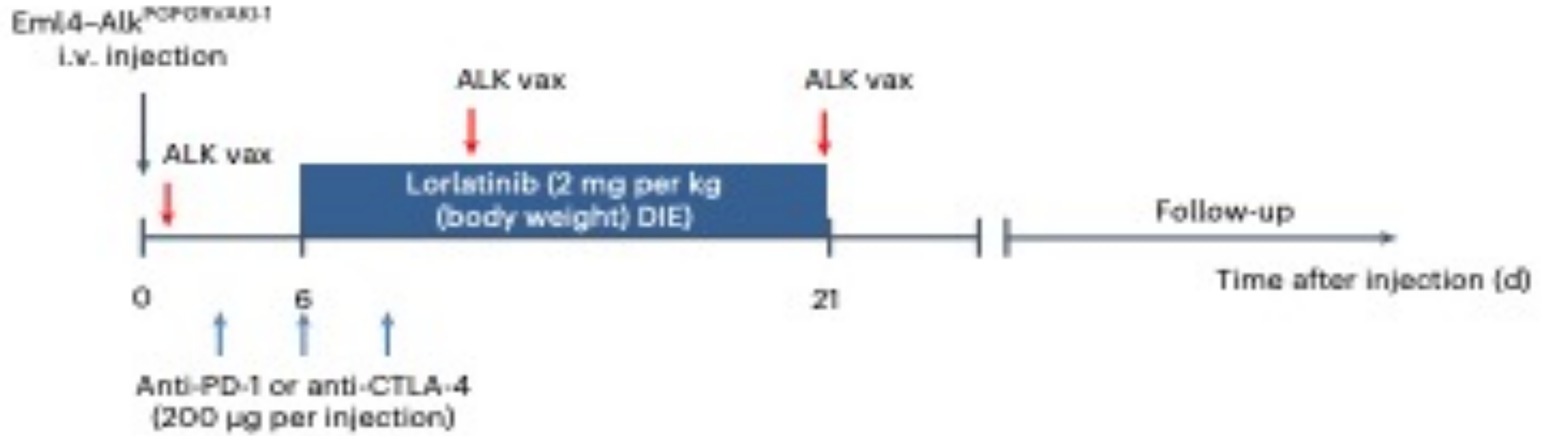
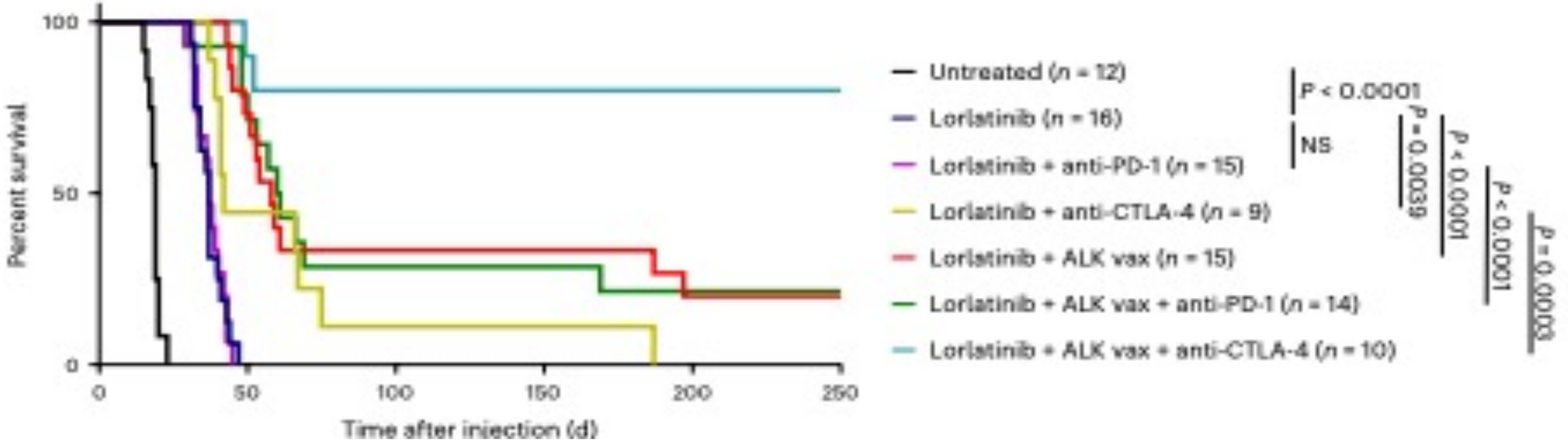
Check for updates

Ines Mota[1], Enrico Patrucco[2], Cristina Mastini[2], Navin R. Mahadevan[3,4], Tran C. Thai[3], Elisa Bergaggio[1], Taek-Chin Cheong[1], Giulia Leonardi[1], Elif Karaca-Atabay[1], Marco Campisi[1,3], Teresa Poggio[2], Matteo Menotti[2], Chiara Ambrogio[2], Dario L. Longo[2,5,6], Susan Klaeger[7], Hasmik Keshishian[7], Zsófia M. Sztupinszki[8,9], Zoltan Szallasi[8,9,10], Derin B. Keskin[3,7,11,12,13], Jonathan S. Duke-Cohan[3,14], Bruce Reinhold[3,14], Steven A. Carr[7], Catherine J. Wu[3,7,15], Kelly D. Moynihan[16], Darrell J. Irvine[16,17], David A. Barbie[3], Ellis L. Reinherz[3,9], Claudia Voena[2], Mark M. Awad[3,15], Rafael B. Blasco[1] ✉ & Roberto Chiarle[1,2] ✉

ALK Vaccine Imparts Sensitivity to Anti-PD-1 and CTLA-4 in an Eml4-Alk Mouse Model with Lorlatinib





Mota Nat Cancer 2023

Conclusions I

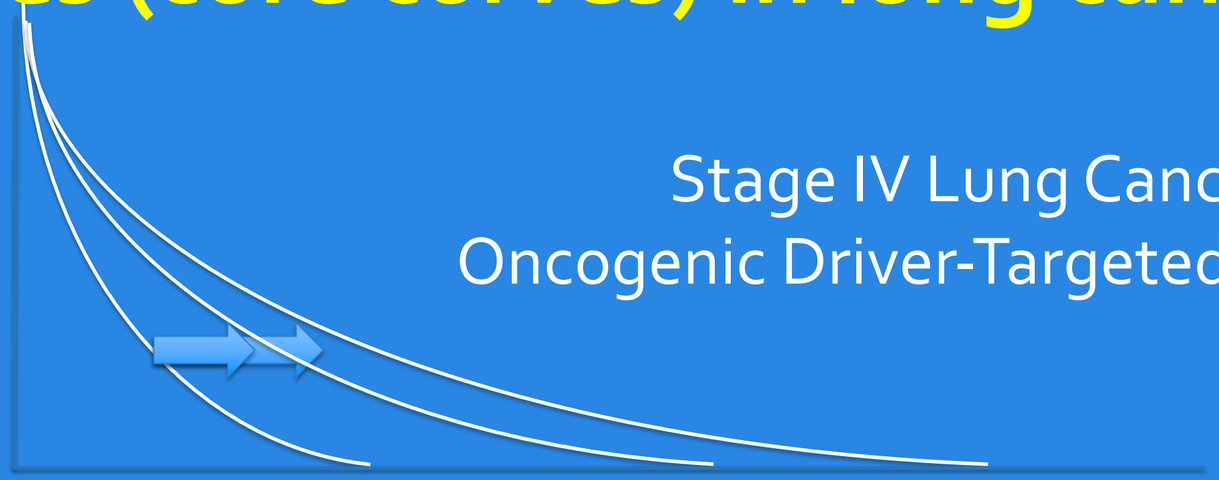
MaTOS™
Masters in Thoracic Oncology Summit
Albuquerque, New Mexico | November 16 - 19, 2023

- Products of driver oncogenes are targets for therapy.
- Oncogenic drivers are detected in half of lung adenocarcinomas and discovered drugs that can block their downstream effects.
- Agents targeting *EGFR*, *ALK*, *ROS1*, *RET*, *NTRK*, *MET* exon 14, and *BRAF* are standard initial therapies. Drugs targeting *HER2*, *KRAS G12C*, *MET* and *HER2* amplification, and *EGFR* exon 20 provide benefit after progression on chemotherapy.
- With targeting, side effects in general are different, less frequent, and not as severe as with cytotoxic chemotherapies

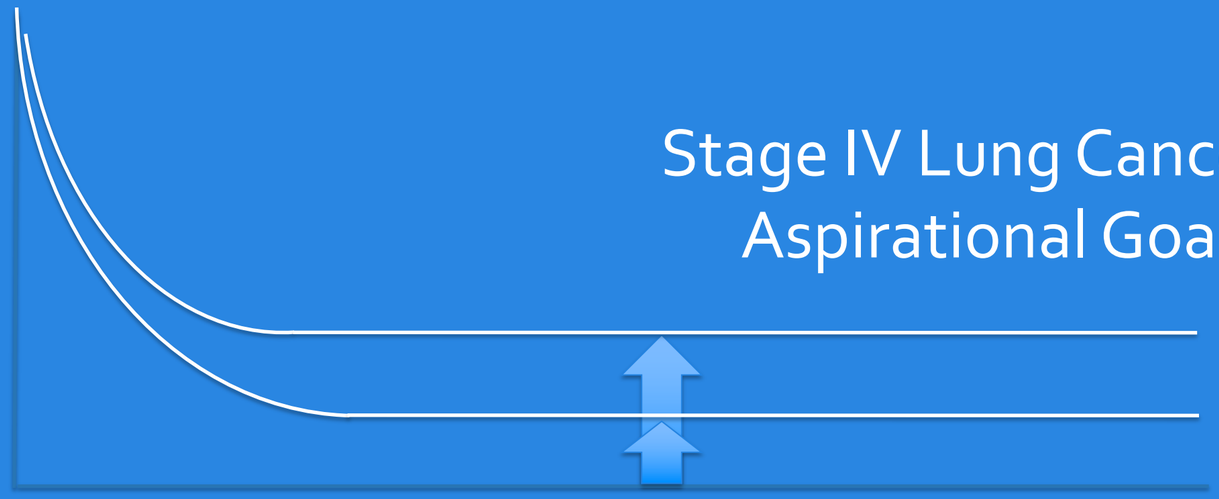
Conclusions II

- RIP for chemotherapy premature. Cytotoxic chemotherapy adds benefit with targeted therapies
- *ALK*- and *EGFR*-targeted therapies improve outcomes when combined surgery. Likely will work with concurrent chemotherapy and radiation and neoadjuvantly.
- Agents with new targets and mechanisms and greater selectivity and potency are in testing
- Ask yourself if there is a path to cure for each patient

Bending the disease free and progression free survival curves (cure curves) in lung cancers



Stage IV Lung Cancers
Oncogenic Driver-Targeted Therapies



Stage IV Lung Cancers
Aspirational Goal

Hellmann JAMA Oncology 2015