Targeted Therapies in Lung Cancer

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Agenda (~22 minutes of fun)

- Finding oncogene-driven lung cancer
- Choosing between first line agents for oncogenes
- How only 2nd line and beyond agents for some oncogenes are trying to get to first line
- Acquired resistance strategies
- Potential paradigm changes – Consolidation, Chemo and Antibody Drug Conjugates
- Early-stage cancer use [cf Bunn]

Finding oncogene-driven lung cancer

Standard 1st line management stage IV NSCLC: USA

NSCLC

EGFR clasical Sensitizing Mt

3RD gen EGFR TKI (osi)

BRAF V600E

BRAF/MEK combo (dabr

FDA licensed June 2017

NTRK rearranged

NTRK TKI (larotrectinib/entrectinib)

FDA licensed Nov 2018/August 2019

ALK rearranged

NEXT GEN ALK TKI (alec/brig)

Brigatinib (May 22nd 2020)

Lorlatinib (March 3rd 2021)

ROS1 rearranged

ROS1 TKI (criz/entrec)

PDL1 any level Platinum-doublet chemotherapy + IO +/- bev +/- pem continuation (depending on histology and label)

PDL1 ≥50% IO

Other actionable change in trials or off-label

Egfr ramu/erlotinib (May 29th 2020)

MET exon 14 Capmatinib (May 6th 2020)

RET rearranged Selpercatinib (May 8th 2020)

RET rearranged Pralsetinib (Sept 4th 2020)

MET exon 14 Tepotinib (Feb 3rd 2021)

Unive
Ansc

Standard 2ND line management stage IV NSCLC: USA

NSCLC

Post Platinum-doublet
Whether post PDL1 debatable for oncogenes except BRAF and KRAS (based on, ANONG OTHER THINGS, smoking status)

EGFR exon 20 ins
Mobocertinib >1st line
(Sept 15th 2021)

EGFR exon 20 ins
Amivantamab >1st line
(May 21st 2021)

KRAS G12C
Sotorasib >1st line
(May 28th 2021)

HER2 ins
trastuzumab deruxtecan
>1st line
(Aug 12th 2022)

Docetaxel +/- Ramu

No single gene testing please

- There are now 12 different molecularly specific FDA approvals in lung cancer (if you count T790M, uncommon EGFR mutations and EGFR exon 20 insertions separately from common EGFR mutations) covering 9 different genes

- 5 mutations:
  - EGFR, HER2, BRAF V600E, KRAS G12C, MET exon 14
- 4 gene rearrangements:
  - ALK, ROS1, RET, NTRK
- - Other oncogenic changes without licensed therapy but still clinically or trial actionable also exist and can be found with broad molecular profiling – eg NRG1 rearrangements, MET amplification

- If there is an oncogene in a never smoker ignore the PDL1!
- If you have to start with chemo while waiting, if you suspect an oncogene don't give IO in Cycle 1

Immunotherapy Has Low Efficacy in NSCLC With Genomic Alterations[1]

IMMUNOTARGET Registry: Main Results for All Cohorts According to Biomarker Subtype

Driver	n	RR	PFS	OS	Impact (+/-) on PFS of				Comments
					PDL1	Smoking	Nb line	Subtype	
Total		19%	2.8	13.3					Outcome consistent with registration trials for ICI
KRAS	271	26%	3.2	13.5	+	X	X	X	Clear benefit across all subgroups
EGFR	125	12%	2.1	10	+	X	X	+/-(1)	Could be considered in PDL1 + after TKIs exhaustion
BRAF	43	24%	3.1	13.6	NA	+	X	X	Could be considered in smokers
MET	36	16%	3.4	18.4	NA	X	NA	X	Could be considered after conventionnal treatment
HER2	29	7%	2.5	20.3	NA	+	X	NA	
ALK	23	0	2.5	17	NA	-	X	NA	Poor outcome. New biomarker needed.
RET	16	6%	2.1	21.3					
ROS1	7	17%	-	-					

+ : positive impact on PFS
X : non-significant impact on PFS
- : negative impact on PFS

1. Mazieres J et al. *Ann Oncol*. 2019;30:1321-1328.

JTO 2022

IASLC

ORIGINAL ARTICLE

Hypersensitivity Reactions to Selpercatinib Treatment With or Without Prior Immune Checkpoint Inhibitor Therapy in Patients With NSCLC in LIBRETTO-001

Check for updates

Caroline E. McCoach, MD, PhD,[a,b,*,*] Christian Rolfo, MD, PhD, MBA,[c,d] Alexander Drilon, MD,[e] Mario Lacouture, MD,[e] Benjamin Besse, MD,[f] Koichi Goto, MD, PhD,[g] Viola W. Zhu, MD, PhD,[h] Daniel S. W. Tan, MBBS, PhD,[i] Stephanie Farajian, RN, BSN,[a] Laura A. Potter, BA,[a,j] Jennifer F. Kherani, MD,[k] Victoria Soldatenkova, MS,[l] Elizabeth A. Olek, DO, MPH,[k] Catherine E. Muehlenbein, MPH, MBA,[l] Keunchil Park, MD, PhD[m]

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Occurs 7% cases
Of these:
77% are post –IO

Single gene testing

- Challenges memory
- Wastes tissue
- Wastes money

- Panel testing is solution
- cfDNA has PPV not NPV but quicker than tissue NGS
- DNA supplemented with RNA extraction increases sensitivity for MET exon 14 and gene rearrangements
- NGS variably calls amplification (issue for future approvals not now)

Choosing between first line agents for oncogenes

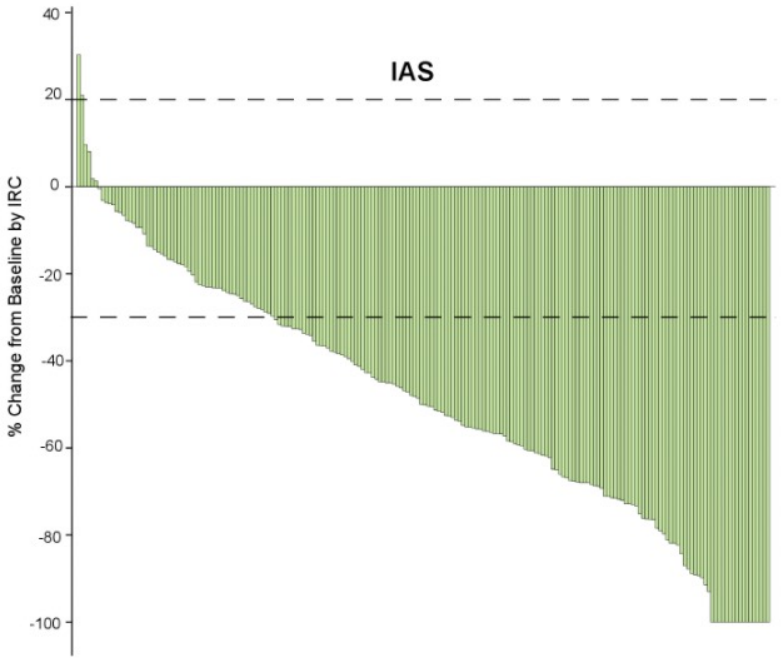
Usually still the oncology basics

- Efficacy>Safety/tolerability>Convenience

But at the end of the day its efficacy and toxicity in YOUR patient that matters

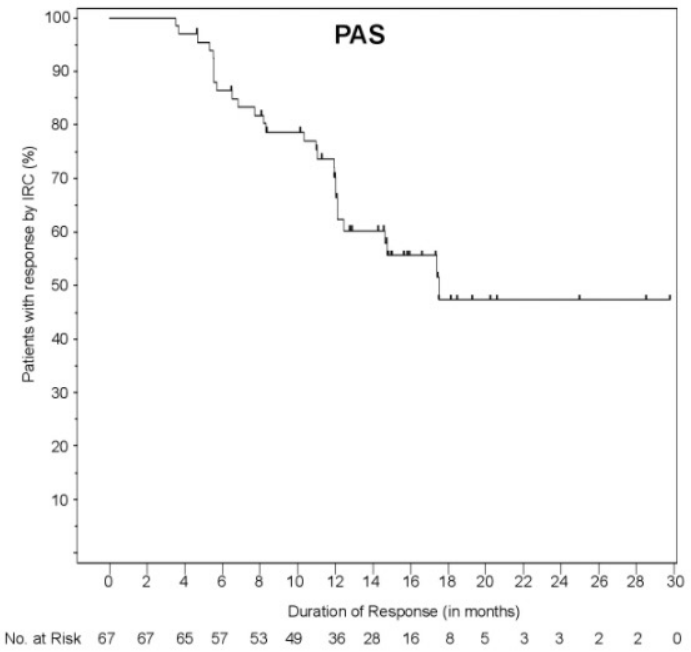
LIBRETTO: Selpercatinib

PLATINUM CHEMOTHERAPY TREATED (PAS or IAS)



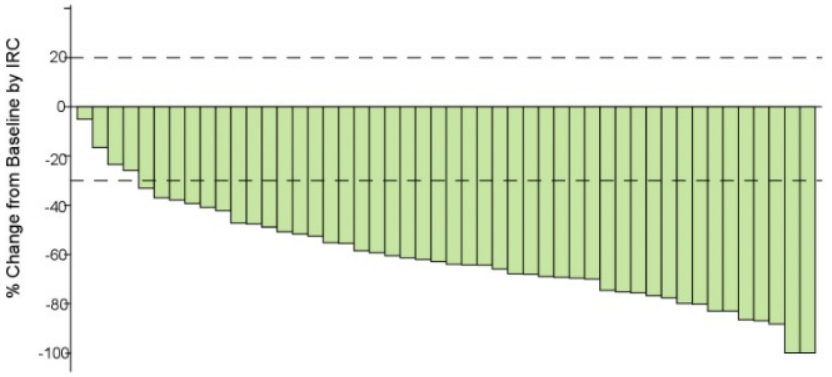
Note: The IAS is a larger population, including the PAS as well as additional patients. Eighteen patients were not included because they had only non-target lesions or did not have a post-baseline target lesion measurement based on IRC. A Kaplan-Meier plot depicting duration of response for IAS is available in the supplement via the QR code.

- With a median follow-up of 15.7 months, 58% (39/67) of responses are ongoing

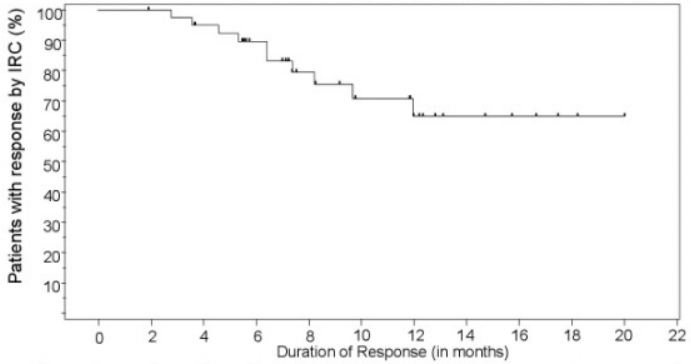


Note: The PAS population, a subset of the IAS, is the more mature dataset. The waterfall plot for PAS is available in the supplement via the QR code.

TREATMENT-NAÏVE



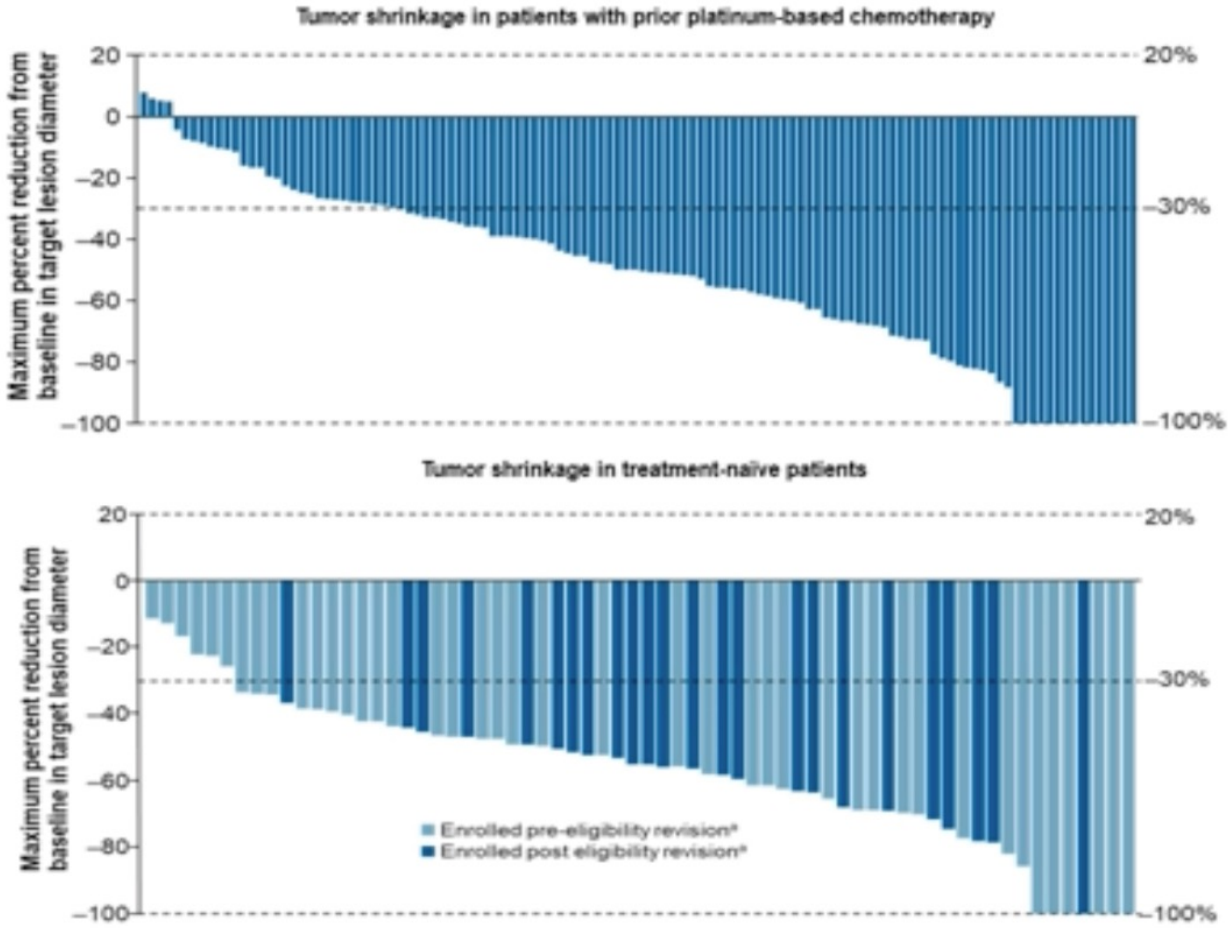
- With a median follow-up of 9.8 months, 76% (31/41) of responses are ongoing



1. Besse B et al. ASCO 2021 Abstract 9065.

ARROW: Pralsetinib

	Measurable disease population					
		Treatment-naïve			Prior treatment	
	RET fusion–positive NSCLC (n=216)	All (n=68)	Pre-eligibility revision (n=43)[a]	Post eligibility revision (n=25)[a]	Prior platinum (n=126)	Prior non-platinum (n=22)
ORR, % (95% CI)	**69** (62–75)	**79** (68–88)	**74** (59–87)	**88** (69–98)	**62** (53–70)	**73** (50–89)
Best overall response, n (%)						
CR	9 (4)	4 (6)	4 (9)	0	5 (4)	0
PR	139 (64)	50 (74)	28 (65)	22 (88)	73 (58)	16 (73)
SD	50 (23)	9 (13)	7 (16)	2 (8)	37 (29)	4 (18)
PD	10 (5)	3 (4)	3 (7)	0	5 (4)	2 (9)
NE	8 (4)	2 (3)	1 (2)	1 (4)	6 (5)	0
DCR, % (95% CI)[b]	92 (87–95)	93 (84–98)	91 (78–97)	96 (80–100)	91 (85–96)	91 (71–99)
CBR, % (95% CI)[c]	77 (71–82)	82 (71–91)	79 (64–90)	88 (69–96)	74 (65–81)	77 (55–92)
mDOR, mo (95% CI)	22.3 (15.1–NR)	NR (9.0–NR)	11.0 (7.4–NR)	NR (NR–NR)	22.3 (15.1–NR)	NR (9.2–NR)



1. Curigliano et al, ASCO 2021

BRIEF REPORT

Brief Report: Chylothorax and Chylous Ascites During RET Tyrosine Kinase Inhibitor Therapy

Or Kalchiem-Dekel, MD,[a,b] Christina J. Falcon, MPH,[a] Christine M. Bestvina, MD,[c] Dazhi Liu, PharmD,[a] Lauren A. Kaplanis, BSN,[a] Clare Wilhelm, PhD,[a] Jordan Eichholz, BA,[a] Guilherme Harada, MD,[a] Lori J. Wirth, MD,[d] Subba R. Digumarthy, MD,[e] Robert P. Lee, MD,[a,b] David Kadosh, MD,[a] Robin B. Mendelsohn, MD,[a,b] Jessica Donington, MD,[c] Justin F. Gainor, MD,[d] Alexander Drilon, MD,[a,b] Jessica J. Lin, MD[d,*]

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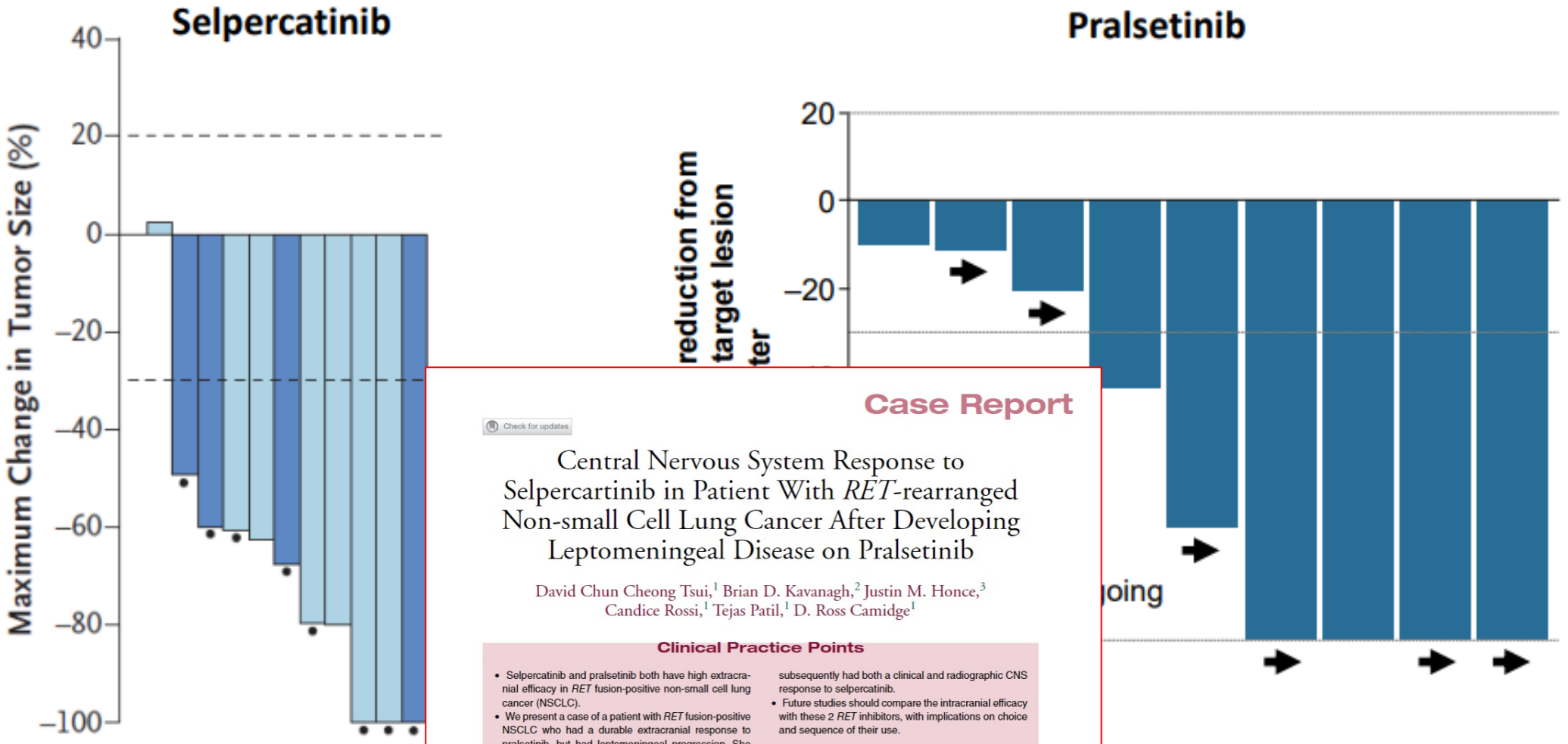
7% with selp
0% with pral

CNS Activity of Selective RET TKIs



Case Report

Check for updates

Central Nervous System Response to Selpercartinib in Patient With *RET*-rearranged Non-small Cell Lung Cancer After Developing Leptomeningeal Disease on Pralsetinib

David Chun Cheong Tsui,[1] Brian D. Kavanagh,[2] Justin M. Honce,[3] Candice Rossi,[1] Tejas Patil,[1] D. Ross Camidge[1]

Clinical Practice Points

- Selpercatinib and pralsetinib both have high extracranial efficacy in *RET* fusion-positive non-small cell lung cancer (NSCLC).
- We present a case of a patient with *RET* fusion-positive NSCLC who had a durable extracranial response to pralsetinib, but had leptomeningeal progression. She subsequently had both a clinical and radiographic CNS response to selpercatinib.
- Future studies should compare the intracranial efficacy with these 2 *RET* inhibitors, with implications on choice and sequence of their use.

Clinical Lung Cancer, Vol. 23, No. 1, e5–e8
Keywords: NSCLC, RET, selpercatinib, pralsetinib, leptomeningeal

Drilon A, et al. NEJM 2020; Curigliano G, et al. AIMO 2020

Usually still the oncology basics

- Efficacy>Safety/tolerability>Convenience

For some oncogene subgroups, even this is changing

Side-by-Side and Like-with-Like comparisons: ALEX Alectinib and ALTA-1L Brigatinib 1st line. Progression-Free Survival Outcomes Within Trials Over Time EQUIVALENT

ALEX: Alectinib vs Crizotinib[1]

Enrollment: Aug 2014 – Jan 2016

Median duration of follow-up in experimental arm:

18.6 months

	Alectinib (n=152)[1]	Crizotinib (n=151)
PFS (INV), months	NR	11.1
HR (95% CI)	0.47 (0.34-0.65)	
PFS (IRC), months	25.7	10.4
HR (95% CI)	0.50 (0.36-0.70)	

27.8 months

	Alectinib (n=152)[2]	Crizotinib (n=151)
PFS (INV), months	34.8	10.9
HR (95% CI)	0.43 (0.32-0.58)	
PFS (IRC), months	--	--
HR (95% CI)	--	

37.8 months

	Alectinib (n=152)[3]	Crizotinib (n=151)
PFS (INV), months	34.8	10.9
HR (95% CI)	0.43 (0.32-0.58)	
PFS (IRC), months	--	--
HR (95% CI)	--	

ALTA-1L: Brigatinib vs Crizotinib[7]

Enrollment: Apr 2016 – Aug 2017

Median duration of follow-up in experimental arm:

11.0 months

1st interim analysis	Brigatinib (n=137)[7]	Crizotinib (n=138)
PFS (INV), months	NR	9.2
HR (95% CI)	0.45 (0.30-0.68)	
PFS (IRC), months	NR	9.8
HR (95% CI)	0.49 (0.33-0.74)	

24.9 months

2nd interim analysis	Brigatinib (n=137)[8]	Crizotinib (n=138)
PFS (INV), months	29.4	9.2
HR (95% CI)	0.43 (0.31-0.61)	
PFS (IRC), months	24.0	11.0
HR (95% CI)	0.49 (0.35-0.68)	

- IRC assessed HR ALEX:ALTA-1L at (closest possible) comparable follow up time points: 0.5 and 0.49
- INV assessed HR: 0.43 and 0.43
- 24 month INV-assessed PFS rate: 57% and 56%
- Median PFS (IRC) point estimate:

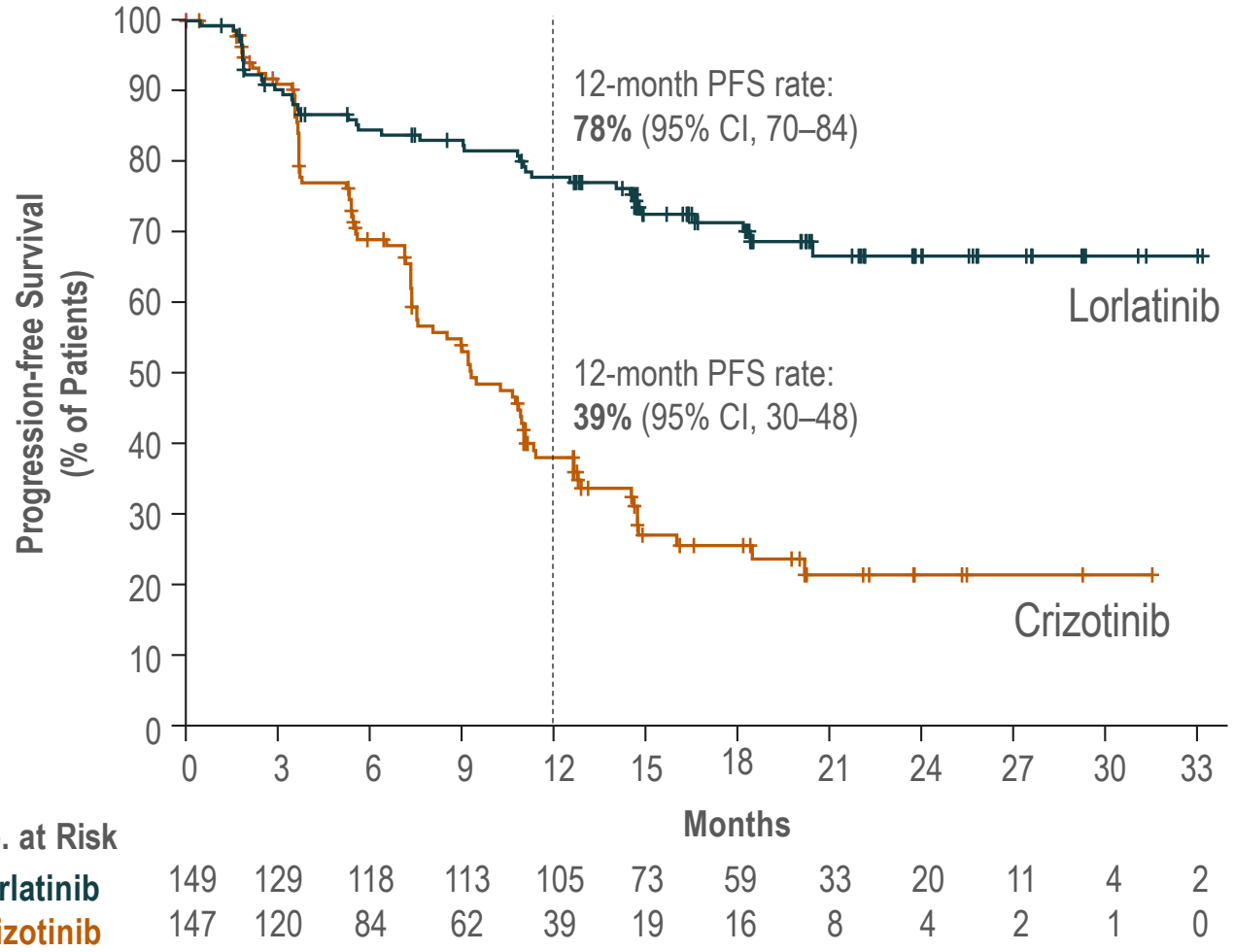
ALEX 25.7 and ALTA-1L 24 mo

- Median PFS (INV) point estimate:

ALEX 34.8 (17.7–NE) and ALTA-1L 29.4 mo (21.2–NR)

Peters et al, NEJM 2017; Camidge et al, JTO 2019; Camidge et al, NEJM 2018; Camidge et al, ESMO ASIA 2019

Primary Endpoint: PFS by BICR



	Lorlatinib (n=149)	Crizotinib (n=147)
Patients with event, n (%)	41 (28)	86 (59)
Median PFS, months (95% CI)	NE (NE–NE)	9.3 (7.6-11.1)
HR (95% CI) 1-sided P value*	**0.28** (0.19-0.41) <0.001	

*By stratified log-rank test.

FDA label extension
March 3rd 2021

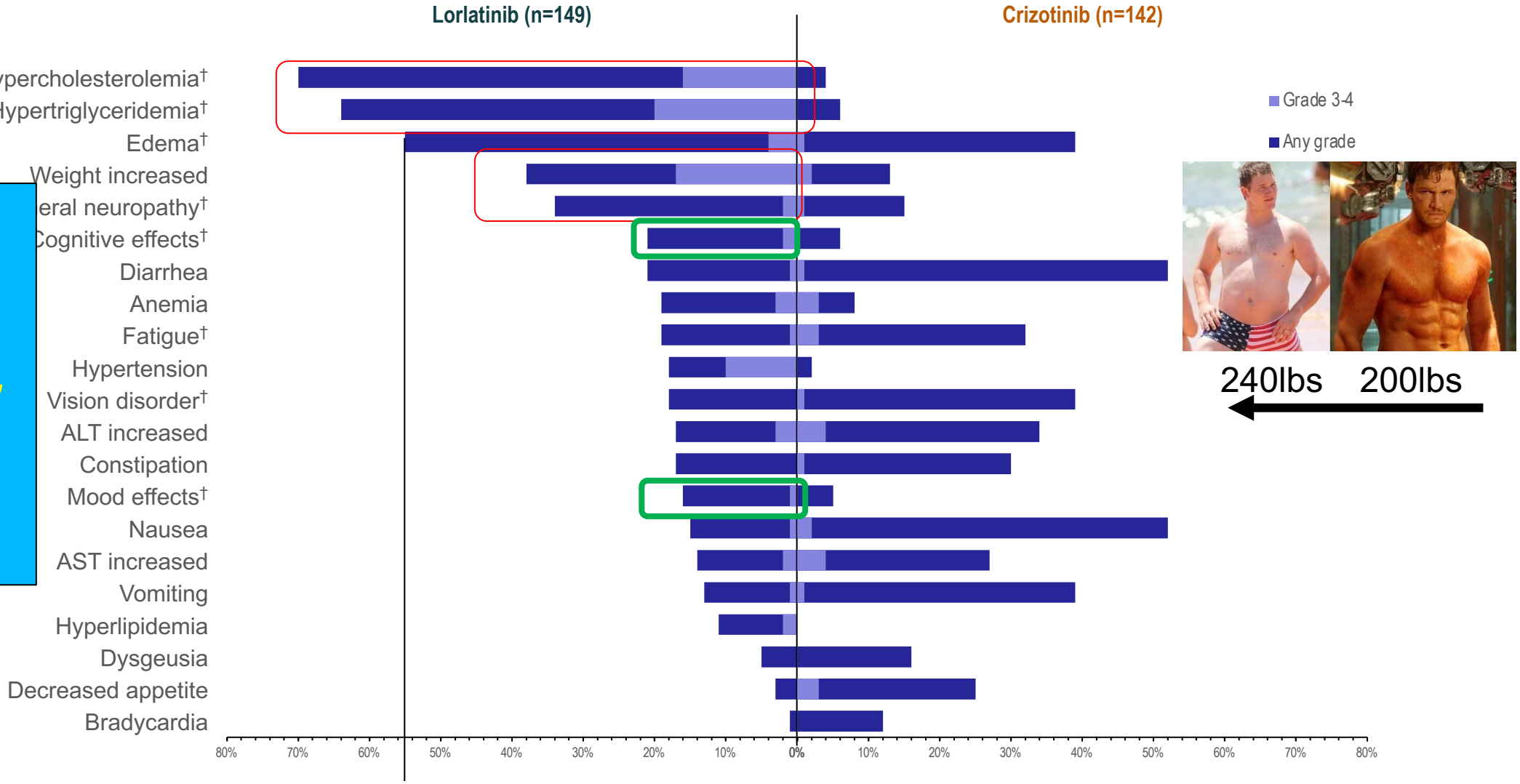
BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NE, not estimable; PFS, progression-free survival

VIRTUAL 2020 ESMO congress

All Causality Adverse Events with ≥10% Difference in Frequency

"I think lorlatinib should come with a psychologist."

ALK + Patient Advocate



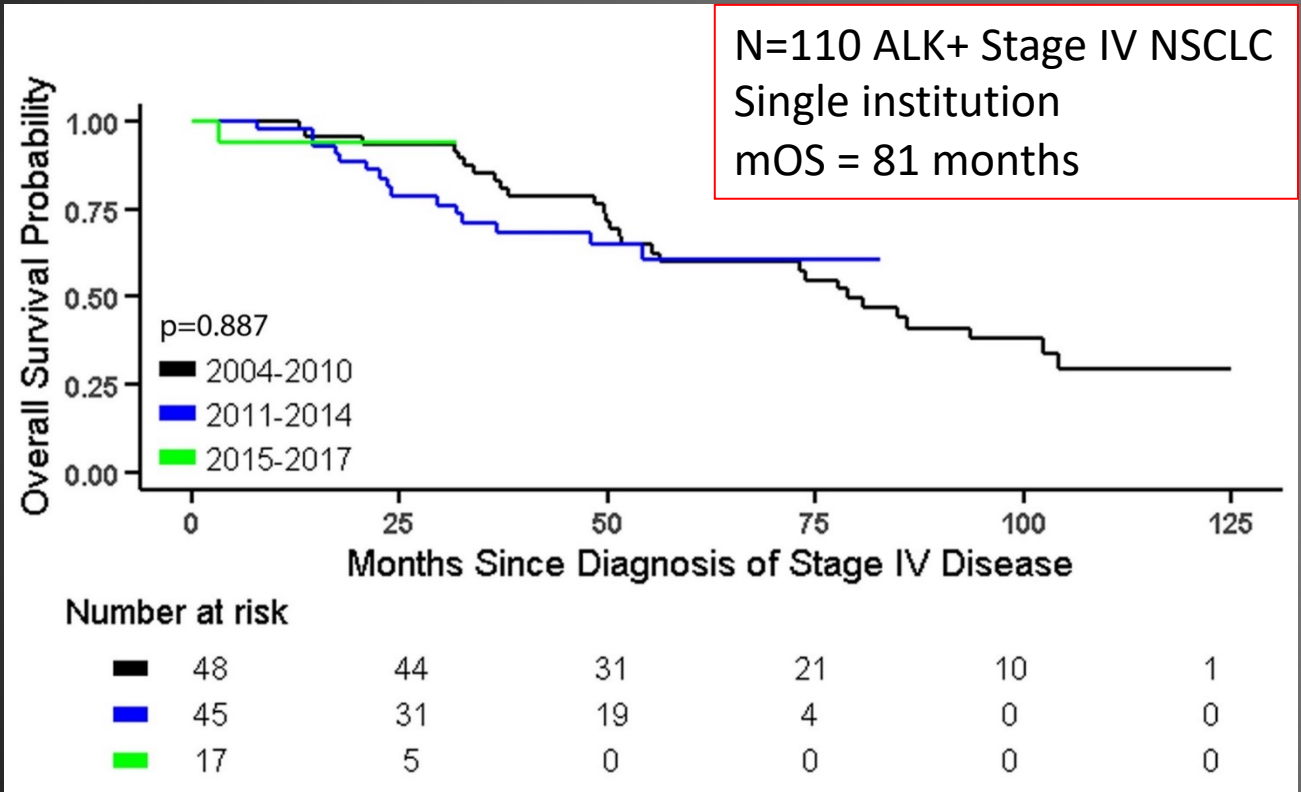
†Cluster term

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

ALK+ NSCLC Treatment Goals

Goals:

Prolonged disease control | Prolonged life | Good quality of life



- No significant difference in OS time between patients who received crizotinib first (median 86 months [n = 40]) and those who received a non-ALKI systemic therapy before crizotinib (median 79 months [n = 65]) (p = 0.653)
- Year of diagnosis of stage IV disease (2004–2010, 2011–2014, and 2015–2017) was not associated with OS (p = 0.887)
- The median OS time was 86 months from diagnosis of stage IV disease for patients who received a next-generation ALKI at some point after crizotinib and 52 months for patients who did not (p = 0.085)

Pacheco JM, et al. *J Thorac Oncol.* 2019;14(4):691-700.

How only 2nd line and beyond agents for some oncogenes are trying to get to first line

Path to 1st line

- In absence of other data – Keynote 189 is mental comparator
- If your ORR is 20-40% (ami, mobo, sotorasib) only three paths to 1st line
  - Define higher ORR subpopulation
  - Combine with something targeted rationally
  - Combine with chemo, chemo-io, or io

Hard studies as control arm good and delta may be small
Also may be TKI –io combo issues

Safety by Dose: Pembrolizumab Concurrent

TRAE, n (%)	Sotorasib 120 mg (N = 5)		Sotorasib 360 mg (N = 8)		Sotorasib 720 mg (N = 2)		Sotorasib 960 mg (N = 4)	
	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3	Any	Grade ≥ 3
All TRAEs	5 (100)	4 (80)	7 (88)	6 (75)	2 (100)	2 (100)	3 (75)	3 (75)
Hepatotoxicity	**2 (40)**	**2 (40)**	**3 (38)**	**2 (25)**	**2 (100)**	**2 (100)**	**3 (75)**	**3 (75)**
ALT increased	2 (40)	1 (20)	3 (38)	1 (13)	2 (100)	2 (100)	3 (75)	3 (75)
AST increased	2 (40)	2 (40)	3 (38)	0	2 (100)	2 (100)	3 (75)	1 (25)

- **Higher rate of TRAEs than with either monotherapy[6–8], with no fatal TRAEs**
- **At lower doses of sotorasib, there was a trend towards less liver enzyme elevations, although sample sizes were limited**
- **Given the safety data for this combination, sotorasib lead-in was explored**

Hepatotoxicity included autoimmune hepatitis, ALT increased, AST increased, ALP increased, bilirubin increased, and GGT increased.
ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; TRAE, treatment-related adverse event.

Li BT, et al. Presented at World Conference on Lung Cancer (WCLC) 2022 Annual Meeting, August 6-9, 2022; Vienna, Austria.

Safety Summary: Lead-in versus Concurrent

	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or IO discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, months (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, months (min, max)‡	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Hepatotoxicity grade ≥ 3, median onset, days (range)	50 (28, 93)	67 (36, 147)	73 (45, 127)	51 (29, 190)

- **Lead-in had lower incidence of Grade 3-4 TRAEs and TRAEs leading to discontinuation than concurrent**
- **Grade 3-4 hepatotoxicity first occurrence was outside DLT window† in 88% of patients; 97% of events resolved with corticosteroids, treatment modification, and/or discontinuation**
- **The incidence of hepatotoxicity TRAEs was similar in IO-naïve versus IO-pretreated patients**

Hepatotoxicity included ALT increased, AST increased, ALP increased, bilirubin increased, GGT increased; also hepatitis, liver function test increased, drug-induced liver injury, transaminases increased for sotorasib+atezolizumab; also hepatic enzyme increased, immune-mediated hepatitis for sotorasib lead-in+pembrolizumab; also autoimmune hepatitis for sotorasib+pembrolizumab concurrent.
*Grade 4 TRAEs were ALT increased (n = 1; related to sotorasib and atezolizumab), and AST increased (n = 1; related to sotorasib).
‡Duration of combination calculated for patients receiving both sotorasib and IO; one patient in a lead-in cohort did not receive IO and not included.
†DLT window was 21 days following initiation of combination treatment. IO, immune-oncology therapy.

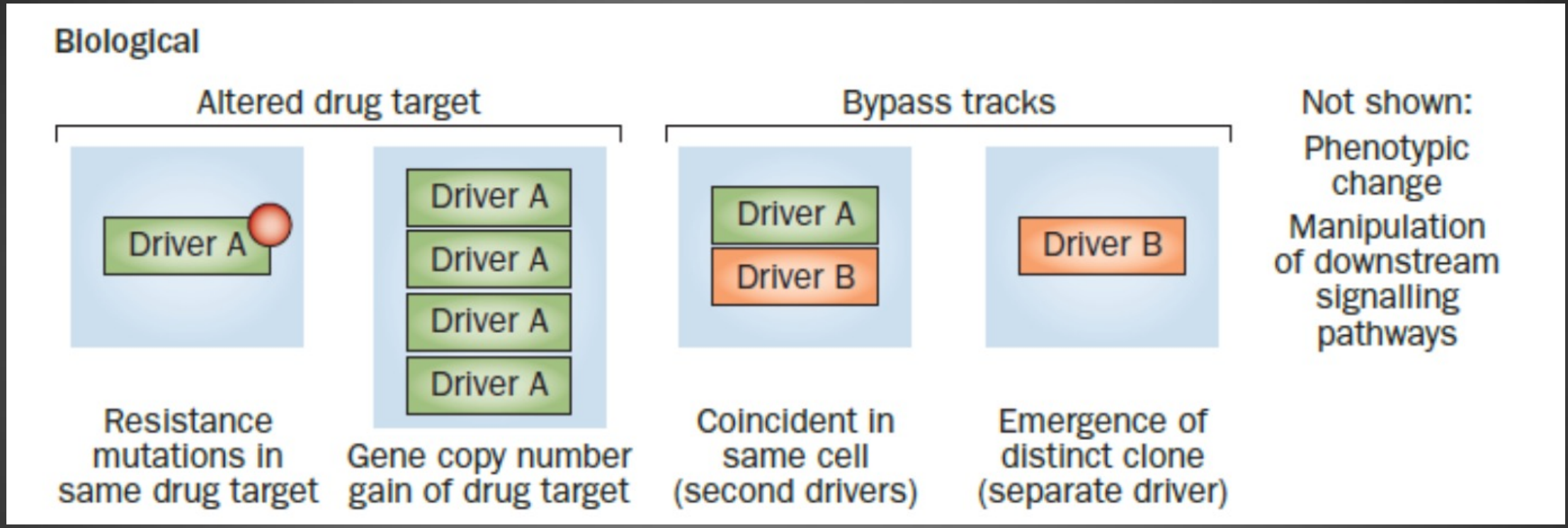
Li BT, et al. Presented at World Conference on Lung Cancer (WCLC) 2022 Annual Meeting, August 6-9, 2022; Vienna, Austria.

Future for G12C in 1st line?

- If takes several weeks to manifest – haven't seen enough adagrasib data on combo to compare – if not class effect then await phase III combo with ada
- If class effect – look out for 1st line phase IIIs of G12Cin plus chemo vs chemo-io in group least likely to miss the IO – ie low PDL1, STK11, KEAP 1, etc

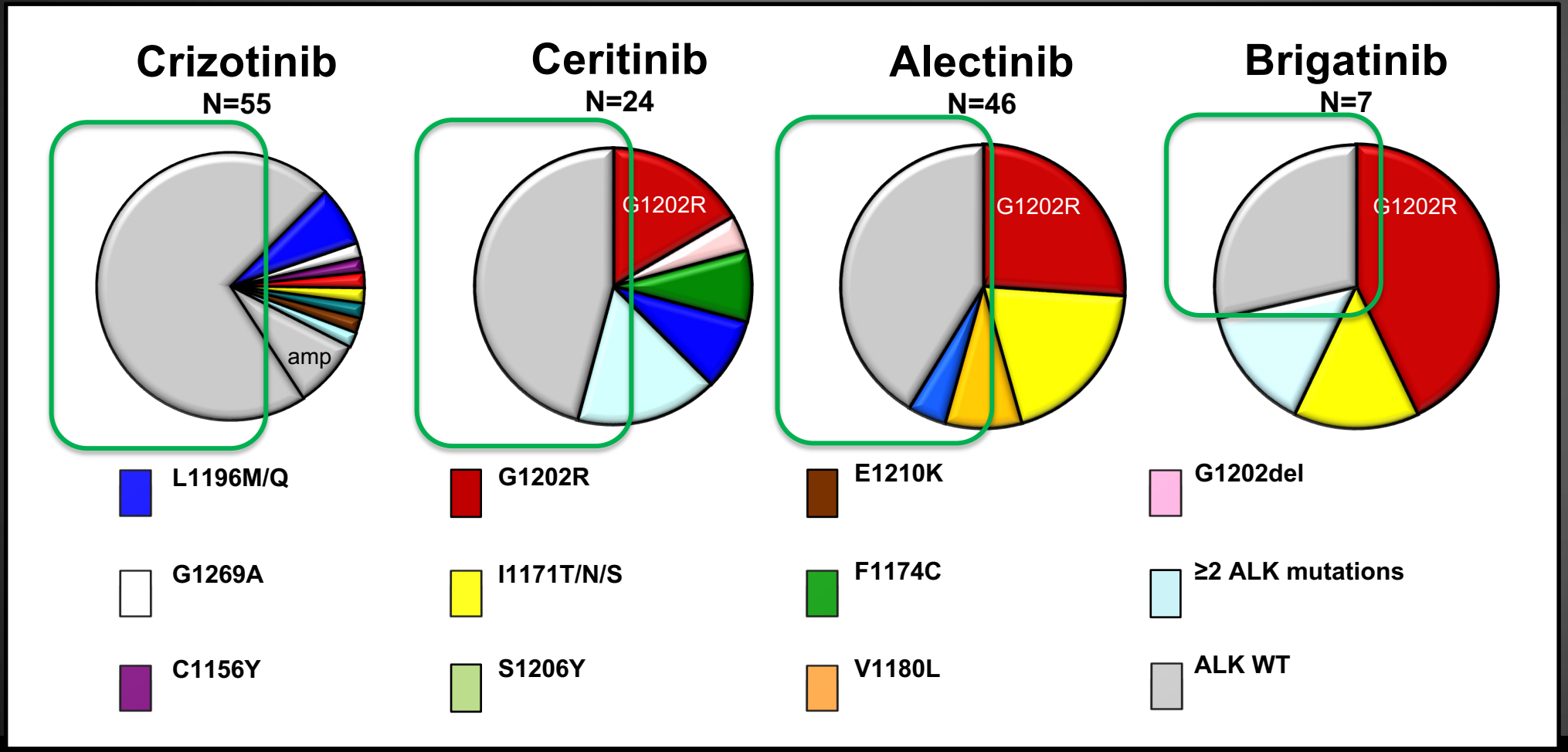
Acquired resistance strategies

Acquired Resistance: Biological



Camidge, Pao, Sequist,
Nature Reviews Clinical Oncology 2014

Elephant in the room….



NOT ALL REMAIN ADDICTED TO ALK ALONE
- 2ND DRIVERS!!

Gainor et al. *Cancer Discov.* 2016;6:1118-1133.
Lin et al. *J Clin Oncol*. 2018;36:9093

TPX-0131, A Next-Gen ALK Inhibitor

TPX-0131 is a next-generation ALK inhibitor entering IND-enabling studies. It has been designed with a novel compact macrocyclic structure and has shown preclinical potent inhibition of wildtype and numerous ALK mutations, including the clinically observed G1202R solvent-front mutation and the G1202R/L1196M compound mutation.

Medical Need

Multiple FDA-approved ALK inhibitors are available to patients for the treatment of ALK+ non-small cell lung cancer (NSCLC), yet none are approved to treat solvent-front mutations that lead to drug resistance.

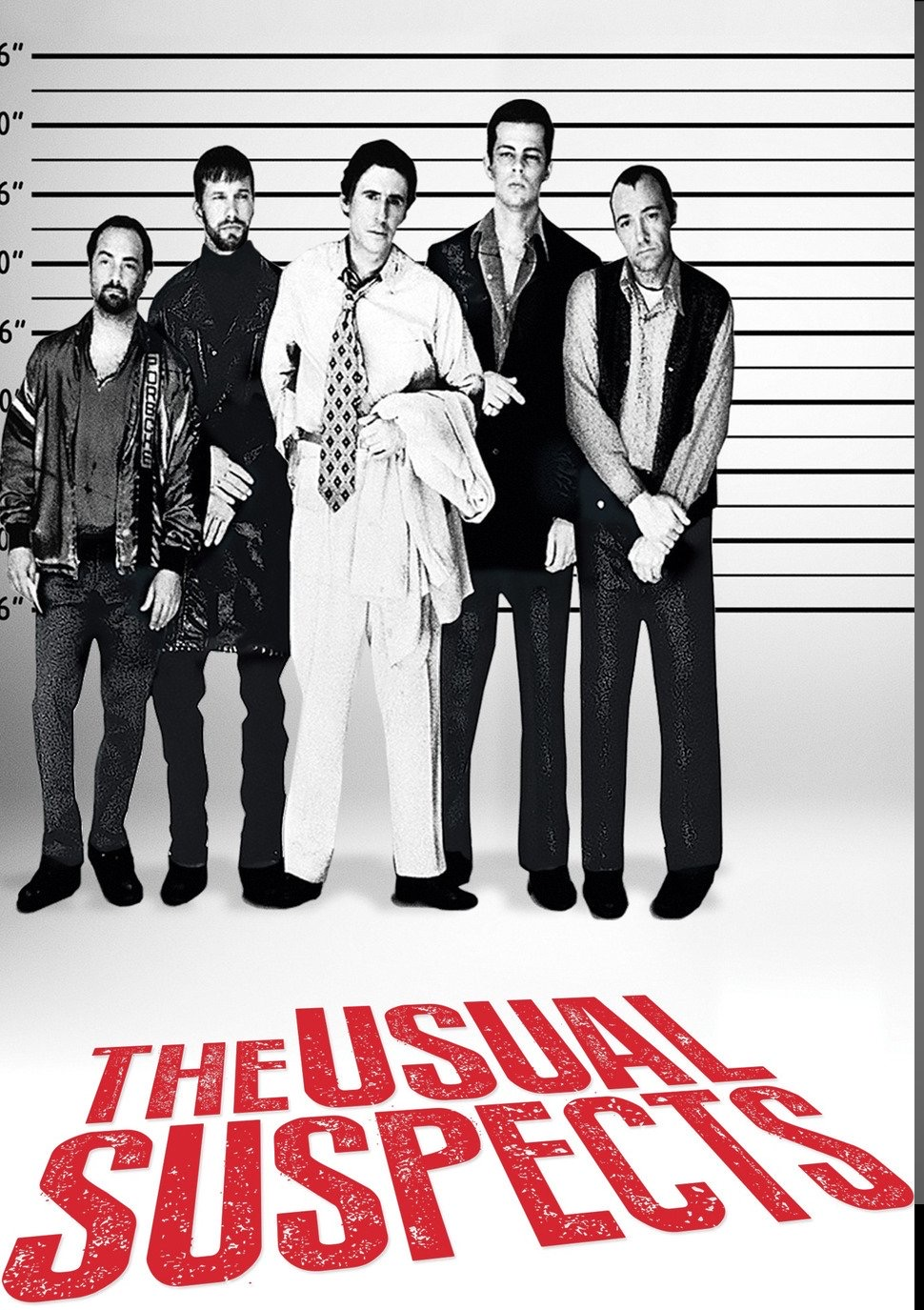
Targeting Known Mechanisms of Resistance

ALK-driven tumors are estimated to represent up to 7 percent of driver oncogenes in NSCLC and of patients who develop a resistance mutation, G1202R has been reported in approximately 42 percent.

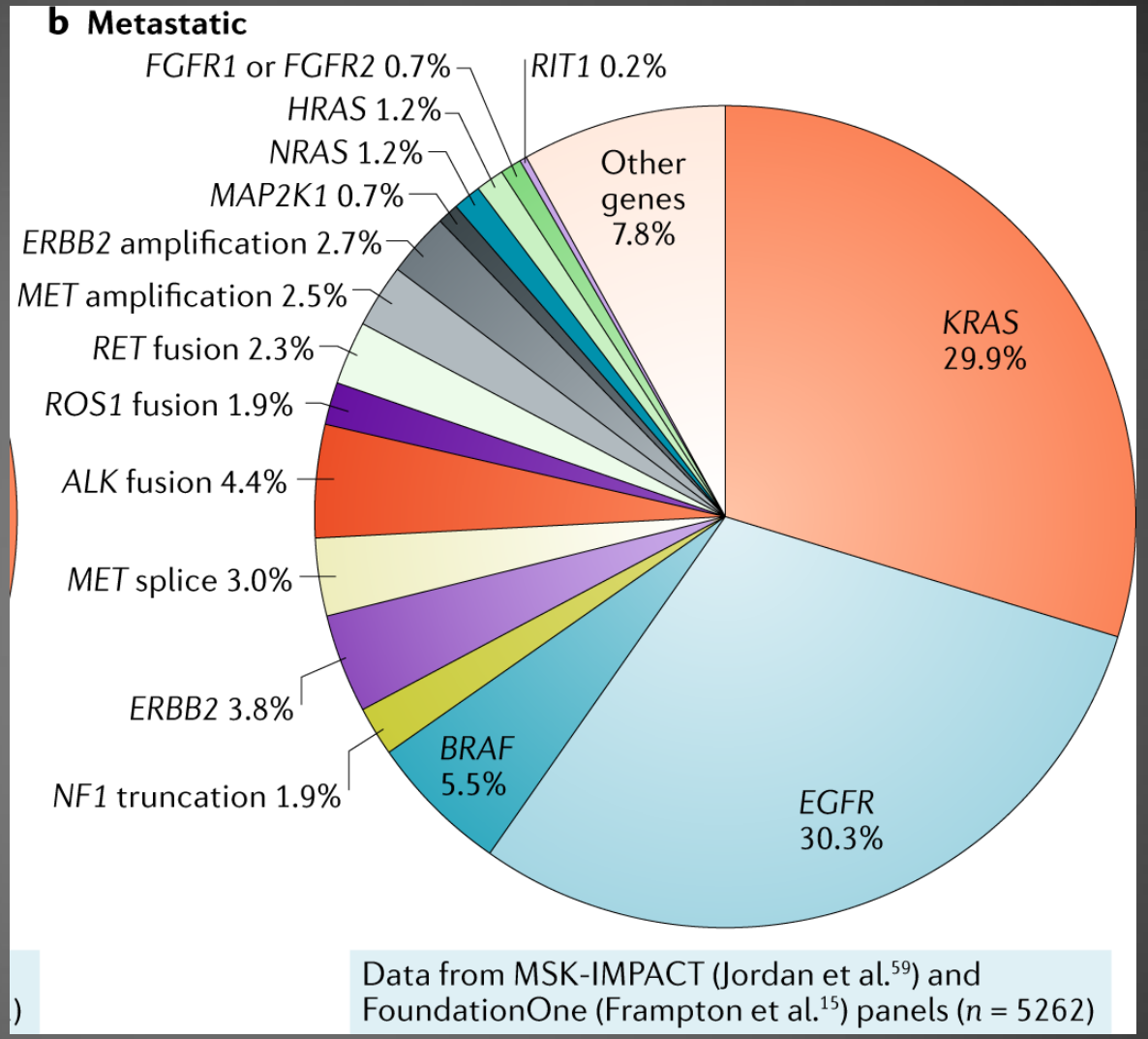
Compound mutation

Nuvalent Pipeline

Indication	Drug Candidate	Resistance or Activating Mutation (s)	Discovery	IND Enabling	P
ROS1 NSCLC	NUV-520	G2032R D2033N L2026M S1986F			
ALK NSCLC	NUV-655	G1202R G1202R/L1196M G1202R/G1269A			



THE USUAL SUSPECTS



Results with Therapy Associations

BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
PD-L1 (22c3)	IHC	Protein	Positive, TPS: 3%	BENEFIT	pembrolizumab	Level 1
PD-L1 (28-8)	IHC	Protein	Positive | 1+, 1%	BENEFIT	nivolumab/ipilimumab combination	Level 1
PD-L1 (SP263)	IHC	Protein	Positive, TC: 1+, 2%	BENEFIT	atezolizumab (adjuvant)	Level 1
BRAF	Seq	DNA-Tumor	Pathogenic Variant Exon 15 | p.V600E	BENEFIT	dabrafenib and trametinib combination therapy	Level 2
					vemurafenib	Level 2
EGFR	Seq	DNA-Tumor	Pathogenic Variant Exon 19 | p.L747 _A755 delinsNNNN	BENEFIT	afatinib, dacomitinib, erlotinib¶, gefitinib, osimertinib	Level 2
ALK	Seq	RNA-Tumor	Fusion Not Detected	LACK OF BENEFIT	alectinib, brigatinib, ceritinib, crizotinib, lorlatinib	Level 2
KRAS	Seq	DNA-Tumor	Mutation Not Detected	LACK OF BENEFIT	sotorasib	Level 2

Optimally combining targeted therapies is not a pound cake recipe

Wikipedia:
Pound cake is a type of cake traditionally made with a pound of each of four ingredients: flour, butter, eggs, and sugar.

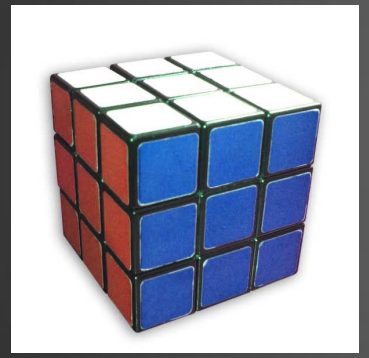
Patient level dose optimization schemes required
"Single patient phase I trials" strongly suggested

-Initial dose/schedule strategy should be based on expected overlapping toxicities and drug-drug interaction potential

Potential paradigm changes – Consolidation, Chemo and Antibody Drug Conjugates

Works in progress: Maximal cytoreduction/consolidation up front.

Lots of people
Any puzzle



One person
One puzzle

original report

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

Daniel R. Gomez, MD[1]; Chad Tang, MD[1]; Jianjun Zhang, MD, PhD[1]; George R. Blumenschein Jr, MD[1]; Mike Hernandez, MS[1]; J. Jack Lee, PhD[1]; Rong Ye, MS[1]; David A. Palma, MD, PhD[2]; Alexander V. Louie, PhD, MSc[2]; D. Ross Camidge, MD, PhD[3]; Robert C. Doebele, MD, PhD[3]; Ferdinandos Skoulidis, MD, PhD[1]; Laurie E. Gaspar, MD[3]; James W. Welsh, MD[1]; Don L. Gibbons, MD[1]; Jose A. Karam, MD[1]; Brian D. Kavanagh, MD, MPH[3]; Anne S. Tsao, MD[1]; Boris Sepesi, MD[1]; Stephen G. Swisher, MD[1]; and John V. Heymach, MD, PhD[1]

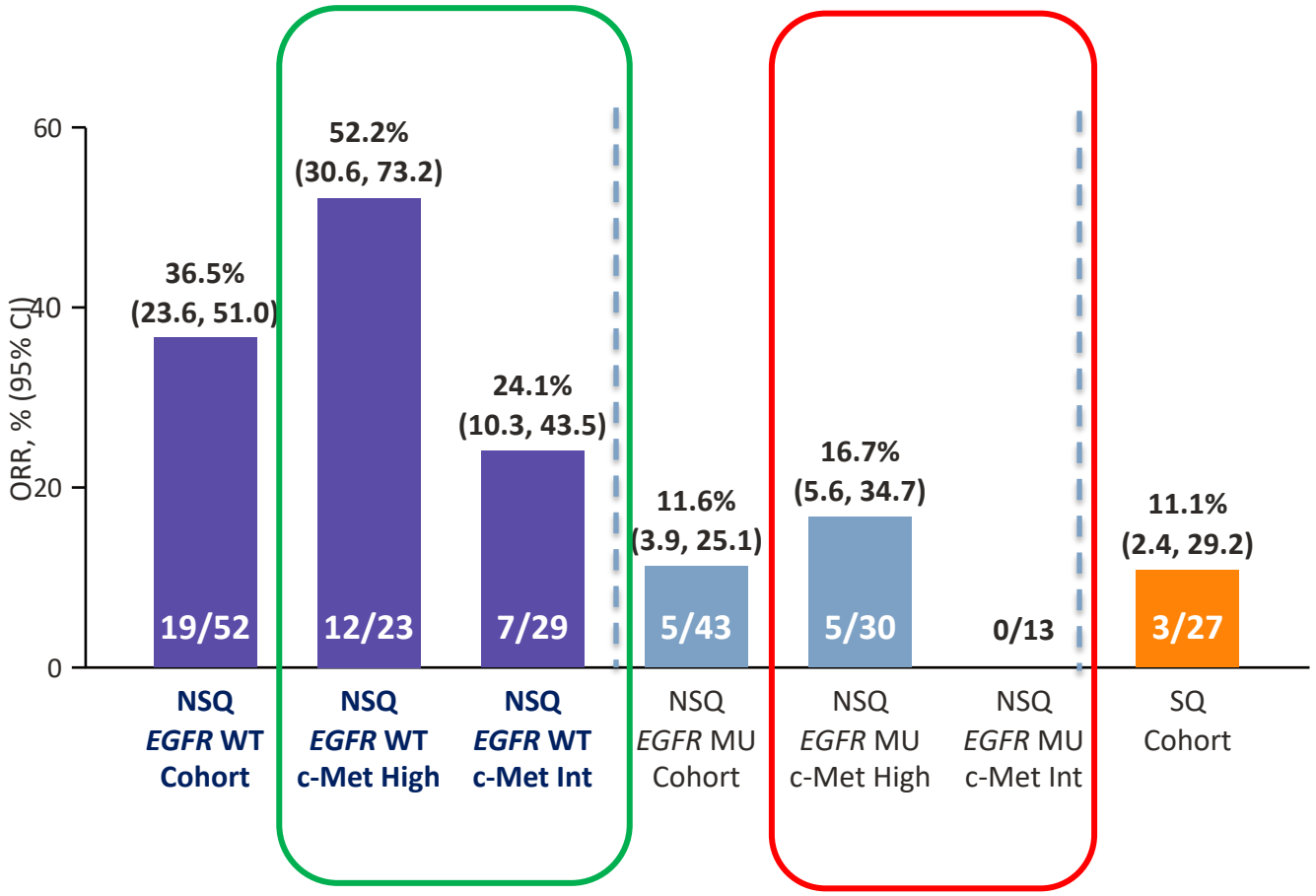
original reports

Gefitinib Versus Gefitinib Plus Pemetrexed and Carboplatin Chemotherapy in *EGFR*-Mutated Lung Cancer

Vanita Noronha, MBBS, MD, DM[1]; Vijay Maruti Patil, MBBS, MD, DM[1]; Amit Joshi, MBBS, MD, DM[1]; Nandini Menon, MBBS, MD, DNB[1]; Anuradha Chougule, PhD[1]; Abhishek Mahajan, MBBS, MD, MRes[1]; Amit Janu, MBBS, DMRD, DNB[1]; Nilendu Purandare, MBBS, DNB[1]; Rajiv Kumar, MBBS, MD[1]; Sucheta More, BAMS, MSc[1]; Supriya Goud, BAMS[1]; Nandkumar Kadam, BSc[2]; Nilesh Daware, HSc[2]; Atanu Bhattacharjee, MSc, PhD[1]; Srushti Shah, BHMS, PDCR[1]; Akanksha Yadav, MSc[1]; Vaishakhi Trivedi, MSc[1]; Vichitra Behel, MTech[1]; Amit Dutt, PhD[3]; Shripad Dinanath Banavali, MBBS, MD[1]; and Kumar Prabhash, MBBS, MD, DM[1]

M14-239 Interim Analysis 4: ORR per Central Review and DoR

Primary efficacy by cohort/group



Primary efficacy analysis set (≥12 weeks follow-up)

NSCLC Cohort	N	# Events / # confirmed responses	Median DOR, mo (95% CI)
c-Met OE NSQ *EGFR* WT	52	8/19	6.9 (4.1, –)
c-Met High	23	5/12	6.9 (2.4, –)
c-Met Intermediate	29	3/7	– (4.1, –)
c-Met OE NSQ *EGFR* mutant	43	2/5	– (3.0, –)
c-Met High	30	2/5	– (3.0, –)
c-Met Intermediate	13	NA	Not applicable
c-Met OE SQ	27	2/3	4.4 (3.0, –)

CI, confidence interval; EGFR, epidermal growth factor receptor; Int, intermediate; MU, mutant; NSQ, non-squamous; DOR duration of response; ORR, overall response rate; SQ, squamous; WT, wild-type.

Camidge DR, et al. ASCO 2022; Poster presentation P9016.

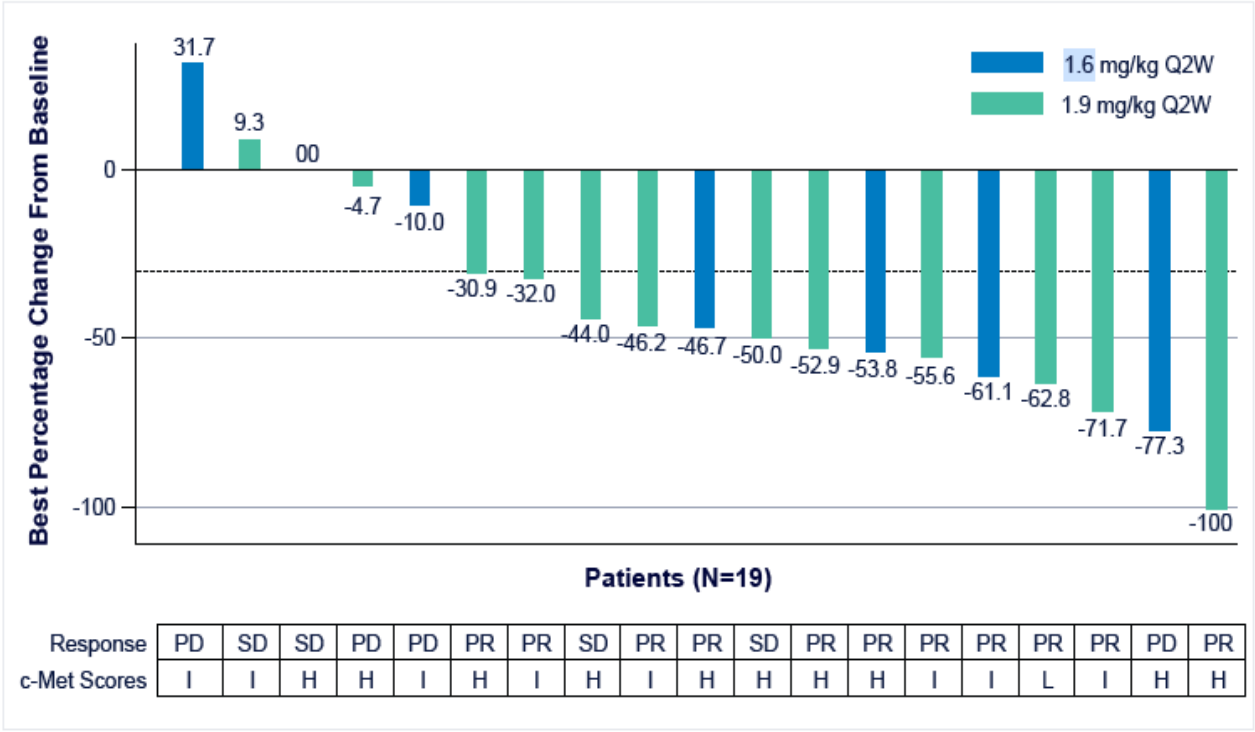
Interim ORR and Best Overall Response

M14-237: Data for Teliso-V + Osimertinib Cohort (N=25)

Category	N	ORR, * n (%) [95% CI]
Teliso-V dose		
1.6 mg/kg	7	3 (43) [10, 82]
1.9 mg/kg	12	8 (67) [35, 90]
Total	19†	11 (58) [34, 80]
c-Met level		
High (≥50%, 3+ staining)	10	5 (50) [19, 81]
Int (25-49%, 3+ staining)	8	5 (63) [25, 92]
Total	18†	10 (56) [31, 79]
***EGFR* mutation**		
L858R	9	5 (56) [21, 86]
Del19	9	6 (67) [30, 93]
Total	19†	11 (58) [34, 80]
Last prior regimen		
Contained Osi	8	4 (50) [16, 84]
Did Not Contain Osi	11	7 (64) [31, 89]
Total	19	11 (58) [34,80]

Response

c-Met Scores

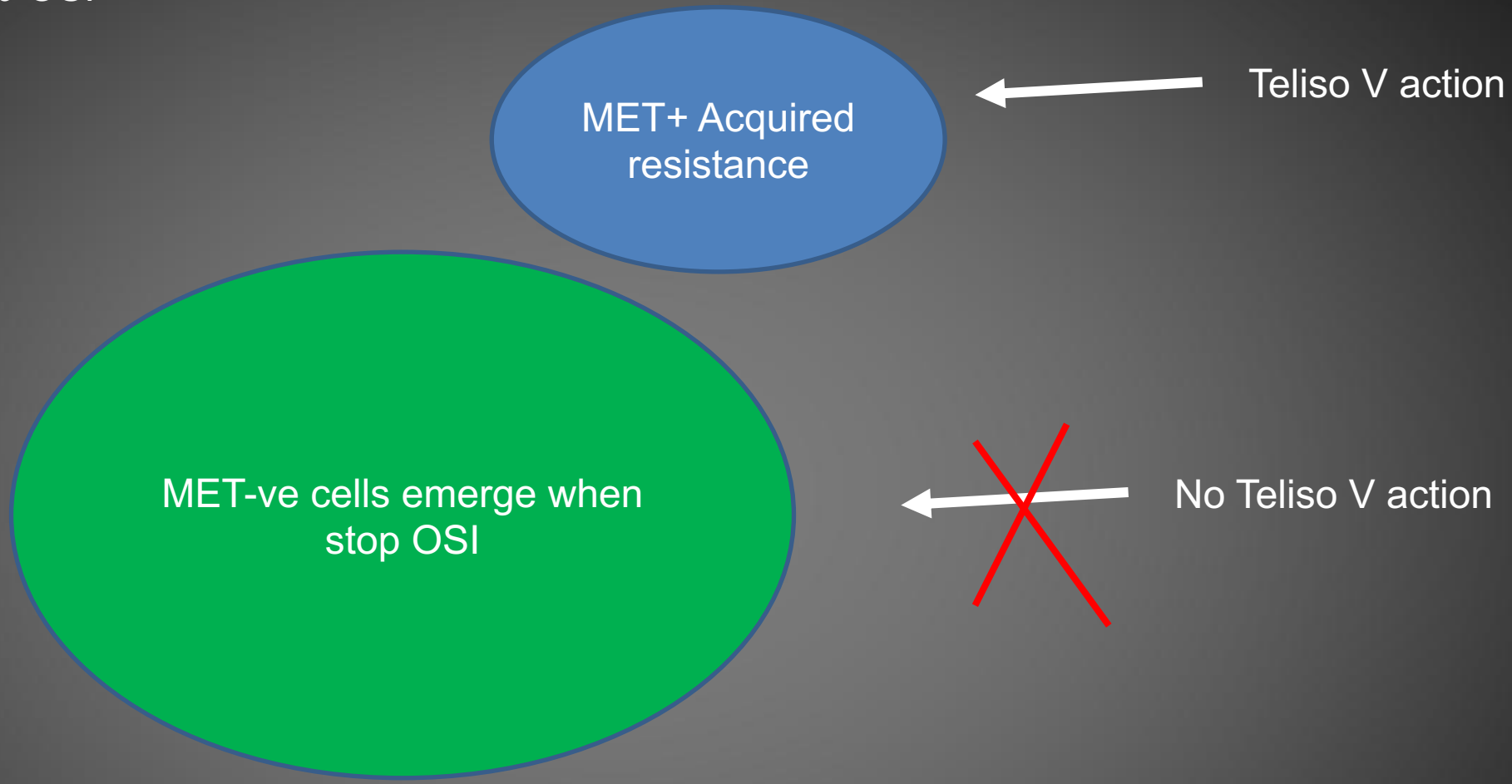


H, c-Met high (≥50%, 3+ staining); I, c-Met intermediate (25–49%, 3+ staining); L, c-Met low (<25, 3+ staining); PD, progressive disease; PR, partial response; Q2W, every 2 weeks; SD, stable disease.

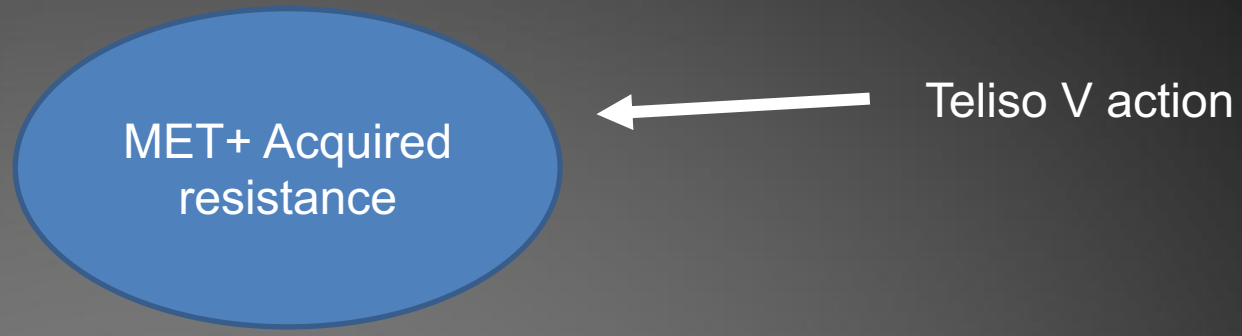
*RECIST v1.1; ORR (confirmed responses, all PR); data not mature for duration of response and progression-free survival. † As of December 2021, 25 patients enrolled, 19 with available RECIST assessment. ‡ c-Met IHC score <25% 3+, n=1. †G719S mutation, n=1.
EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; Int, intermediate; ORR, objective response rate; Osi, Osimertinib; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; Teliso-V, telisotuzumab vedotin.

Goldman J, *et al.* ASCO 2022; Poster presentation P9013.

PD on OSI when stop OSI



PD on OSI when keep OSI going



Met –ve cells suppressed

ADCs in 2L+ EGFR wt NSCLC (+/- CDx/patient identification)

Future development is focused on EGFRm in the 2L post EGFR TKI NSCLC given increased ORR

- P1/2, cohort 2: HER3-ADC (patritumab deruxtecan, payload ≈ 8) in 2L+ EGFRwt NSCLC, post IO + chemo or targeted therapy [Abstract #9017]
- **ORR** = 27% (EGFRwt), 29% (EGFRwt, w/ other driver mut)
  - ORR for EGFRm: 39% (reported at ASCO 2021)
- **mPFS** = 5.4mos (EGFRwt)
- **Gr3+ TRAEs** 72%; **discontinuation** 11%; **ILD** 11% (no Gr3+)
- Future development in 2L EFGRm, NSCLC post TKI:
  - Single arm P2 [HERTHENA-Lung01] readout expected in H2 2023.
  - P3 [HERTHENA-Lung02] readout expected in H2 2024

Camidge theory:
If HER3 not enriched in Acquired Resistance but lineage marker, Patri+Osi (ongoing) wont bump ORR like Teliso V combo did

ORR of 39% vs 11% with monotherapy in AR Setting suggests it's a lineage marker

Devil's Thumb Ranch, Colorado 2020

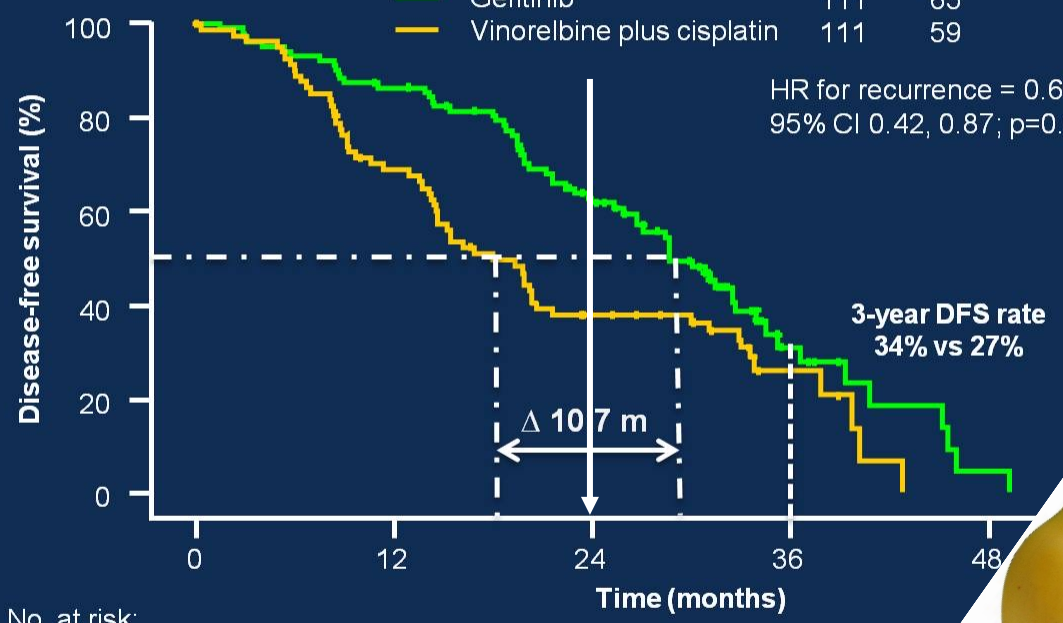
Questions?

Ross.Camidge@cuanschutz.edu

Early-stage cancer use

Primary endpoint: DFS (ITT population)

Group	N	Events	Median, months (95% CI)
Gefitinib	111	65	28.7 (24.9, 32.5)
Vinorelbine plus cisplatin	111	59	18.0 (13.6, 22.3)

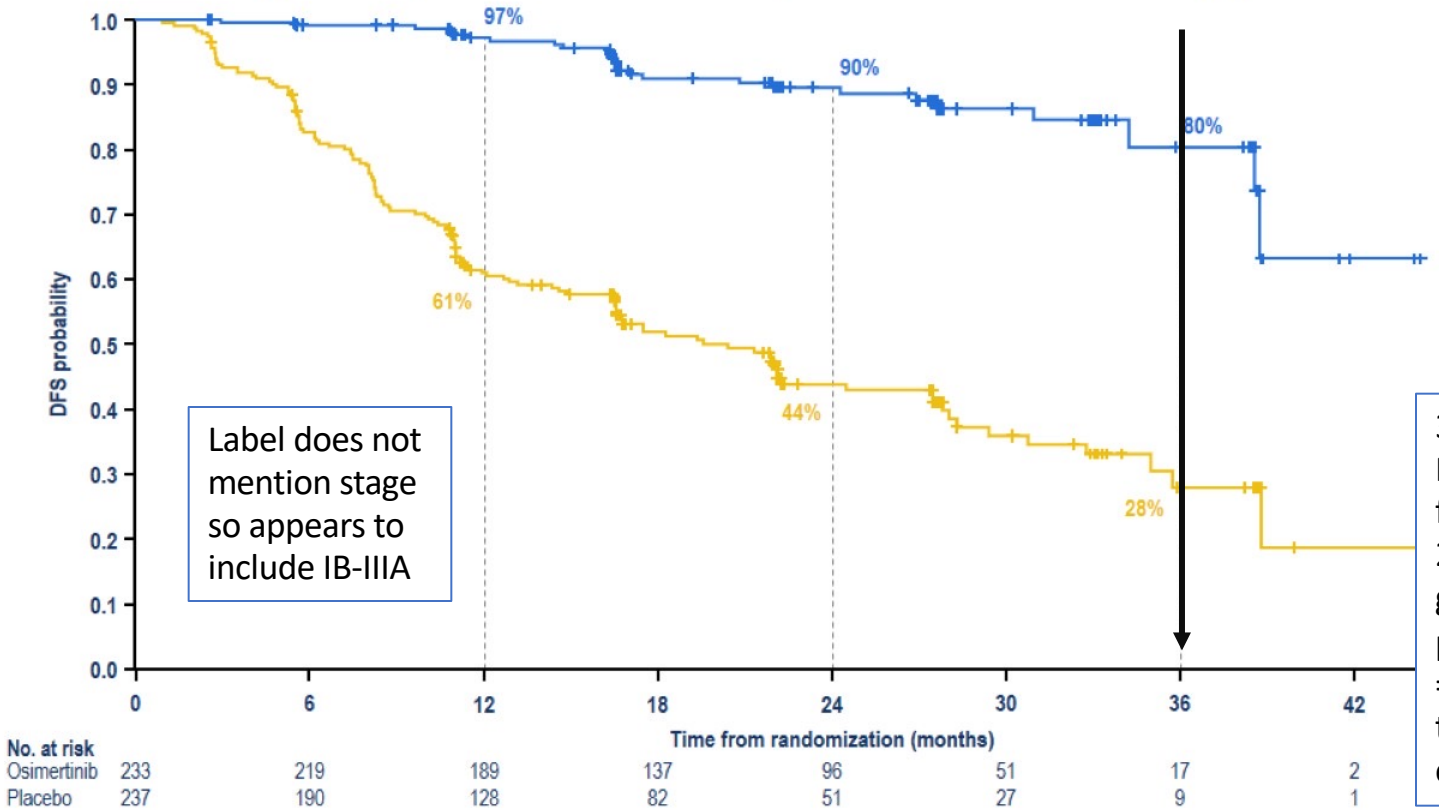


No. at risk:				
Gefitinib	111	88	57	10
Vinorelbine plus cisplatin	111	54	26	5

Abstract 8500 presented by Y-L Wu
Guangdong Lung Cancer Institute , Gu

Presented By Yi-Long Wu at 2017 ASCO Annual Meeting CTONG 1104

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



Median DFS, months (95% CI)	
– Osimertinib	NR (38.8, NC)
– Placebo	20.4 (16.6, 24.5)
HR (95% CI)	0.17 (0.12, 0.23); p<0.0001

Maturity 33%:
osimertinib 11%, placebo 55%

Label does not mention stage so appears to include IB-IIIA

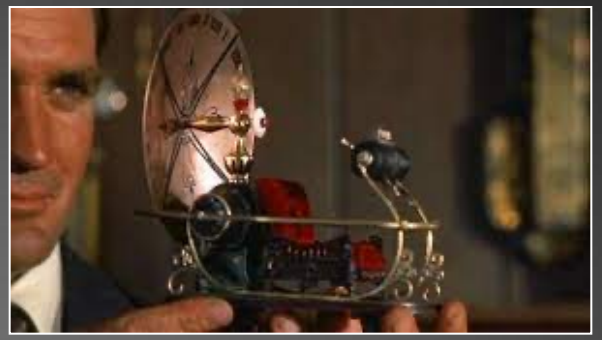
3 year therapy.
Median follow up for disease-free survival 22.1 months osimertinib group and 14.9 months placebo group.
= 61% patients on therapy at time of analysis

ADAURA data cut-off: January 17, 2020.
Median follow-up: osimertinib 22.1, placebo: 15.0 months;
DFS by investigator assessment; Tick marks indicate censored data.
NC, not calculable; NR, not reached.

Targeted adjuvant approach - controversy

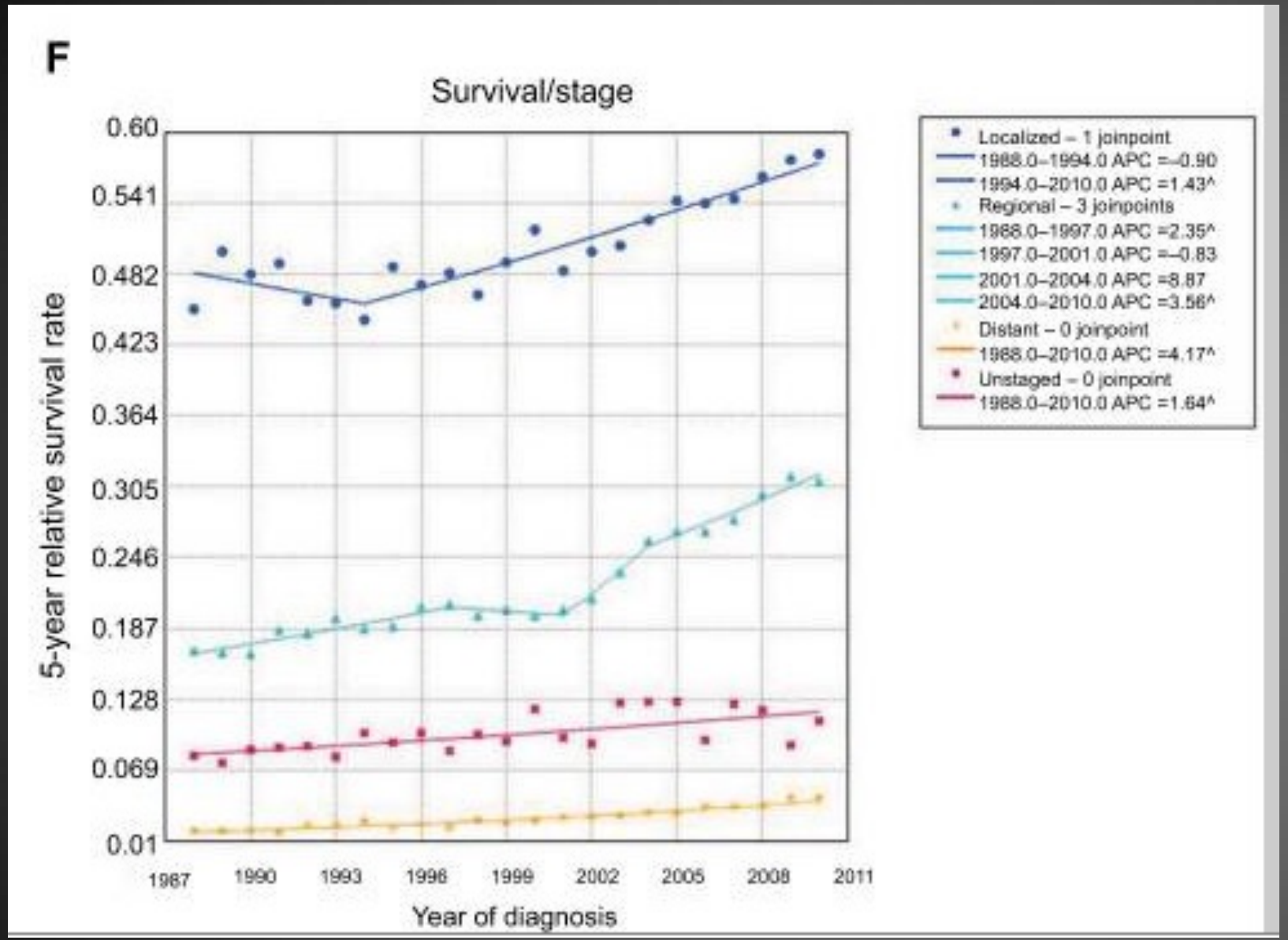
- Some patients already cured (true for all adjuvant indications)
- No OS benefit shown yet
  - ‘Surely huge DFS will equal OS benefit..’
  - ‘Do we even need chemo?’
  - ‘What if not cured and issues when stop drug…’
  - Middle ground – the Oncology Time Machine benefit…

The oncology time machine of adjuvant TKIs



- If no change in cure rate
- Can there still be an OS advantage?
- Beyond access differences in trial vs real world among participants
  - ?still advantage to ‘deal with this later’ – use as ‘oncology time machine’ to re-emerge when medicine more advanced?
  - PD after adjuvant therapy stopped not likely acquired resistance if many months have passed before disease emerges
  - Likely there are people we should NOT stop drug in (upfront long-term therapy of microscopic metastatic disease?)

Camidge. The magic of ADAURA? JTO 2022



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ORIGINAL RESEARCH

Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades

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