AIGOM:CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2023?

Sessione I - NSCLC avanzato: malattia oncogene addicted

Superamento della Resistenza a Osimertinib nei Pazienti con *EGFR* Mutato

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Disclosures

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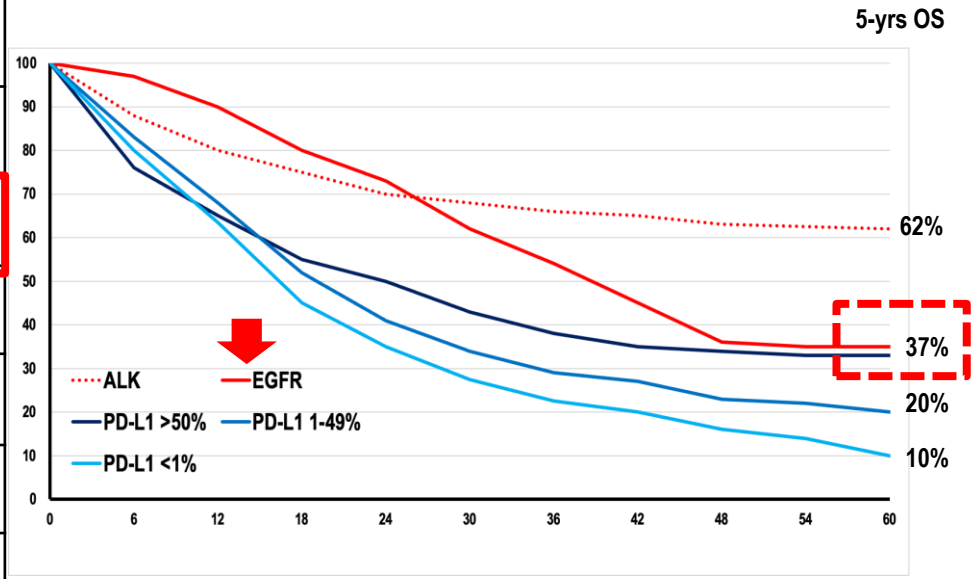
- Travels / Hospitality:
  - *Roche, Astra-Zeneca, BMS, MSD.*

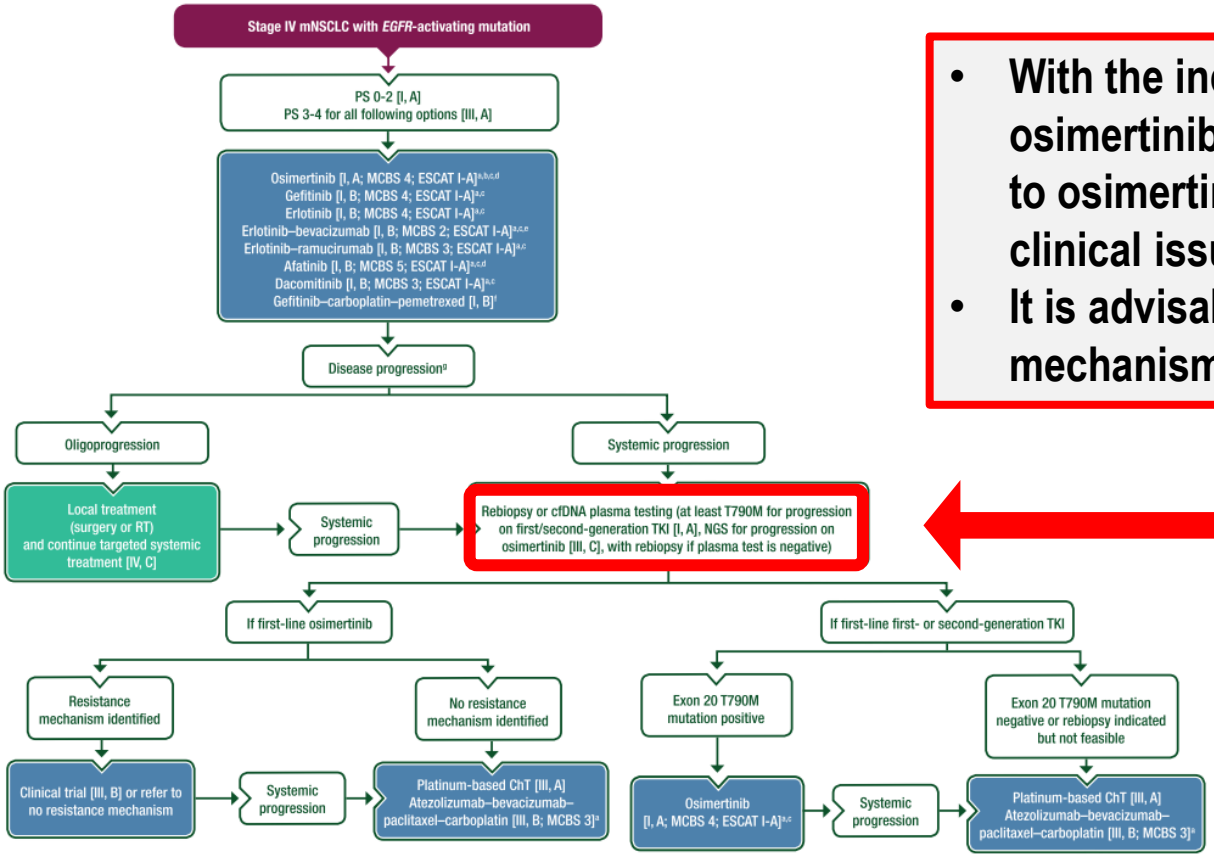
Advanced NSCLC: Estimated Prognostic Horizon(s) according to Biomarker and Current Best 'Matched' Treatment in RCTs*

Addiction	Biomarker	Current Options	Data Source	Median OS (months)	Estimated OS @5 yrs
YES	*ALK+*	*Alectinib* *Brigatinib*	Phase 3 Phase 3	*N.R.*	62%
YES	*ROS1+*	*Crizotinib* *Entrectinib*	Phase 1b Pooled Ph.1b	*48 mo.*	45%
YES	*EGFR+*	*Osimertinib*	Phase 3	*40 mo.*	35-40%
YES	*BRAF+*	*Dabrafenib + Trametinib*	Phase 2	*18-20 mo.*	22%
NO	*PD-L1 >50%*	*PEMBRO* *Atezolizumab* *Cemiplimab*	Phase 3 Phase 3 Phase 3	*24 mo.*	30-35%
NO	*PD-L1 1-49%*	*4 Chemo + PEMBRO* *2 Chemo + NIVO-IPI*	Phase 3 Phase 3	*19 mo.*	20%
NO	*PD-L1 <1%*	*4 Chemo + PEMBRO* *2 Chemo + NIVO-IPI*	Phase 3 Phase 3	*16 mo.*	10%



**** Pending Important Limitations/Variability with regard to Histology, Data Maturity and Follow-Up***

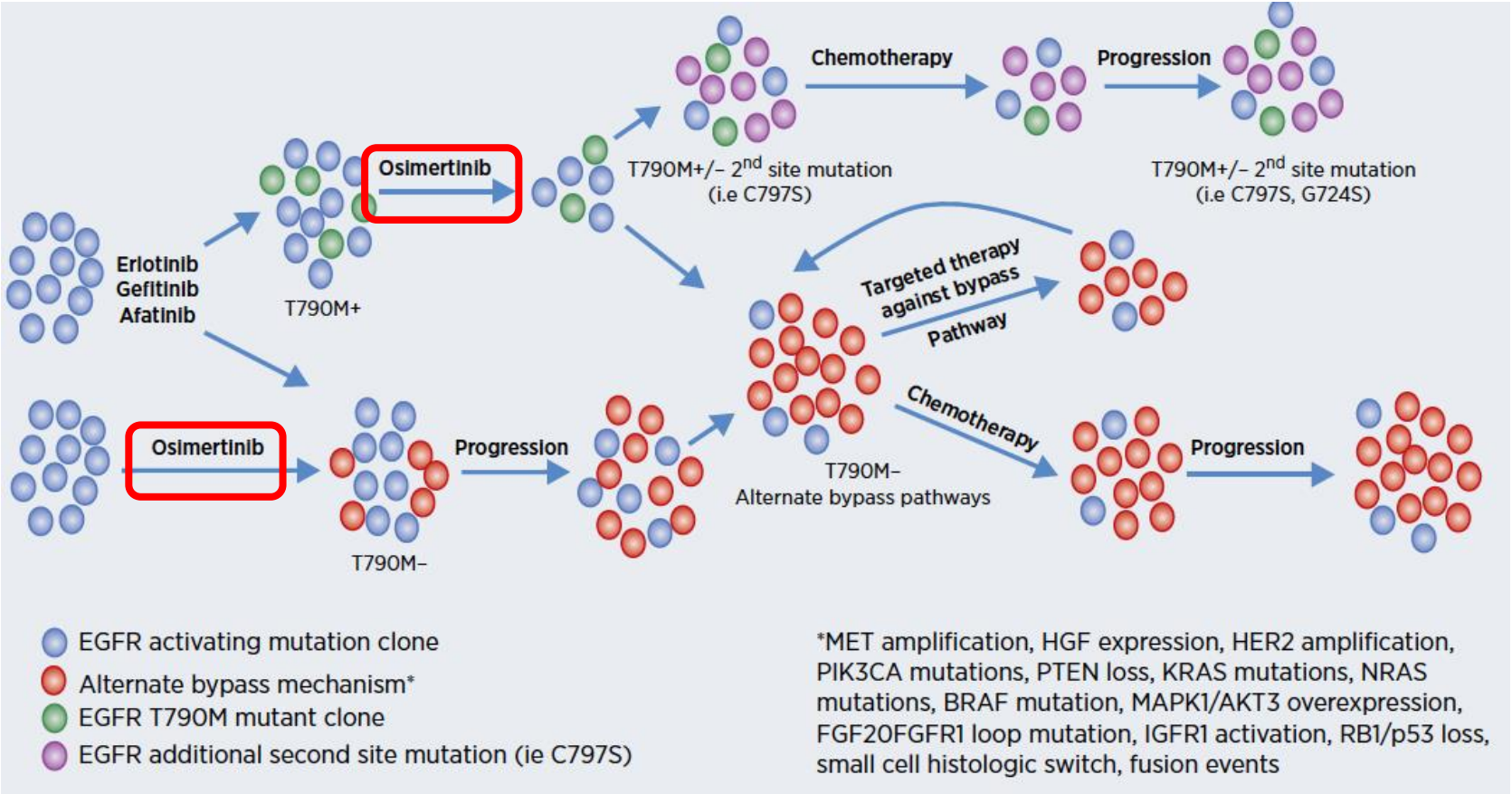
Testing Resistance Mechanisms



- **With the increasing use of first-line osimertinib, management of resistance to osimertinib has become a major clinical issue …**
- **It is advisable to test for resistance mechanisms when feasible.**

Oncogene-addicted metastatic NSCLC ESMO Clinical Practice Guideline 2023

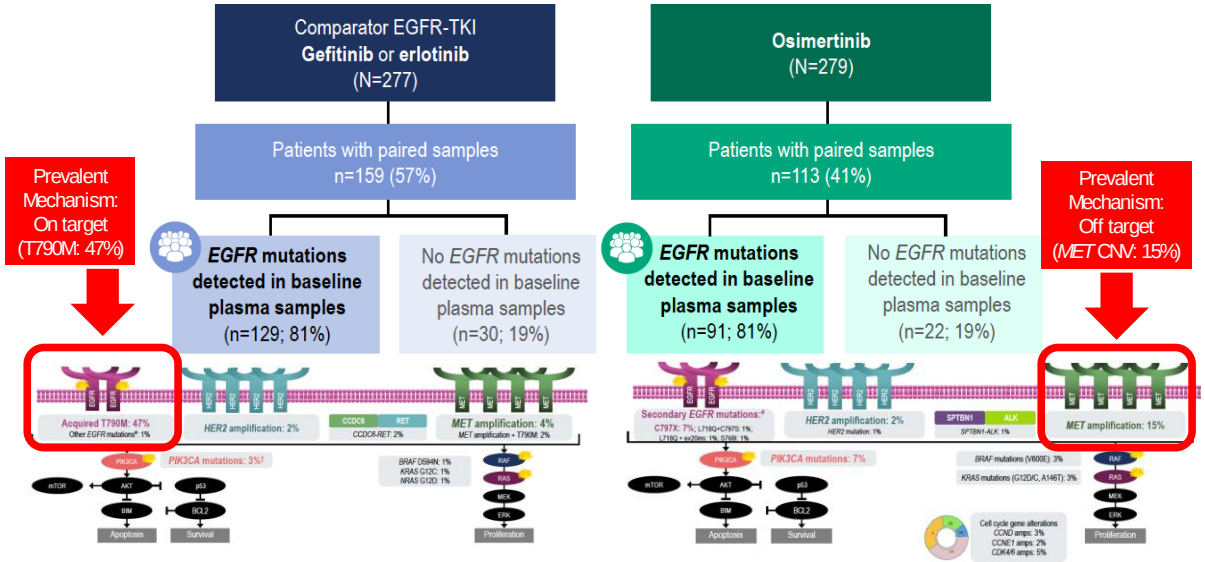
Clonal Evolution of *EGFR* Mutant NSCLC on Therapy

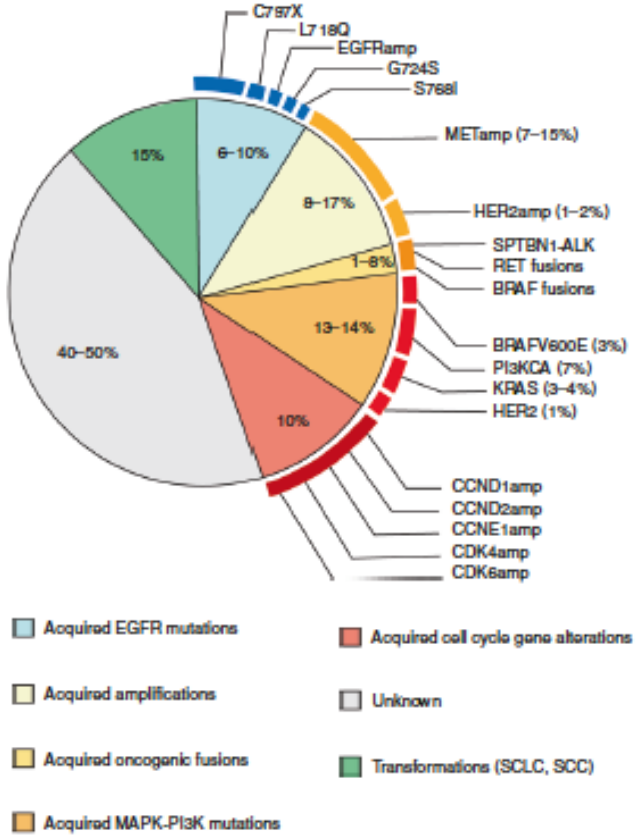


Murtuza et al, Cancer Res 2019

Resistance Mechanisms to First Line Osimertinib

FLAURA: Acquired alterations in GEF/ERL vs. OSI Arms



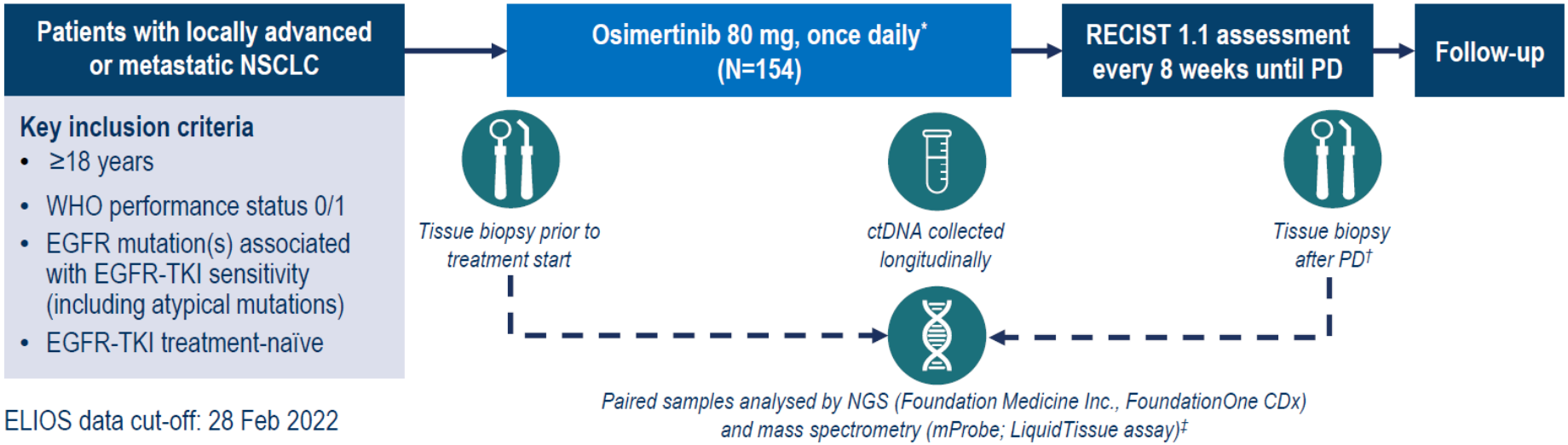


Ramalingham S et al, ESMO 2018

Leonetti et al, Br J Cancer 2019

Resistance Mechanisms to 1L Osimertinib: ELIOS

Phase 2 open-label, multicenter, single-arm trial to characterize resistance to 1L osimertinib
Primary endpoint: proportion of patients with a given tumour genetic and proteomic marker at PD



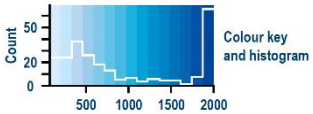
ELIOS data cut-off: 28 Feb 2022

- **Only 39% (46/115) of patients with PD on osimertinib provided an evaluable biopsy pair**
- **Most common failure: no biopsy (patient/anatomic factors), technical failure of NGS on either baseline or PD biopsy**

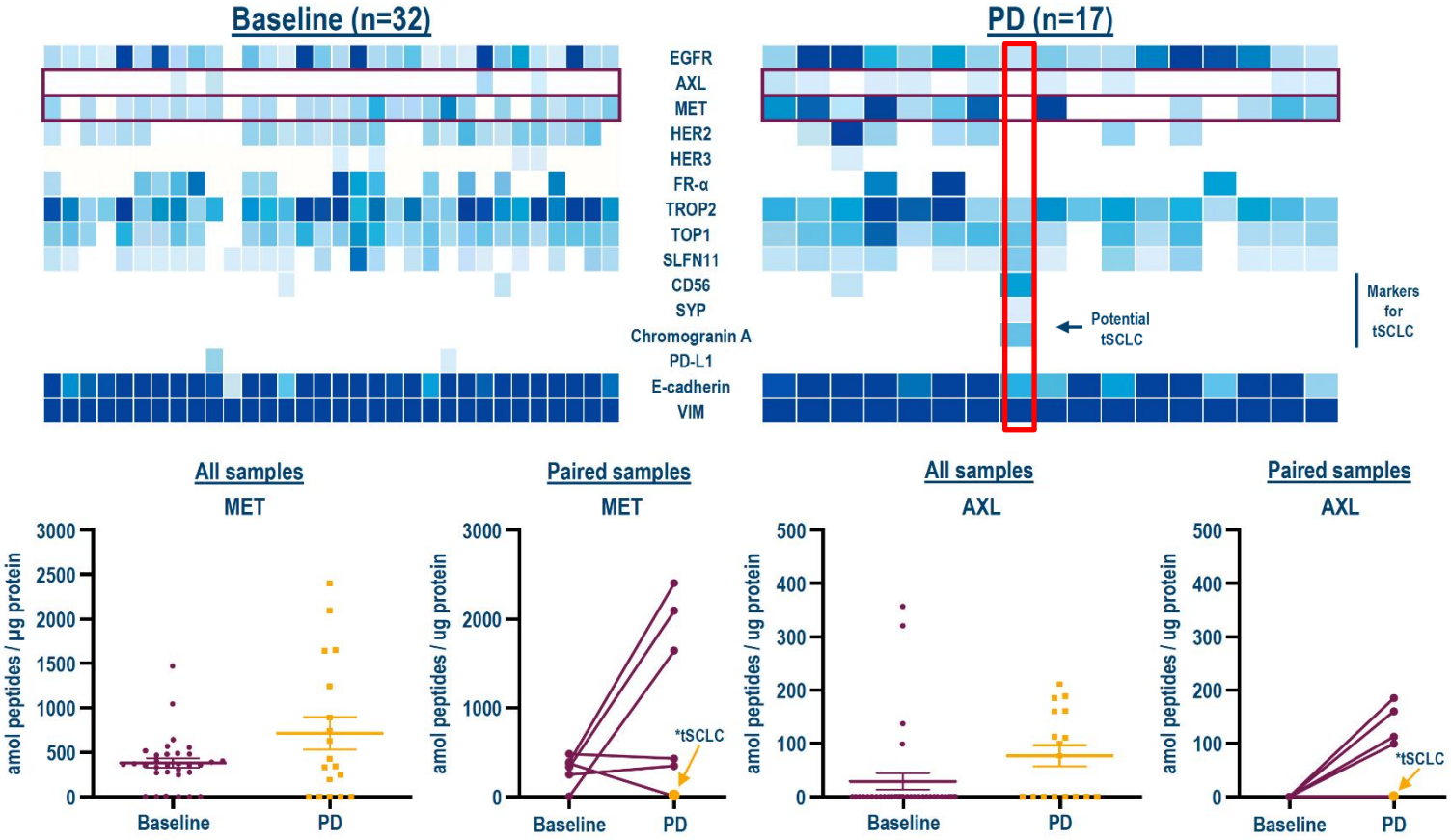
Piotrowska Z et al, ESMO 2022

ELIOS: Multicentre, Phase II, Molecular Profiling Study

Heatmap of protein expression based on mass spectrometry



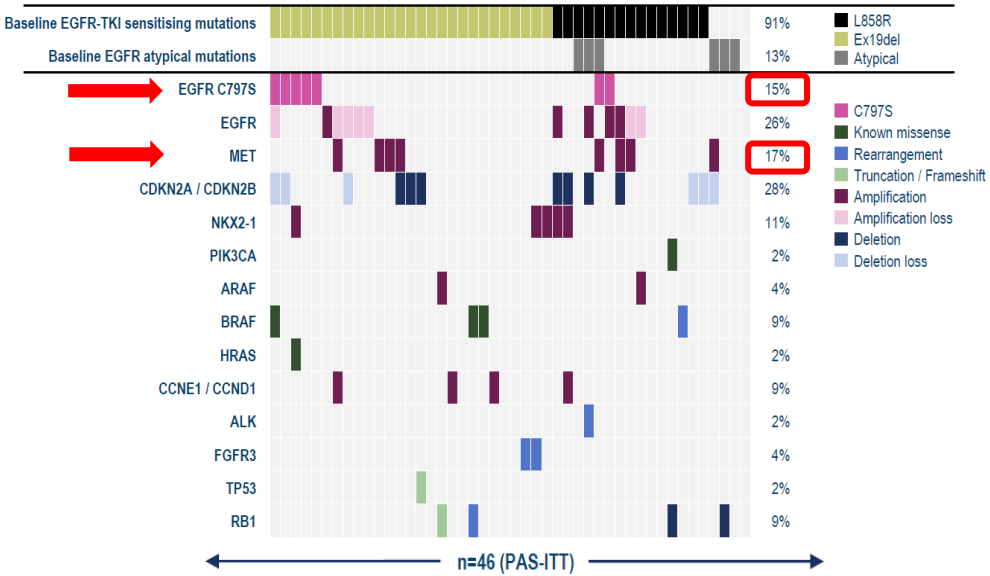
Upregulation of MET and AXL in a subset of PD tumours

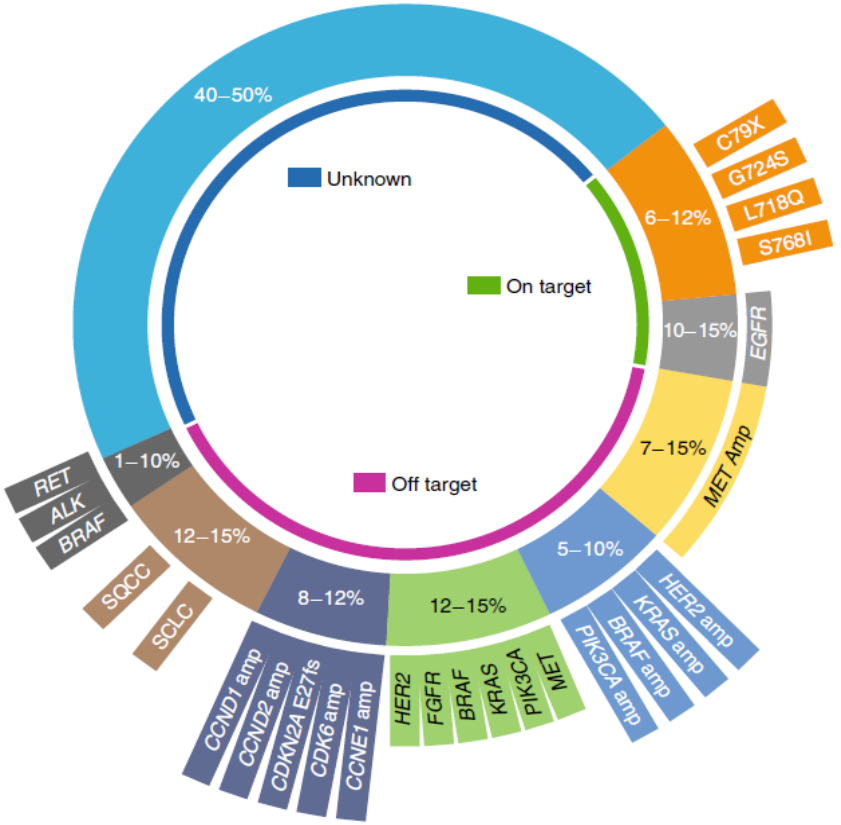


Piotrowska Z et al, ESMO 2022

Resistance Mechanisms to 1L Osimertinib

ELIOS study
N = 46 (PAS-ITT)



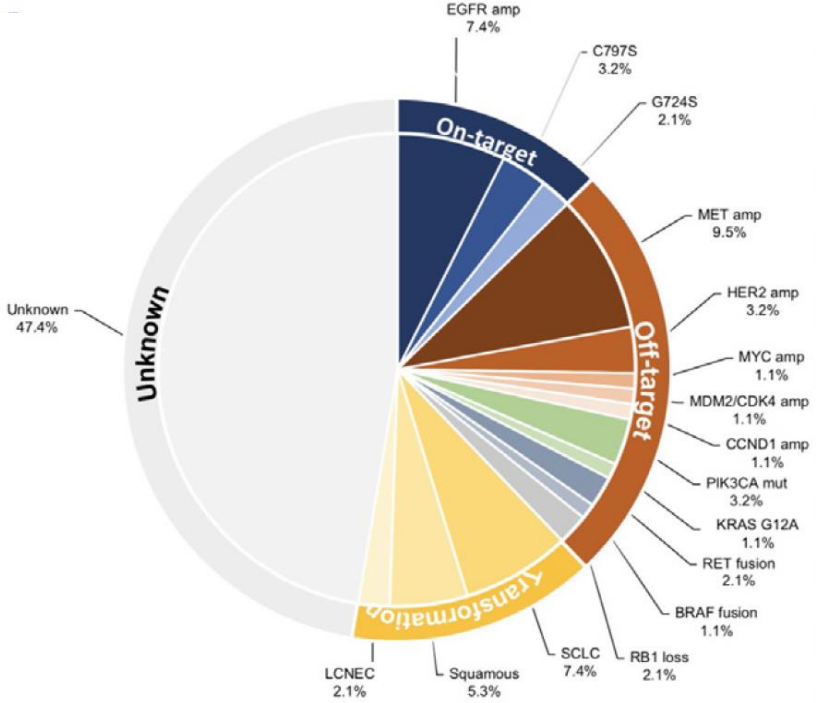


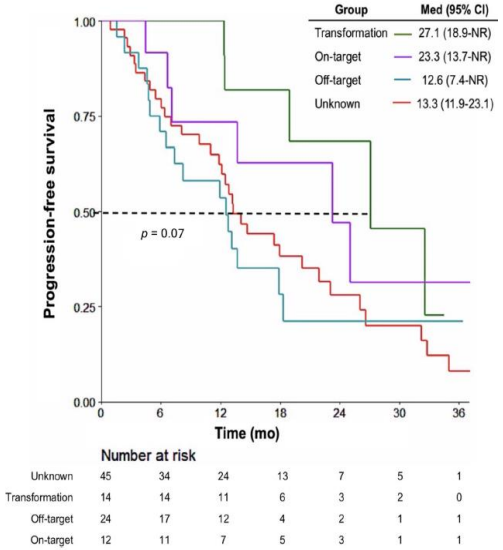
Piotrowska Z et al, ESMO 2022

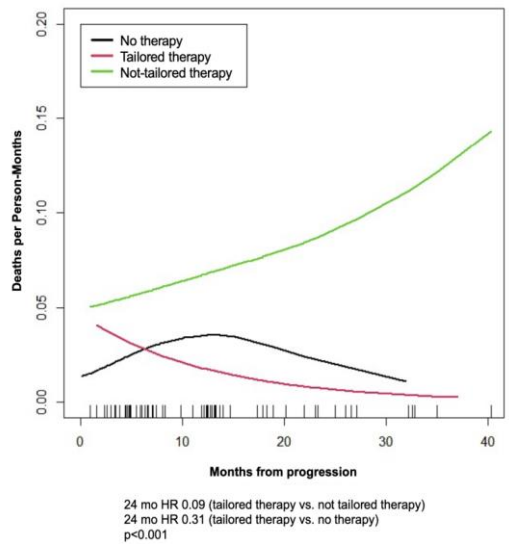
Passaro A et al, Nat Cancer 2021

Resistance Mechanisms to 1L Osimertinib: RWD

- Real-world cohort of patients with EGFR-mutant NSCLC treated with 1L osimertinib at MSKCC (n=327)
- N=95 patients with postprogression biopsies





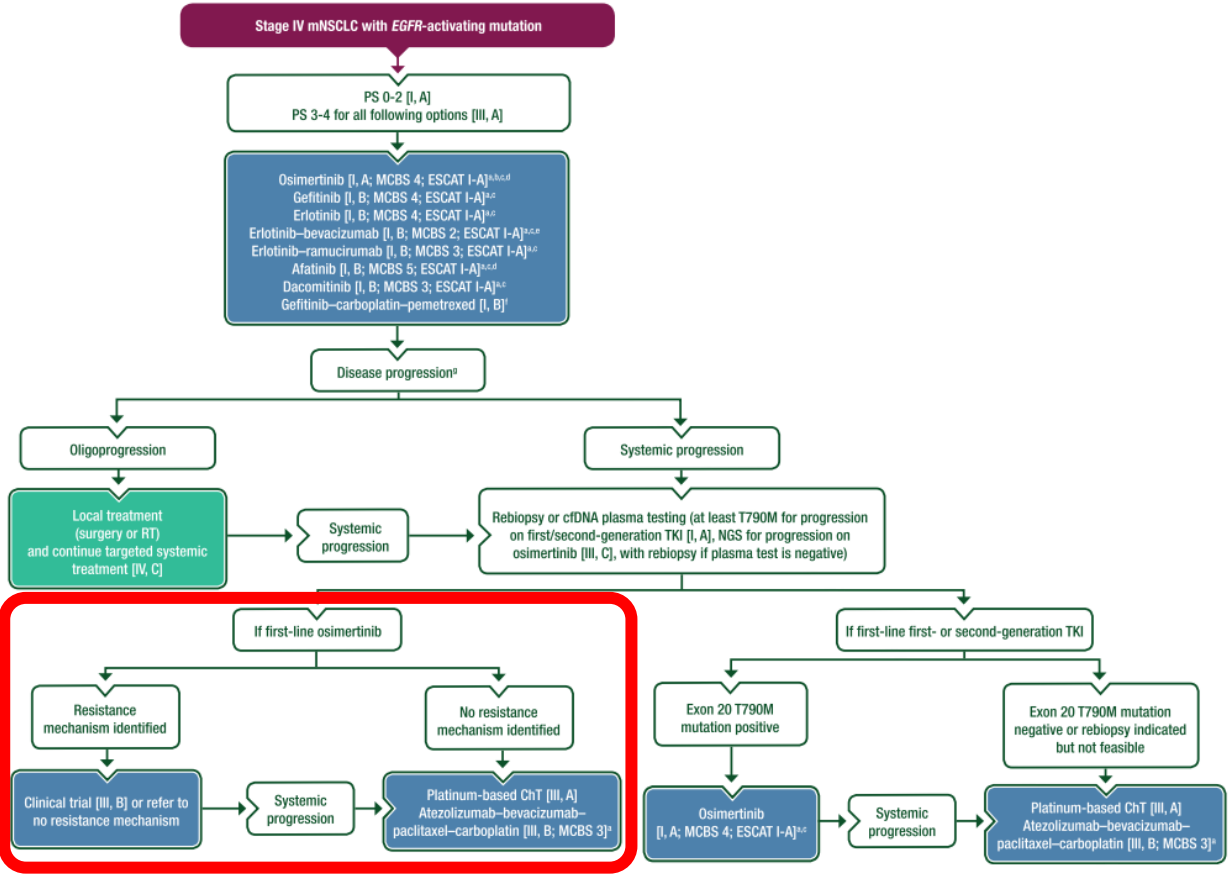


- Improved OS with treatment adaptation on the basis of identified mechanisms of resistance at PD using tissue-based genomic analysis

Choudhury NJ et al JTO 2023

Recommended Strategies at Progression

- **Preferably, patients progressing on osimertinib are enrolled in a clinical trial, if possible, standard treatment is platinum-doublet Chemotherapy**



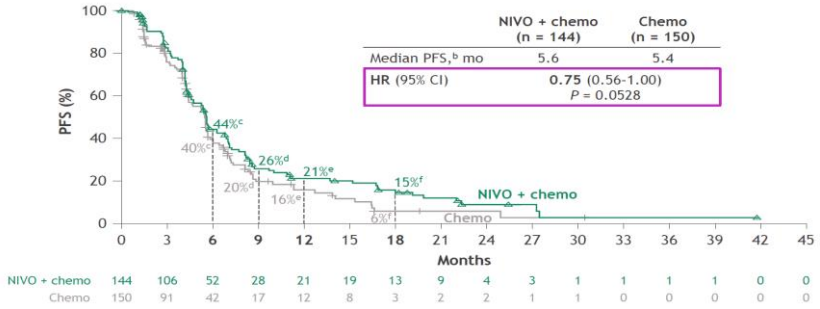
Oncogene-addicted metastatic NSCLC ESMO Clinical Practice Guideline 2023

Classical Chemotherapy-based Strategies

Platinum-doublet Chemo ✓

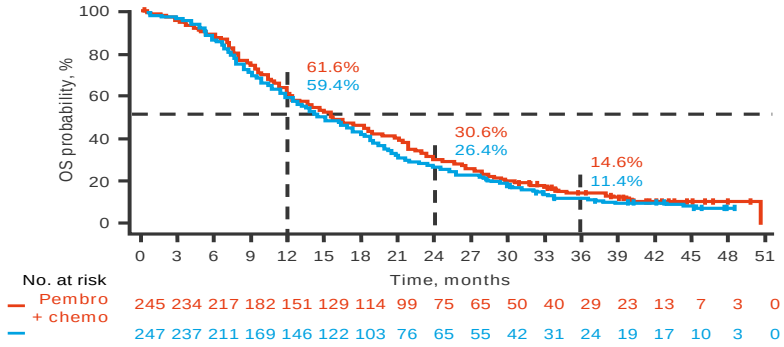
Platinum-doublet Chemo – I-O ✗ ➡

Checkmate-722: Chemo +/- Nivo in NSQ NSCLC



Mok T et al, ESMO-Asia 2022

Keynote-789: Platin-Pem +/- Pembro in NSQ NSCLC



Yang J et al, ASCO 2023

Classical Chemotherapy-based Strategies

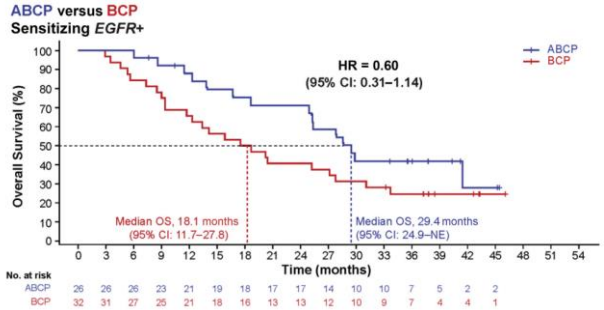
Platinum-doublet Chemo ✓

Platinum-doublet Chemo – I-O ✗

Platinum-doublet Chemo – I-O + Antiangiogenics ✓ →

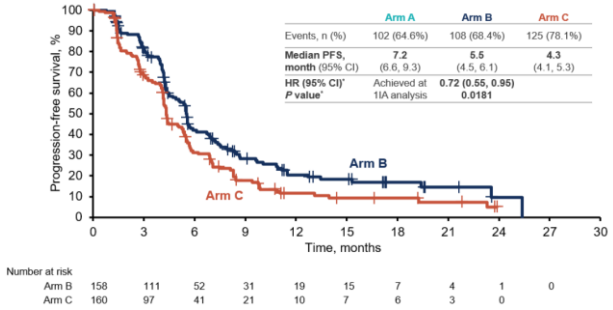
N.B.: Impower 151: as Im150 (50% EGFR+): Negative

IMPower-150: Carbo-Taxol-Beva +/- Atezo in NSQ NSCLC



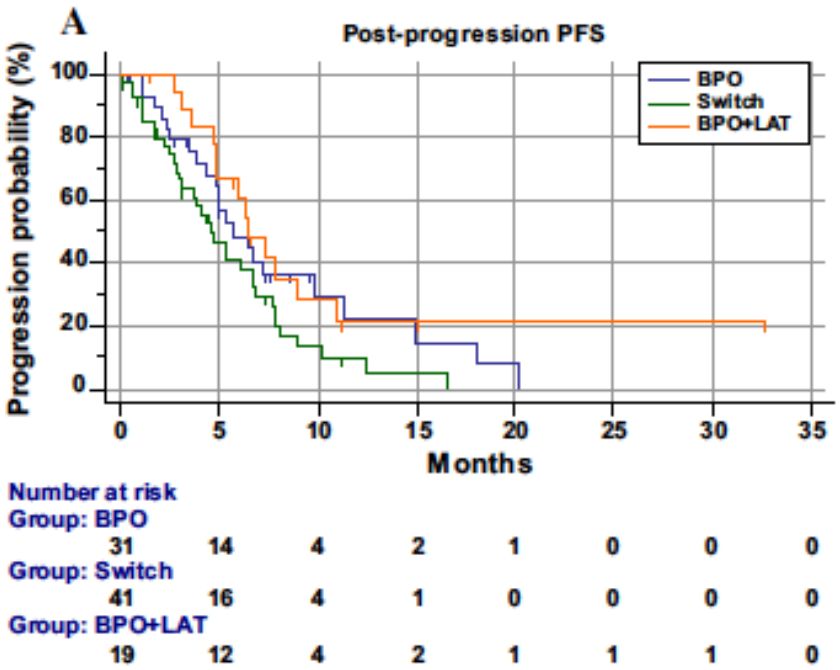
Nogami N et al JTO 2022

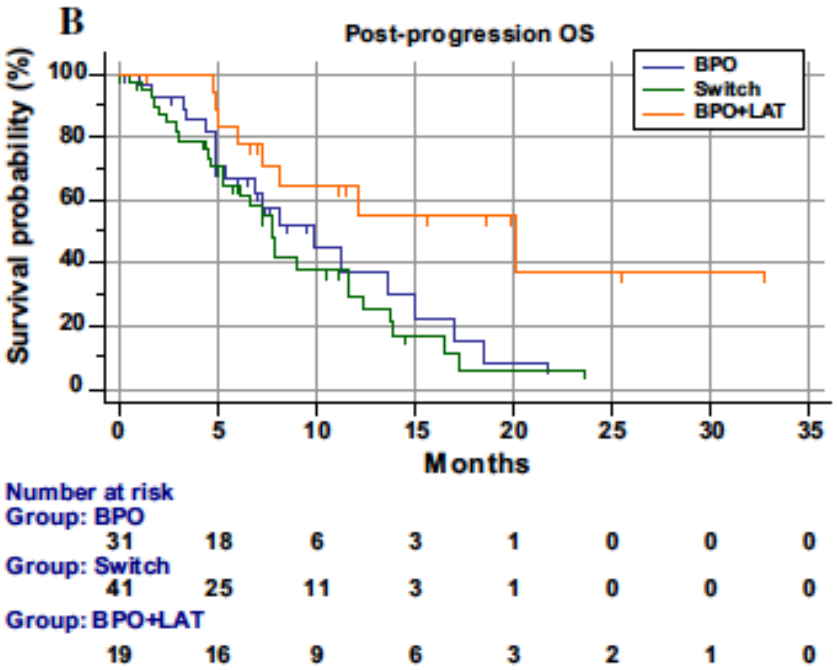
ORIENT-31: Platinum-Pem + / - Sintilimab + / - IBI305



Lu S et al, Lancet Respir Med 2023

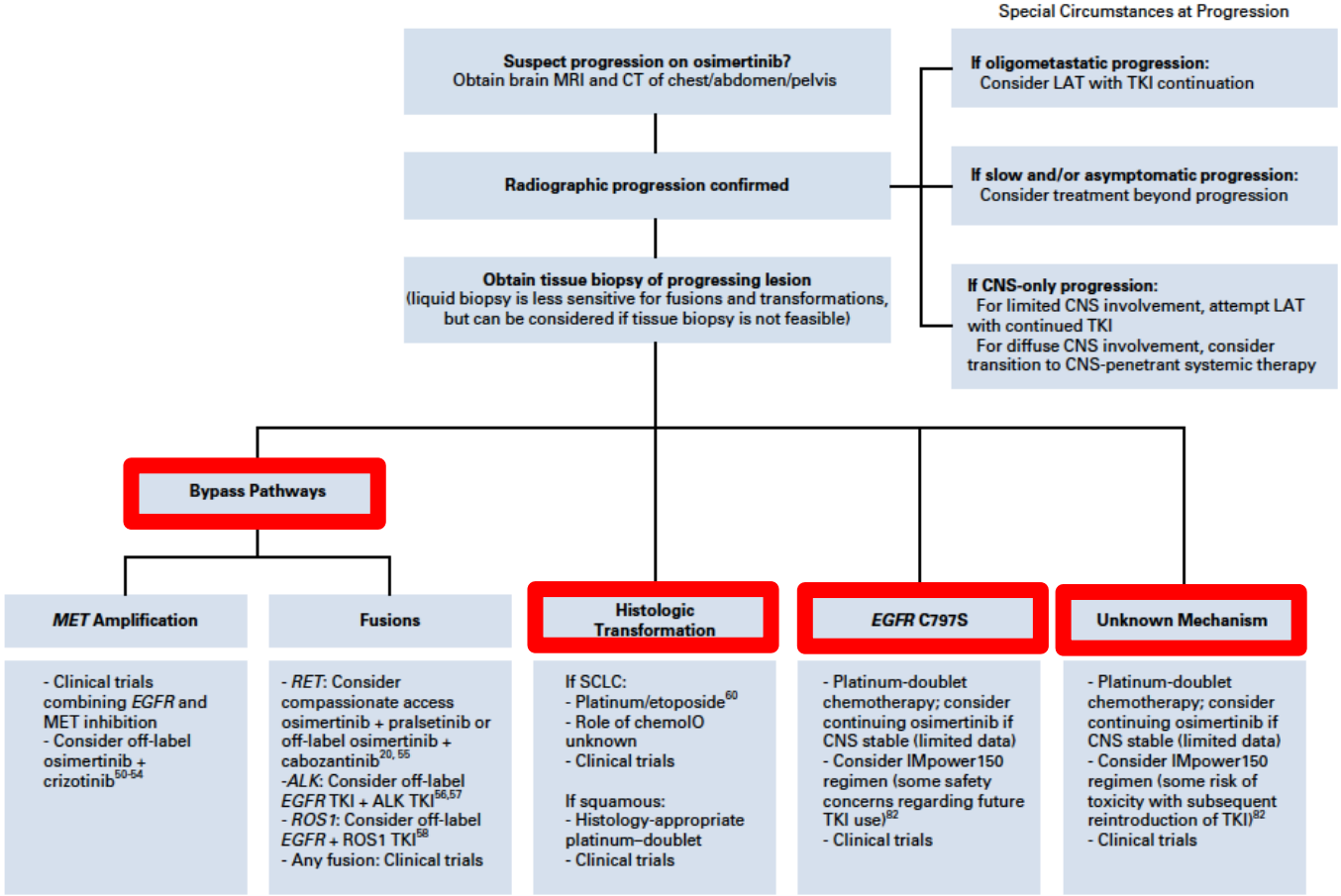
Is There a role for Osimertinib beyond Progression? RWD





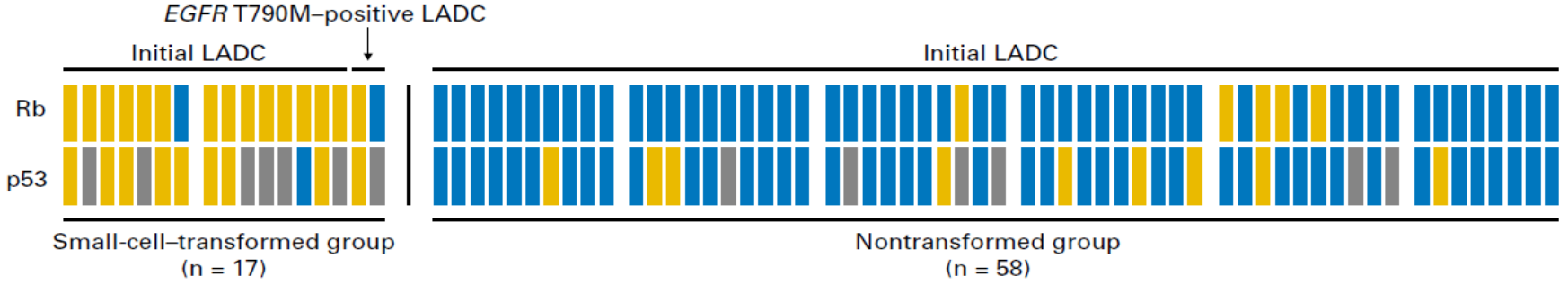
Cortellini A et al, Clin Transl Oncol 2019

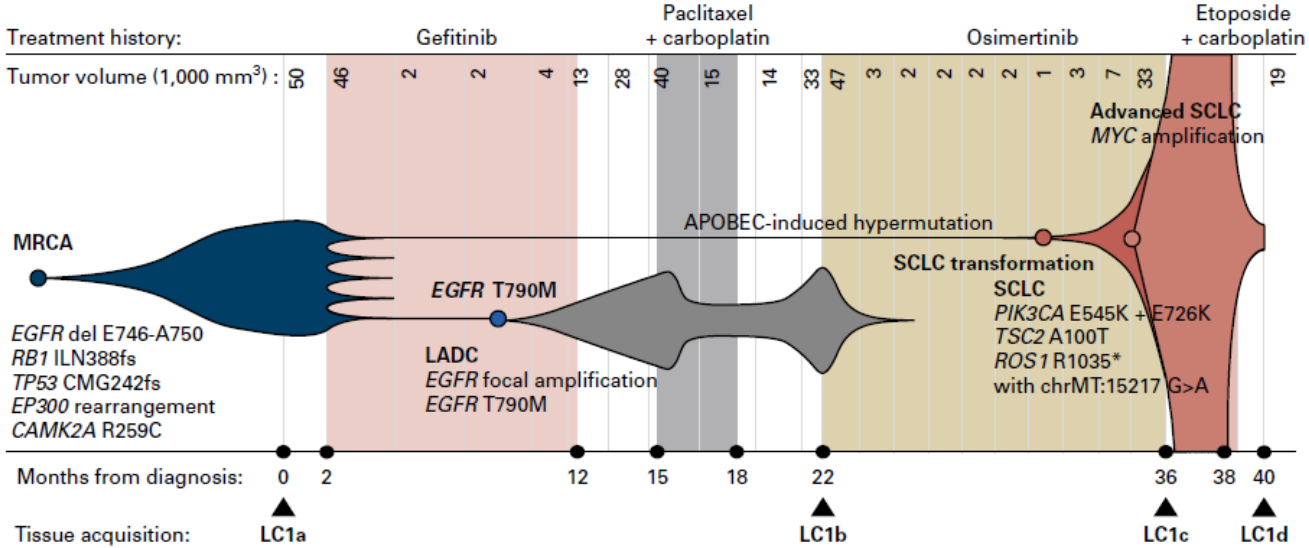
Management of *EGFR*-mutant NSCLC progressing on Osimertinib



Piper-Vallillo AJ et al, J Clin Oncol 2020

Clonal History/Genomic Predictors of SCLC Switch in *EGFR*-driven NSCLC

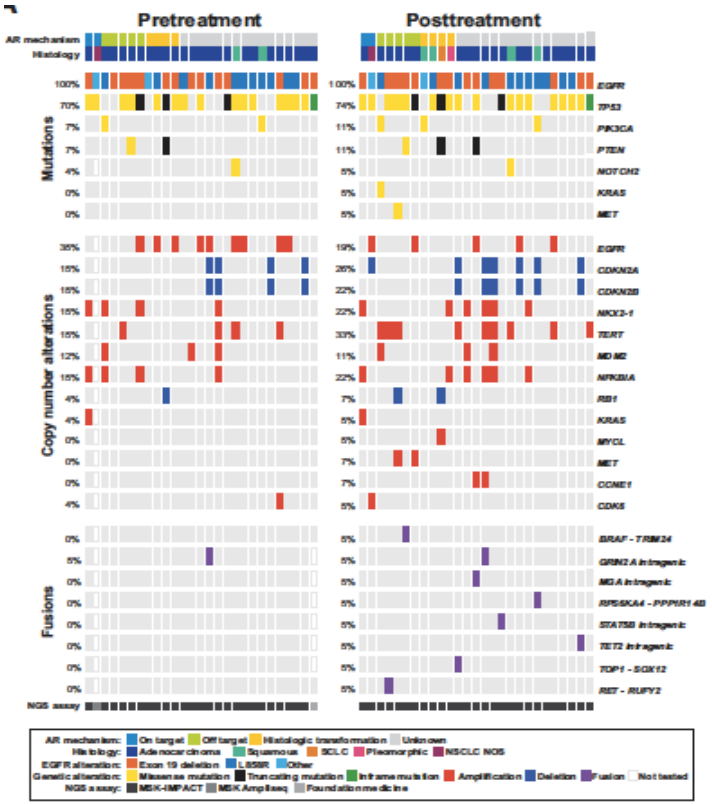


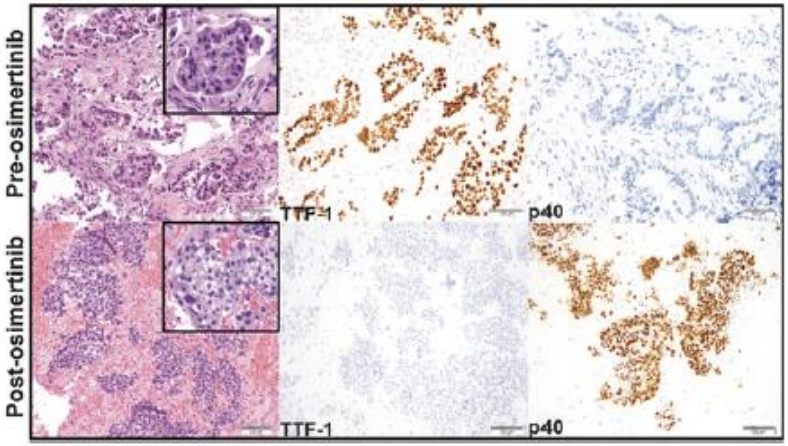


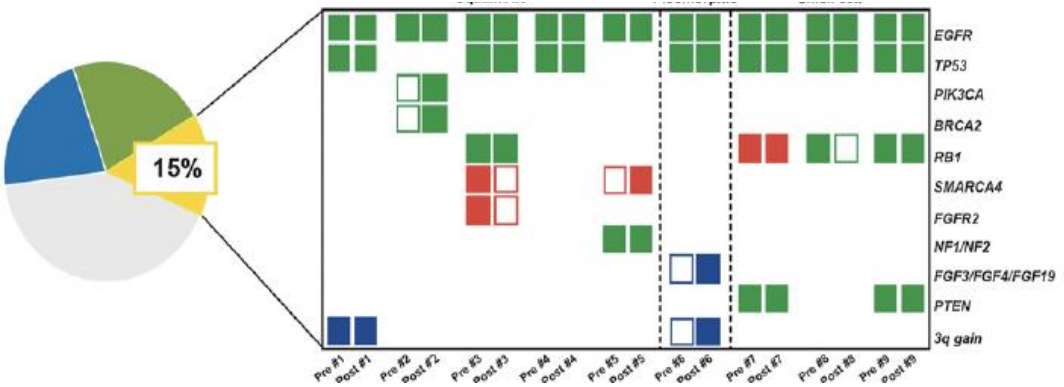
- **SCLC Switch:**
  - **5-10% of EGFR+ NSCLC**
- **EGFR+ NSCLC with pre-treatment RB1/TP53 alterations**
  - **43X risk of SCLC Switch**

Lee JK et al, J Clin Oncol 2017

Squamous Histology Shift After Osimertinib



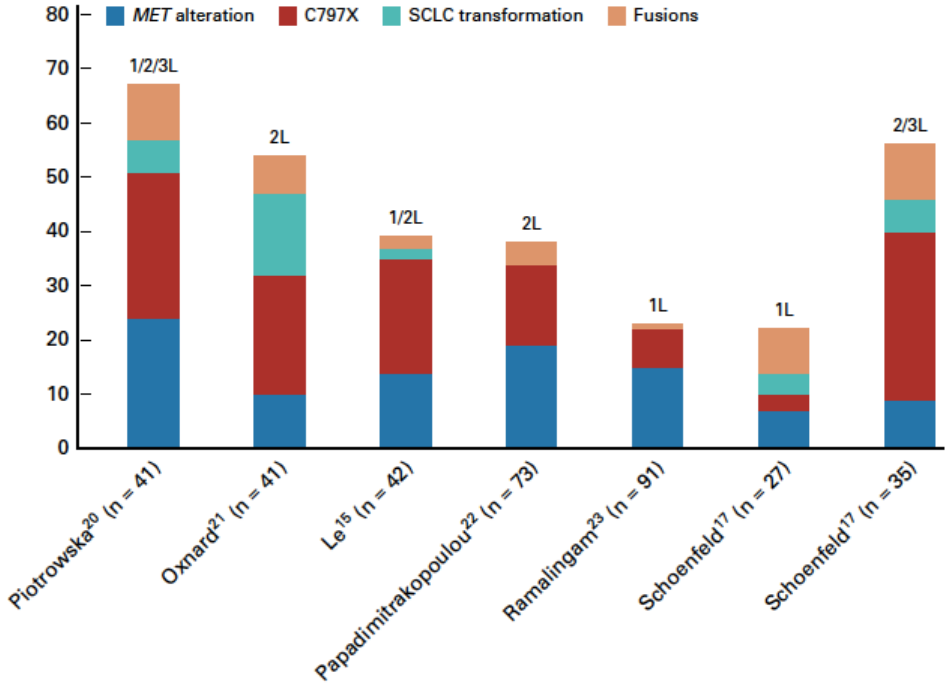




Schoenfeld AJ et al, Clin Cancer Res 2020

Mechanisms of Resistance to Osimertinib

The 4 Most Common Mechanisms of Resistance (% of pts)



Mechanisms of Resistance according to Setting/Line

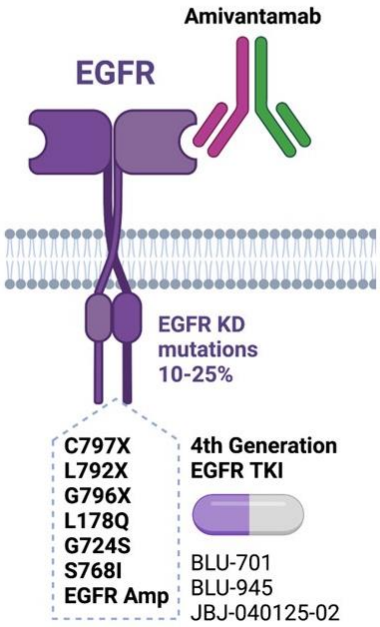
	FLAURA	AURA3	Le *et al.*	Piotrowska *et al.*
N	91	83	42	41
% T790M loss	(N/A)	49	50	63
Acquired changes (%)				
EGFR mut	9	17	26	24
MET amp	15	19	15	19
HER2 amp	2	5	2	5
PIK3CA mut	7	1	5	12
BRAF mut	3	3		
KRAS mut	3		2	
Fusions	1	3	5	10
SCLC/SqCC			5	7
Other	60	52	40	23

Piper-Vallillo AJ et al, J Clin Oncol 2020

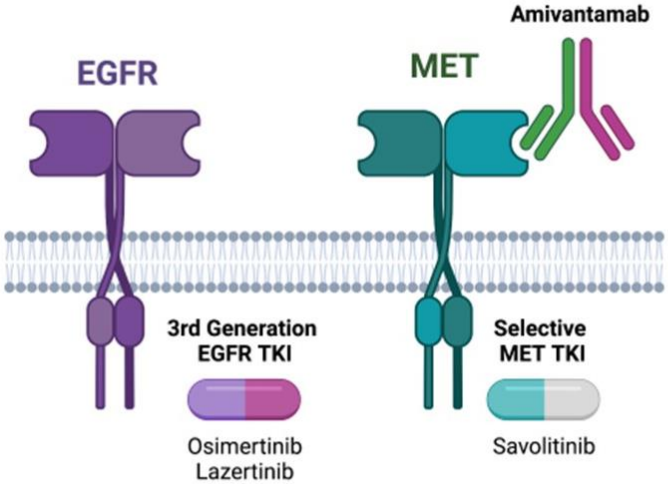
Rudin C, Discussant at ESMO 2018

Investigational Treatment Strategies to Overcome Resistance

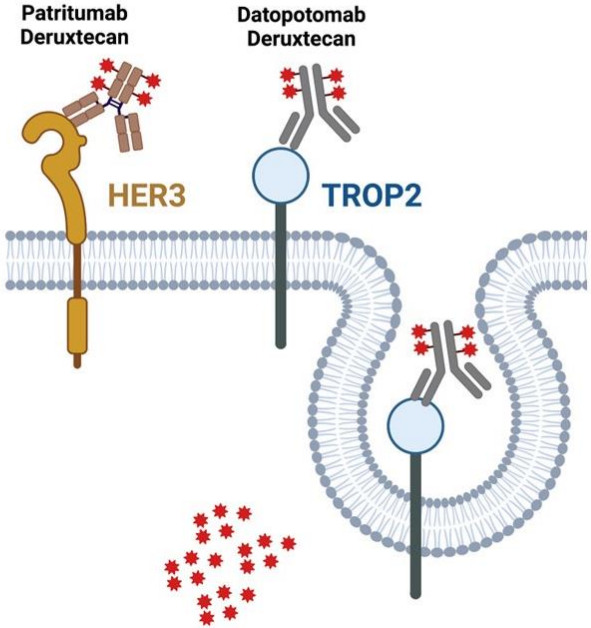
On-Target resistance



Bypass resistance



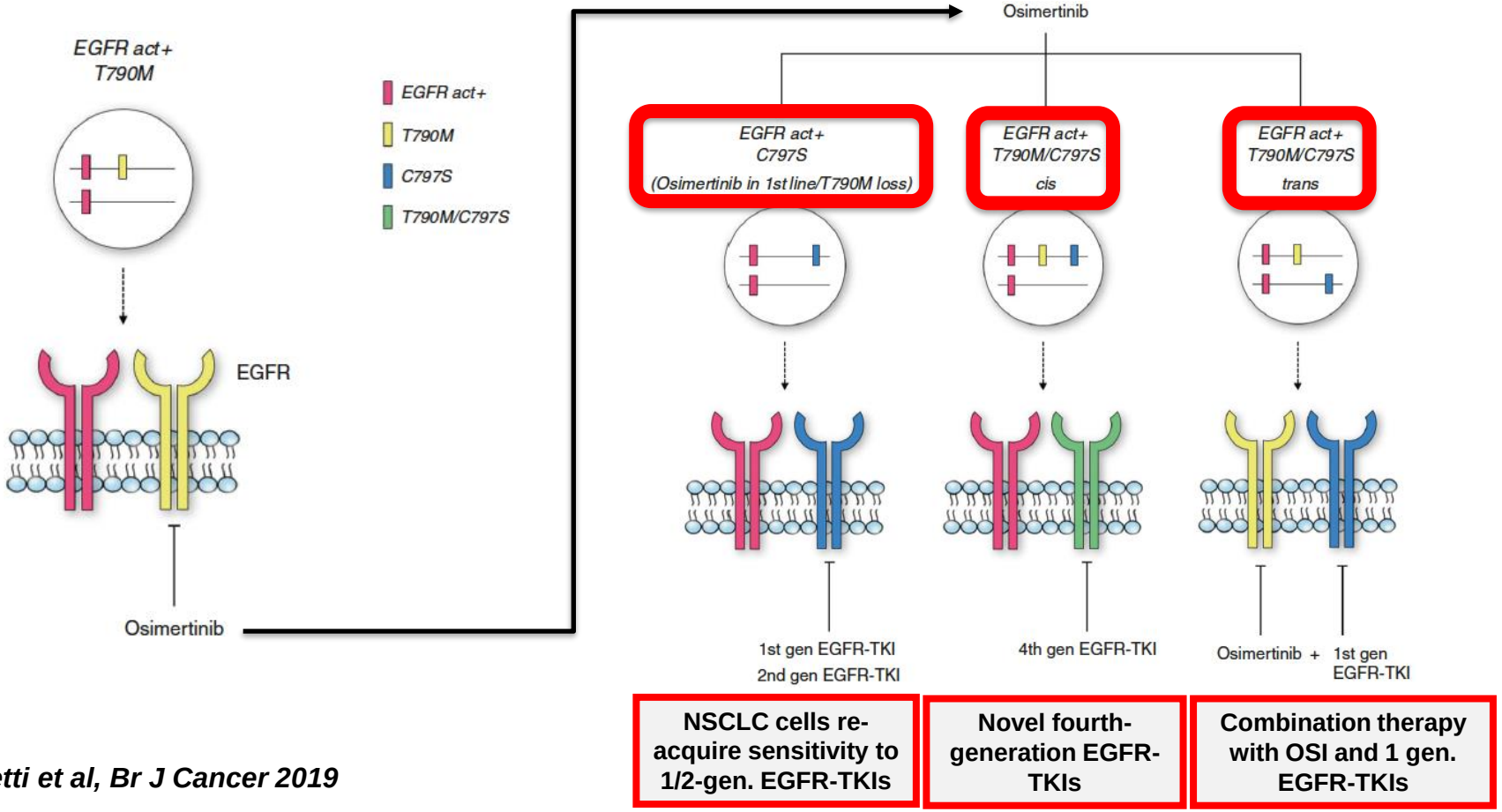
Delivering Targeted Chemotherapy - ADCs



BC Cho et al. Presnted at ASCO 2021, L. Sequist et al. Lancet Oncology 2020, P. Janne et al Presented at ASCO 2021, EB Garon et al. Presented at ESMO 2021

Modified from Recondo G, ASCO 2022

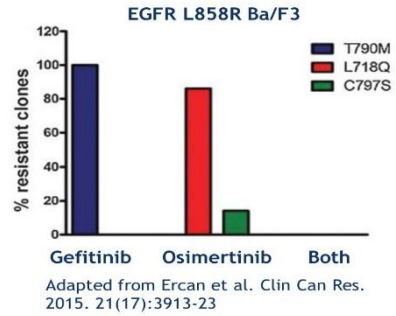
Treatment Opportunities for *EGFR*-driven Resistance to OSI



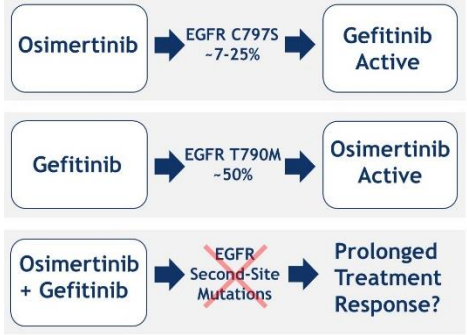
Leonetti et al, Br J Cancer 2019

Combo OSI + GEF: Phase I/II – NCT03122717

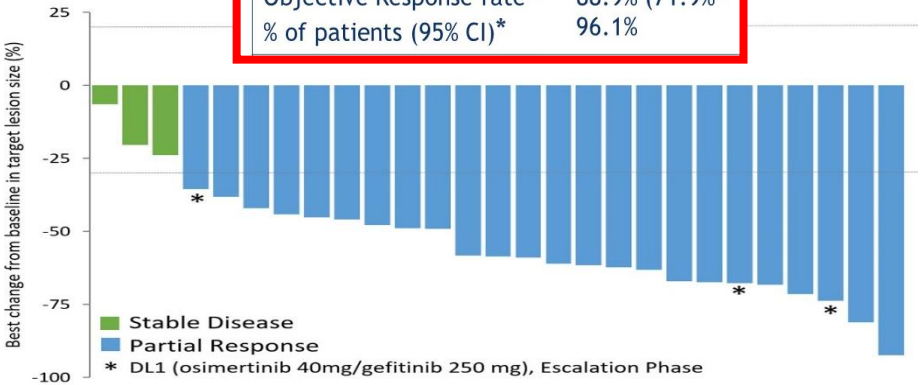
Preclinical Models: Combo prevents acquired secondo-site EGFR resistance mutations



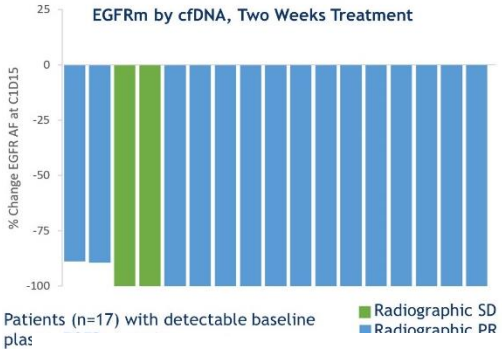
Adapted from Ercan et al. Clin Can Res. 2015. 21(17):3913-23

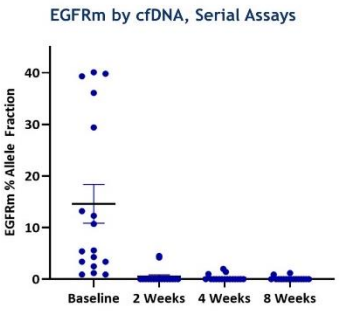


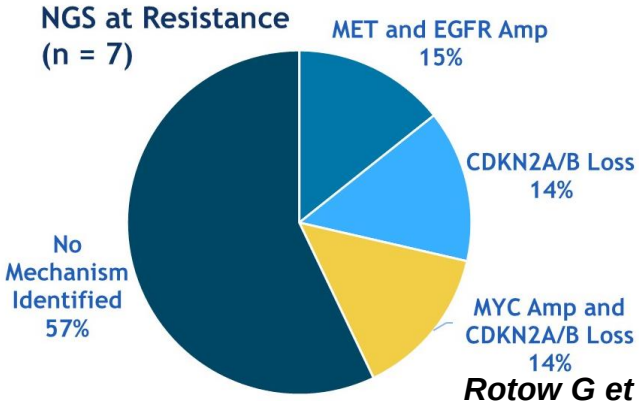
Objective Response rate - % of patients (95% CI)* 88.9% (71.9% - 96.1%)



Patients' Subgroup with EGFR mutations detectable in blood with retest







Rotow G et al, ASCO 2020

Selected Investigational Treatment Strategies

Resistance mechanism	Clinical trial	Intervention(s)	Phase
EGFR C797S	ORCHARD	Osimertinib + gefitinib	2
	SYMPHONY	BLU-945 +/- osimertinib	1/2
	HARMONY	BLU-701 +/- osimertinib (or ChT)	1/2
	NCT04820023	BBT-176	1/2
	NCT05256290	BDTX-1535	1
	NCT05394831	JIN-A02	1/2
MET amplification	SAFFRON	Osimertinib + savolitinib vs ChT	3
	SAVANNAH	Savoltinib +/- osimertinib	2
	INSIGHT2	Tepotinib +(/-) osimertinib	2
ALK fusion	ORCHARD	Osimertinib + alectinib	2
RET fusion	ORCHARD	Osimertinib + selpercatinib	2
BRAF fusion/mutations	ORCHARD	Osimertinib + selumetinib	2
SCLC transformation	ORCHARD	Platinum + etoposide + durvalumab	2
NA	ORCHARD	Platinum + pem + durvalumab / others	2
	COMPEL	ChT + / - osimertinib	3
	HERTHENA-Lung02	Patritumab deruxtecan vs ChT	3
	TROPION-Lung05	Datopotamab deruxtecan	2
	PALOMA-3	Amivantamab + lazertinib	3
	CHRYSALIS-2	Amivantamab + / - lazertinib	1
	MARIPOSA-2	ChT + / - amivantamab + lazertinib	3

Modified from Piotrowska Z, ELCC 2023

Courtesy of Pilotto S

EGFR + *MET* Co-targeting (for Acquired *MET* Ampl.)

	Drugs	Patient population	MET selection	Efficacy	Toxicity	
INSIGHT2	**Osimertinib + Tepotinib**	s/p 1L osimertinib Stable treated CNS dx	MET FISH MET NGS	ORR 54.5% ORR 50%	Any grade/grade ≥3 One patient grade 5 pneumonitis	Diarrhea 31/0% Edema 24/4% Paronychia 17/1% Nausea 14/0%
SAVANNAH	**Osimertinib + Savolitinib** ★	Prior 3rd gen EGFR TKI	MET FISH MET IHC NET NGS	ORR 49% (high MET) mPFS 7.6mo DoR 9.3mo	Any grade/grade ≥3 4% hypersensitivity reaction with savolitinib	Nausea 49/3% Anorexia 34/4% Fatigue 35/4% Edema 32/2% Diarrhea 28/3%
	Osimertinib + Teliso-V	Prior osimertinib L858R/Exon19del 57% 3+ prior lines 86% prior chemo	MET IHC 43% high 57% intermed	58% 50% 63%	Grade ≥3 TEAE Anemia 12% Pulmonary embolism 12%	Any grade Neuropathy 36% Edema 24% Anemia 20% Fatigue 20% Nausea 20%

★ **SAFFRON (ph III) ongoing [osi + savolitinib vs ChT]**

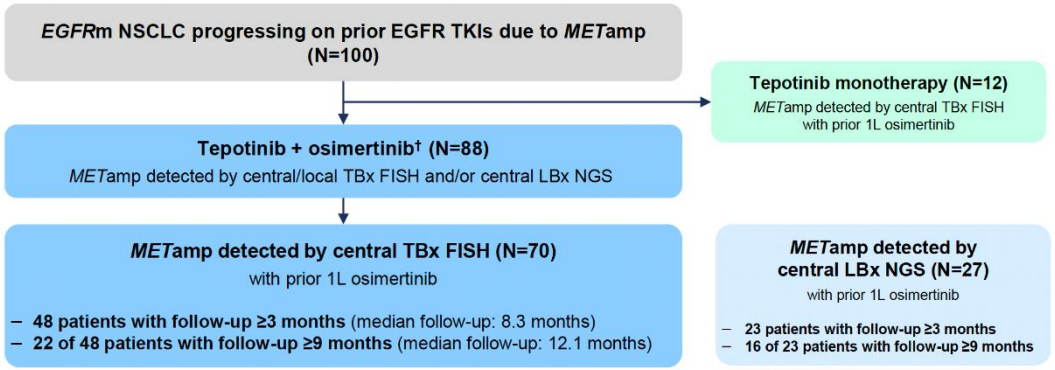
- **Multiple studies have established MET amp as a clear driver of resistance to EGFR TKIs and**
- **MET + EGFR inhibition as a valid therapeutic strategy**

Mazieres J et al, ESMO 2022; Myung Ju A et al, WCLC 2022; Goldman JW et al, ASCO 2022

INSIGHT 2: Multicentre, Phase IIR, Open-Label, After OSI 1L

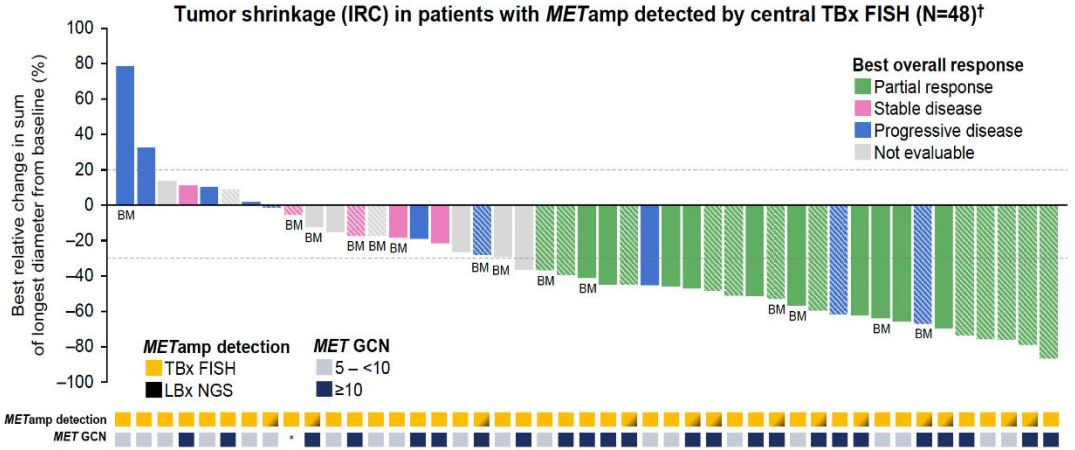
Key inclusion criteria

- Locally advanced or metastatic NSCLC with activating *EGFR* mutation
- Acquired resistance to 1L osimertinib
- *MET*amp detected by either central or local* FISH testing (TBx) or central NGS testing (LBx)†
- ECOG PS of 0 or 1
- Stable, treated brain metastases allowed



Tepotinib plus osimertinib (IRC)

	*MET*amp by central TBx FISH		*MET*amp by central LBx NGS	
Follow-up	≥9 months (N=22)	≥3 months (N=48)	≥9 months (N=16)	≥3 months (N=23)
ORR (95% CI)	**54.5%** (32.2, 75.6)	**45.8%** (31.4, 60.8)	**50.0%** (24.7, 75.3)	**56.5%** (34.5, 76.8)
BOR, n (%)				
PR	12 (54.5)	22 (45.8)	8 (50.0)	13 (56.5)
SD	2 (9.1)	5 (10.4)	1 (6.3)	1 (4.3)
PD	4 (18.2)	10 (20.8)	5 (31.3)	5 (21.7)
NE	4 (18.2)	11 (22.9)*	2 (12.5)	4 (17.4)



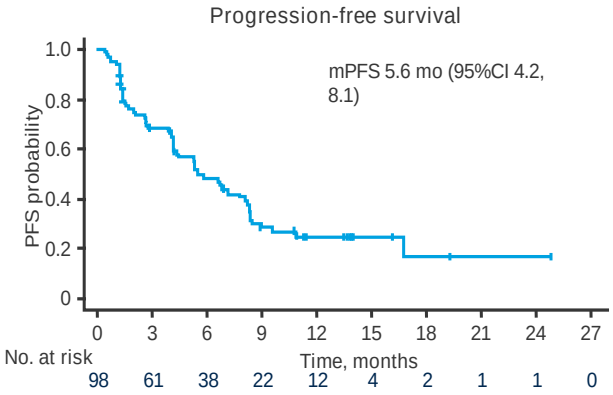
Mazieres J et al, ESMO 2022

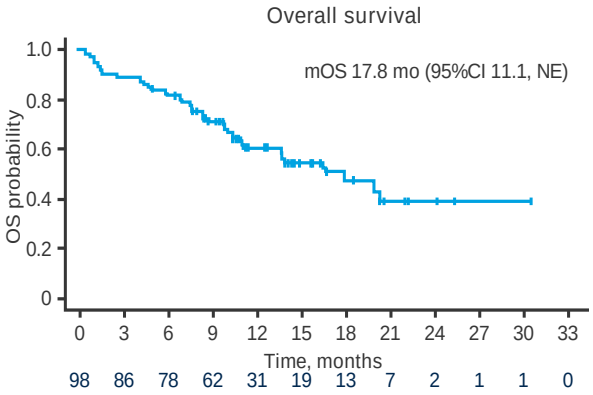
INSIGHT 2: Multicentre, Phase IIR, Open-Label, After OSI 1L

Response	Tepotinib + osimertinib (n=128)
ORR, % (95%CI)	50.0 (39.7, 60.3)
BOR, n (%)	
PR	49 (50.0)
SD	13 (13.3)
PD	23 (23.5)
NE	13 (13.3)
mDoR, mo (95%CI)	8.5 (6.1, NE)

Intracranial responses	TBx FISH (n=24)
ORR, % (95%CI)	29.2 (12.6, 51.1)
BOR, n (%)	
CR	6 (25.0)
PR	1 (4.2)
SD	12 (50.0)
PD	2 (8.3)
NE	3 (12.5)
DCR, % (95%CI)	79.2 (57.8, 92.9)
mDoR, mo (95%CI)	NE (3.6, NE)
mPFS, mo (95%CI)	7.8 (3.9, NE)

Grade ≥3 AEs, n (%)	Tepotinib + osimertinib (n=128)
Any	44 (34.4)
Peripheral edema	6 (4.7)
Appetite decreased	5 (3.9)
Nausea	3 (2.3)
Lipase increased	3 (2.3)
Anemia	2 (1.6)
ALT increased	2 (1.6)
Diarrhea	1 (0.8)
Paronychia	1 (0.8)
Hypoalbuminemia	1 (0.8)
Vomiting	1 (0.8)

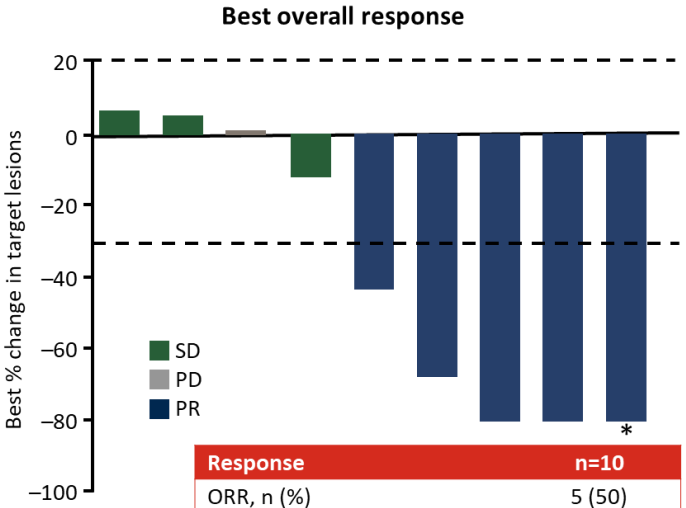




Kim TM J et al, WCLC 2023

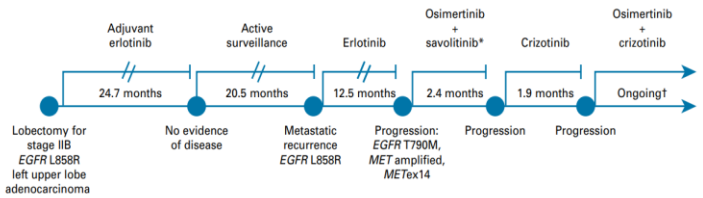
Targeting Bypass Resistance Mechanisms

Osimertinib + Selpercatinib [RET fusion]

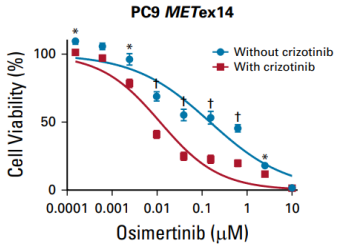


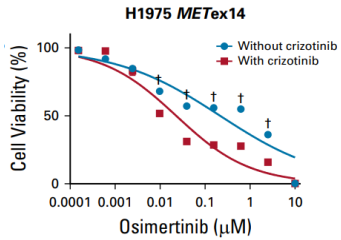
Response	n=10
ORR, n (%)	5 (50)
PR*	5 (50)
SD	3 (30)
PD	2 (20)
DCR, n (%)	8 (80)
Median depth of response, n	-43

Osimertinib + Crizotinib [METex14]



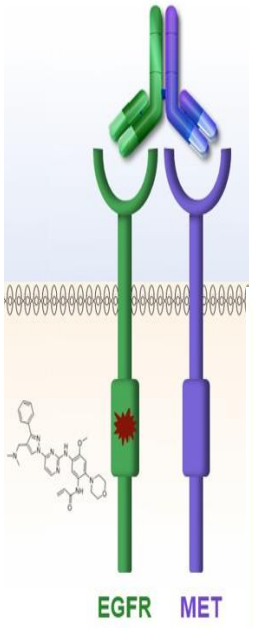
	Timing of test	Type of test	Sample	Result
Molecular testing	Diagnosis stage IIB	Hotspot genotyping (a)	Tumor	*EGFR* L858R detected
	Metastatic recurrence	Digital PCR (b)	Tumor	*EGFR* T790M negative
		NGS by MSK-IMPACT (c)	Tumor	*EGFR* L858R
	Progression during erlotinib treatment	Digital PCR (b)	cfDNA	*EGFR* T790M positive
		Digital PCR (b)	Tumor	*EGFR* T790M negative
		NGS by MSK-IMPACT (c)	Tumor	*EGFR* L858R with amplification (FC, 3.8); *MET* exon 14 splicing variant (c.2888-1G>A) with amplification (FC, 2.5)
		FISH (d)	Tumor	*MET* amplification





Rotow et al, WCLC 2021; Suzawa K et al, JCO Precision Oncol 2019

Amivantamab + Lazertinib

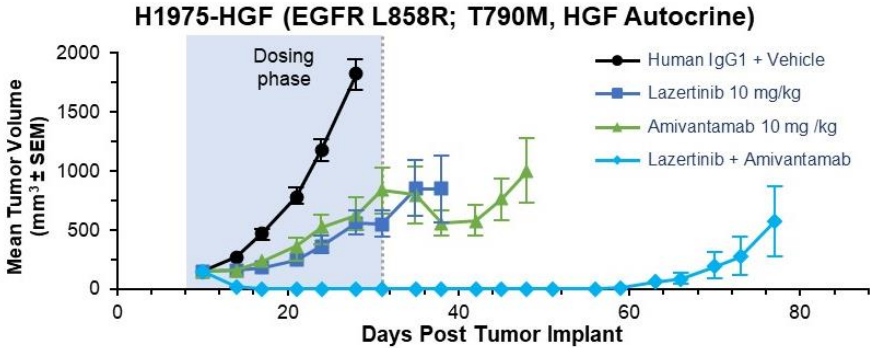


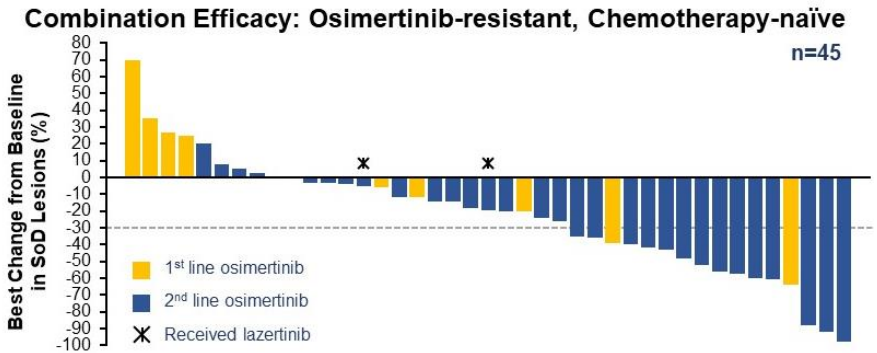
Amivantamab (am-e-van-tuh-mab)

- Fully human bispecific antibody that targets EGFR and MET
- Fc portion has immune cell-directing activity[1]
- Demonstrated clinical activity across diverse EGFRm NSCLC[2-4]
- Granted Breakthrough Therapy Designation for EGFRm Exon20ins NSCLC post-chemotherapy in US and China

Lazertinib (la-zer-tin-ib)

- Potent 3rd-gen TKI with efficacy in activating EGFR mutations, T790M, and CNS disease[5-6]
- Low rates of EGFR-related toxicity such as rash and diarrhea[5]
- Low cardiovascular safety risk[7]
- Safety profile that supports combination with other anti-EGFR molecules





Cho BC et al, ESMO 2020

Amivantamab + Lazertinib [CHRYSALIS-2]

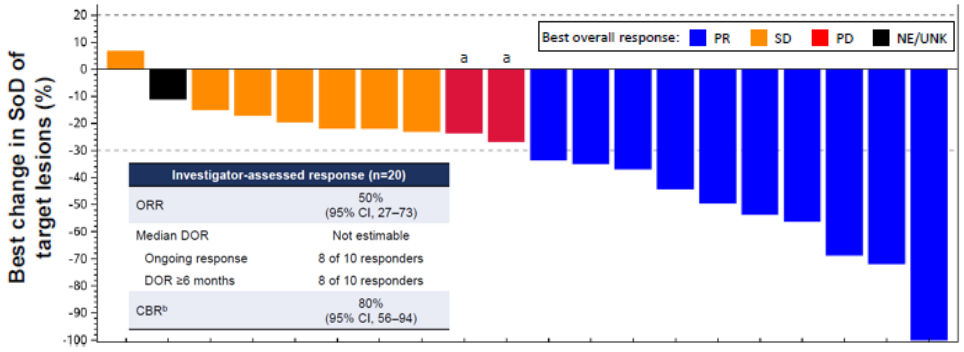
CHRYSALIS-2 (NCT04077463)

Eligibility
EGFR-mutated, advanced NSCLC post-TKI (max of 3 prior lines)

Dosing (21-day cycle)	
Lazertinib	240 mg daily
Amivantamab	1400/1750[b] mg on C1 D1/D2, C1D8, C1D15, C2D1; 1750/2100[b] mg C3+ Q3W
Chemotherapy	Carboplatin (AUC5; stopped after 4 cycles)
	Pemetrexed (500 mg/m^2) until disease progression

Endpoints

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

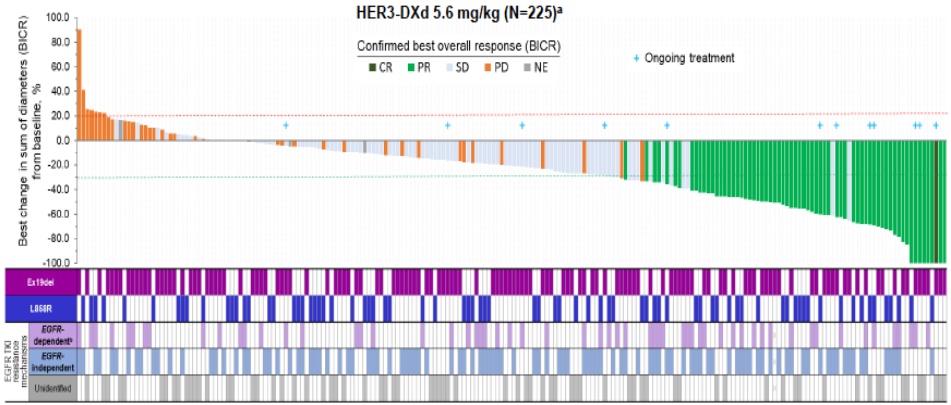


AEs (≥20%) by preferred term, n (%)	Total[a]	Grade ≥3
Associated with EGFR inhibition		
Rash	15 (75)	1 (5)
Paronychia	12 (60)	0
Stomatitis	12 (60)	0
Dermatitis acneiform	8 (40)	2 (10)
Diarrhea	6 (30)	1 (5)
Associated with MET inhibition		
Hypoalbuminemia	8 (40)	2 (10)
Other		
Neutropenia	18 (90)	14 (70)
IRR	13 (65)	0
Fatigue	10 (50)	5 (25)
Nausea	10 (50)	0
COVID-19	8 (40)	0
Thrombocytopenia	8 (40)	5 (25)
Constipation	7 (35)	0
Decreased appetite	7 (35)	1 (5)
Leukopenia	7 (35)	4 (20)
Alanine aminotransferase increased	6 (30)	0
Anemia	6 (30)	2 (10)
Pulmonary embolism	6 (30)	1 (5)
Aspartate aminotransferase increased	5 (25)	0
Back pain	5 (25)	0
Epistaxis	5 (25)	0
Hemorrhoids	5 (25)	0
Peripheral sensory neuropathy	5 (25)	0

Lee S-H et al, WCLC 2023

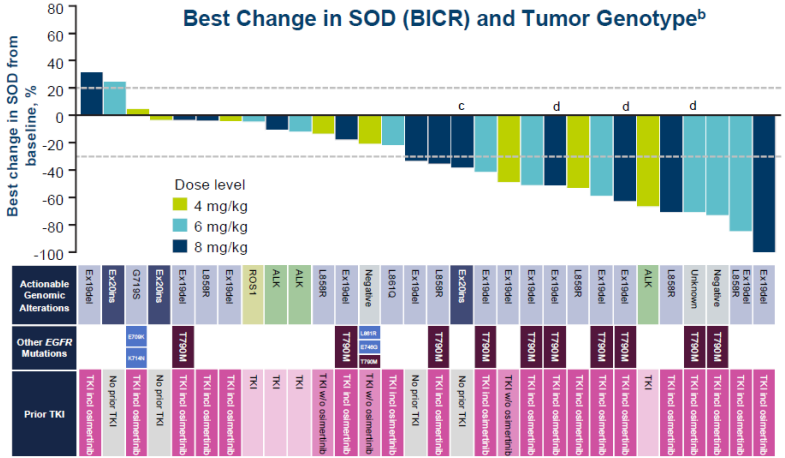
Antibody Drug Conjugates (ADCs)

Patritumab Deruxtecan (HER3-DXd)



N = 225
ORR 30%, mPFS 5.5 ms, OS 11.9 ms

Datopotomab Deruxtecan (TROP2-DXd)



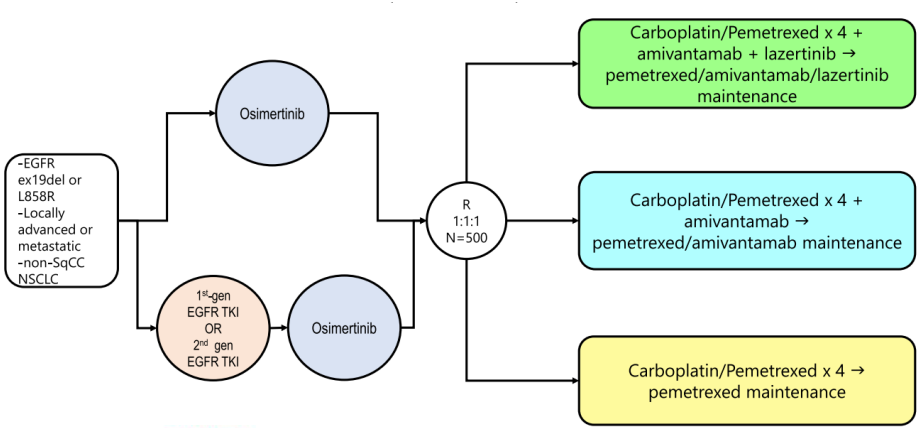
N = 34
ORR 35%, mDoR 9.5 m

Janne PA et al, WCLC 2023; Yu et al, JCO 2023

Garon EB et al, ESMO 2021

Amivantamab + Lazertinib [ph. III post-osi]

MARIPOSA-2 (NCT04988295)



MADRID 2023 ESMO congress

Primary endpoint: Progression-Free Survival

Phase 3 MARIPOSA-2 Study Meets Dual Primary Endpoint Resulting in Statistically Significant and Clinically Meaningful Improvement in PFS for amivantamab plus ChT With and Without Lazertinib versus ChT Alone in Patients with EGFR-Mutated NSCLC after Disease Progression on Osimertinib

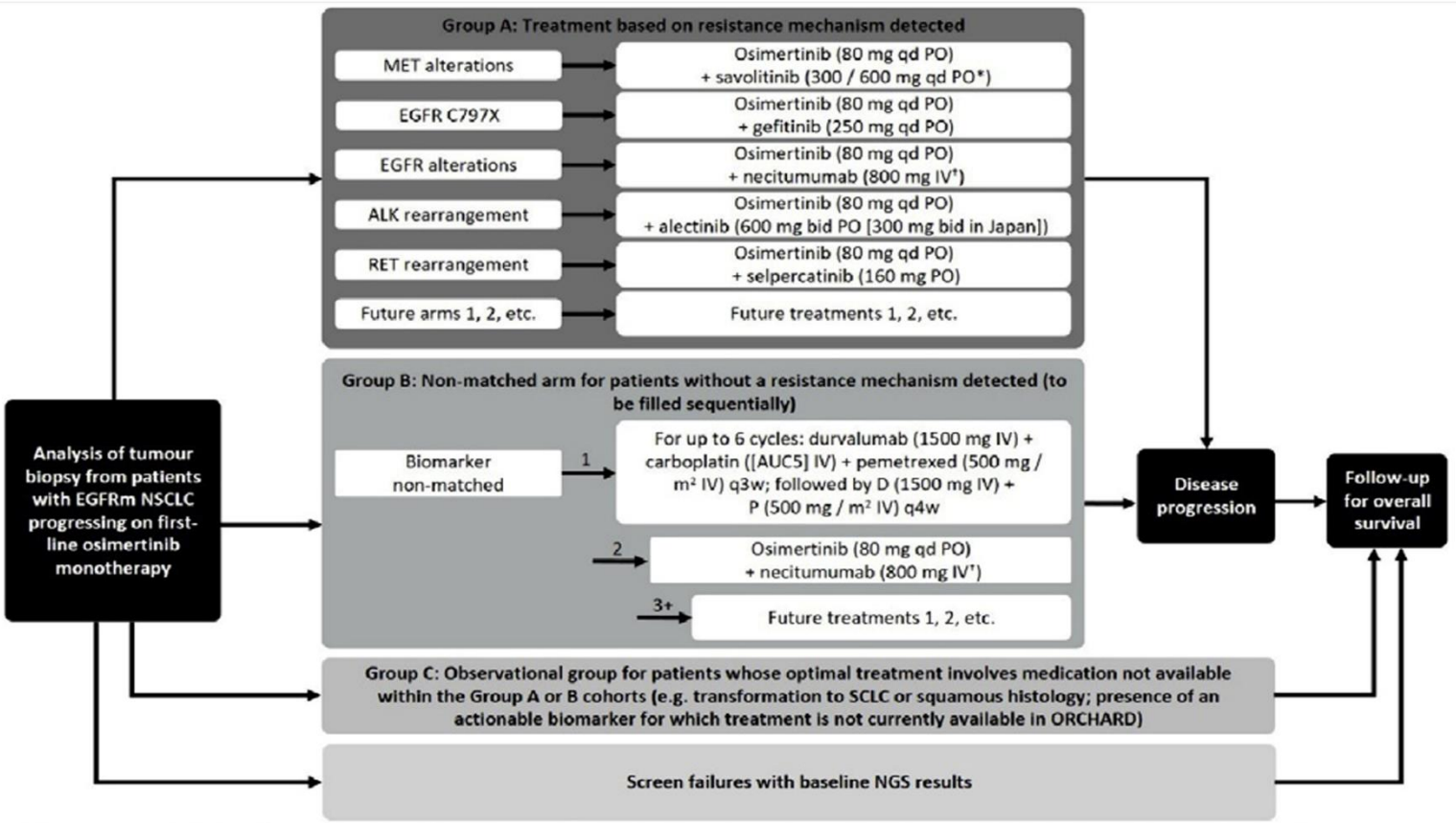
See Presidential Symposium @ESMO 2023!

PALOMA-3 (NCT05388669)

A Study of Lazertinib With Subcutaneous Amivantamab Compared With Intravenous Amivantamab in Participants With Epidermal Growth Factor Receptor (EGFR)-Mutated Advanced or Metastatic Non-small Cell Lung Cancer

Nagasake M, Lung Cancer: Targets and Therapy 2022
https://clinicaltrials.gov/ct2/show/NCT05388669

ORCHARD: Biomarker-Driven Ph. 2 Platform Study

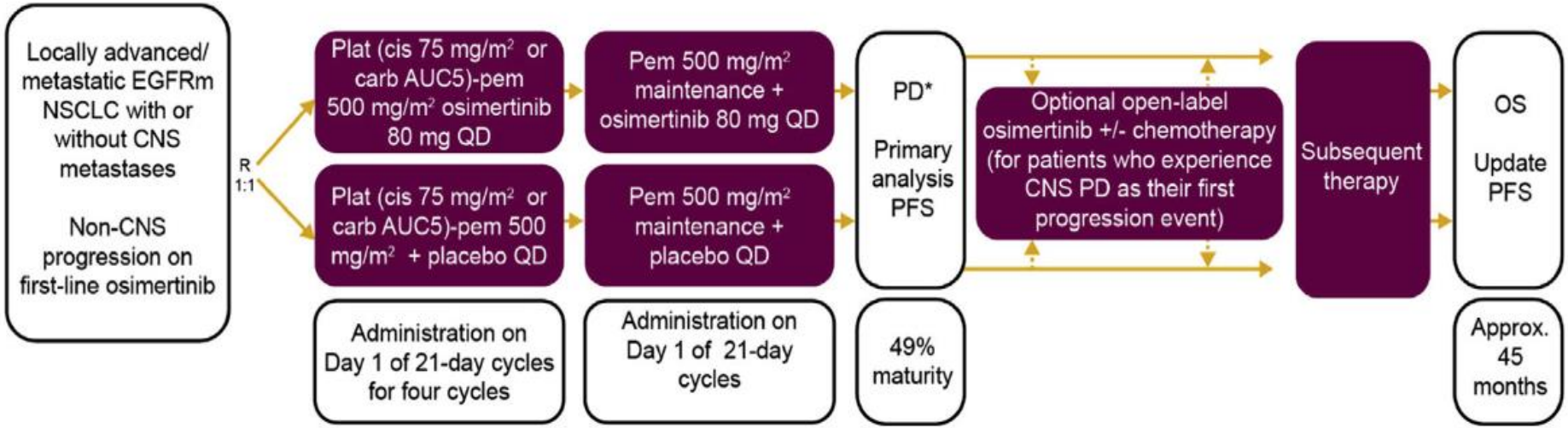


DOI: https://doi.org/10.1016/j.jtho.2021.01.1084

Adding Chemotherapy to Osimertinib

COMPEL (NCT04765059)

Continuing osimertinib with carbo/pem is an appealing strategy (i.e. BM, slow progressors)



Sequist L et al, WCLC 2021

(Main) 3 Open Questions

Tissue **vs./&** **Liquid**

Tailored **vs.** **Agnostic**

Anticipating **vs.** **Sequencing**

Crucial and Ethical Implications for:

Treatment Tailoring

Patients' Prognosis, QoL

Modified from Pilotto S