16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

GECP lung cancer research

DEBATE: Pros and Cons combination EGFR treatments

Cons

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Disclosures of Financial Relationships

- ✓ Honoraria
  - ✓ MSD Oncology, Pfizer, Astellas Pharma, Roche, Novartis, Janssen-Cilag, Bristol-Myers Squibb, Astra Zeneca
- ✓ Consulting of Advisory Role
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  - ✓ MSD Oncology, Astra Zeneca
- ✓ Research Funding
  - ✓ Miratti Therapeutics, Astra Zeneca, Bayer, OncoMed, Astellas Pharma, Janssen-Cilag, Roche, Abbvie, Boehringer-Ingelheim, Pfizer, PharmaMar, Bristol-Myers Squibb, Novartis, Celgene, Ignyta
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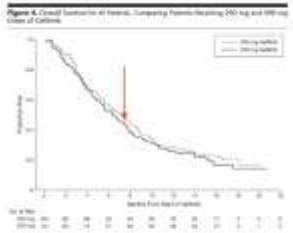
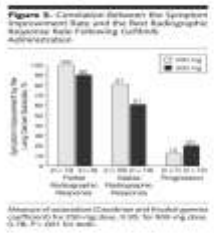
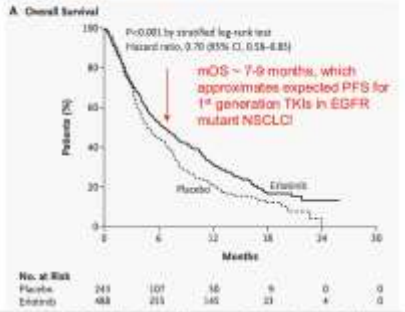
Initial Forays into EGFR Therapy







	Erlotinib (N = 488)	Placebo (N = 243)
Median survival	6.7 mo	4.7 mo
1 year survival	31.2%	21.5%
Objective response rate	8.9%	<1%

PFS = progression-free survival; mOS = mean overall survival.
Ranson M, et al. *J Clin Oncol*. 2002;20(9):2240-2250. Kris MG, et al. *JAMA*. 2003;290(16):2149-58. Shepherd FA, et al. *N Engl J Med*. 2005;353(2):123-132.

Targeting *EGFR* mutations in NSCLC: a twenty years successful story

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

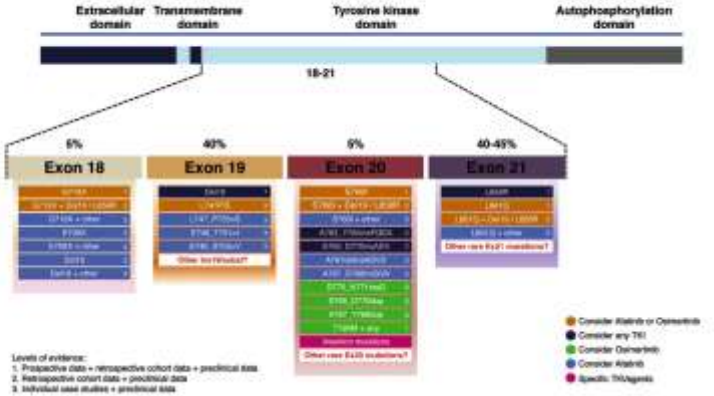
J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,2*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[2] Paula Herman,[1] Frederic J. Kaye,[3] Neal Lindeman,[4] Titus J. Boggon,[1,2] Katsuhiko Naoki,[1] Hidefumi Sasaki,[5] Yoshitaka Fujii,[5] Michael J. Eck,[1,6] William R. Sellers,[1,2,6,+] Bruce E. Johnson,[1,7+] Matthew Meyerson[1,2,6+]

The NEW ENGLAND JOURNAL of MEDICINE

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

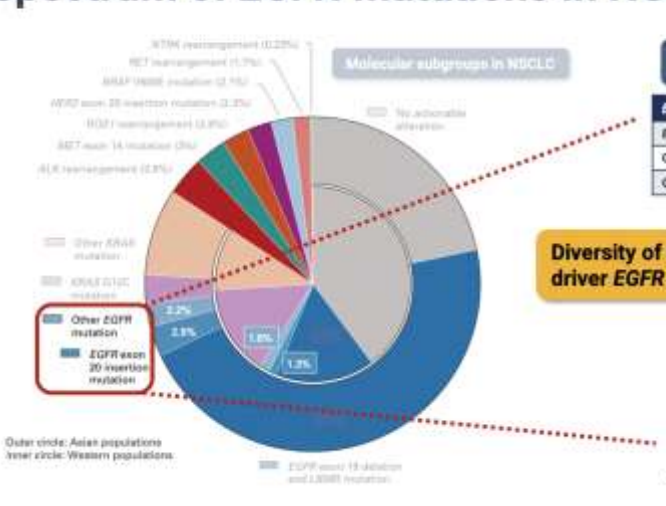
May 2004: Two independent Boston groups[1,2] first reported sustained responses to the EGFR TKI in patients harboring mutations in the kinase domain of the EGFR gene (exon 19 del and exon 21 L858R)

[1]Paez JG, et al. *Science* 2004; [2]Lynch TJ, et al. *NEJM* 2004



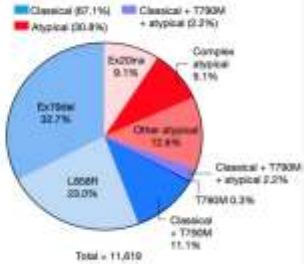
Passaro A, et al. *J Thorac Oncol* 2021

Spectrum of *EGFR* mutations in NSCLC

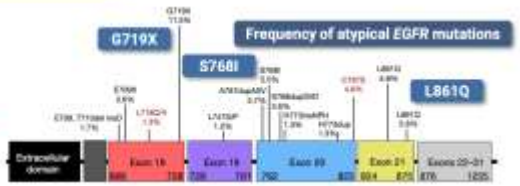


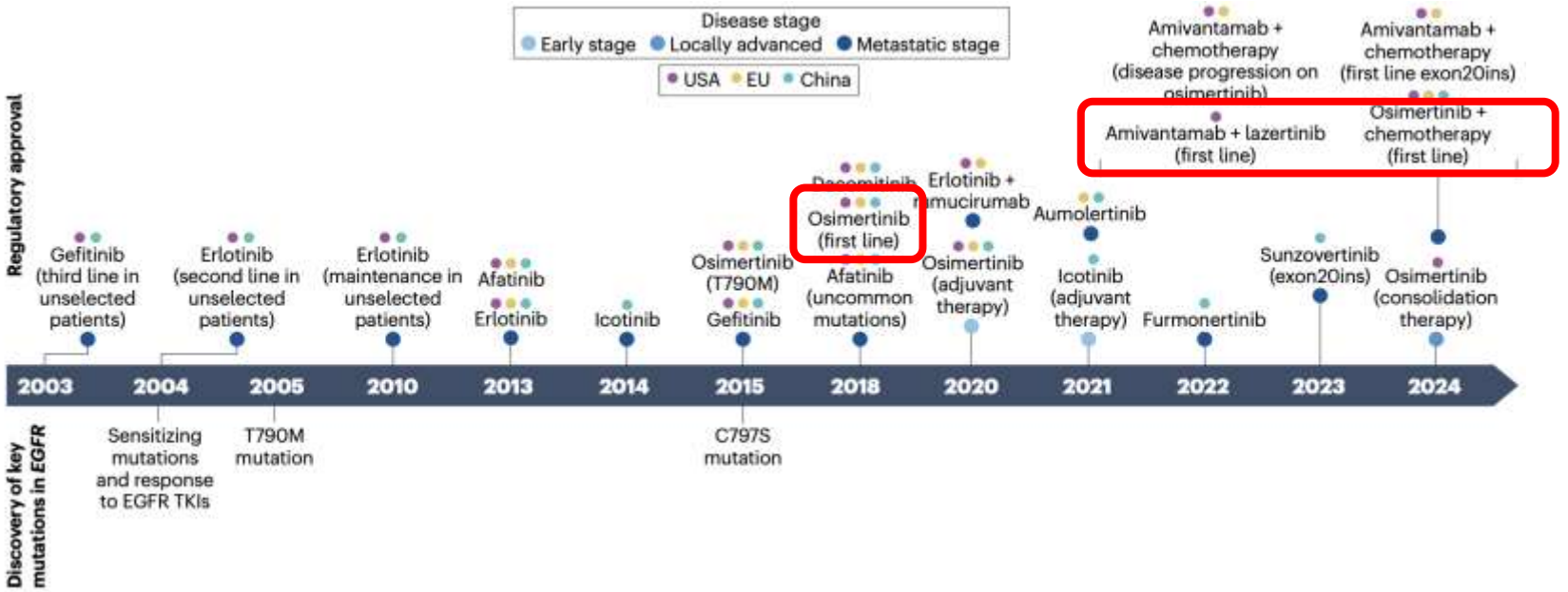
Breakdown of *EGFR* mutations: classical vs atypical

EGFR mutation	%
EGFR exon 20 insertion	9.1%
Complex atypical (uncommon)	9.1%
Other atypical (uncommon)	12.6%



Diversity of oncogenic driver *EGFR* mutations





Phase III, double-blind, randomized trial in previously untreated EGFR+ advanced NSCLC: osimertinib vs standard of care (SOC) EGFR-TKI

Newly diagnosed advanced NSCLC with confirmed exon 19 deletion or L858R EGFR mutation:

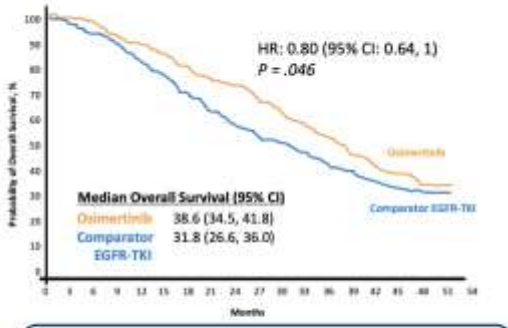
- **Osimertinib 80 mg once daily**
- *Cross over to open-label osimertinib permitted with disease progression and T790 mutation*
- **SOC oral EGFR-TKI** *(gefitinib 250 mg once daily or erlotinib 150 mg once daily)*

Continuation of First-Line Trial Drug

Patients continuing to receive first-line trial drug — number (%)	Osimertinib (N=279)	SOC EGFR-TKI (N=277)
At 12 mo	194 (70)	131 (47)
At 24 mo	118 (42)	45 (16)
At 36 mo	78 (28)	26 (9)

Primary endpoint: Osimertinib showed significantly longer progression-free survival
18.9 months vs. 10.2 months (HR 0.46; P<0.001)

Secondary Endpoint: Overall Survival

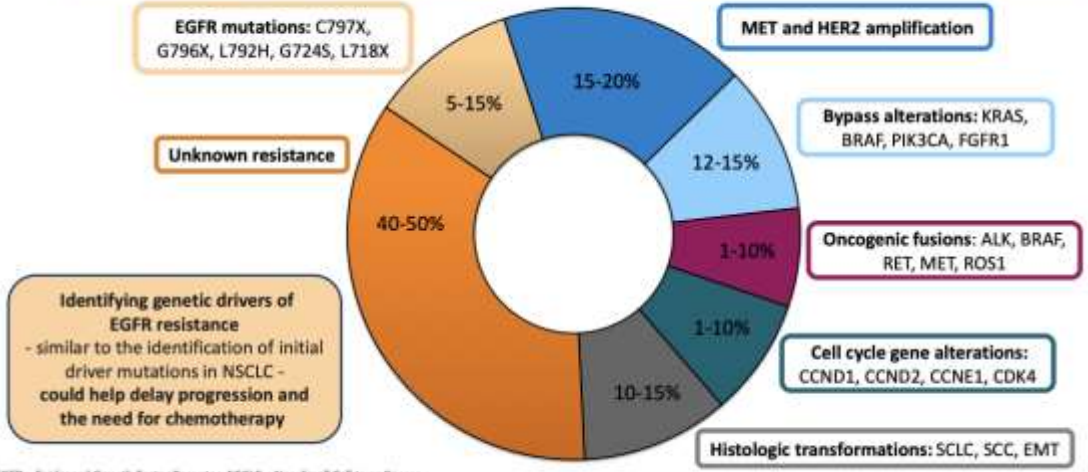


Osimertinib is recommended as first-line therapy in advanced/metastatic NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Mutations *(category 1, preferred); NCCN*

SOC = Standard of Care; PFS = Progression-Free Survival; CI = Confidence Interval; HR = Hazard Ratio; EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Cancer

Ramalingam SS, et al. *N Engl J Med.* 2020; 382:41-50. Soria JC, et al. *N Engl J Med.* 2018; 378:113-125.

Mechanisms of Resistance to First-Line Osimertinib Treatment



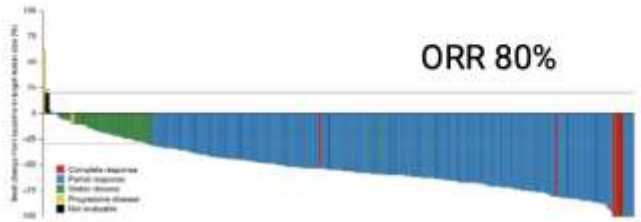
Identifying genetic drivers of EGFR resistance
- similar to the identification of initial driver mutations in NSCLC -
could help delay progression and the need for chemotherapy

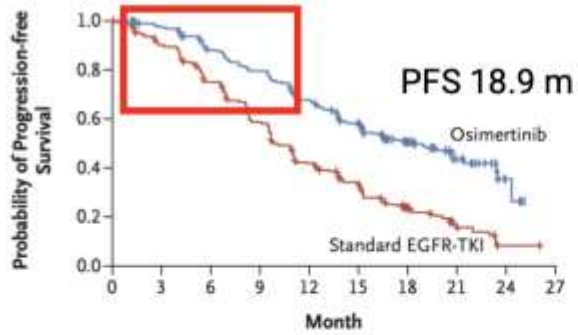
EGFR = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Cancer

Kaira K, et al. *Transl Lung Cancer Res.* 2024;13:1177–1182; Feldt S, et al. *Cancers (Basel).* 2023;15:2998.

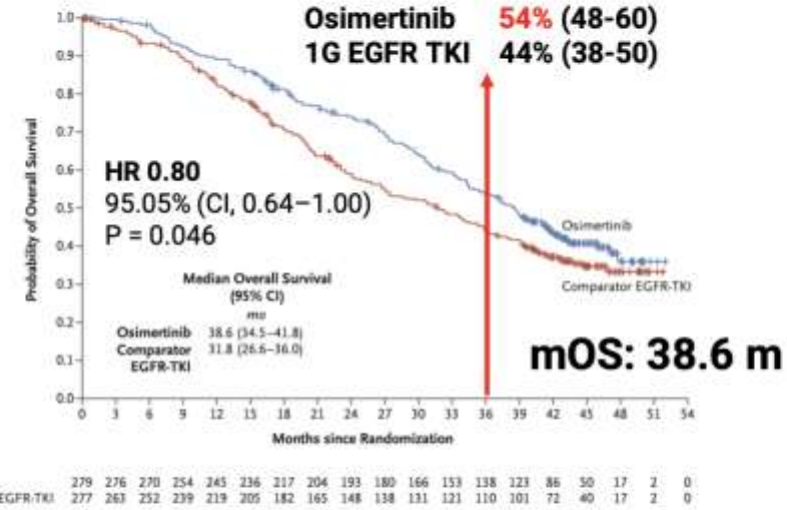
Why the need for upfront combinations?

Early progressors





Current SoC: Osimertinib



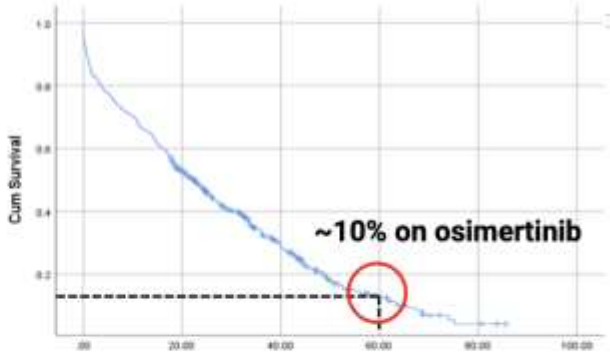
Patient's continuing to receive 1L drug (%)

	Osimertinib	1G TKI
12 m	70%	47%
24 m	42%	16%
36 m	28%	9%

Few long term responders

FLAURA
12.9% remain on osi > 4.5 yrs

NCCS data
n=506, Stage IV, 2018-2023



Dr Tan Wei Chong , NCCS Data Science Core

Soria et al. NEJM 2018; Ramalingam et al. NEJM 2020; Garassino et al. Lung Cancer 2025

Strategies to improve first-line treatment (Phase III trials)

- Antiangiogenics + TKI
  - NEJ026 Erlotinib + Bevacizumab vs Erlotinib
  - ARTEMIS Erlotinib + Bevacizumab vs Erlotinib
  - RELAY Erlotinib + Ramucirumab vs. Erlotinib
  - BEVERLY Erlotinib + Bevacizumab vs Erlotinib

  Negative Results

  - RAMOSE Osimertinib + Ramucirumab vs Osimertinib

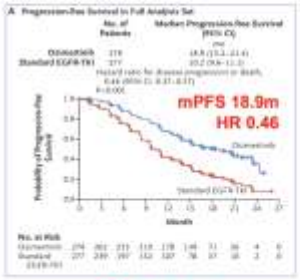
  ↑ PFS (phase II trial)
- Chemotherapy + TKI
  - FLAURA 2 Osimertinib + CHT vs. Osimertinib
- Bispecific Ab + TKI
  - MARIPOSA Amivantamab + Lazertinib vs. Osimertinib

  Positive Results

EGFR MUTATIONS (EX19DEL, L858R): BREAKING THE ESTABLISHED COMFORT ZONE

The familiar standard:

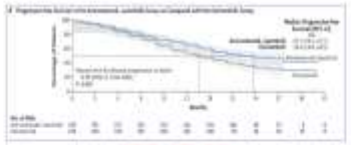
Osimertinib
vs. 1st gen. EGFR-TKI (FLAURA)



mOS: 38.6m

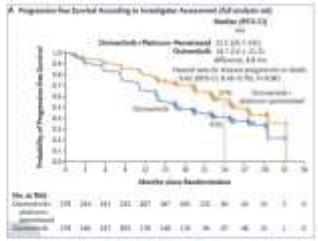
The challengers:

Lazertinib + amivantamab
vs. osimertinib (**MARIPOSA**)



PFS: HR 0.7

Osimertinib + chemotherapy
vs. osimertinib (**FLAURA2**)

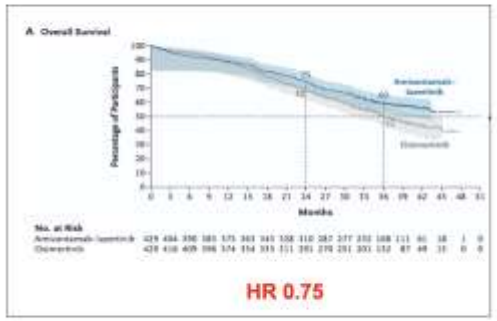


PFS: HR 0.62

> Both combinations clearly superior in PFS (primary endpoint)

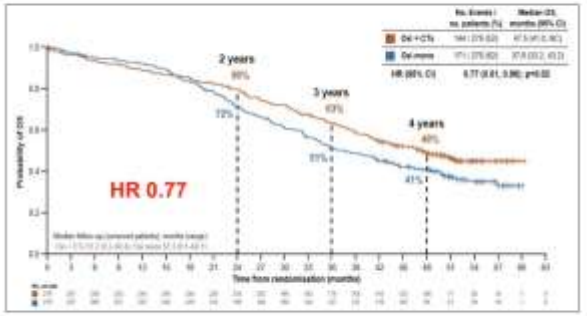
PFS BENEFIT TRANSLATES INTO OS ADVANTAGE

MARIPOSA



mOS Amivantamab – Lazertinib: NR (95% CI, 42.9-NE)
Osimertinib: 36.7 (95% CI, 33.4-41.0)

FLAURA2



mOS Osimertinib + CTx: 47-5 (95% CI, 41.0-NR)
Osimertinib mono: 37.6 (95% CI, 33.2-43.2)

IMPROVED EFFICACY COMES AT THE COST OF HIGHER TOXICITY

	Osimertinib + chemotherapy	Osimertinib	Lazertinib + Amivantamab	Osimertinib
SAEs	38%	19%	49%	33%
Grade ≥ 3 tox.	64%	27%	75%	43%
Interruption of trial drug	Osimertinib: 11%	Osimertinib: 6%	35%	14%

Most prominent toxicities in FLAURA-2 chemotherapy-associated:
- Anemia: 46% vs. 8%
- Diarrhoea: 43% vs. 41%
- Nausea: 43% vs. 10%

Most prominent toxicities in MARIPOSA amivantamab-associated:
- Paronychia: 68% vs. 28%
- Infusion-related reaction: 63% vs. 0%
- Rash: 62% vs. 31%
- Pulmonary embolism: 17% vs. 5%

COCOON
PALOMA 3
VTE PROPHYLAXIS

Toxicity management improved by prophylactic skin care, s.c. formulation, anticoagulation

> Are there subgroups that could be spared from toxicity ?

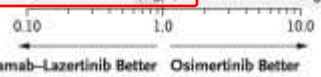
What is the tradeoff with upfront combination treatment?

	Osimertinib	Osimertinib-Pemetrexed-carboplatin	Amivantamab-Lazertinib
Study	FLAURA	FLAURA2	MARIPOSA
Efficacy	PFS 18.9 m **OS 38.6 m v 31.8 m**	PFS 25.5 m △9.9 m **OS 47.5 m v 37.6 m (HR 0.77)**	PFS 23.7 m △12 m+ **OS Not reached v 36.7 m (HR 0.75)**
Side effects (all grades)	Diarrhoea 42% Rash 22% Paronychia 27% Neutropenia 4% Neutrophil count decreased 7% Anaemia 11%	Diarrhoea 46% Rash 30% Paronychia 26% Neutropenia 25% Neutrophil count decreased 24% Anaemia 48% (G3 20%) Creatinine increase 14%	Diarrhoea 32% Rash 64% Paronychia 69% Infusion related reaction 65% Peripheral edema 38% Venous thromboembolism 40% Anaemia 27%
Supportive care	Emollient cream, steroid creams	Emollient cream, steroid creams Cytopenias/ mouthwashes	Emollient cream, steroid creams Prophylactic antibiotics, anticoagulation
Schedule	Daily oral tablet Visit every 2-3 months	Daily oral tablet, Iv Infusion once every 3 weeks	Daily oral tablet, Infusion/ subcut once per week for first 4 weeks; once every 2 weeks thereafter
Financial	$	$$	$$$$

MARIPOSA

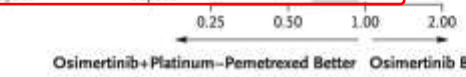
B Subgroup Analysis of Overall Survival

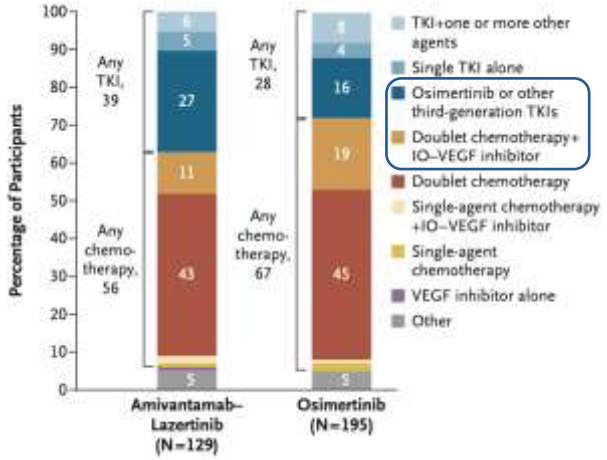
Subgroup	Amivantamab–Lazertinib (no. of participants)	Osimertinib (no. of participants)	Hazard Ratio for Death (95% CI)
All participants	429	429	0.75 (0.61–0.92)
Age at randomization			
<65 yr	235	237	0.53 (0.40–0.70)
≥65 yr	194	192	1.11 (0.84–1.48)
<75 yr	378	376	0.75 (0.60–0.93)
≥75 yr	51	53	0.79 (0.47–1.33)
Sex			
Female	275	251	0.73 (0.56–0.95)
Male	154	178	0.81 (0.60–1.09)
Race			
Asian	250	251	0.75 (0.58–0.98)
Non-Asian	177	177	0.74 (0.54–1.00)
Weight			
<80 kg	376	368	0.78 (0.63–0.97)
≥80 kg	53	61	0.62 (0.36–1.07)
ECOG performance-status score			
0	141	149	0.88 (0.61–1.28)
1	288	280	0.70 (0.55–0.89)
History of smoking			
Yes	130	134	0.78 (0.55–1.10)
No	299	295	0.74 (0.58–0.95)
History of brain metastases			
Yes	178	173	0.67 (0.50–0.90)
No	251	256	0.82 (0.62–1.08)
EGFR mutation			
Exon 19 deletion	257	257	0.66 (0.50–0.86)
L858R substitution	171	172	0.90 (0.67–1.21)

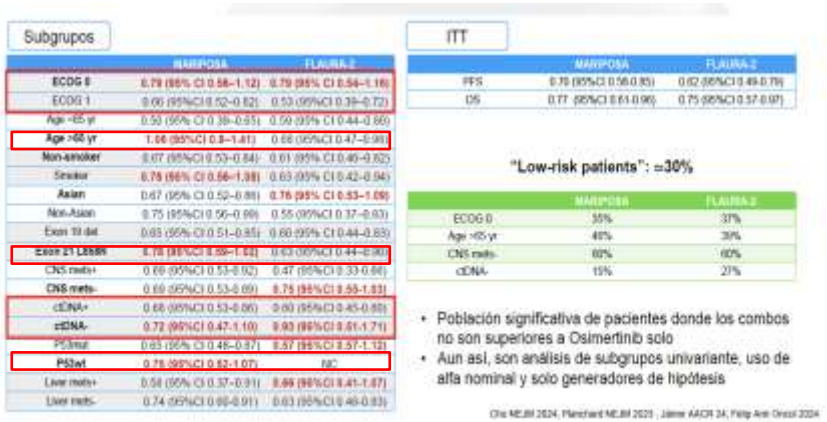


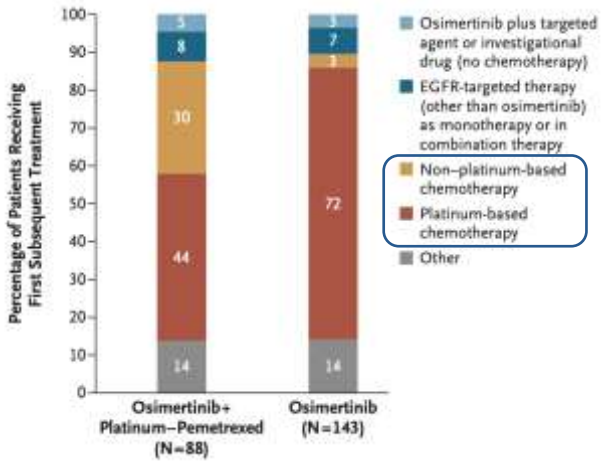
FLAURA 2

Subgroup	Osimertinib+Platinum–Pemetrexed (no. of events/no. of patients)	Osimertinib (no. of events/no. of patients)	Hazard Ratio for Death (95% CI)
Overall			
Stratified log-rank analysis	144/279	171/278	0.77 (0.61–0.96)
Unadjusted Cox proportional-hazards analysis	144/279	171/278	0.76 (0.61–0.95)
Sex			
Male	65/106	72/109	0.84 (0.60–1.17)
Female	79/173	99/169	0.71 (0.53–0.96)
Race			
Asian Chinese	34/71	39/69	0.76 (0.48–1.20)
Asian non-Chinese	65/107	66/107	1.00 (0.71–1.40)
Non-Asian	45/101	66/102	0.56 (0.39–0.82)
Method used for tissue testing			
Central	65/121	73/119	0.81 (0.58–1.14)
Local	79/158	98/159	0.73 (0.54–0.98)
Age			
<65 yr	80/174	95/166	0.71 (0.53–0.95)
≥65 yr	64/105	76/112	0.87 (0.63–1.22)
History of smoking			
Yes	52/91	60/97	0.83 (0.57–1.20)
No	92/188	111/181	0.73 (0.55–0.96)
EGFR mutation at randomization			
Exon 19 deletion	78/172	95/169	0.76 (0.56–1.02)
L858R mutation	66/106	74/107	0.76 (0.55–1.07)
WHO performance-status score			
0	47/101	55/102	0.82 (0.55–1.20)
1	97/178	116/176	0.73 (0.56–0.96)
CNS metastases at baseline			
Yes	71/116	79/110	0.72 (0.52–0.99)
No	73/163	92/168	0.77 (0.57–1.05)

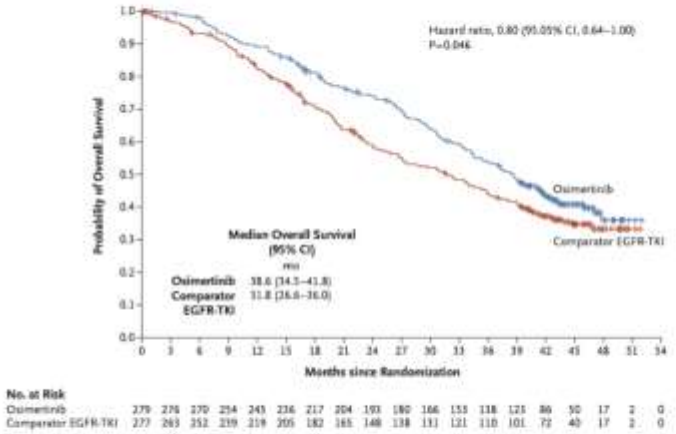






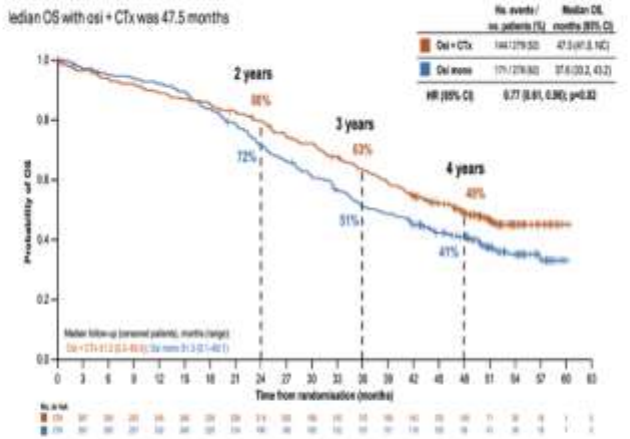


Osimertinib (FLAURA)



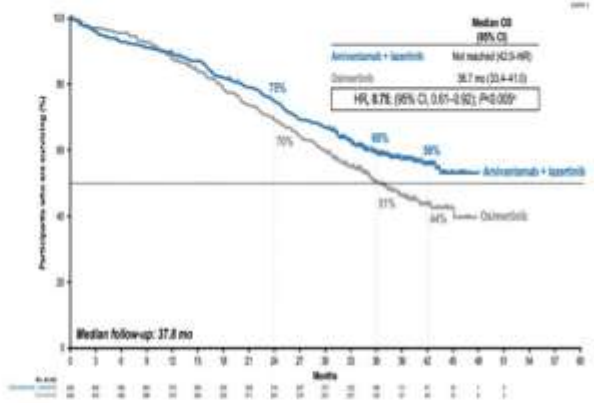
OS: 38.6 v 31.8 months
HR 0.8 (0.64 – 1.00) p=0.046

Osimertinib-pemetrexed-plt (FLAURA-2)



OS: 47.5 v 37.6 months
HR 0.77 (0.61-0.96) p=0.02

Lazertinib + Amivantamab (MARIPOSA)

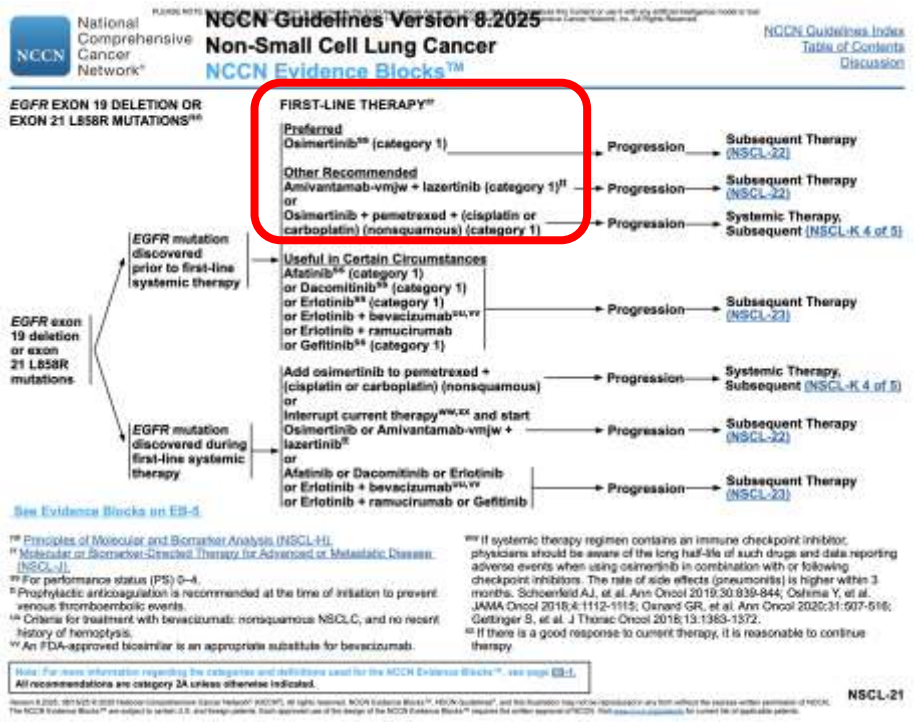


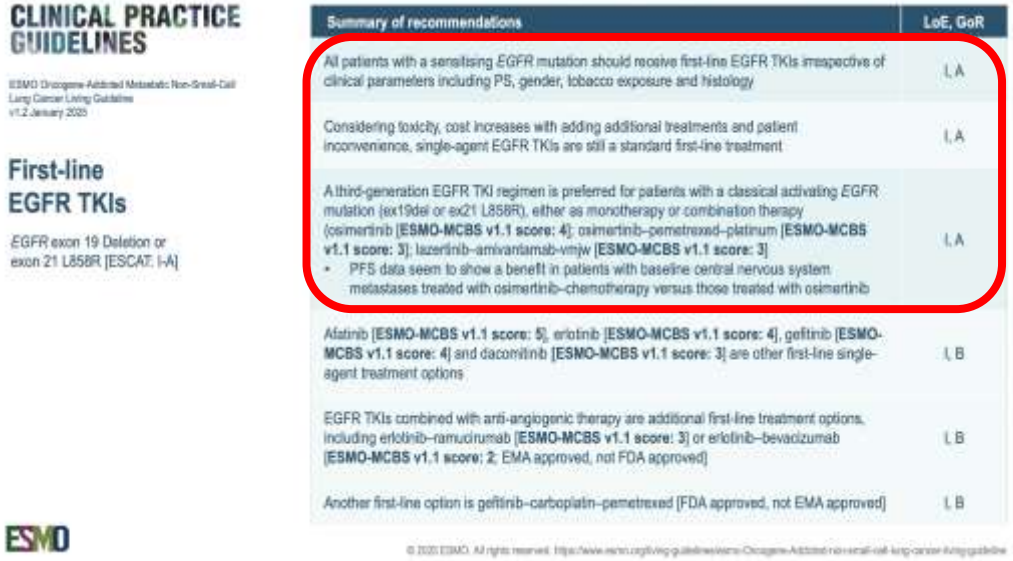
OS: Not reached v 36.7 months
HR 0.75 (0.61 – 0.92) p<0.005

Questions

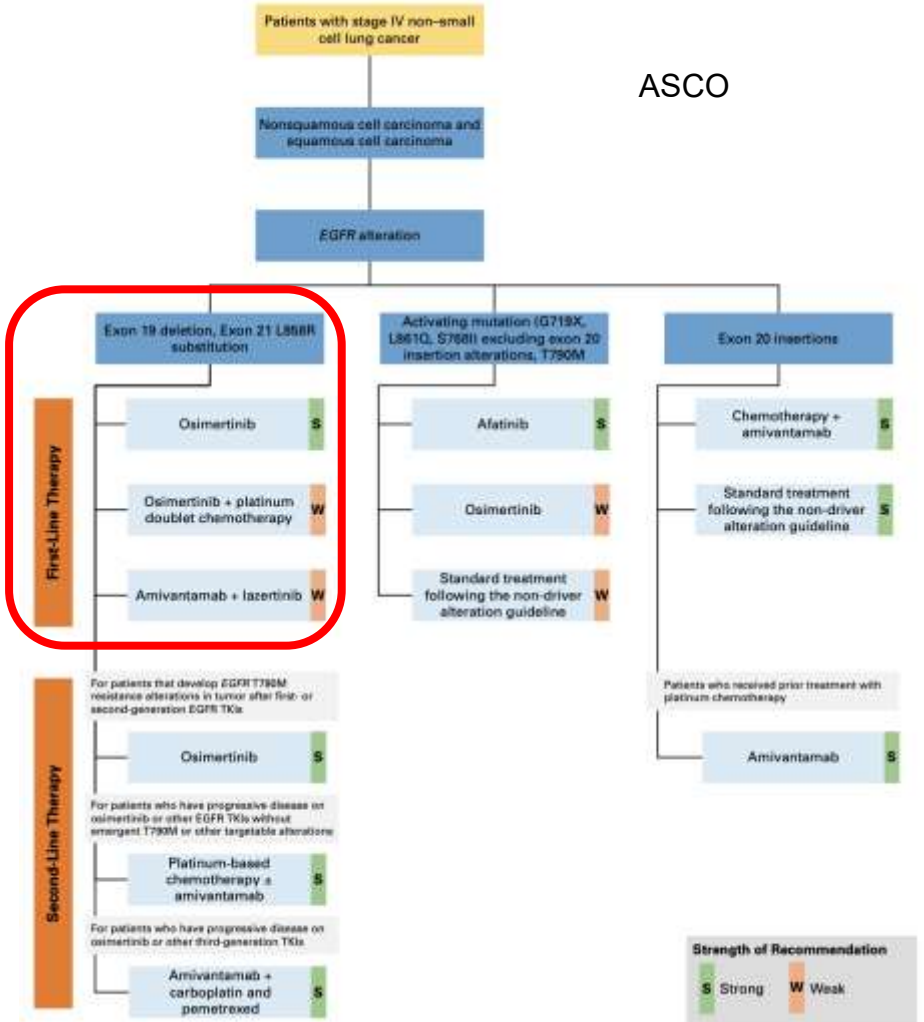
1. Is there still a role for single agent osimertinib?
2. If we opt for combinations: Who should receive it? When is the best time? Which combination?
3. How do we move forward from here?

Guidelines





ASCO



Overall Survival in EGFR-Mutant Advanced NSCLC Treated With First-Line Osimertinib: A Cohort Study Integrating Clinical and Biomarker Data in the United States

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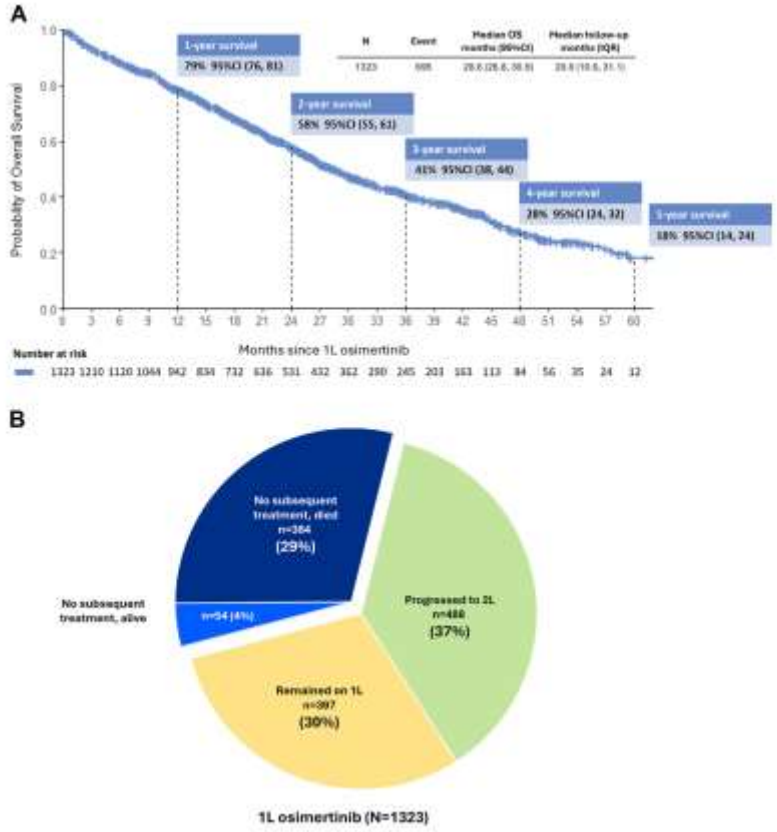
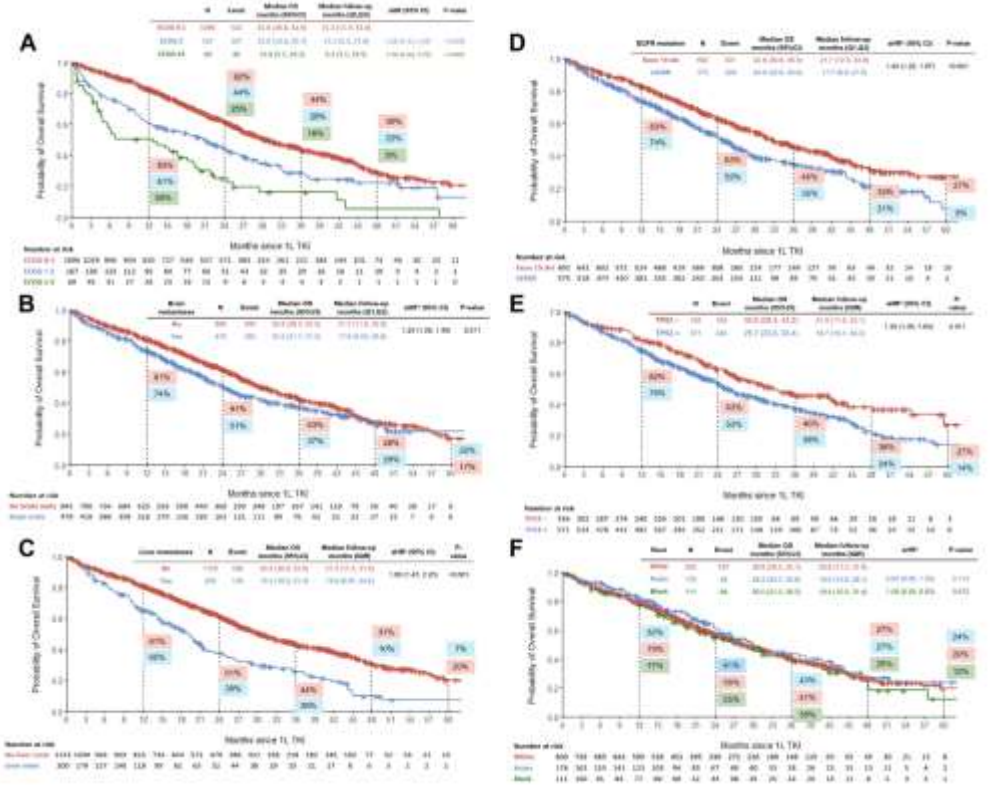




Risk Factors	Prevalence	aHR (95% CI)	*p* value
Age ≥ 65 y	66%	1.26 (1.07-1.50)	0.007
Brain metastases	36%	1.24 (1.05-1.45)	0.011
TP53 test positive	63%	1.30 (1.06-1.60)	0.011
EGFR L858R[a]	48%	1.43 (1.22-1.67)	<0.001
Liver metastases	15%	1.91 (1.57-2.32)	<0.001
ECOG PS ≥ 2	17%	1.78 (1.47-2.16)	<0.001

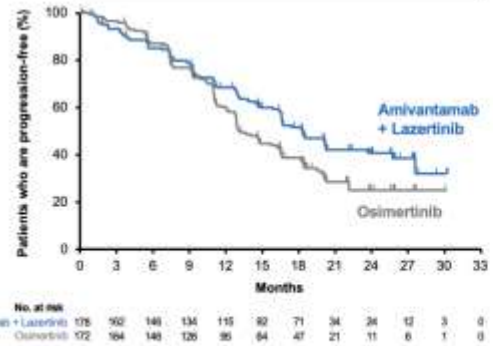
[a]Compared with exon 19 deletions.
aHR, adjusted hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Score.

BRAIN METATASIS

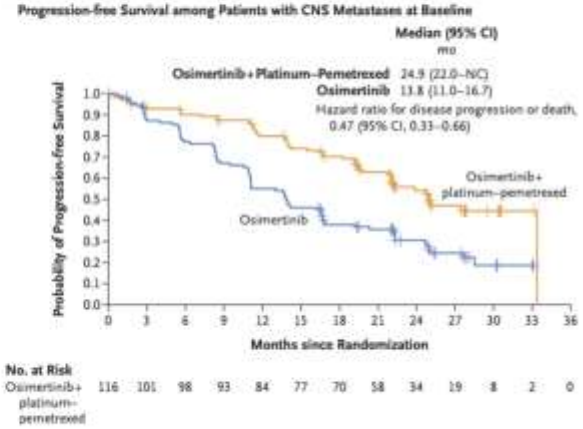
MARIPOSA

With History of Brain Metastases	Median PFS (95% CI)
Amivantamab + Lazertinib	18.3 mo (16.6–23.7)
Osimertinib	13.0 mo (12.2–16.4)

HR, **0.69** (95% CI, 0.53–0.92)



FLAURA 2



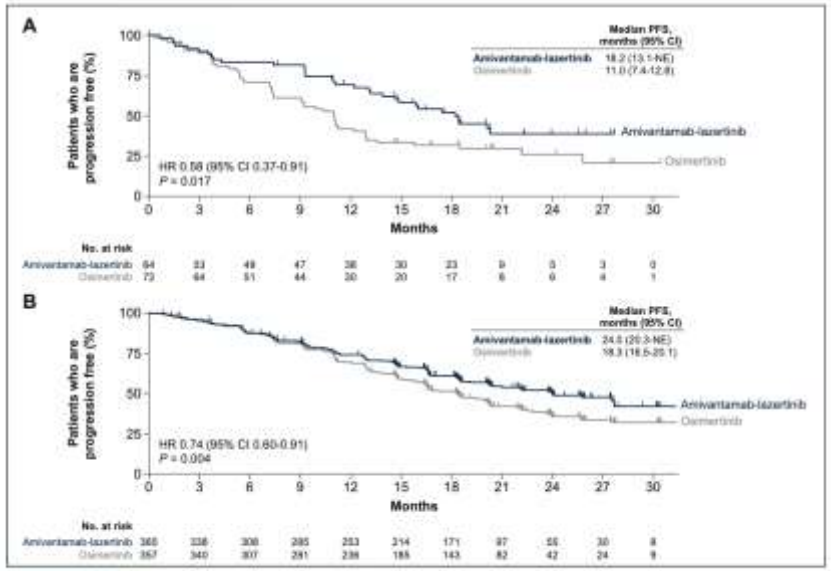
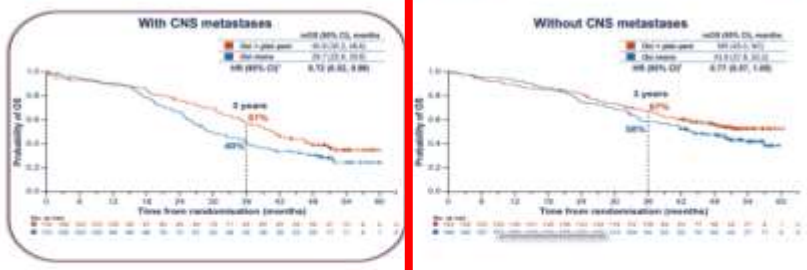


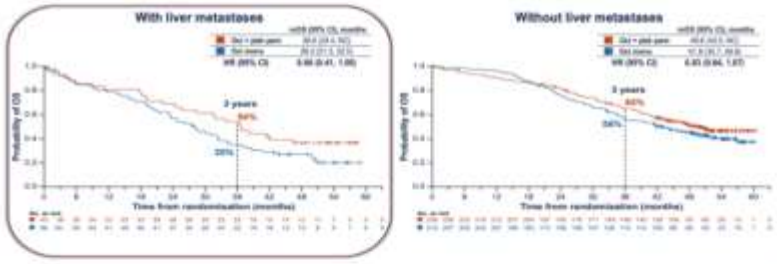
Figure 4. **Progression-free survival for patients with and without baseline liver metastases.** Shown are Kaplan-Meier estimates of progression-free survival for subgroups of patients with baseline liver metastases (A) and without baseline liver metastases (B). Tick marks indicate censoring of data.
CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

BONE AND VISCERAL METASTASIS

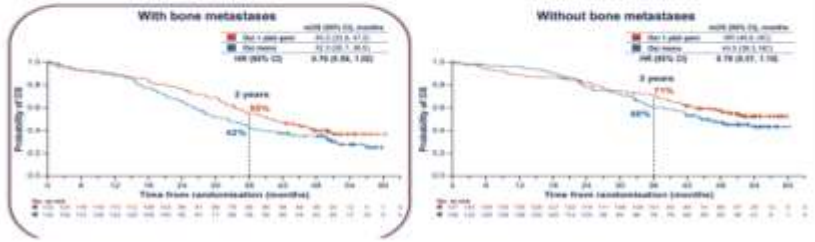
Poorer prognostic factor: CNS metastases at baseline



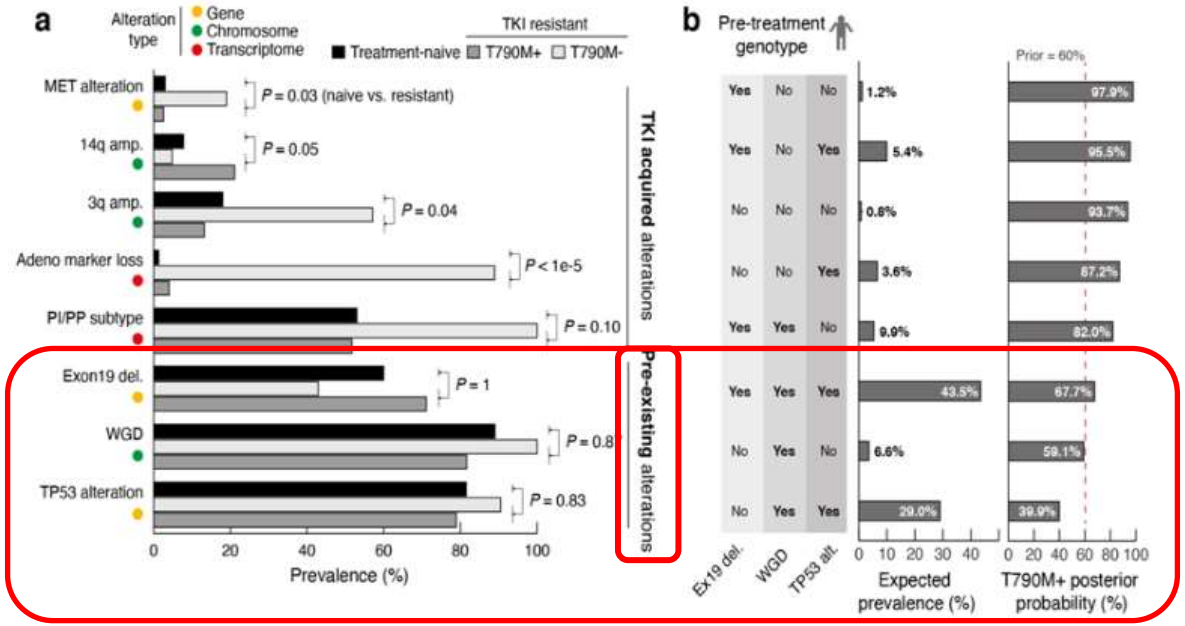
Poorer prognostic factor: liver metastases at baseline



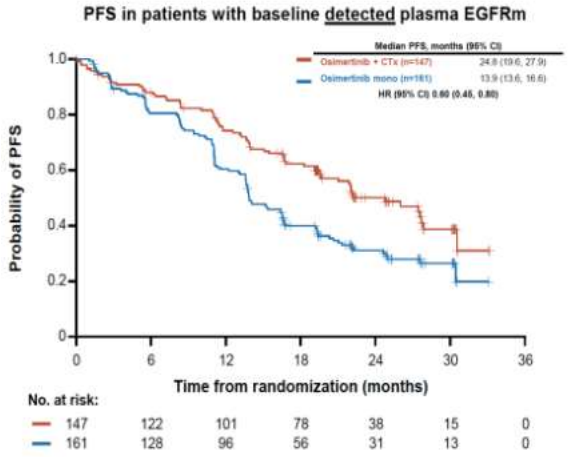
Poorer prognostic factor: bone metastases at baseline

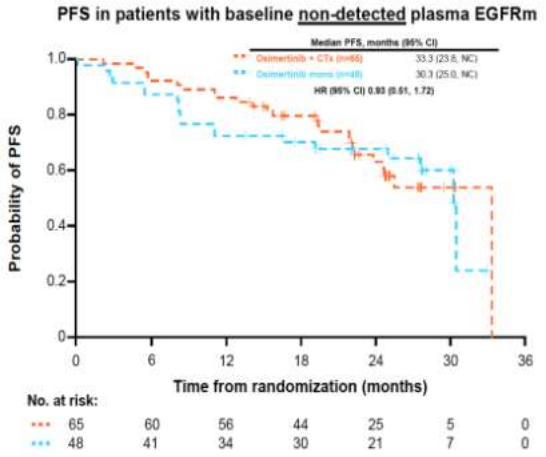


Baseline Molecular



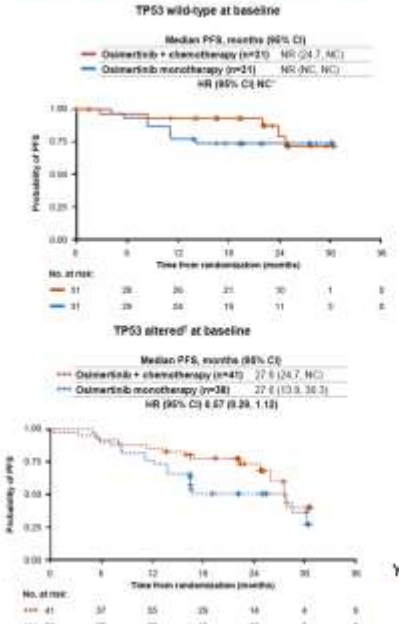
ctDNA





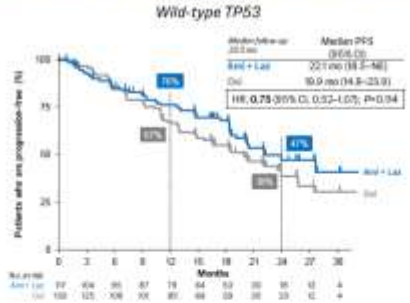
TP53 and PLASMA EGFRm

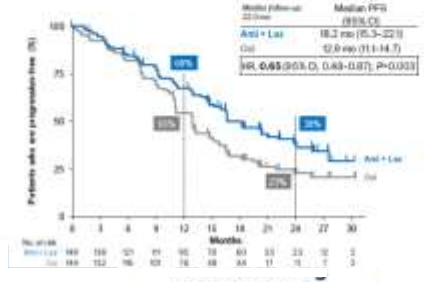
FLAURA2: Osimertinib ± Chemo



Yang JC, et al. WCLC 2024

MARIPOSA: Amivantamab + Lazertinib

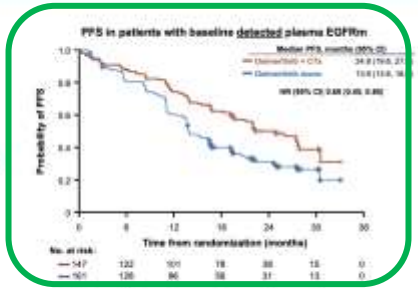


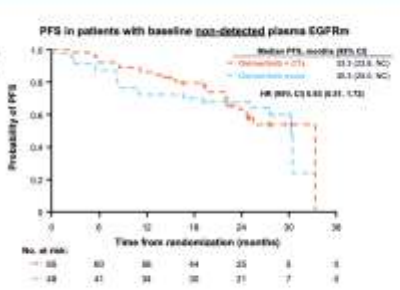


Felip E, et al. ASCO 2024

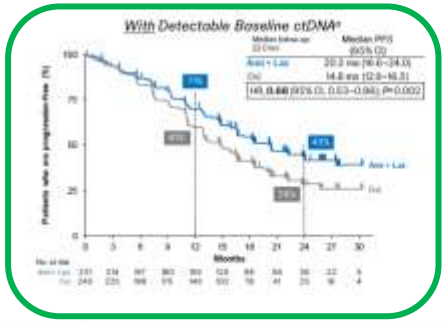
HIGH RISK PATIENTS BENEFIT MOST FROM COMBOS: baseline ctDNA+

FLAURA2: Osimertinib ± Chemo





Jänne PA, et al. AACR 2024



MARIPOSA: Amivantamab + Lazertinib

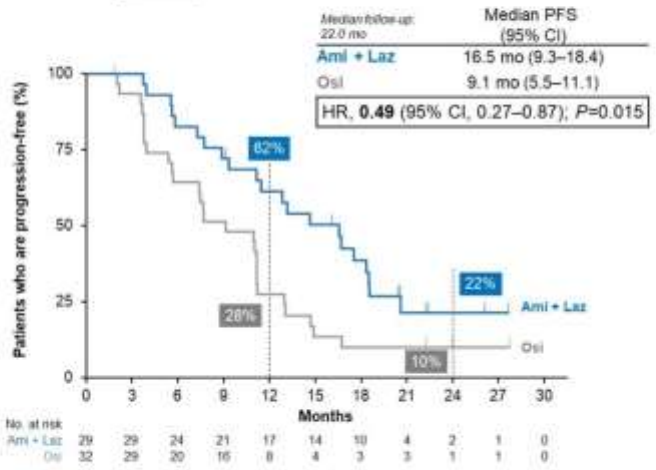
Felip E, et al. ASCO 2024

PFS without and with Cleared EGFRm ctDNA[a] at Wk 9 (C3D1)

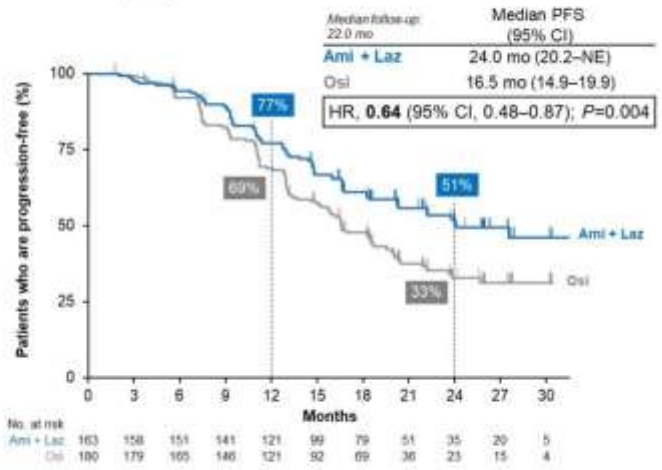
- Osimertinib showed a median PFS of 9.1 mo in patients without cleared *EGFR*m ctDNA[a] at Week 9
- Amivantamab + lazertinib reduced the risk of progression or death by 51% in this subgroup

DYNAMIC ctDNA CLEARANCE

Without Cleared EGFRm ctDNA[a] at Week 9

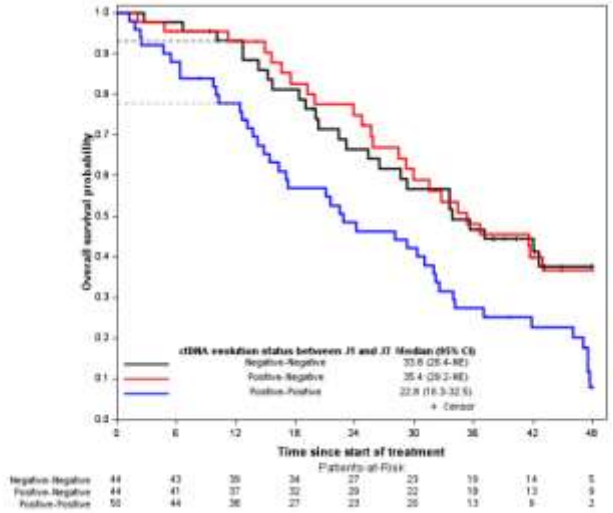


With Cleared EGFRm ctDNA[a] at Week 9



Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; Osi, osimertinib.

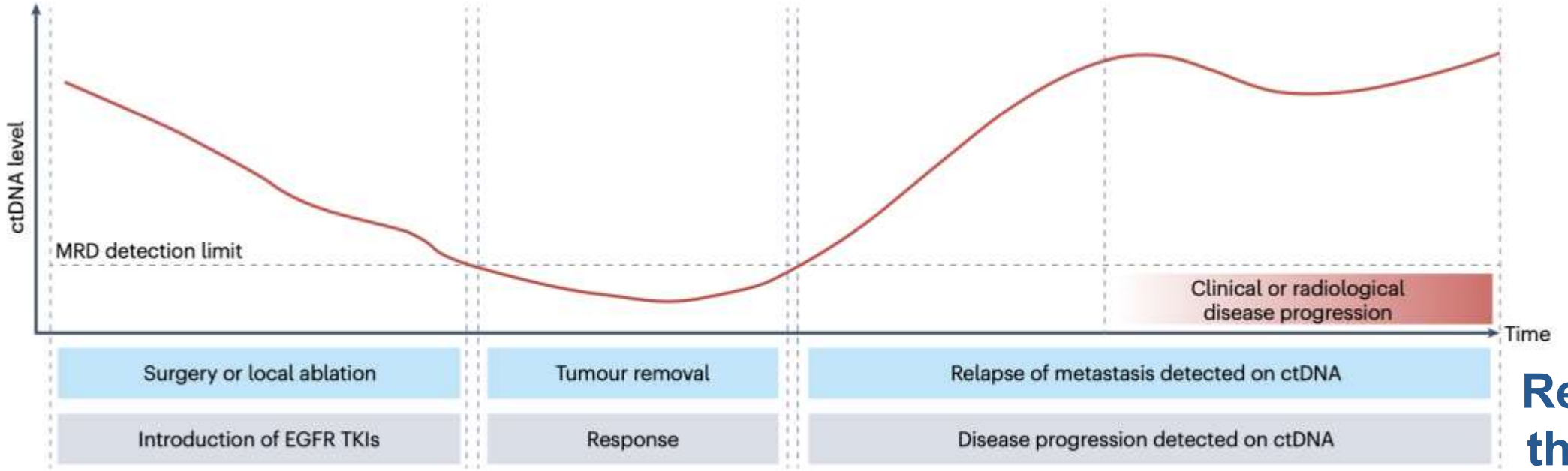
Felip E, et al. *JCO*. 2024;42:8504-8504.



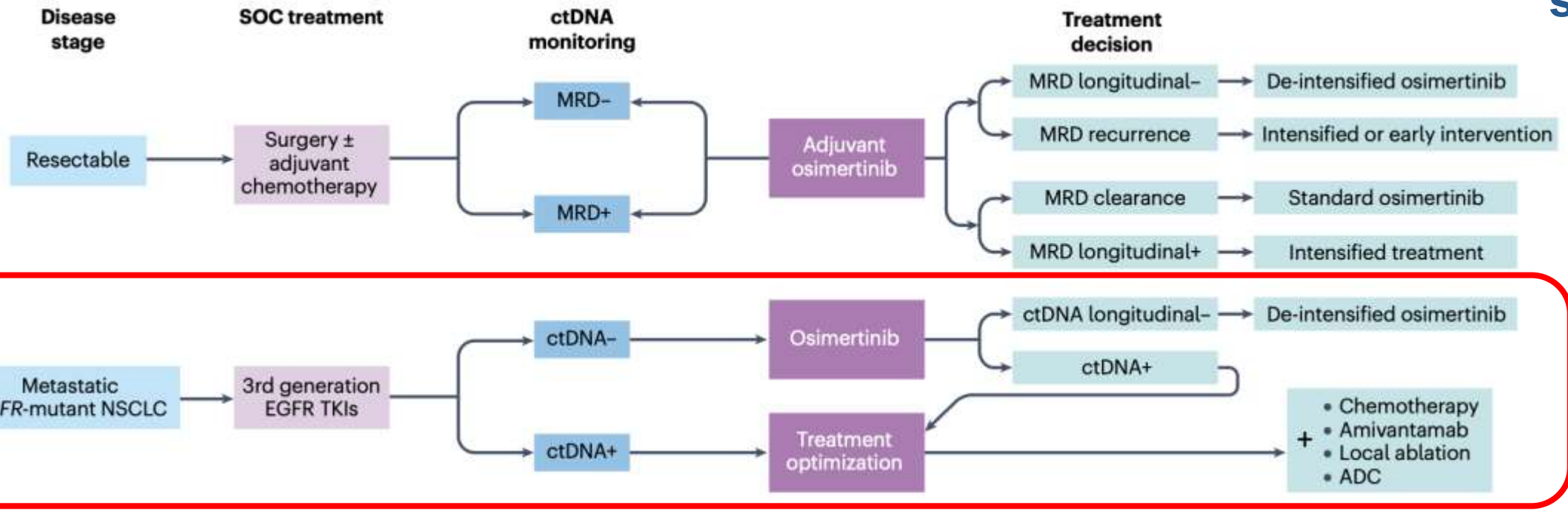
1957P : Day-7 ctDNA Response as a Prognostic Marker in EGFR-Mutant NonSmall Lung Cancer (NSCLC) under Osimertinib: The French Study MELROSE

J. Bennouna [1], E. Pons-Tostivint [2], C. Sagan [3], J. Cadranel [4], C. Audigier Valette [5], P. Tomasini [6], P. Masson [7], H. Curcio [8], N. Girard [9], A. Cortot [10], O. Molinier [11], I. Monnet [12], M. Marcq [13], T. Urban [14], D. Moro Sibilot [15], H. Lena [16], S Charpentier [17], A. Le Thuaut [18], M.G. Denis [17],

[1] Medical Oncology, Hopital Foch, Suresnes; [2] Medical Oncology, CHU Nantes; [3] Anatomopathology, CHU Nantes; [4] Pneumology, Hopital Tenon, Paris; [5] Hopital Sainte-Musse, Toulon; [6] Thoracic Oncology, APHM Hopital Nord, Marseille; [7] Pneumology, CH Cholet; [8] Medical Oncology, Centre Baclesse, Caen; [9] Medical Oncology, Institut Curie, Paris; [10] Pneumology, CHU Lille; [11] Pneumology, CH Le Mans; [12] Pneumology CHI Créteil; [13] Pneumology, CH La Roche Sur Yon; [14] Pneumology, CHU Angers; [15] Pneumology, CHU Grenoble; [16] Pneumology, CHU Rennes; [17] Plateforme de biologie des cancers, CHU Nantes; [18] Centre d'Investigation Clinique, CHU Nantes



Relevance of the Dinamyc study of ctDNA



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ORIGINAL RESEARCH
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What Matters Most to Lung Cancer Patients? A Qualitative Study in Italy and Belgium to Investigate Patient Preferences

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Patients' attitudes and preferences toward delayed disease progression in the absence of improved survival

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Balancing benefits and risks in lung cancer therapies: patient preferences for lung cancer treatment alternatives

OPEN ACCESS

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GECP lung cancer research

Results: Patients highlighted themes reflecting: 1) positive effects or expected gains from treatment such as greater life expectancy and maintenance of daily functioning, 2) negative effects or adverse events related to therapy that negatively impact patients' daily functioning such as fatigue and 3) uncertainty regarding the duration and type of treatment effects. These overarching themes were consistent among patients from Belgium and Italy, suggesting that treatment aspects related to efficacy and safety as well as the psychological impact of lung cancer treatment are common areas of concern for patients, regardless of cultural background or country.

Abstract

Background: Cancer patients' attitudes toward progression-free survival (PFS) gains offered by treatment are not well understood, particularly in the absence of overall survival (OS) gains. The objectives were to describe patients' willingness to accept treatment that offers PFS gains without OS gains, to compare these findings with treatments offering OS gains, and to qualitatively summarize patients' reasons for their preferences.

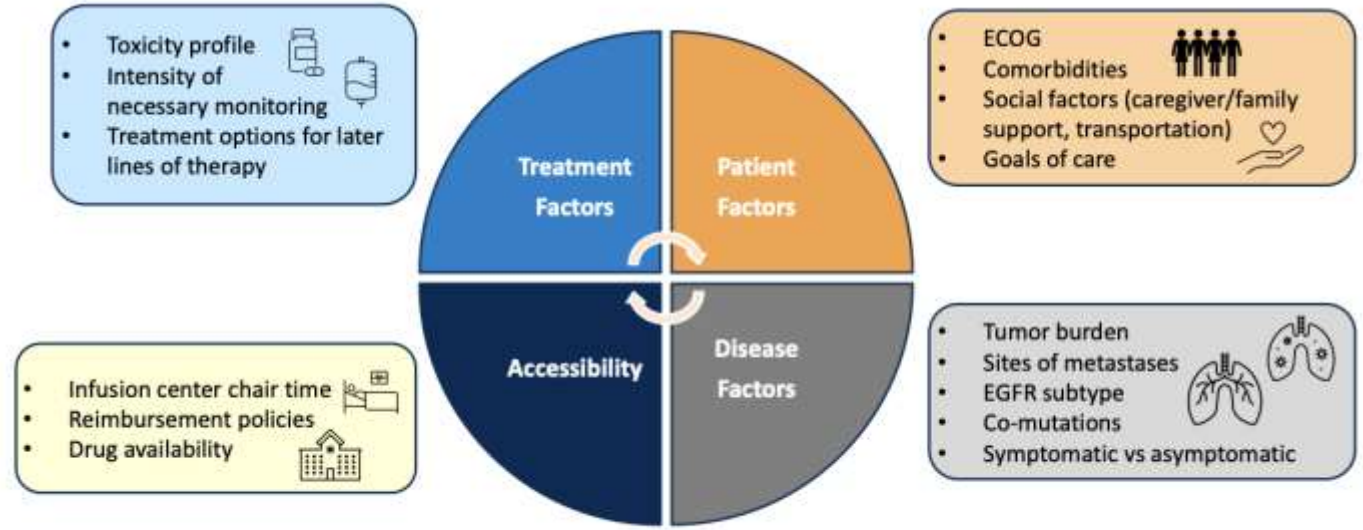
Methods: A multicenter, cross-sectional, convergent mixed-methods study design recruited patients who had received at least 3 months of systemic therapy for incurable solid tumors. A treatment trade-off exercise determined the gains in imaging PFS that patients require to prefer additional systemic treatment for a scenario of a newly diagnosed, asymptomatic, incurable abdominal tumor. A qualitative, descriptive, thematic analysis explored factors influencing patients' decisions, and a narrative method integrated the quantitative and qualitative findings.

Results: In total, 100 patients participated (63% were older than 60 years of age). If additional treatment with added toxicity offered no OS advantage, 17% would prefer it for no PFS benefit; 26% for some PFS benefit (range, 3-9 months), whereas 51% would decline it regardless of PFS benefit. Similarly, 71% preferred additional treatment offering a 6-month OS advantage dependent on described toxicity levels ($P = .03$). A spectrum of reasons for these preferences reflected the complexity of participants' attitudes and values.

Conclusions: Prolongation of time to progression was not universally valued. Most patients did not prefer treatments that negatively affect quality of life for PFS gains alone. Implications for individual decision making, policy, and trials research are discussed.

least 5 years from the diagnosis of cancer. Similarly, patients were willing to accept a switch in the mode of administration or complete loss of hair to obtain an increase in survival.

Conclusion: In this study, the proportion of respondents who systematically preferred survival over all other treatment attributes was particularly high. Age, objective health literacy and locus of control accounted for heterogeneity in patients' preferences. Evidence on how NSCLC patients trade between survival and other NSCLC attributes can support regulators and other stakeholders on assessing clinical trial evidence and protocols, based on patients' conditions and socio-demographic parameters.



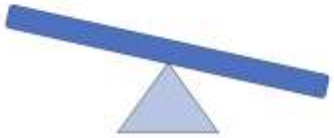
EGFR = Epidermal Growth Factor Receptor; ECOG = Eastern Cooperative Oncology Group

Saw SP, et al. *Am Soc Clin Oncol Educ Book*. 2024;44:e432516.

BALANCING EFFICACY, TOXICITY AND PATIENT FACTORS

Patient preference

Osimertinib mono



Consider

Combination therapy
FLAURA2, MARIPOSA

- **Good performance state**
- **No contraindications against combination therapies**
- **Brain metastases or other clinical risk factors**
- TP53 mutations
- Baseline EGFRmut in ctDNA

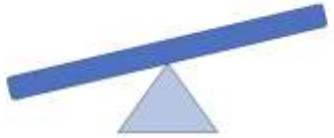
BALANCING EFFICACY, TOXICITY AND PATIENT FACTORS

Patient preference

Consider

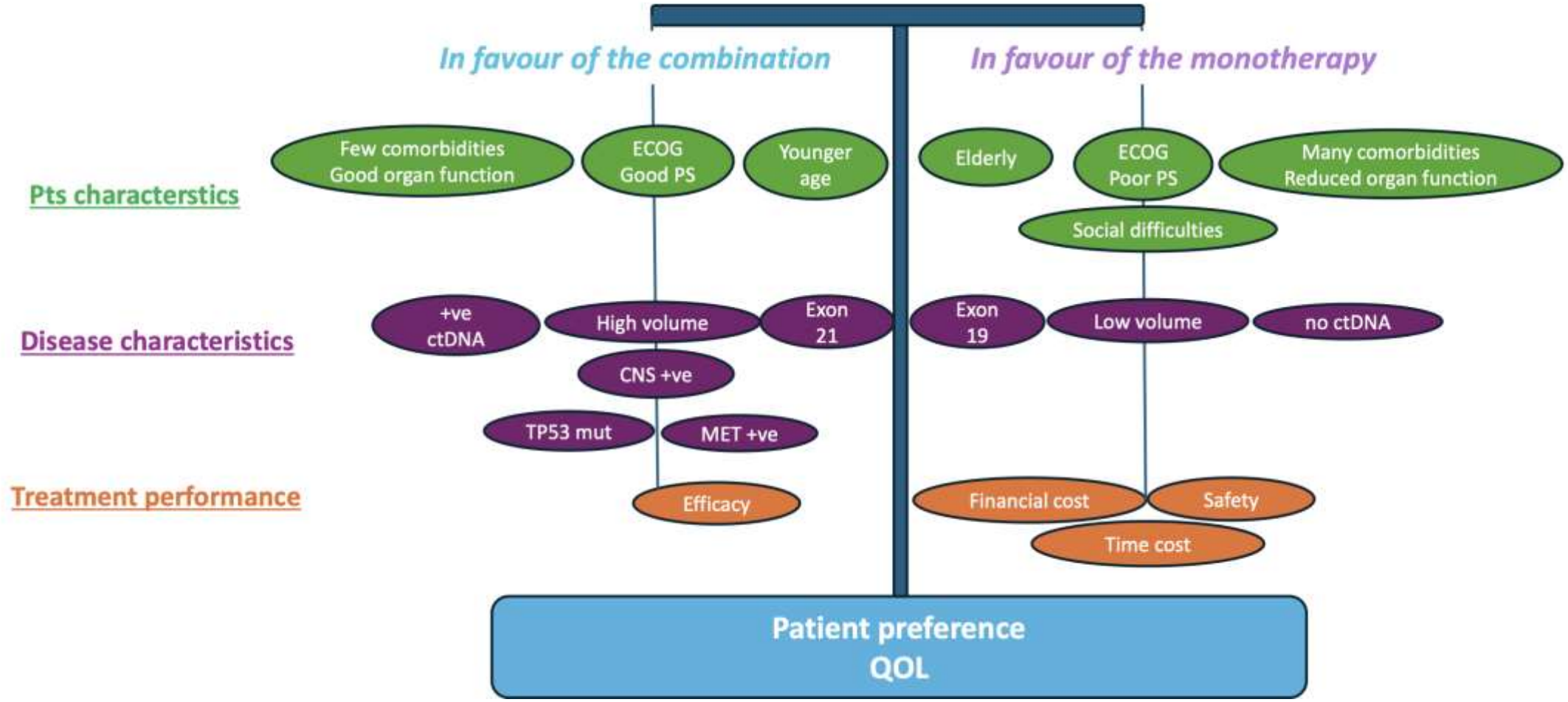
Osimertinib mono

- **Comorbidities precluding combination therapies**
- **> 75 years**
- **No brain metastases or other clinical risk factors**
- Absence of TP53 mutations
- Lack of baseline EGFRmut in ctDNA



Combination therapy
FLAURA2, MARIPOSA

How to choose the best strategy?

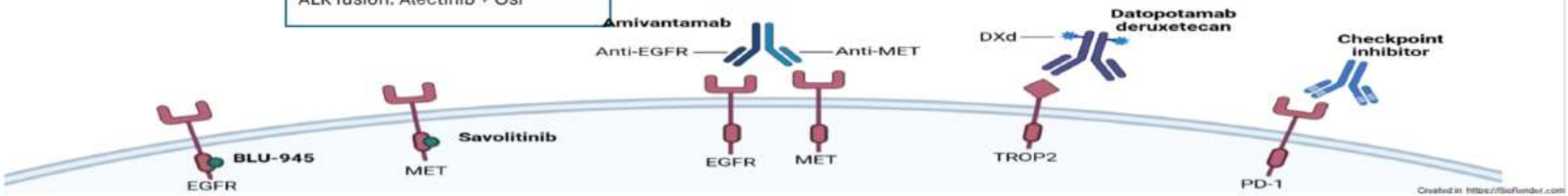


Testing for resistance mechanisms and assessing the posible therapeutic options available upon progression is critical to define an optimal management approach for patients

Genotype-matched strategies

Mechanism-agnostic strategies *(non-genotype based)*

On-target inhibition	Bypass pathway inhibition	On-target + bypass pathway inhibition	Targeting tumor-associated antigen	Targeting common escape routes
EGFR TKI/mAB	**Resistance-matched agents**	**Biespecific mAB/ADC targeting EGFR + bypass pathway**	**ADCs**	**mAB**
C797X mut: Gefitinib Gefitinib + Osi	cMET amp: Savolitinib + Osi Capmatinib + Osi Tepotinib + Osi cMET over-exp: Teliso V +/- Osi	Amivantamab (EGFR + cMET)	Datopotomab DXd (TROP2) Sacituzumab tirumotecan	Ivonescimab (PDL1 + VEGF) + Chemo
EGFR alt: Necitumumab + Osi 4G EGFR TKI	HER2 over-exp: TDM1 + Osi	Izalontamab brengitecan (EGFR + HER3)	Patritumab DXd (HER3)	Anti PD1/L1 + Antiangiogenic + Chemo
	RAS-MAPK act: Selumetinib + Osi			
	ALK fusion: Alectinib + Osi			

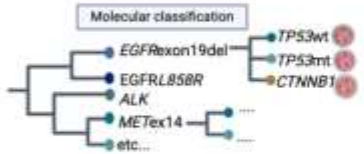


Navigating patients through tough decisions

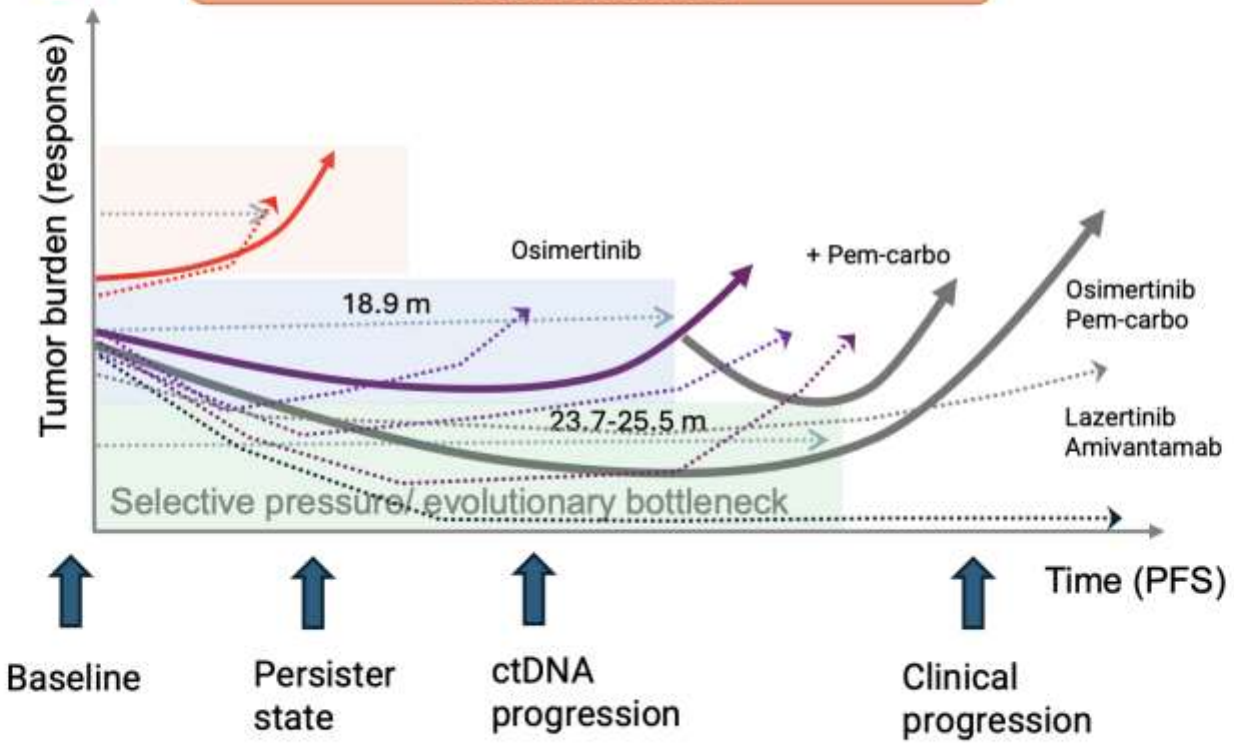
Baseline features

Current
- EGFR subtype
- Brain metastases

Emerging
- Co-alterations e.g cMET, TP53
- WGD (sub/clonal)
- PI/ PP/ TRU
- TME
- ADC targets
- Ecotypes



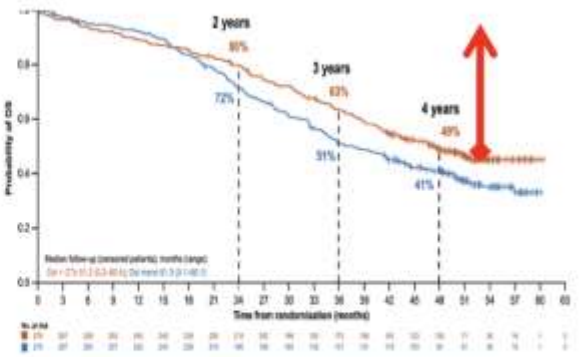
On treatment adaptive features



Longitudinal sampling

Outcomes

Real time feedback
Adaptive trials
Real world evidence
Proof of mechanism readouts
Surrogate endpoints
Patient centric



FINAL COMMENTS

- Therapeutic combinations for advanced EGFR-mutated NSCLC have shown superior scientific evidence over osimertinib monotherapy, impacting PFS and OS.

- The increased adverse effects with combinations should also be considered.

- Osimertinib monotherapy still has a role in a broad group of patients characterized by:
  - Older age
  - Poorer functional status
  - More comorbidities
  - Absence of p53 and MET amplification
  - No detectable basal ctDNA
  - Low tumor volume
  - Social and geographical difficulties

- In addition to economic considerations, we must never forget safety, continuous hospital visits, and consulting patients about their preferences (CLINICAL BENEFIT vs SCIENTIFIC EVIDENCE)

- In the future, we believe that the determination of biomarkers and dynamic ctDNA will allow for better therapeutic selection.

TAKE HOME MESSAGES

- Initiation of therapeutic combinations in frontline setting improves PFS and overall survival in EGFR mutated NSCLC
  - Osi + Chemo: Median OS: 47,5 m vs. 37,6 m [HR: 0,77 (0,61-0,96) p= 0,02]
  - Amivantamab + Lazertinib: Median OS: NE vs. 36,7m [HR: 0,75 (0,61-0,92) p= 0,005]
- Osimertinib monotherapy still has its role in a large group of patients
- Real-world studies are needed to assess the beneficial effect of the combinations in these clinical trials
- Predictive biomarker for this combination treatment will be important
- The patterns of resistance that develop after each régimen may further refine our clínical decisión making and treatment sequening
- First-line treatment selection can be tailored according to clinical characteristics and shared decisión making

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU

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