Metastatic Non-Small Cell Lung Cancer. A 2024 update.

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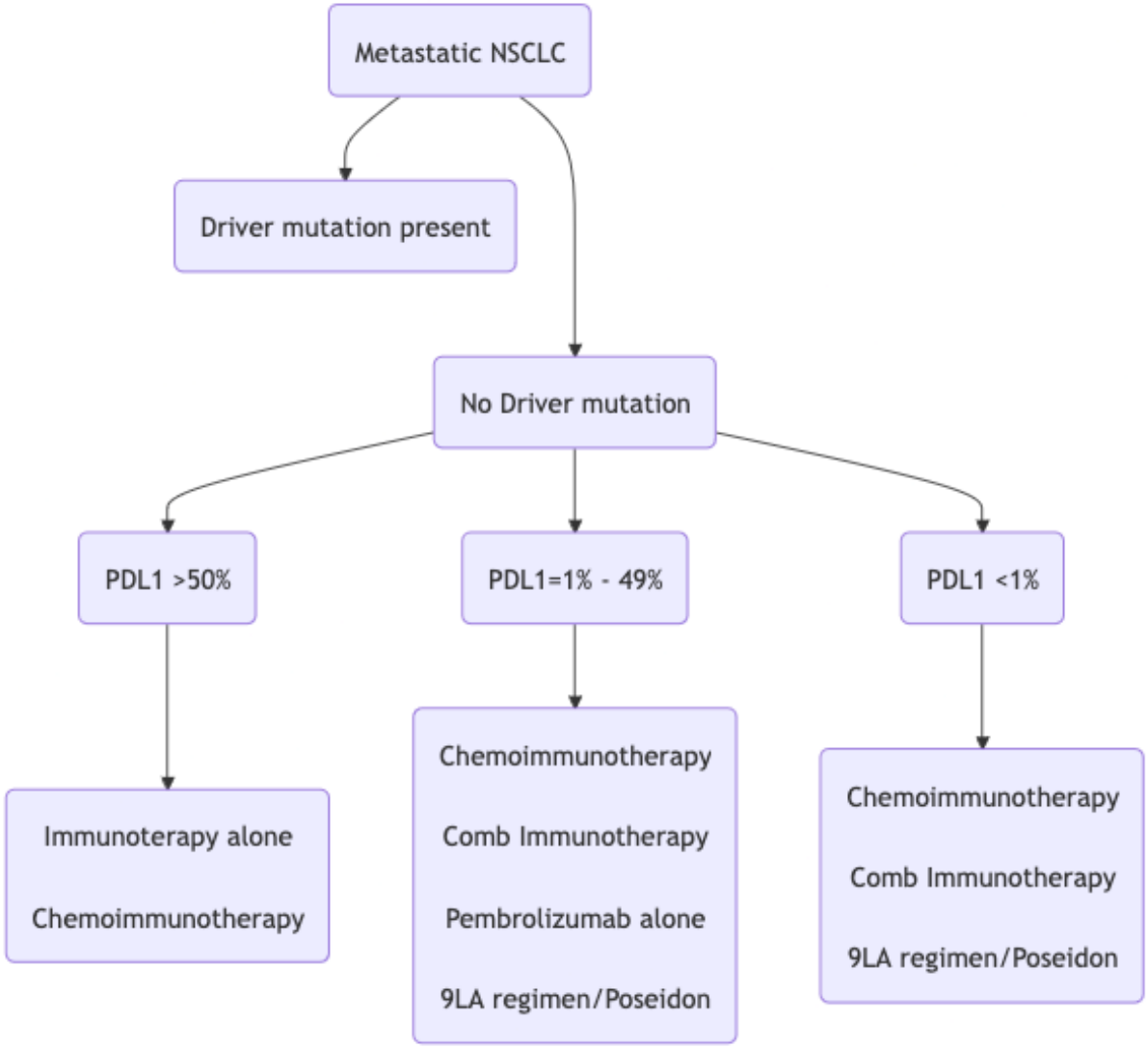
Background

- Several phase 3 studies have been reported in the last couple of years.
- Several FDA approvals have occurred in 2024.
- Field is in flux with no clear standards and many options.

Initial treatment

- Depends on clinical, molecular and patient characteristics.
- All patients should have NGS to look for driver mutations. Circulating CT-DNA and tissue based NGS are complimentary.

Treatment algorithms



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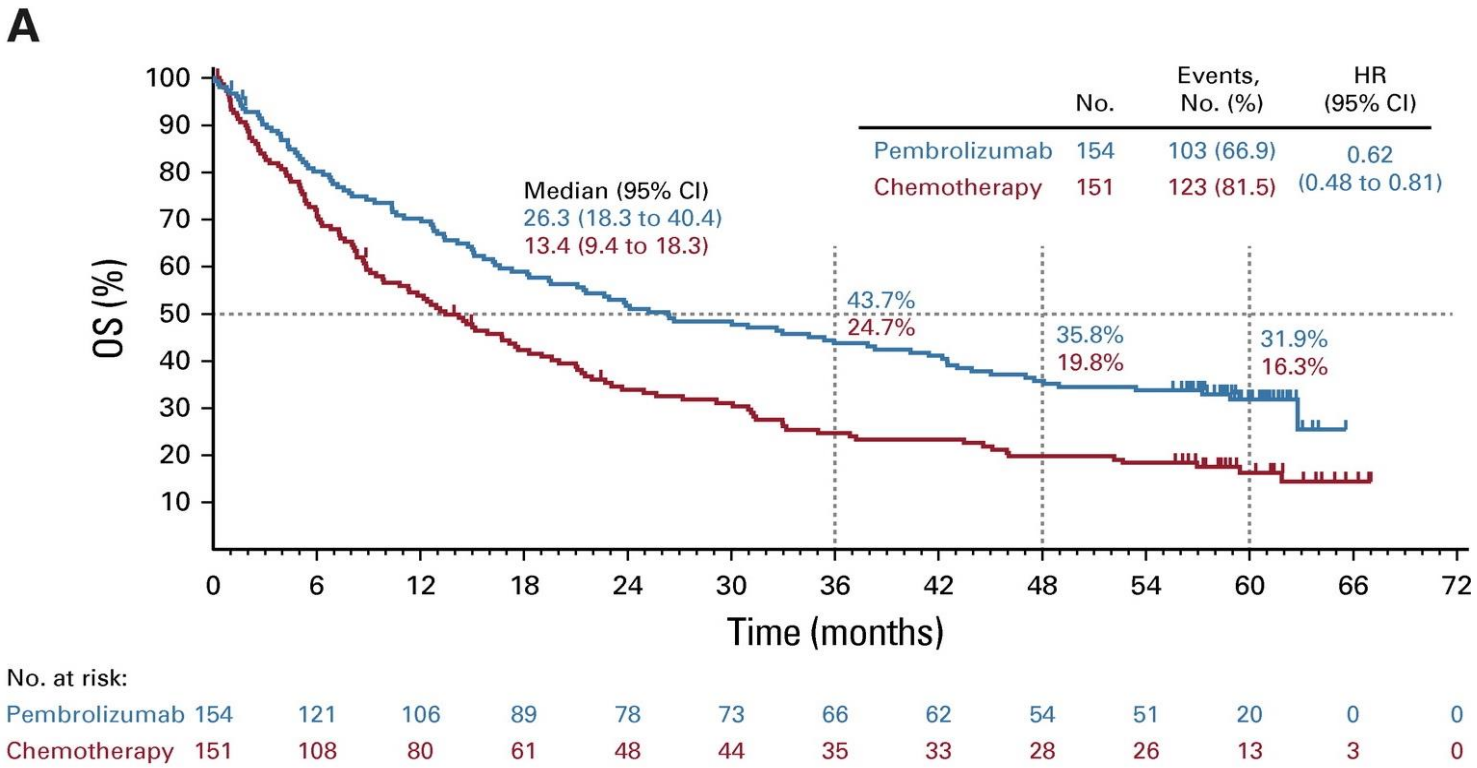

Published in: Martin Reck; Delvys Rodríguez-Abreu; Andrew G. Robinson; Rina Hui; Tibor Csőszi; Andrea Fülöp; Maya Gottfried; Nir Peled; Ali Tafreshi; Sinead Cuffe; Mary O'Brien; Suman Rao; Katsuyuki Hotta; Ticiana A. Leal; Jonathan W. Riess; Erin Jensen; Bin Zhao; M. Catherine Pietanza; Julie R. Brahmer; *Journal of Clinical Oncology* 2021 392339-2349.
DOI: 10.1200/JCO.21.00174

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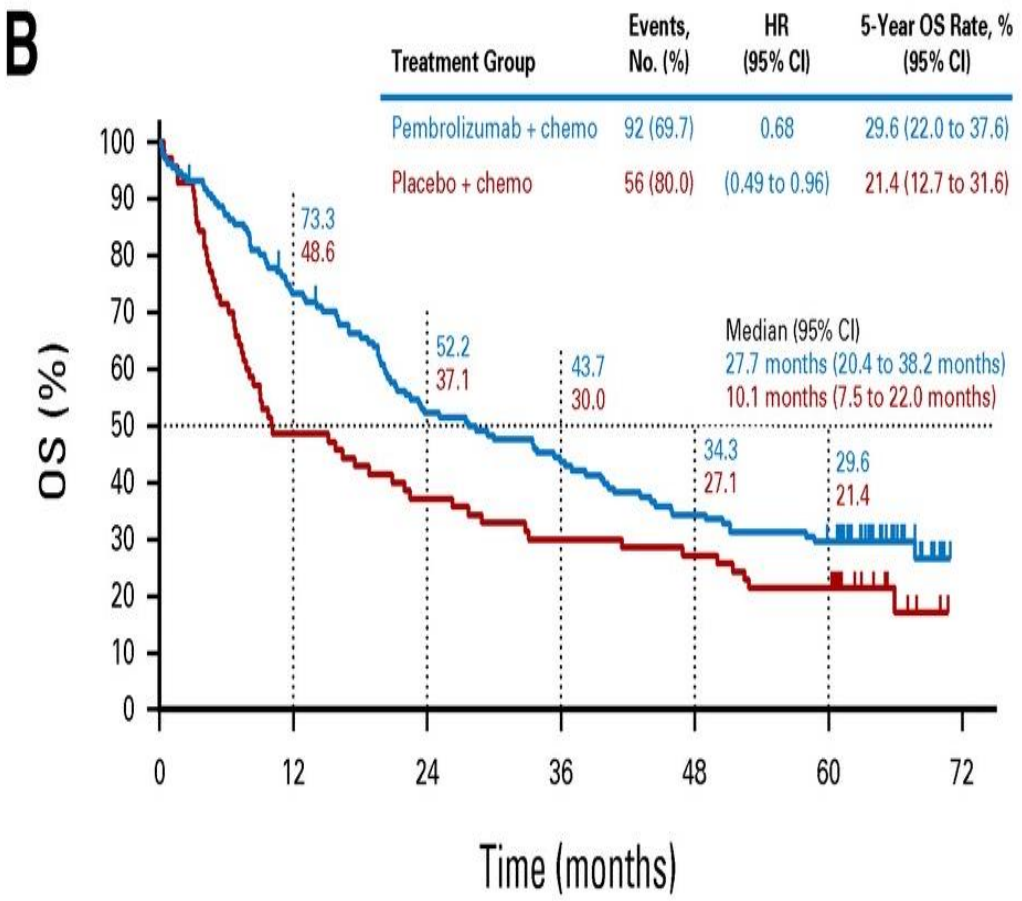
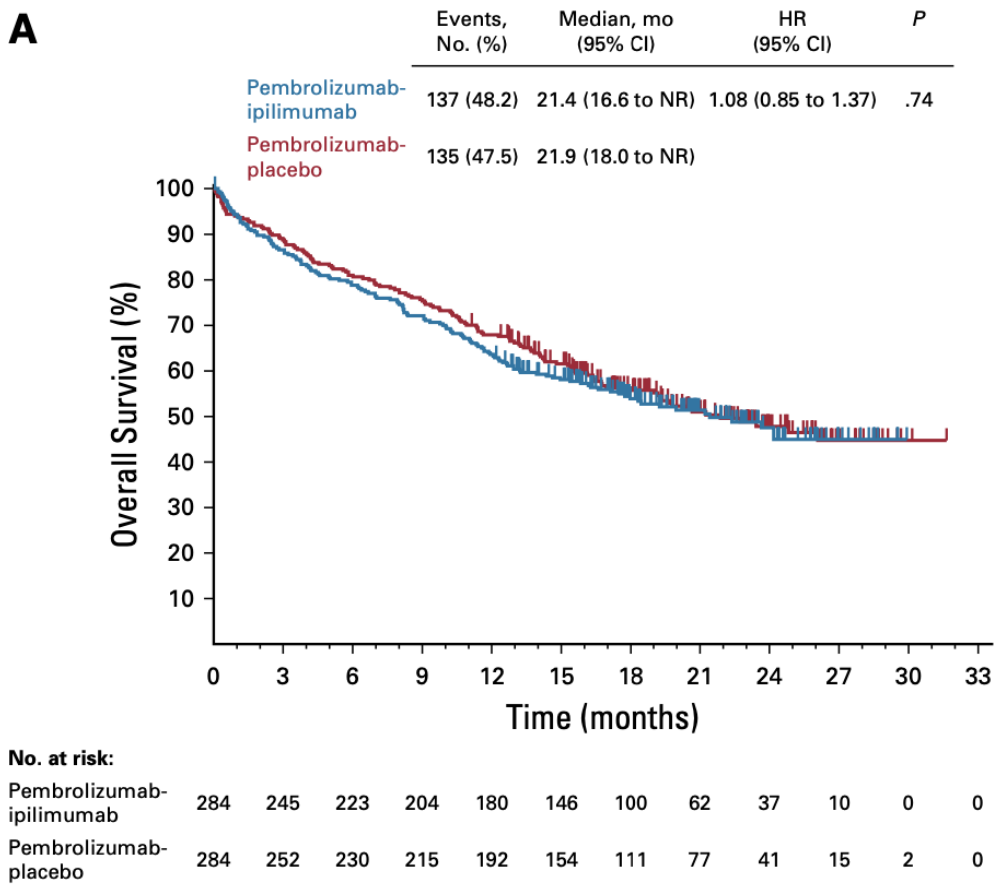


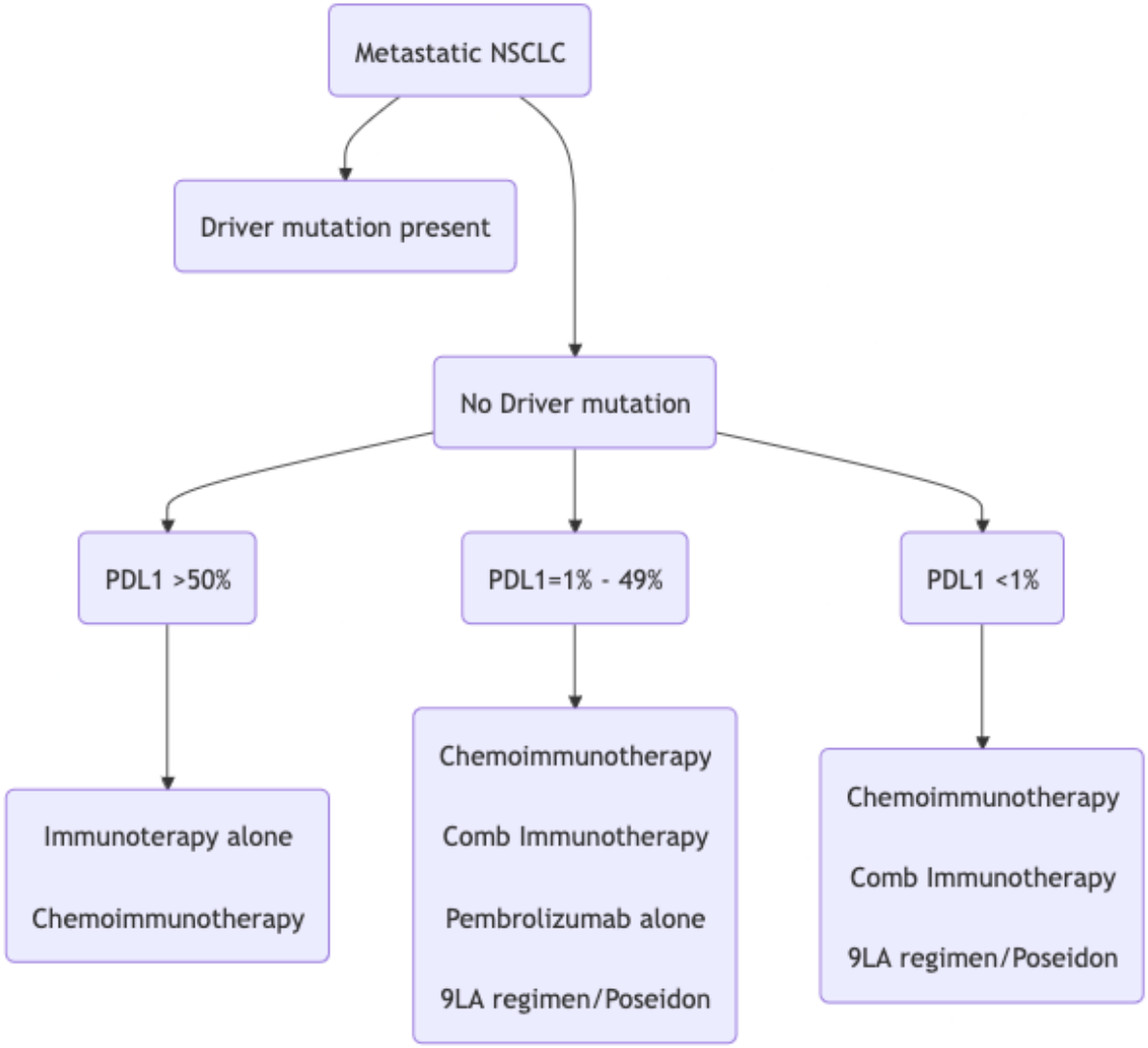
Published in: Marina C. Garassino; Shirish Gadgeel; Giovanna Speranza; Enriqueta Felip; Emilio Esteban; Manuel Dómine; Maximilian J. Hochmair; Steven F. Powell; Helge G. Bischoff; Nir Peled; Francesco Grossi; Ross R. Jennens; Martin Reck; Rina Hui; Edward B. Garon; Takayasu Kurata; Jhanelle E. Gray; Paul Schwarzenberger; Erin Jensen; M. Catherine Pietanza; Delvys Rodríguez-Abreu; *Journal of Clinical Oncology* 2023 411992-1998.
DOI: 10.1200/JCO.22.01989

CTLA4 did nothing

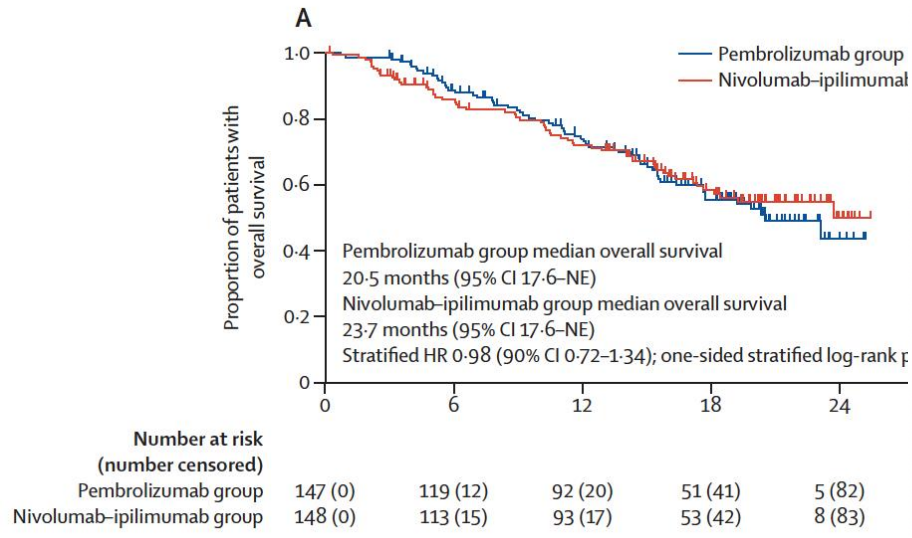


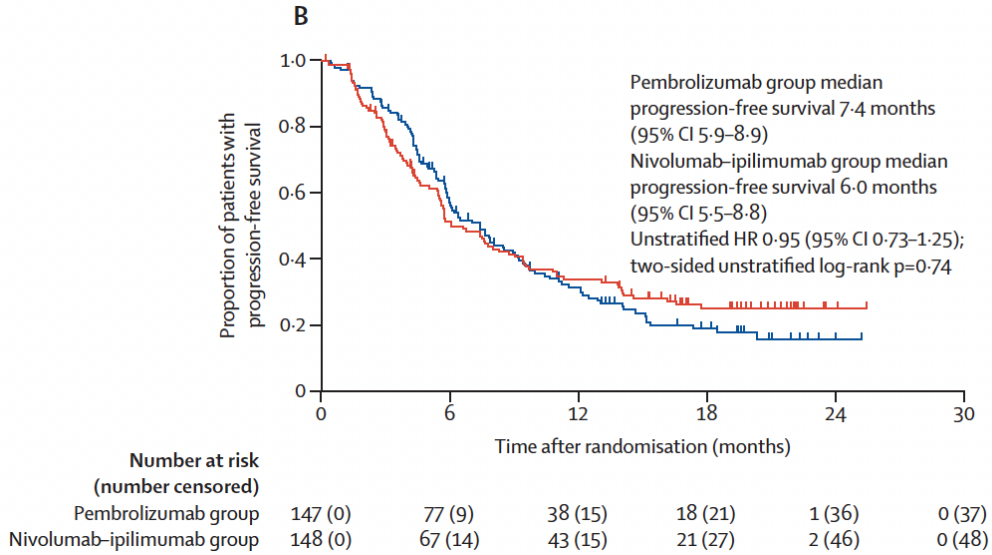
Boyer, M. *et al. J Clin Oncol* **39**, 2327–2338 (2021). PMID (33513313)

Treatment algorithms



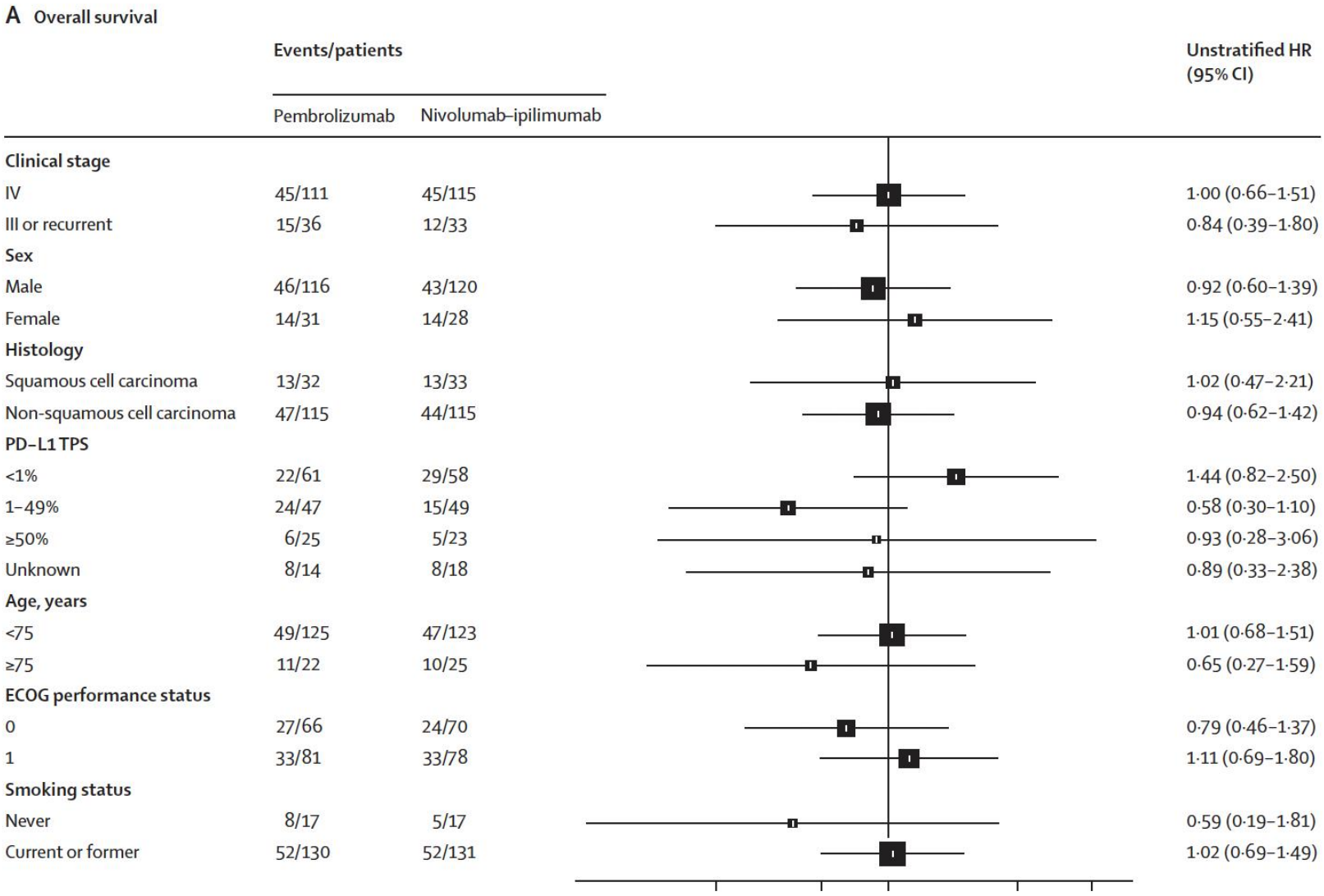
Nippon study





Shiraishi Y. Lancet Respir Med. 2024 PMID: 39159638.

Subgroups



A Overall survival

	Events/patients		Unstratified HR (95% CI)
	Pembrolizumab	Nivolumab–ipilimumab	
Clinical stage			
IV	45/111	45/115	1·00 (0·66–1·51)
III or recurrent	15/36	12/33	0·84 (0·39–1·80)
Sex			
Male	46/116	43/120	0·92 (0·60–1·39)
Female	14/31	14/28	1·15 (0·55–2·41)
Histology			
Squamous cell carcinoma	13/32	13/33	1·02 (0·47–2·21)
Non-squamous cell carcinoma	47/115	44/115	0·94 (0·62–1·42)
PD-L1 TPS			
<1%	22/61	29/58	1·44 (0·82–2·50)
1–49%	24/47	15/49	0·58 (0·30–1·10)
≥50%	6/25	5/23	0·93 (0·28–3·06)
Unknown	8/14	8/18	0·89 (0·33–2·38)
Age, years			
<75	49/125	47/123	1·01 (0·68–1·51)
≥75	11/22	10/25	0·65 (0·27–1·59)
ECOG performance status			
0	27/66	24/70	0·79 (0·46–1·37)
1	33/81	33/78	1·11 (0·69–1·80)
Smoking status			
Never	8/17	5/17	0·59 (0·19–1·81)
Current or former	52/130	52/131	1·02 (0·69–1·49)

Adverse events

	Pembrolizumab group (n=144)			Nivolumab–ipilimumab group (n=146)		
	Non-squamous cell carcinoma (n=112)	Squamous cell carcinoma (n=32)	Total (n=144)	Non-squamous cell carcinoma (n=114)	Squamous cell carcinoma (n=32)	Total (n=146)
Grade 2 or worse	87 (78%)	29 (91%)	116 (81%)	96 (84%)	29 (91%)	125 (86%)
Grade 3 or worse	43 (38%)	16 (50%)	59 (41%)	65 (57%)	22 (69%)	87 (60%)
Grade 4 or worse	5 (4%)	2 (6%)	7 (5%)	12 (11%)	6 (19%)	18 (12%)
Grade 5 (treatment-related death)	2 (2%)	1 (3%)	3 (2%)	9 (8%)	2 (6%)	11 (8%)

Data are n (%).

Table 2: **Numbers of patients with non-haematological toxicities**

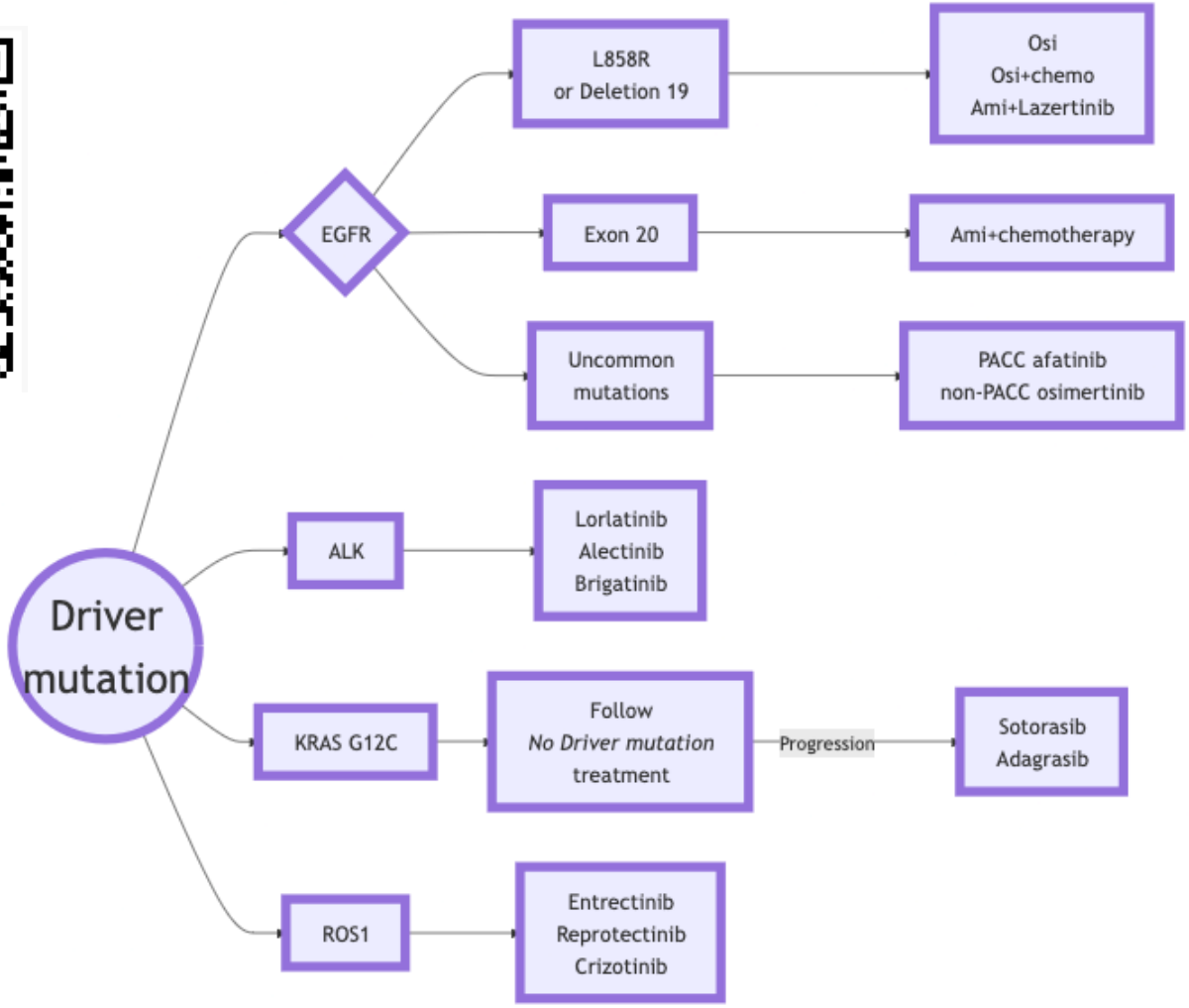
Conclusions Driver negative.

- Depends on PDL1 staining. Not a perfect biomarker.
- In PDL1>50. Immunotherapy alone is an option.
- In others depends on discussion with a patient to understand their values, goals, hope.

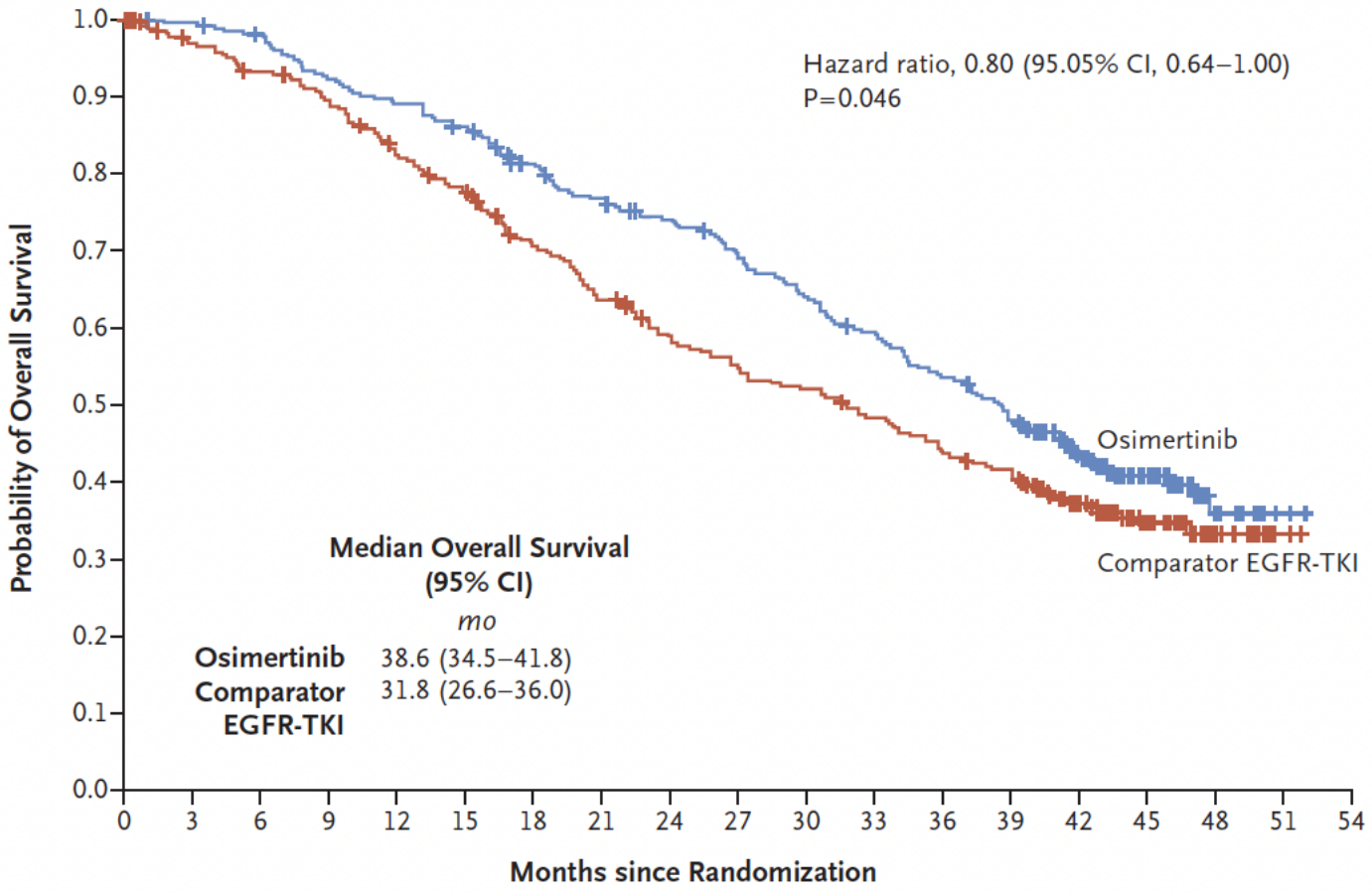
Mutation driven cancers

- When there is a target.
- In the majority of cases.
  - Better responses.
  - Better tolerance.
  - Still palliative.

Driver mutation driven NSCLC



FLAURA OG



No. at Risk

Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Initial treatment of patients with metastatic EGFR+ lung cancer.

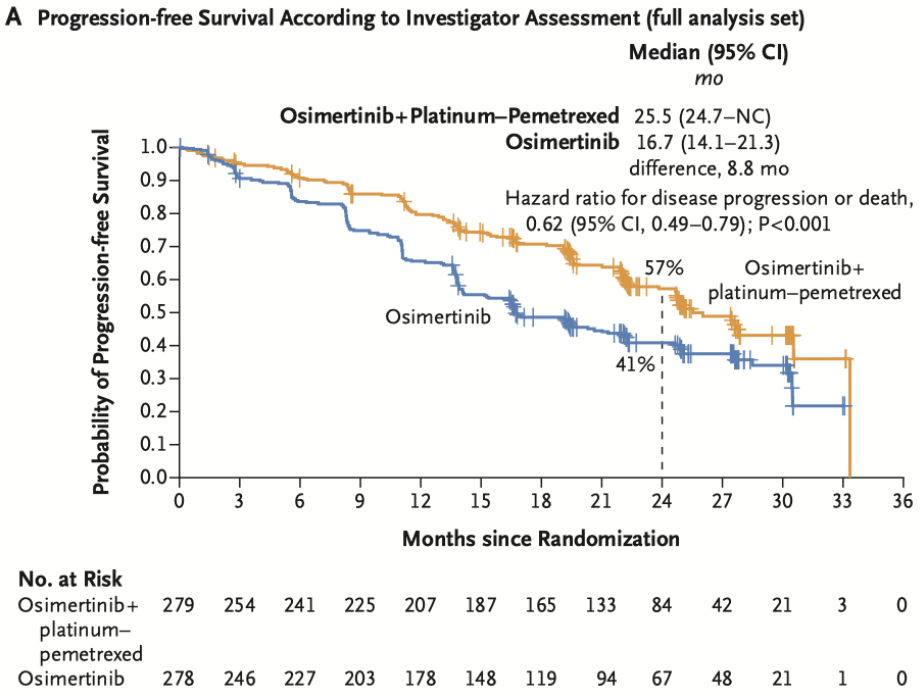
- Patient with EGFR +ve lung cancer have remarkable response to osimertinib; however, this are not long lived (median DOT 20.7 months) and eventually patients progress needing other forms of treatment.
- FLAURA2 was a phase 3 study that compared patients treated with osimertinib vs the experimental arm of osimertinb + carboplatin and pemetrexed.

Planchard, D. *et al.* Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. *N Engl J Med* **389**, 1935–1948 (2023).

Results

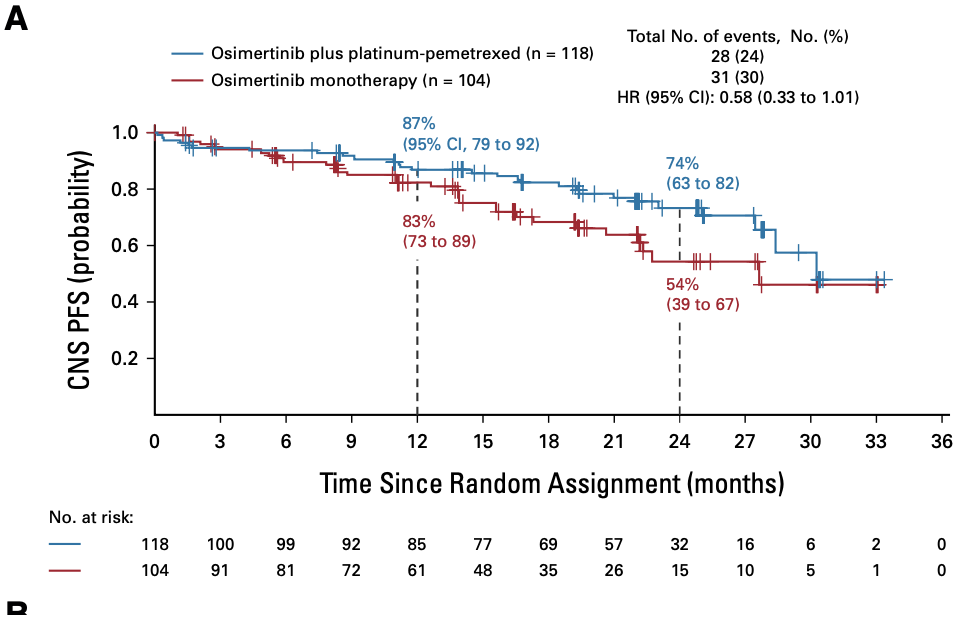
- Eligibility criteria. Del19 or L858R. Metastatic and asymptomatic CNS disease was allowed (41%).
- Primary endpoint. PFS.
- 557 patients were randomized.
- 76% completed the planned 4 cycles of platinum and a median of 12 cycles (range, 1 to 48) of pemetrexed.
- ORR did not differ (83 vs 76%)

Results



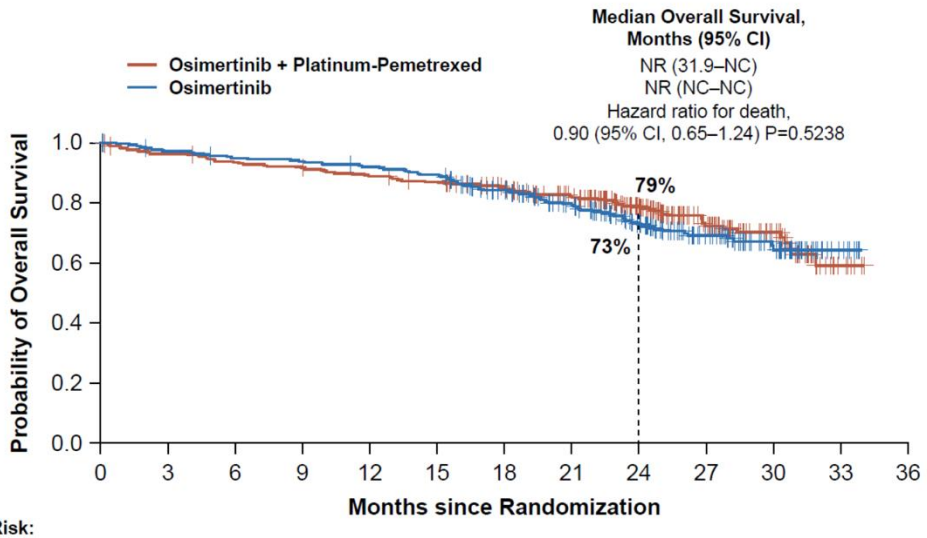
No. at Risk													
Osimertinib+ platinum–pemetrexed	279	254	241	225	207	187	165	133	84	42	21	3	0
Osimertinib	278	246	227	203	178	148	119	94	67	48	21	1	0

PFS in patients with CNS disease



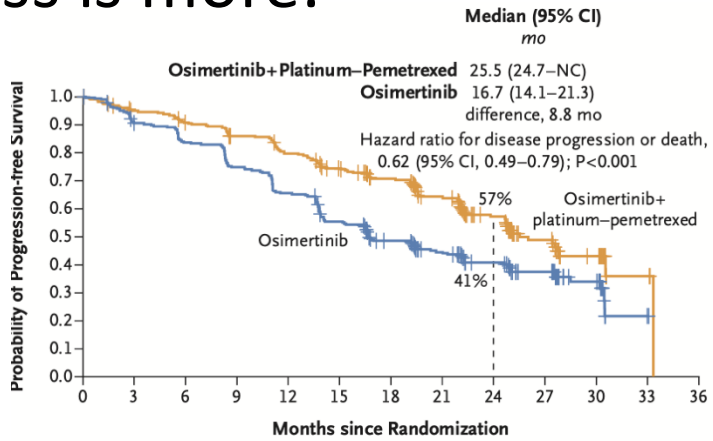
Jänne, P. A. *et al.* CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor-Mutated Advanced Non-Small-Cell Lung Cancer. *J Clin Oncol* JCO2302219 (2023).

Overall survival



So now what?

- Clearly an option that improves PFS compared to osi alone. Unknown if this will translated into an OS advantage compared to sequential treatment.
- Who are the patient that would benefit from a more aggressive treatment? Large burden of disease? Significant CNS disease?
- Who are those patient that are likely to stay on osi for a few years, those years where less is more.



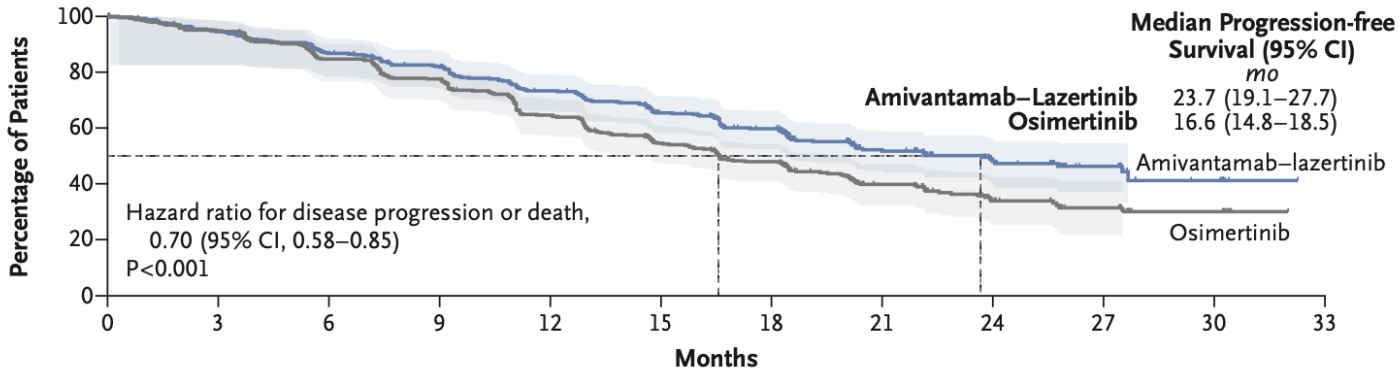
Ami + Lazertinib

- Amivantamab, an EGFR-MET bispecific antibody.
- Lazertinib is a 3rd gen TKI against EGFR.
- Active in the second line setting.
- RCT compared to osimertinib.

Cho, B. C. *et al*. Amivantamab plus Lazertinib in Previously Untreated EGFR - Mutated Advanced NSCLC. *New England Journal of Medicine*(2024).

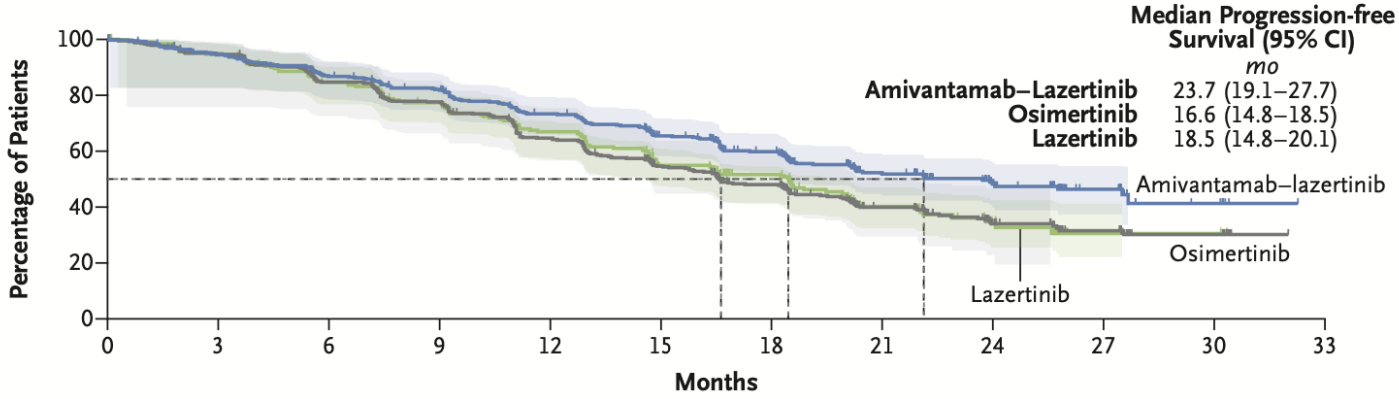
Results

A **Progression-free Survival in the Amivantamab–Lazertinib Group as Compared with the Osimertinib Group**



No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

B **Progression-free Survival in Amivantamab–Lazertinib Group as Compared with the Osimertinib and the Lazertinib Monotherapy Groups**



No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

Adverse events

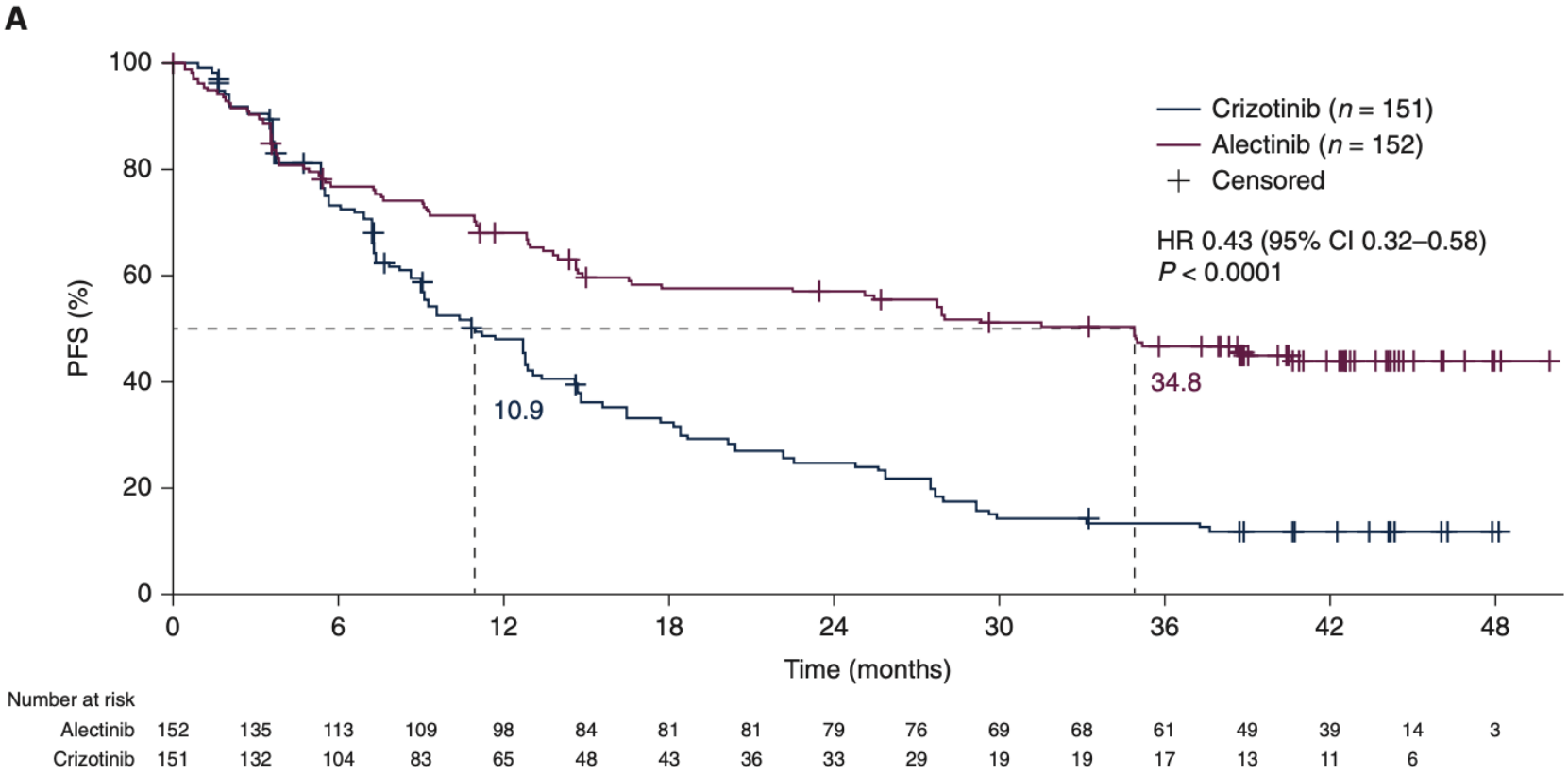
Table 3. Adverse Events.*

Event	Amivantamab–Lazertinib (N = 421)		Osimertinib (N = 428)	
	All	Grade ≥3	All	Grade ≥3
	number of patients (percent)			
Any event	421 (100)	316 (75)	425 (99)	183 (43)
Any serious event	205 (49)		143 (33)	
Any event resulting in death		34 (8)		31 (7)
Event leading to interruption of any trial agent	350 (83)		165 (39)	
Event leading to dose reduction of any trial agent	249 (59)		23 (5)	
Event leading to discontinuation of any trial agent	147 (35)		58 (14)	
Adverse events reported in ≥15% of the patients in either group†				

Conclusions EGFR

- Clearly some patients do extremely well on Osi.
- However others are likely to benefit from escalation of therapy. Who and how?
- In my own practice I continue to use osi as the standard with a discussion with the patient about the other options.

ALK



Mok, T. *et al. Ann Oncol* **31**, 1056–1064 (2020). PMID (32418886)

Lorlatanib

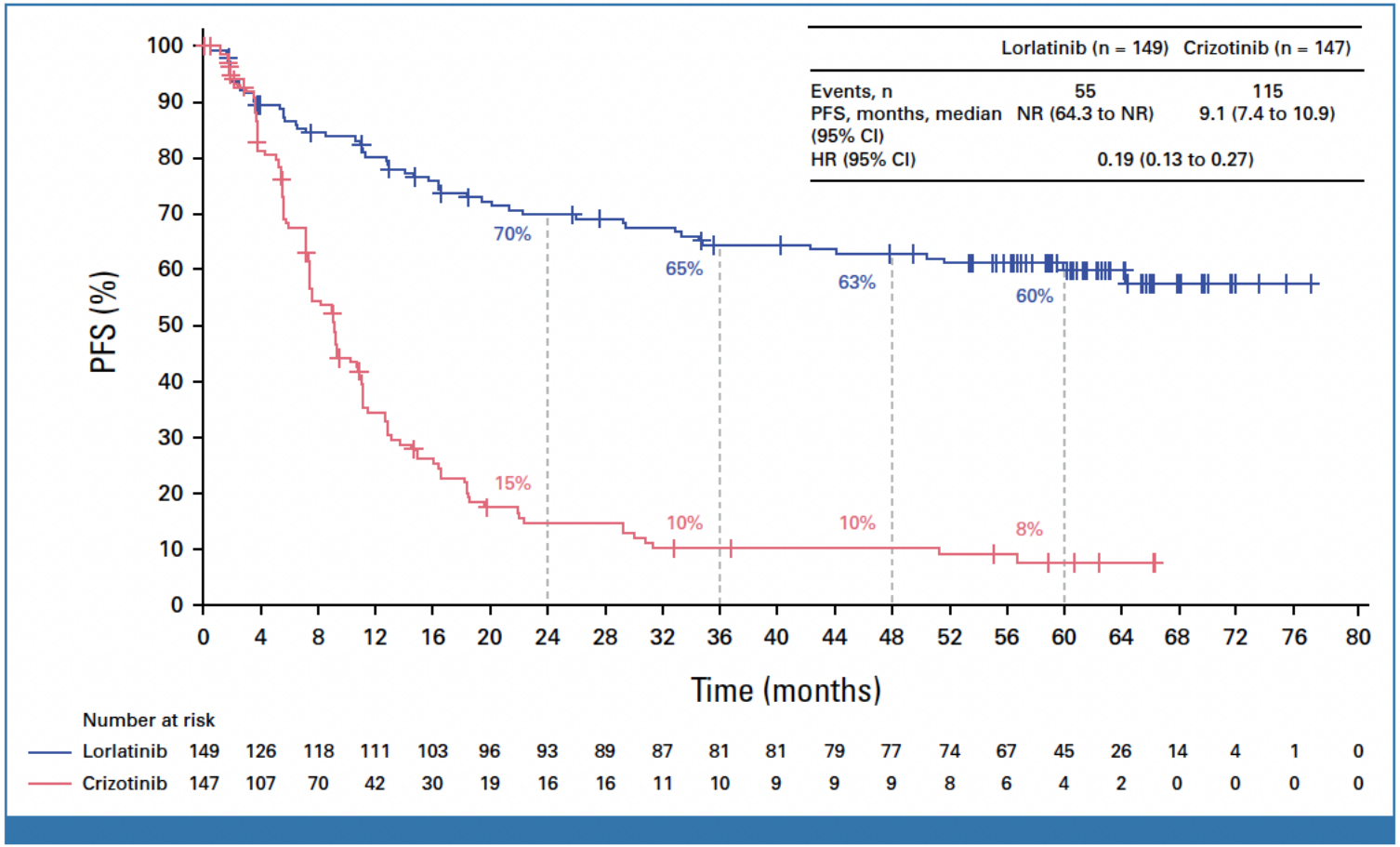


FIG 2. PFS by investigator assessment in the intention-to-treat population. HR, hazard ratio; NR, not reached; PFS, progression-free survival.

Solomon, B. J. *et al. J Clin Oncol* JCO2400581 (2024). PMID (38819031)

Adverse events

TABLE 2. Summary of AEs

Safety Population	Lorlatinib (n = 149)	Crizotinib (n = 142)
All-causality AEs, No. (%)		
Any grade	149 (100)	140 (99)
Grade 3/4	115 (77)	81 (57)
Grade 5	14 (9)	7 (5)
Serious	65 (44)	45 (32)
Leading to temporary drug discontinuation	92 (62)	68 (48)
Leading to dose reduction	34 (23)	21 (15)
Leading to permanent drug discontinuation	16 (11)	15 (11)

TABLE A4. Summary of CNS AEs in the Lorlatinib Group

	Lorlatinib (n = 149)				
Cluster Term	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AEs, No. (%)	63 (42)	36 (24)	18 (12)	8 (5)	1 (1)
Cognitive effects[a]	41 (28)	25 (17)	11 (7)	5 (3)	0
Mood effects[b]	31 (21)	17 (11)	12 (8)	2 (1)	0
Speech effects[c]	9 (6)	6 (4)	2 (1)	1 (1)	0
Psychotic effects[d]	8 (5)	5 (3)	1 (1)	1 (1)	1 (1)

Conclusions

- Multiple options where options were very limited.
- Back to being a good oncologist where we find out our patient's goals, hopes and values and recommend treatment based on these.

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Thank you

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