EARLY STAGE RESECTABLE LUNG CANCER: ADJUVANT IMMUNOTHERAPY

MaTOS

Albuquerque, New Mexico

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Christina Baik MD MPH

Associate Professor of Medicine

Fred Hutchinson Cancer Center

University of Washington

Fred Hutch Cancer Center

UNIVERSITY of WASHINGTON

CHALLENGES OF NEOADJUVANT THERAPY

- Increasing evidence to support the use of neoadjuvant chemo-immunotherapy in resectable NSCLC
- But important to recognize challenges of giving neoadjuvant therapy:
  - Timely referral of patients with resectable disease to medical oncology before surgery
  - Uncommon but some patients develop prohibitive toxicities from neoadjuvant therapy that may result in cancelled or delayed surgery

STUDY	% not going to surgery (chemoIO vs chemo)	% AE leading to surgery cancellation	% AE leading to surgery delay	Immune related AE leading to surgery delay or cancellation
CM-816	17 v 25	1 v 0.6	3.4 v 5.1	Pneumonitis, rash
KN-671	18 v 21	6.3 v 4.2	N/A	Pneumonitis, (sudden cardiac death)
AEGEAN	19 v 19	1.8 v 1.2	3.9 v 4.0	N/A

AEGEAN Heymach *et al.* NEJM 2023; 389(19):1672-1684
CheckMate816: Forde *et al* NEJM 2022 May 26;386(21):1973
KEYNOTE-671: Wakelee *et al.* NEJM 2023; 389(6):491-503

Not common but some patients do have delay or cancellation of surgery due to toxicities

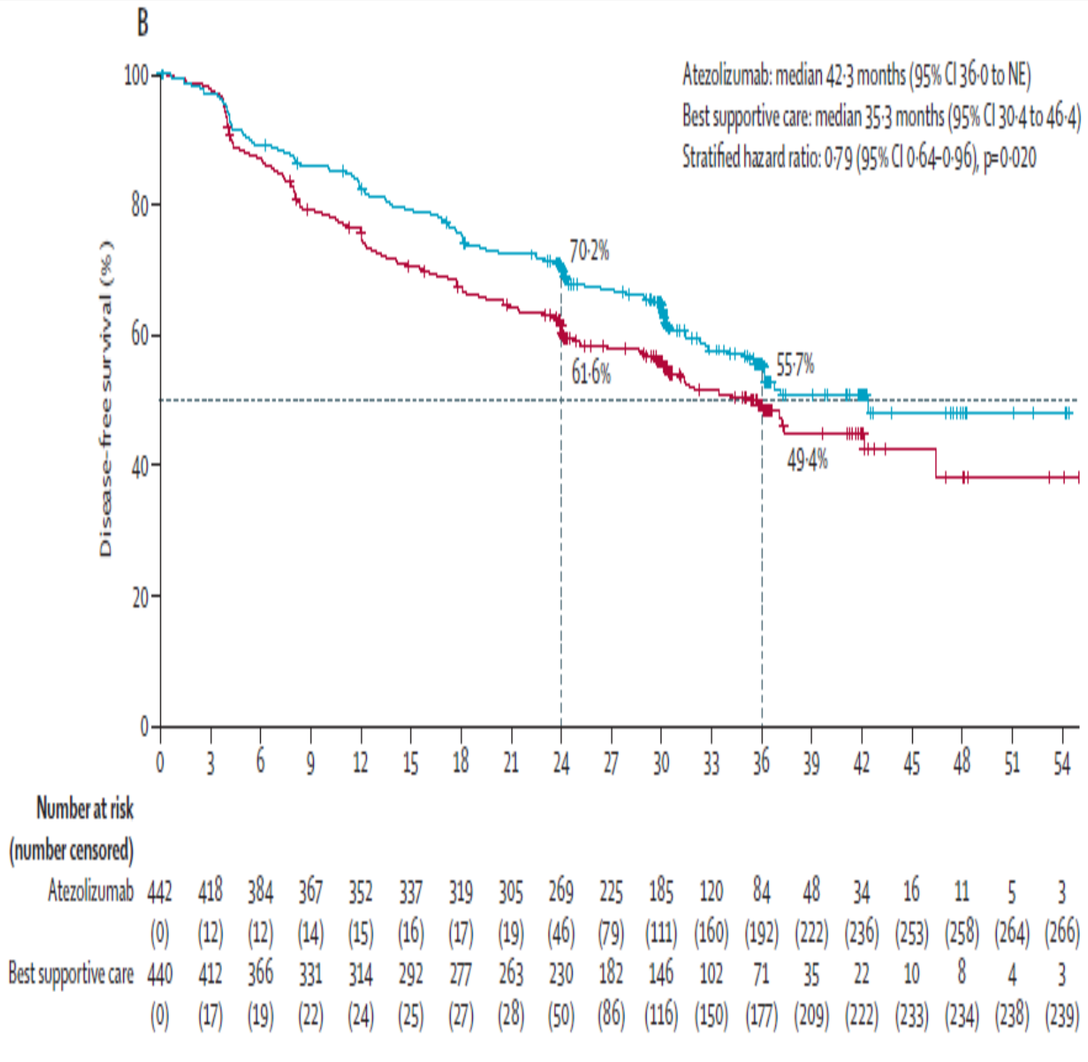
CLINICAL SCENARIO #1: PATIENT SEES MEDICAL ONCOLOGIST BEFORE SURGERY

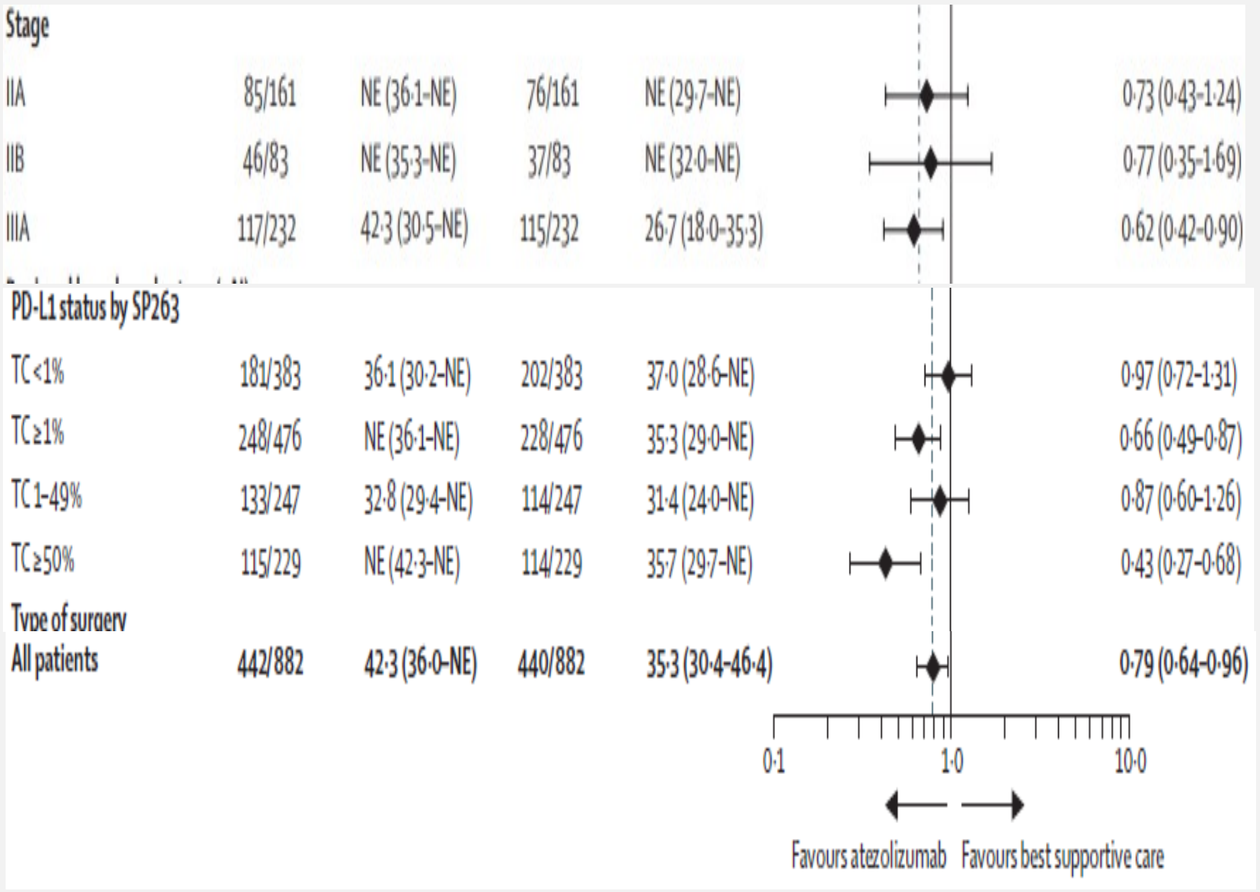
- My personal opinion is that most patients with resectable NSCLC should be offered neoadjuvant chemo-immunotherapy (if no EGFR / ALK)
- When to advocate for adjuvant therapy?
  - Increased risk of immune related toxicity (hx autoimmune disease)
  - Increased risk of chemo related toxicity (e.g. renal insufficiency)
  - Oncogene driven NSCLC (most neoadjuvant trials excluded patients with EGFR / ALK+ NSCLC)

CLINICAL SCENARIO #2: PATIENT SEES MEDICAL ONCOLOGIST AFTER SURGERY

- Who should receive adjuvant immunotherapy?
  - Does PDL-1 expression matter?
  - What about EGFR / ALK or other oncogenic alterations?

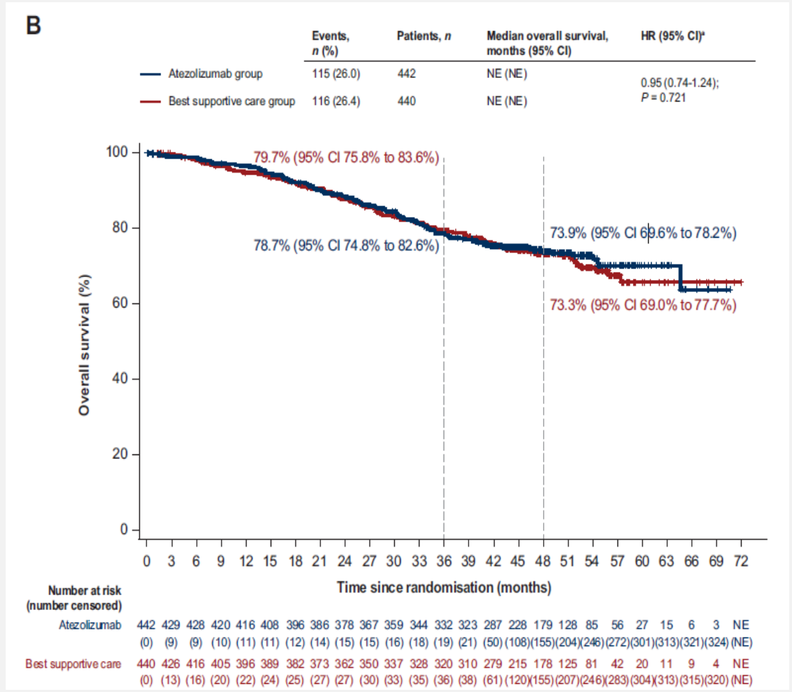
IMPOWER-010: Adjuvant atezolizumab, DFS

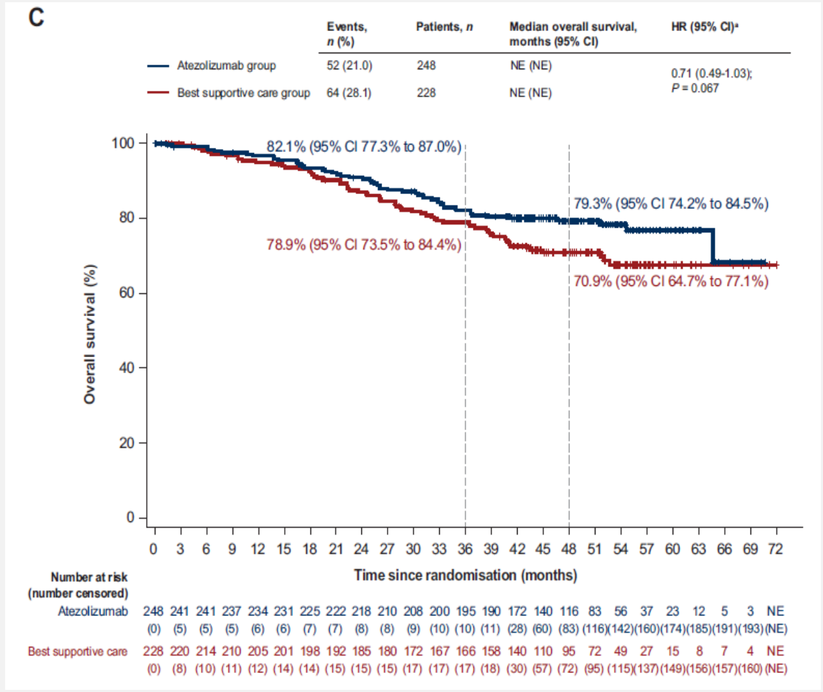


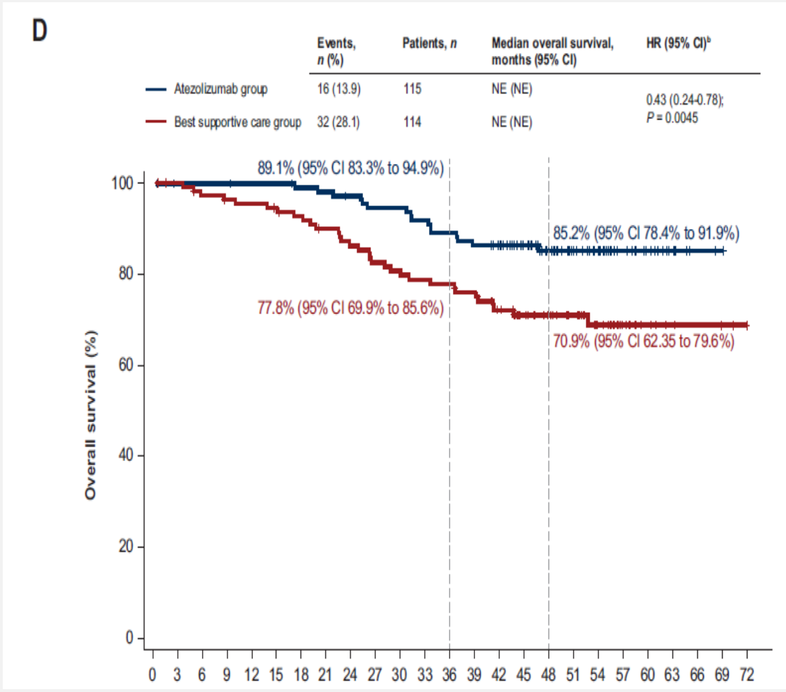


Felip *et al.* Lancet 2021, 9(398):1344-1357 Felip *et al.* Ann Oncol 2023, 34(10):907-919

IMPOWER-010. Overall survival







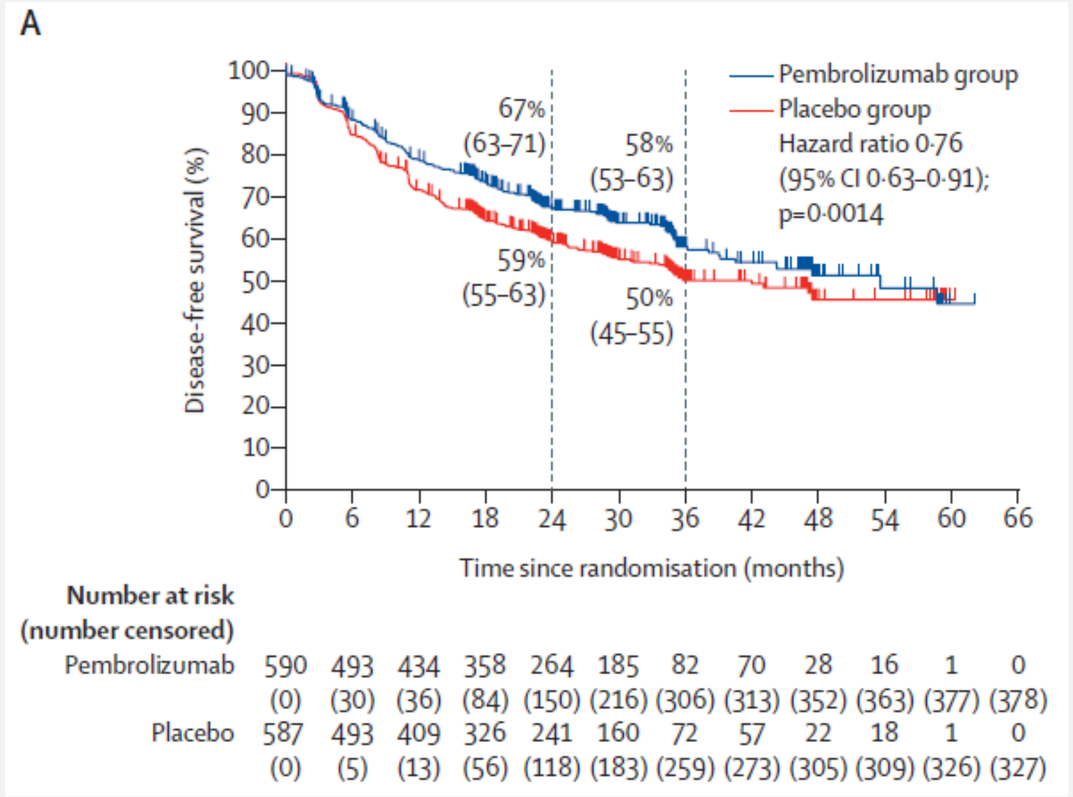
II-IIIA, any PDL1
HR 0.95 (p=0.72)

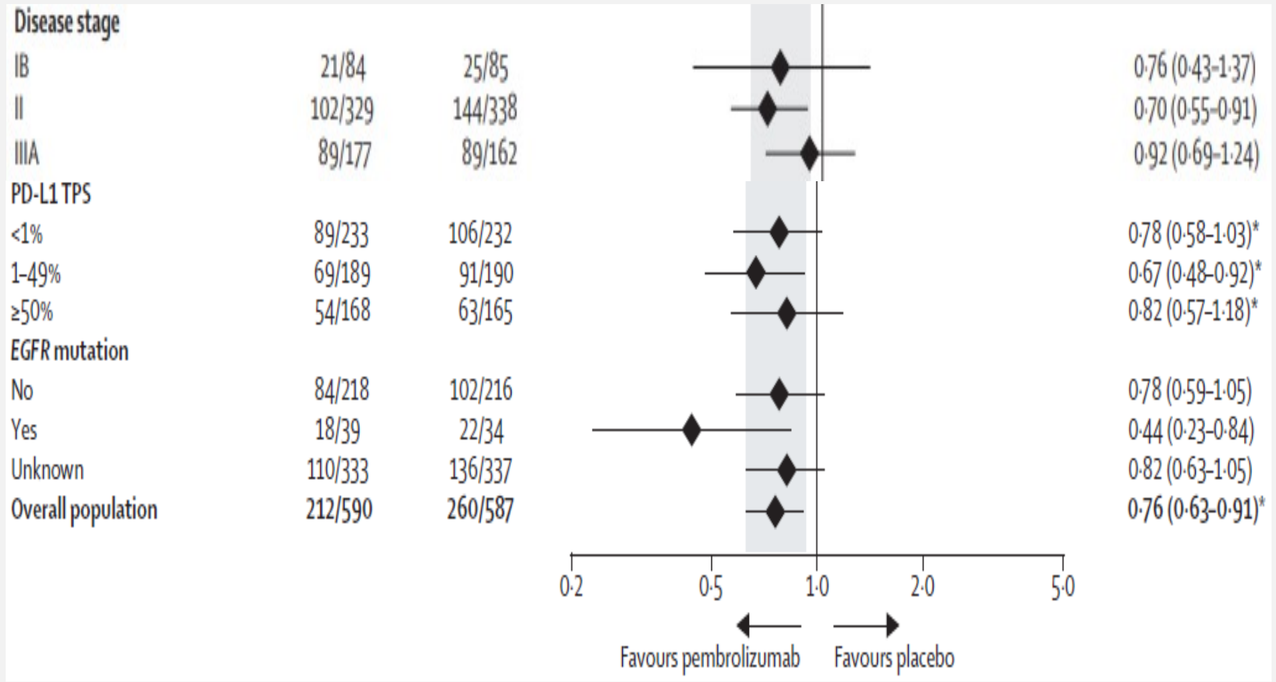
II-IIIA, PDL1 >1%
HR 0.71 (p=0.07)

II-IIIA, PDL1 >=50%
HR 0.43 (p=0.005)

Disease free survival and overall survival benefit of atezolizumab is most compelling in patients with PD-L1 positive (especially high) NSCLC

KEYNOTE-091 / PEARLS: Adjuvant pembrolizumab (interim analysis)





- DFS, ITT (any PD-L1): HR 0.76 (*p*=0.0014)
- DFS, PD-L1 >=50%: HR 0.82 (*p*=0.14)
- OS, ITT: HR 0.87, not statistically significant. Immature data
- FDA approved adjuvant pembro for any PD-L1 expressed NSCLC, stage IB-IIIA
- Subgroup data from this study should be interpreted with caution

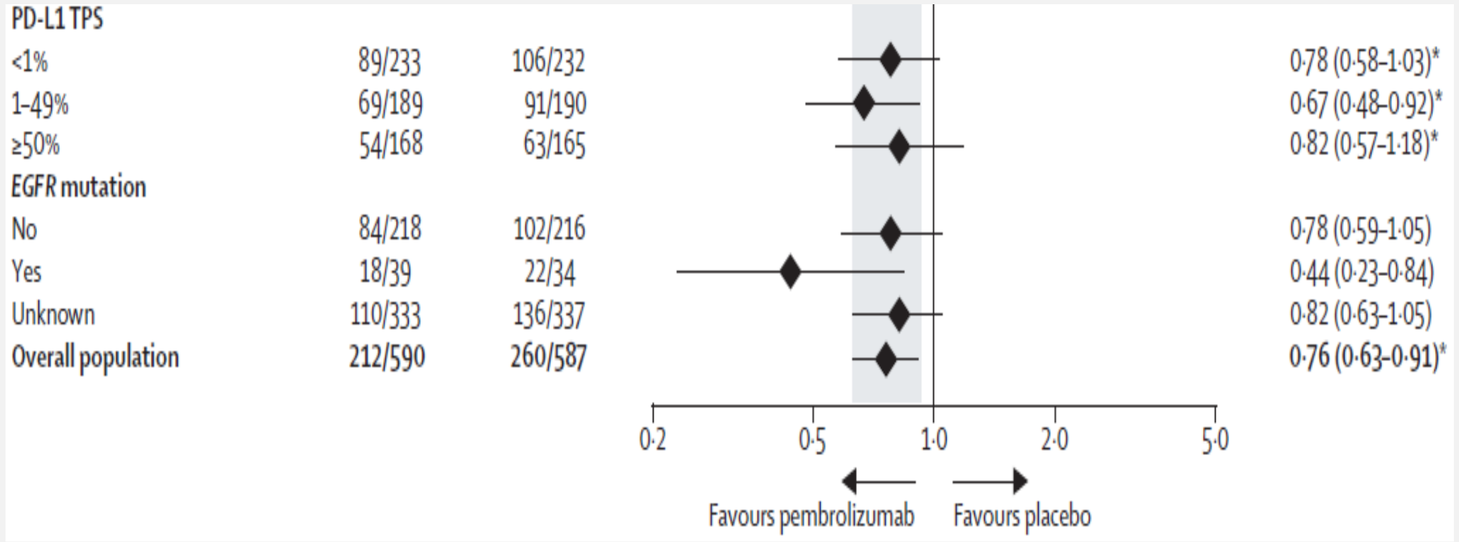
O'Brien et al. Lancet Oncol 2022, 23(10):1274-1286

What about patients with EGFR / ALK+ resected NSCLC?

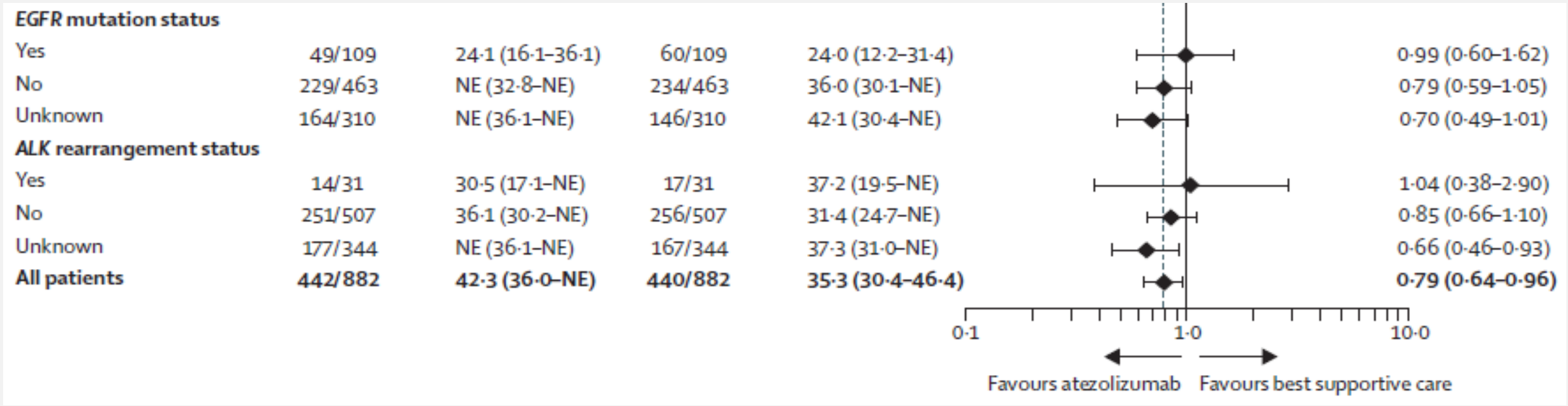
Based on what we know in the literature,
IO likely does not benefit this patient population

Overall body of literature indicate these patients will benefit from adjuvant TKI (ADAURA, ALINA)

ADJUVANT PEMBRO (PEARLS)



ADJUVANT ATEZO (IMPOWER-010)



CLINICAL SCENARIO #3: PATIENT COMES TO SEE MEDICAL ONCOLOGIST AFTER NEOADJUVANT THERAPY AND SURGERY

- Is more adjuvant IO really necessary?

Study name	EGFR/\ ALK (Y/N)	Neoadjuvant regimen	Stages	Adjuvant IO? (duration, mos)	EFS (HR, 95% CI)	OS (HR, 95% CI)	NCT#
KEYNOTE-671	Y (small #)	Chemo + pembro	II-IIIB	Y (app 10)	0.58 (0.46-0.72)	0.73 (0.54-0.99)	NCT03425643
CheckMate-816	N	Chemo + nivo	IB-IIIA	N	0.63 (0.43-0.91)	0.57 (0.3-1.07)	NCT02998528
NADIM	N	Chemo + nivo	IIIA-IIIB	Y (6)	0.47 (0.25-0.88)	0.43 (0.19-0.98)	NCT03838159
NEOTORCH	N	Chemo + toripalimab	II-III	Y (app 10)	0.40 (0.28-0.57)	0.62 (0.38-0.99)	NCT04158440
CM77T	N	Chemo + nivo	IIA-IIIB	Y (12)	0.58 (0.42,0.81)	N/A	NCT04025879
AEGEAN	N	Chemo + durva	IIA-IIIB	Y (12)	0.68 (0.53-0.88)	N/A	NCT03800134
IMPOWER-030	N	Chemo + atezo	IIA-IIIB	Y (12)	N/A	N/A	NCT03456063

What is the toxicity cost during the adjuvant phase? (Adverse events during the adjuvant phase, KN-671)

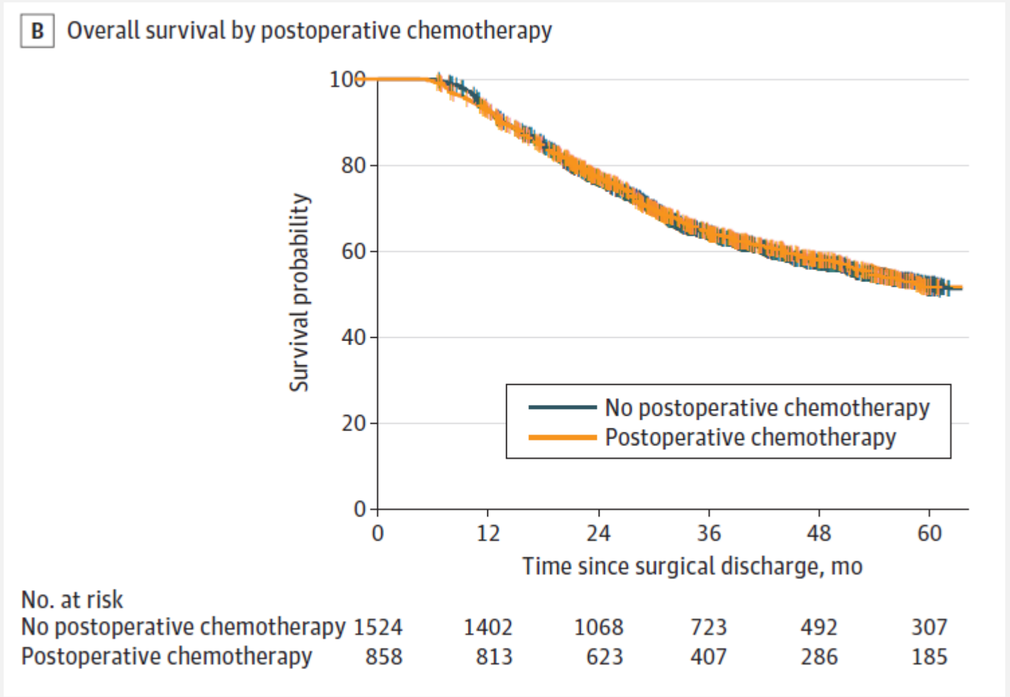
	Pembrolizumab	Placebo
Any treatment related AE, grade 3-5	10%	5.6%
Led to death	0.3% (n=1)	0
Treatment related AE, >5% (gr 3-4)		
Rash	6.2 (0.3)	3.0 (0)
Diarrhea	5.2 (1.0)	4.5 (0)
Hypothyroidism	5.2 (0)	0.7 (0)
Pruritis	8.3 (0.7)	2.2 (0)

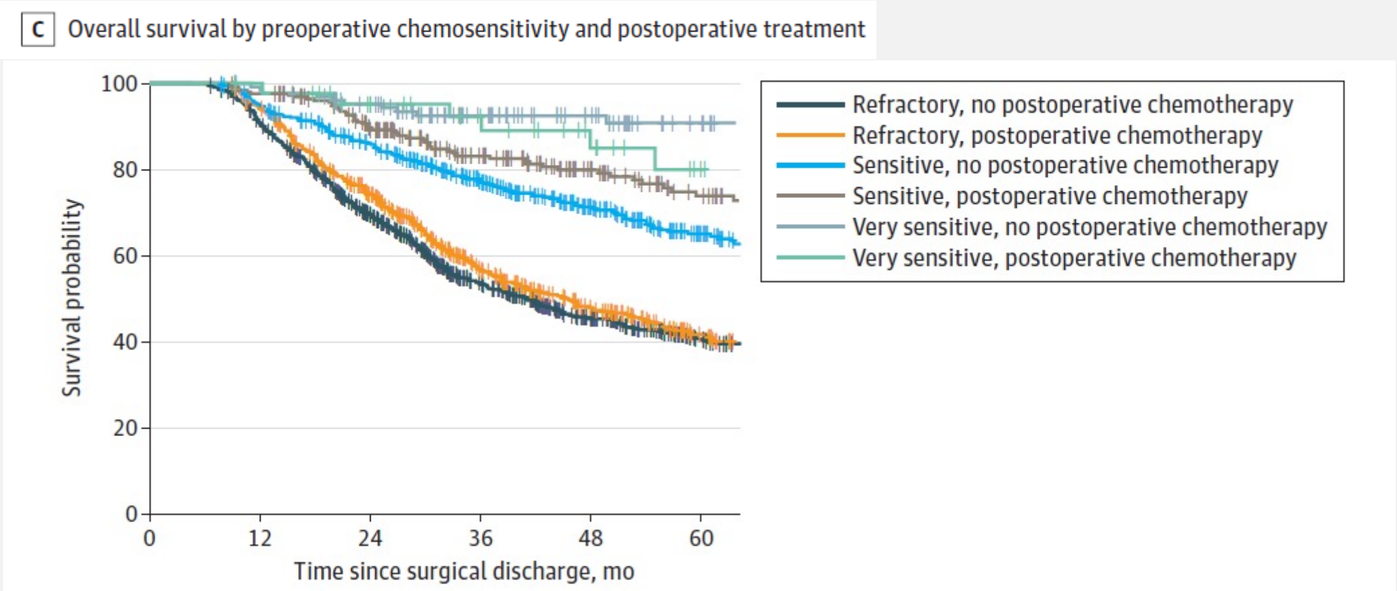
Wakelee *et al.* KN-671. NEJM 2022; 387-691. Supplemental appendix, Table S8

COULD WE BETTER SELECT PATIENTS FOR ADJUVANT THERAPY?

Future strategy: Decision based prior IO sensitivity?

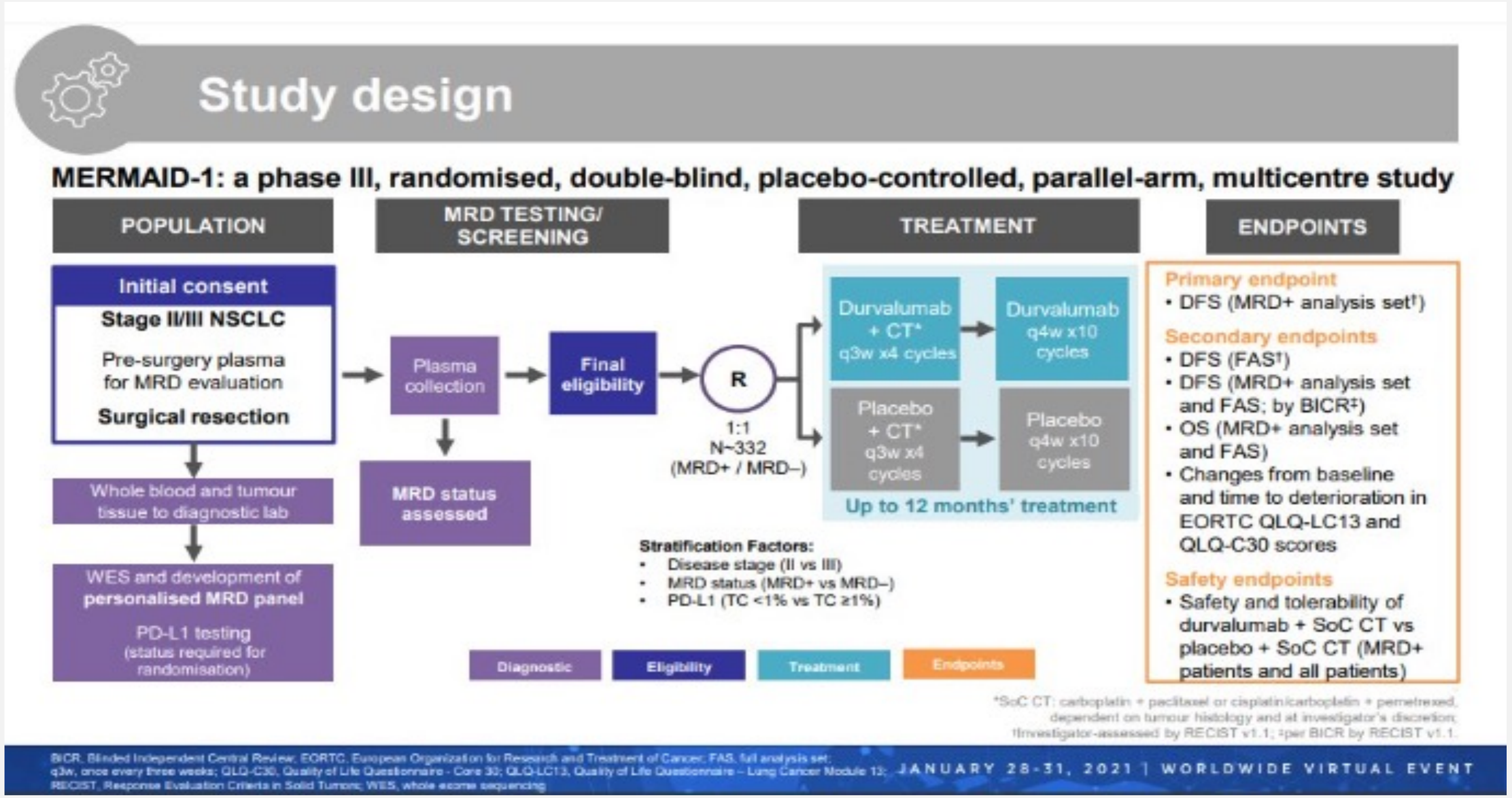
- NCDB analysis of 2382 patients with gastric cancer, who received both neoadjuvant and adjuvant chemotherapy





Deng et al. JAMA Network Open 2021; 4(11): e213540

Future strategy: Selection of patients by post-operative biomarker e.g. MRD



Peters et al. P03.03.WCLC 2021 (NCT04385368)

TAKE HOME POINTS

- Outcome of patients with resectable NSCLC is improving with effective systemic therapies
- Knowing molecular status soon after diagnosis is crucial to best inform therapy decision
- Close communication with thoracic surgery / pulmonology becoming increasingly important to ensure all appropriate patients are offered peri-operative systemic therapy
- Consider adjuvant immunotherapy if patients have not received neoadjuvant therapy
  - Any PD-L1 is appropriate but benefit likely higher with high PD-L1 expression
  - Patients with EGFR / ALK+ NSCLC should receive oncogene targeting therapy
- Unknown whether more adjuvant IO is really beneficial after neoadjuvant chemo-immunotherapy
- Future research direction will be in fine tuning patient selection for adjuvant therapy – stay tuned!

REFERENCES

AEGEAN Heymach *et al*. NEJM 2023; 389(19):1672-1684

CheckMate816: Forde *et al* NEJM 2022 May 26;386(21):1973

CheckMate-77T: Cascone T *et al*. LBA1. ESMO 2023

IMPOWER-010:

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KEYNOTE-671: Wakelee *et al*. NEJM 2023; 389(6):491-503

NADIM: Provencio *et al* NEJM 2023;389(6):504-513

NEOTORCH: Lu *et al* JCO 41,no.36_suppl425126

PERI-OPERATIVE CHEMO-IMMUNOTHERAPY IN RESECTABLE NSCLC

- Increasing evidence to support the use of neoadjuvant chemo-immunotherapy in resectable NSCLC

- But many unanswered questions:
  - Is neoadjuvant chemoimmunotherapy better than adjuvant therapy?
  - Even if better, are there patients who should go to surgery first rather than neoadjuvant therapy?
  - In patients who received neoadjuvant therapy, is adjuvant therapy necessary? If so, who? How long?
  - Amongst patients who did not receive neoadjuvant therapy, should everyone receive adjuvant immunotherapy?
  - Stage III NSCLC: What is our definition of resectability and are there patients who are better served with chemoradiation → consolidation immunotherapy?

IS NEOADJUVANT THERAPY BETTER THAN ADJUVANT ALONE?

- We don’t know but data seems to suggest it
- HR for event-free survival for neoadjuvant therapy is consistently lower than adjuvant studies
- Emerging OS benefit with neoadjuvant therapy but not with adjuvant

NEOADJUVANT

Study name	EGFR/\ ALK (Y/N)	Neoadjuvant regimen	Stages	Adjuvant IO? (duration, mos)	EFS (HR, 95% CI)	OS (HR, 95% CI)	NCT#
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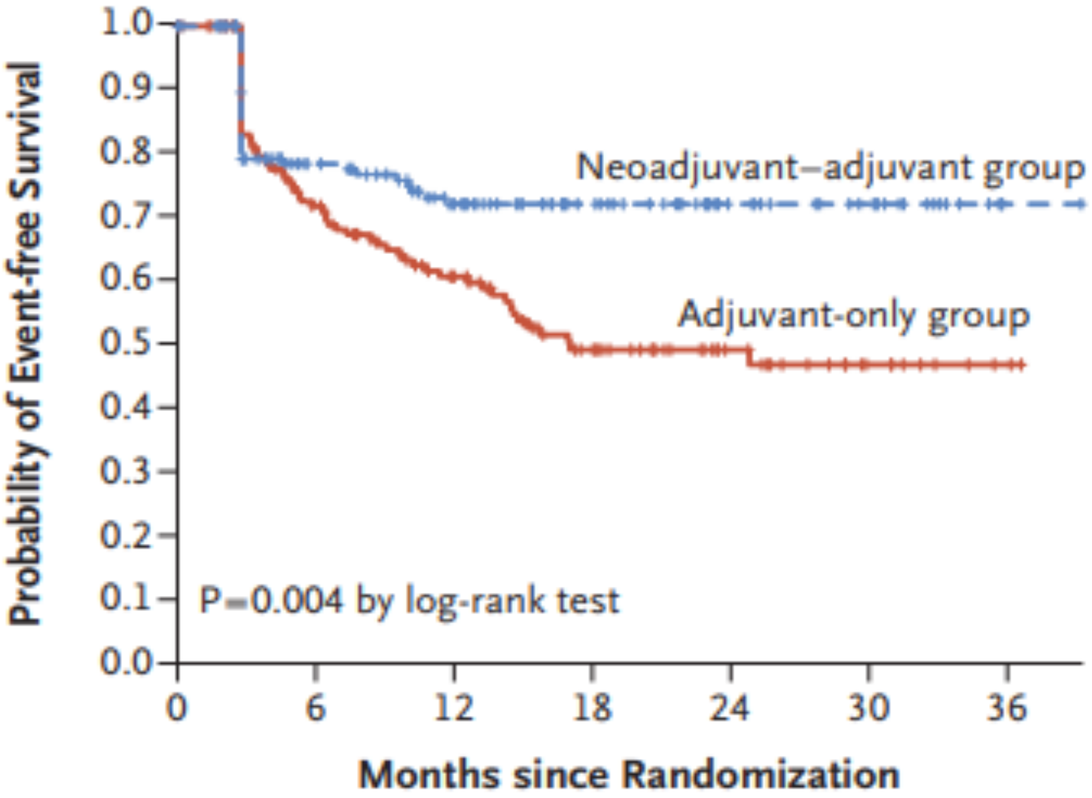
ADJUVANT

Study name	EGFR / ALK	Stages	Duration (mos)	Regimen	EFS	OS	NCT#
IMPower010	Y	II-IIIA	12	Atezolizumab	0.79 (0.64-0.96)	0.95 (0.74-1.24)	NCT02486718
PEARLS	Y	IB-IIIA	12	Pembrolizumab	0.76 (0.63-0.91)	0.87 (0.67-1.15)	NCT02504372



No. at Risk							
Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

S1801: Neoadjuvant-Adjuvant or Adjuvant-only Pembrolizumab in advanced melanoma
(Patel et al. NEJM 2023;388:813-23)

EFS at 2 years 72% vs 49% (p=0004)

CHALLENGE #1: TIMELY REFERRAL FOR SYSTEMIC THERAPY

Physician referral patterns and use of adjuvant therapy among patients with stage IB-IIIA (Kale *et al*. *Journal of Clinical Oncology* 40, no. 28_suppl (October 01, 2022) 114-114)

- SEER-Medicare analysis (2010-2017)
- Resected Stage IB-IIIA
- N=7108
- 74% patients saw a medical oncologist
- Higher stage and shorter time to referral to medical oncology more likely to receive adjuvant therapy

CHALLENGE #1: TIMELY REFERRAL FOR SYSTEMIC THERAPY

Table 3. Proportion of patients by treatment modality (with timing) in resected stages I–III non-small-cell lung cancer. (Table view)

Study (year)	Country	Study period	Total (n)	Patients, n (%)					
				S (±RT)		Neo-CT/CRT		Adj-CT/CRT	
				n	%	n	%	n	%
Stage I									
Arnold (2016)	USA	2003–2009	4293	3581	83.4†	108	2.5‡	604	14.1‡
Rajaram (2016)	USA	2002–2011	55,016	44,563	81.0 §	1540	2.8‡,¶	8913	16.2‡
Stage II									
Arnold (2016)	USA	2003–2009	5407	2737	50.6†	766	14.2‡	1904	35.2‡
Moore (2020)	Canada	2005–2012	245	112	45.7 §	7	2.9‡	126	51.4‡
Stage III									
Arnold (2016)	USA	2003–2009	5547	1909	34.4†	2,053	37.0‡	1585	28.6‡
Moore (2019)	Canada	2005–2012	133	29	21.8#	59	44.4‡‡	45	33.8‡‡
Vinod (2012)	Canada	2000–2007	250	148	59.2§	34	13.6‡,††	68	27.2‡,††

<u>Practice patterns in resectable stages I-III NSCLC</u>

- Systematic review of studies of treatment pattern after 2000 in North America, Europe and Asia
- 20 studies included

Waser *et al*. Future Oncology2022, 18(12):1519-1530

CHALLENGE #1: TIMELY REFERRAL FOR SYSTEMIC THERAPY

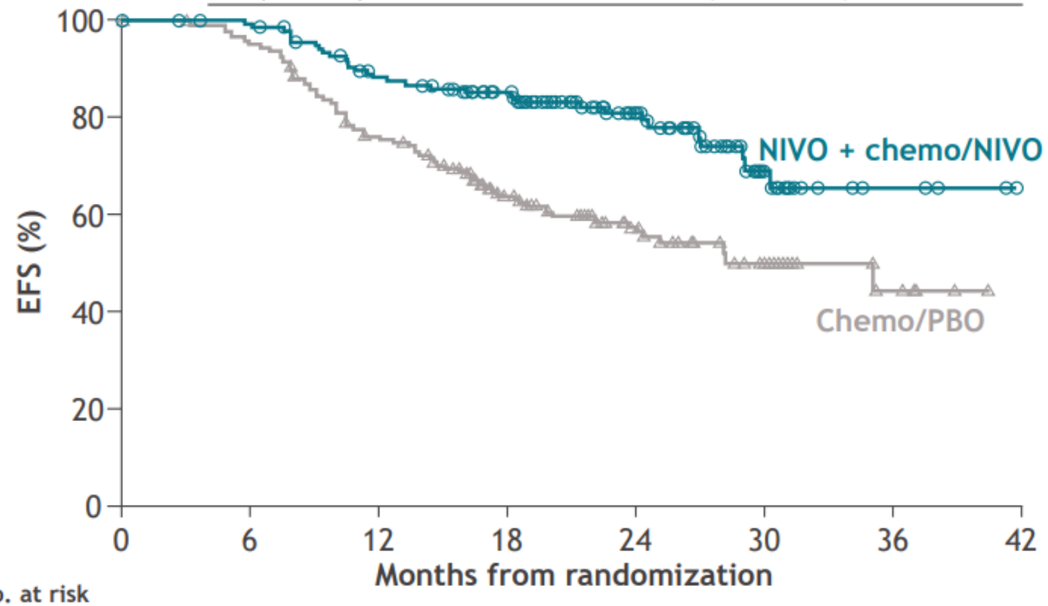
Factors associated with referral to medical oncology… (Kankesan et a. Curr Oncol 2013; 20;30-37)

- n=3354 patient with resected NSCLC in Ontario 2004-2006
- 55% were referred to medical oncology after surgery
- 31% received adjuvant therapy
- Older patients, stage I less likely to be referred to medical oncology

Exploratory analysis: EFS by adjuvant treatment status

Adjuvant

	NIVO + chemo/NIVO (n = 142)	Chemo/PBO (n = 152)
Median EFS, mo (95% CI)	NR (NR-NR)	35.1 (22.0-NR)
HR (95% CI)	0.45 (0.29-0.69)	

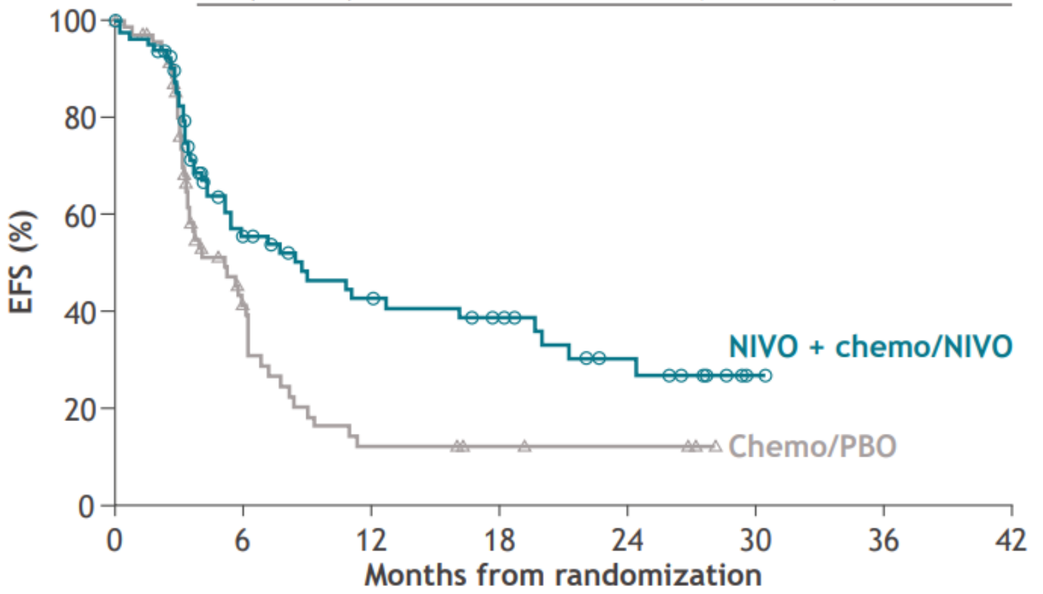


No. at risk

NIVO + chemo/NIVO	142	139	118	97	60	19	4	0
Chemo/PBO	152	144	112	74	41	19	6	0

No adjuvant

	NIVO + chemo/NIVO (n = 87)	Chemo/PBO (n = 80)
Median EFS, mo (95% CI)	8.8 (5.2-19.7)	5.2 (3.4-6.2)
HR (95% CI)	0.55 (0.37-0.83)	



NIVO + chemo/NIVO	87	34	23	18	9	1	0	0
Chemo/PBO	80	21	6	4	3	0	0	0

- NIVO + chemo/NIVO improved EFS vs chemo/PBO with numerically higher benefit in patients who received adjuvant treatment (HR [95% CI], 0.45 [0.29-0.69]) vs those who did not (HR [95% CI], 0.55 [0.37-0.83])[a]

Cascone et al. Chec,Mate 77T LBA1. ESMO 2023