Session 1B: Neo-Adjuvant & Adjuvant Therapy

Moderators: Heather Wakelee, Roy Herbst, Leah Backhus, Taryne Imai

Panel: Ayman Abdul-Ghani, Evan Wu, Nicholas Stollenwerk, Nicholas Villanueva

Case*

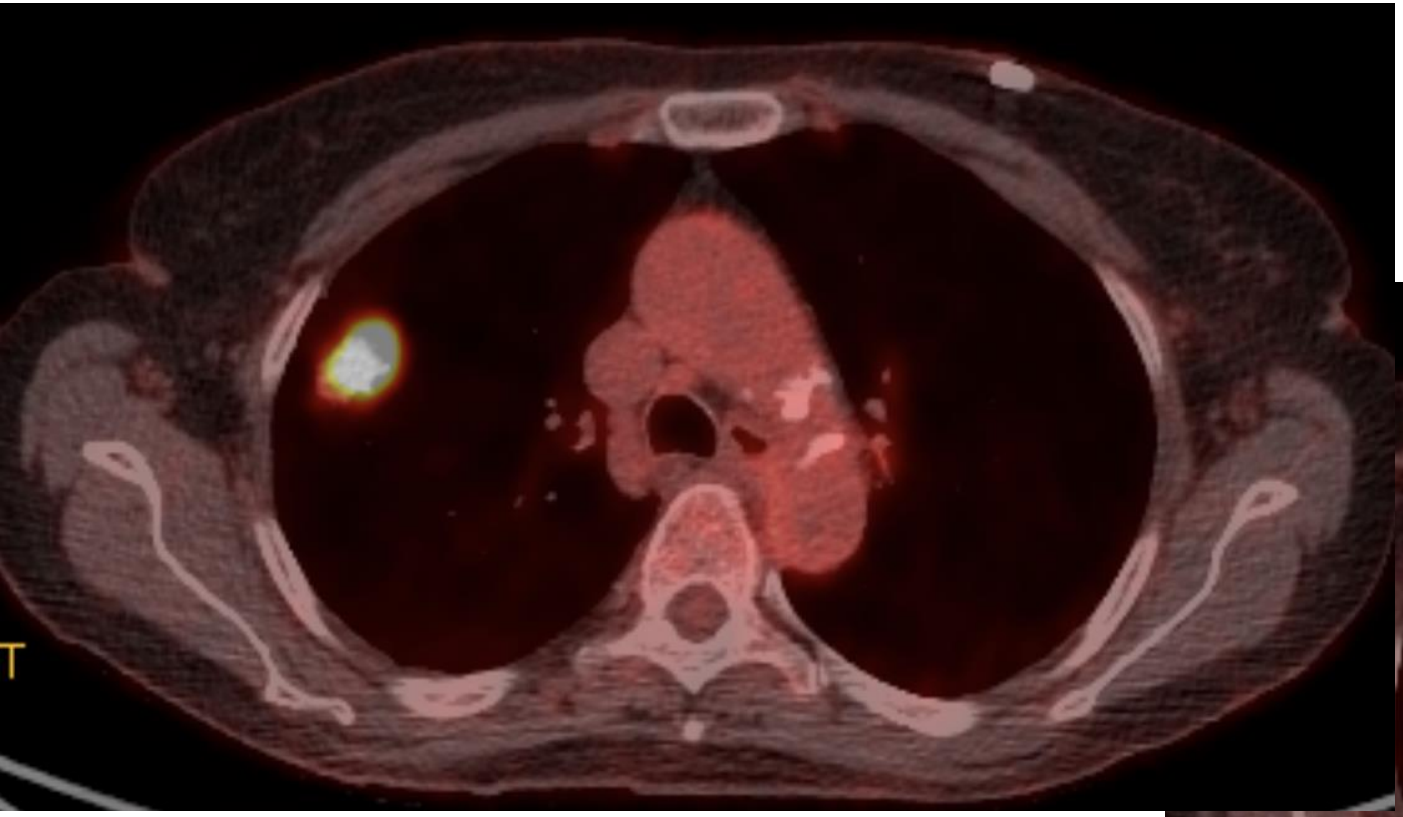
- **AL** is a 73 year old woman, former heavy smoker with a history of CAD, HTN, DM, emphysema, and GERD. Retired flight attendant
- She remains active, walking 3 hours on a treadmill almost daily
- June 2023: Presented to her PCP with persistent but worsening cough with green sputum, treated with antibiotics without resolution
  - CXR revealed 2.2 cm mass RUL
- CT showed a noncalcified spiculated lung nodule 2.1 x 1.4 x 3.2 RUL
- Aug 2023: EBUS confirmed NSCLC, likely adenocarcinoma, LNs negative for malignancy
- Sept 2023: PET: Dominant RUL pulmonary nodule consistent with known primary neoplasm, questionable uptake in right peri-hilar area
- Sept 2023: Brain MRI – no evidence of malignancy
- Sept 2023: Pre-op flexible bronchoscopy and EBUS: LN, station 11R, metastatic carcinoma, compatible with known lung primary

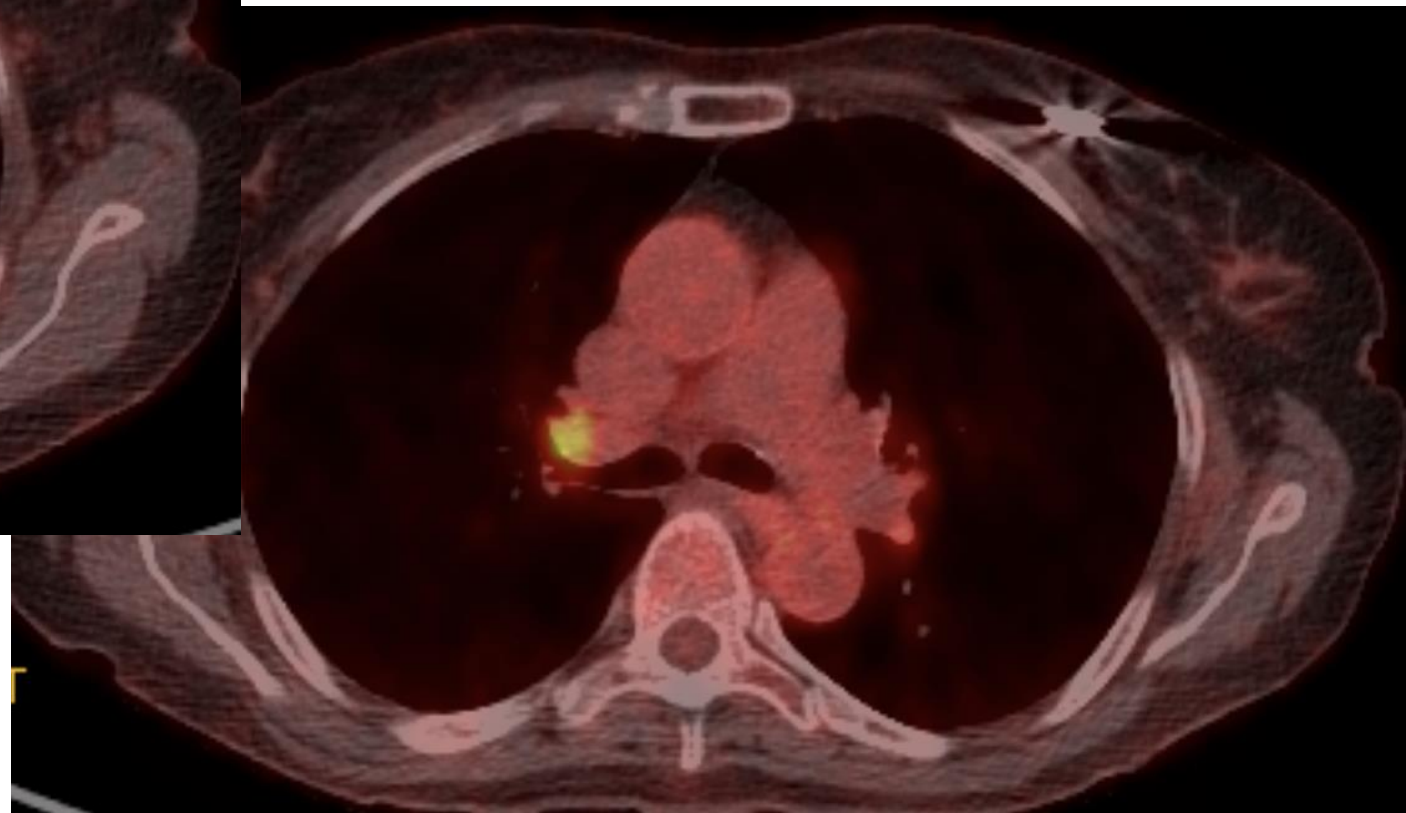
*Cases may have been modified for educational purposes

PET Sept 2023

Lungs: Spiculated lung nodule measuring up to 3.2 cm in periphery of anterolateral right upper lobe with SUV max 10.2

Lymph nodes: Mildly hypermetabolic right suprahilar lymph node measures 1.3 x 1.2 cm with SUV max 3.8





Question

What additional studies should be performed prior to decision on next steps?

- Nothing, proceed to surgery
- Nothing, start neo-adjuvant chemotherapy + IO
- Await tumor molecular and PD-L1 testing results

Case

- Her tumor has a KRAS G12A mutation
- Her tumor has a PD-L1 level of 85%

Question

What would be your preferred option for the patient for treatment at this point?

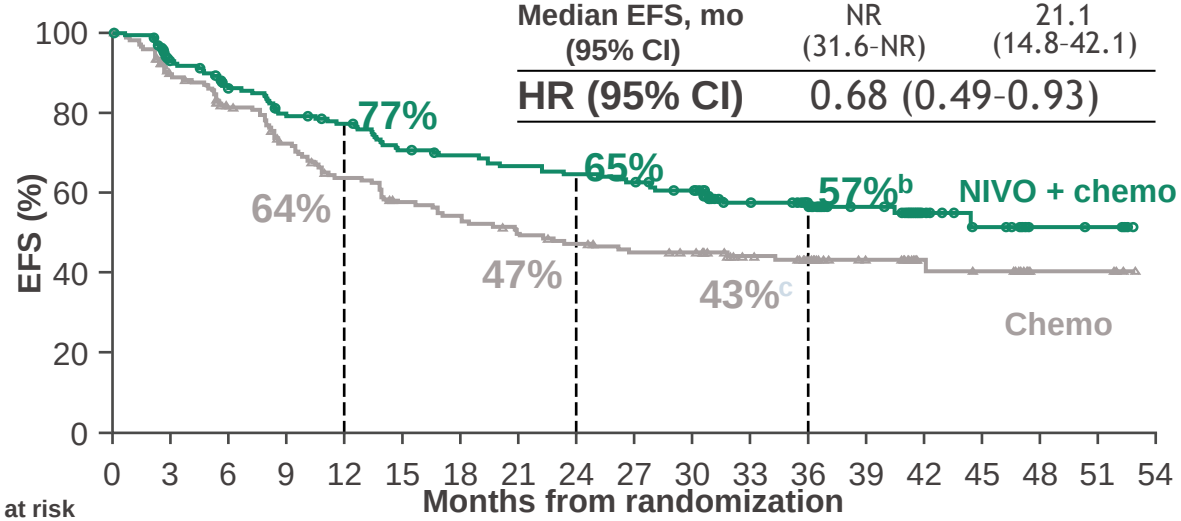
- Surgery then adjuvant KRAS inhibitor
- Surgery then adjuvant IO (IM010, KN091)
- Neo-adjuvant chemo + IO then surgery (CM816)
- Peri-operative chemo+IO then surgery, then adjuvant IO (KN671, CM77T, AEGEAN, etc.)

Who should be part of the decision process?

Neo-Adjuvant IO:
CM816 EFS with neoadjuvant NIVO + chemo vs chemo: 3-year update

EFS

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo (95% CI)	NR (31.6-NR)	21.1 (14.8-42.1)
HR (95% CI)	0.68 (0.49-0.93)	



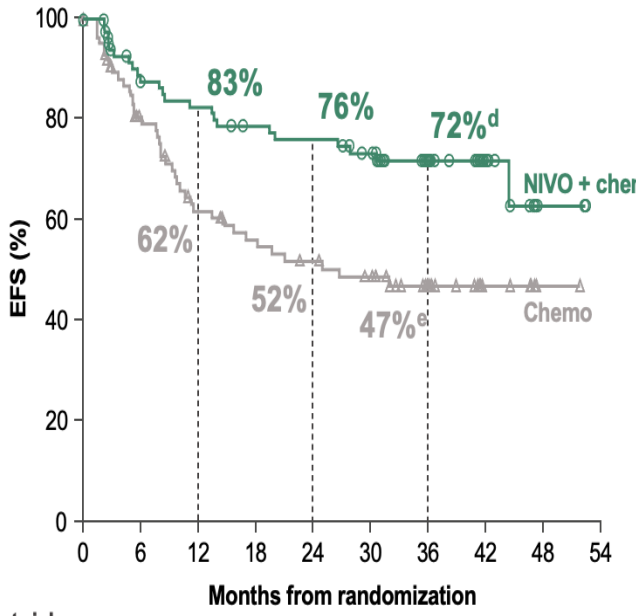
No. at risk

NIVO + chemo	179	152	136	125	119	108	104	100	97	94	88	69	57	38	20	13	6	5	0
Chemo	179	146	128	110	95	84	79	72	67	62	60	48	39	27	15	13	4	4	0

pCR 24%
mPR 37%

EFS

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median EFS, mo (95% CI)	NR (44.4–NR)	26.7 (13.4–NR)
HR (95% CI)	0.46 (0.28–0.77)	

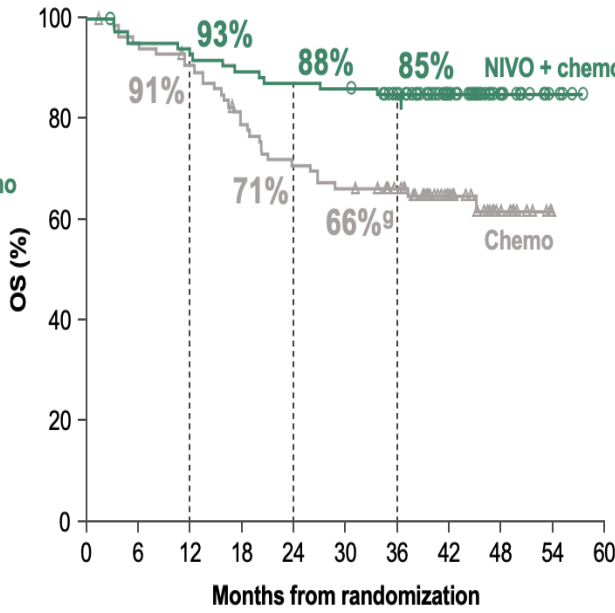


at risk

chemo	89	69	65	60	58	53	37	11	2	0
Chemo	89	61	45	39	35	31	19	7	1	0

OS

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median OS, mo (95% CI)	NR (NR–NR)	NR (45.1–NR)
HR (95% CI)	0.37 (0.20–0.71)	



	89	84	82	79	77	76	66	37	13	4	0
	89	83	79	68	61	57	51	27	10	0	0

Minimum/median follow-up: 32.9/41.4 months.

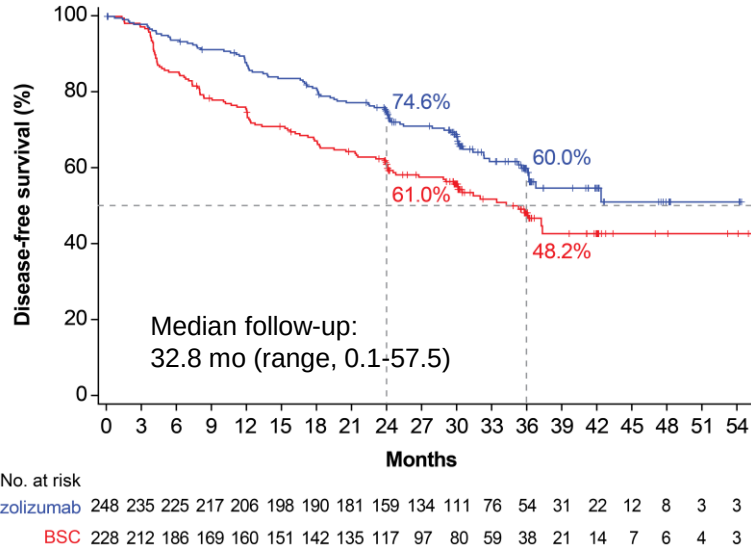
[a]Exploratory analysis. Time from randomization to any disease progression precluding surgery, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause per BICR. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b,c]95% CIs for 3-year EFS rates: [b]48–64; [c]35–51.

Forde, Spicer, Girard, et al. ELCC2023

Provencio ESMO2023

Adjuvant IO: IMpower010 DFS+OS and KEYNOTE-091 DFS

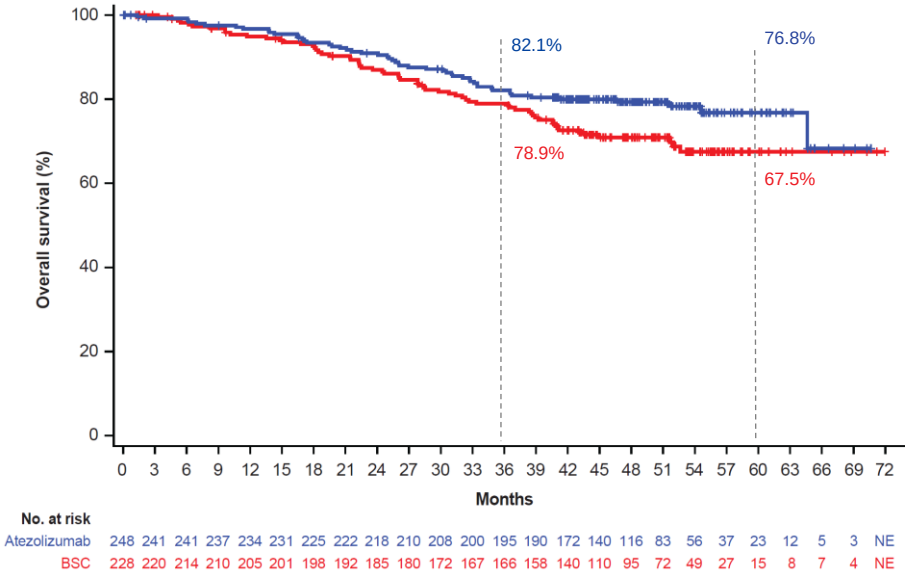
IMpower010PD-L1 TC ≥1% stage II-IIIA population



	Atezolizumab (n=248)	BSC (n=228)
Median DFS (95% CI), mo	NE (36.1, NE)	35.3 (29.0, NE)
Stratified HR (95% CI)	0.66 (0.50, 0.88)	
P value[b]	0.004[c]	

Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021

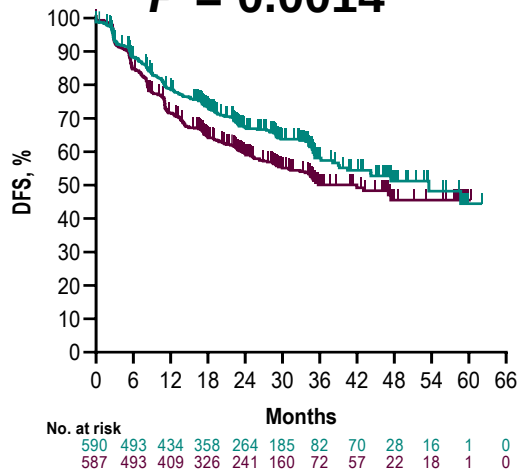
IMpower010: OS: PD-L1 TC ≥1%[a] (stage II-IIIA)



	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0%)	64 (28.1%)
mOS (95% CI), mo	NR	NR
HR (95% CI)	**0.71 (0.49, 1.03)**	

Felip IASLC WCLC 2022 Presidential Plenary

KN091DFS, Overall Population HR 0.76 (95% CI 0.63-0.91) *P* = 0.0014



	Events	Median
Pembro	35.9%	53.6 mo
Placebo	44.3%	42.0 mo

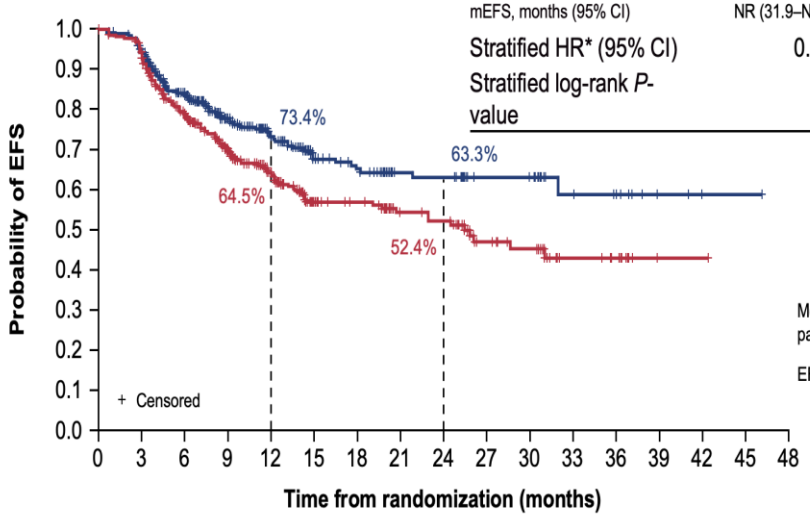
Paz-Ares ESMO plenary 2022, O'Brien ASCO 2022, Lancet Oncol 2023

Peri-Operative IO: EFS from AEGEAN, KN671, and CM77T

AEGEAN: EFS using RECIST v1.1 (BICR) (mITT)

First planned interim analysis of EFS

	D arm	PBO arm
No. events / no. patients (%)	98/366 (26.8)	138/374 (36.9)
mEFS, months (95% CI)	NR (31.9–NR)	25.9 (18.9–NR)
Stratified HR* (95% CI)	0.68 (0.53–0.88)	
Stratified log-rank *P*-value	0.003902	



Median follow-up (range) in censored patients: 11.7 months (0.0–46.1)

EFS maturity: 31.9%

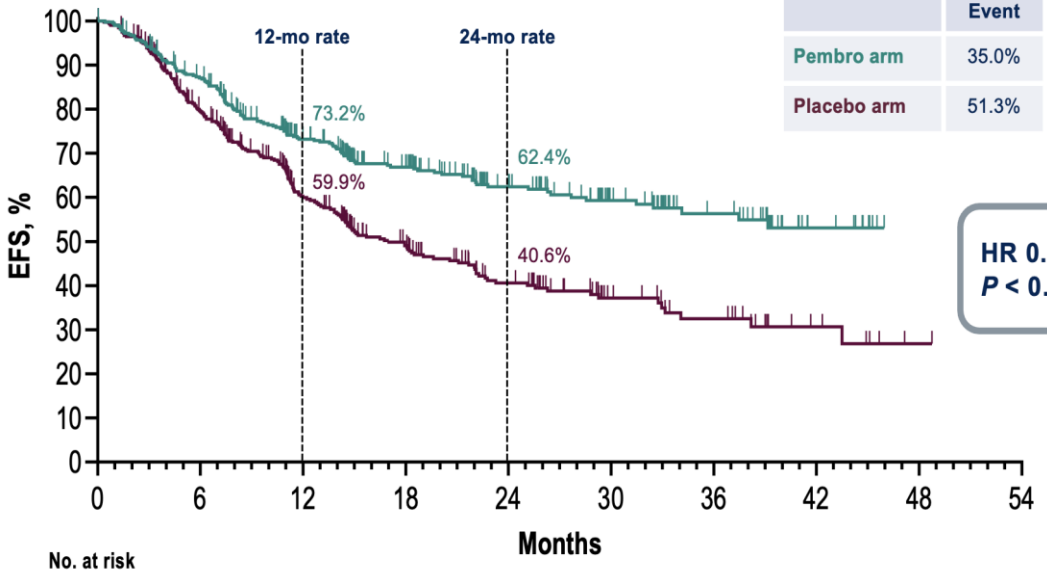
17% pCR
33% mPR

No. at risk:																
D arm	366	336	271	194	140	90	78	50	49	31	30	14	11	3	1	1	0
PBO arm	374	339	257	184	136	82	74	53	50	30	25	16	13	1	1	0	0

Heymach AACR 2023
NEJM 2023

KN671 - EFS

	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)



HR 0.58 (95% CI, 0.46-0.72)
P < 0.00001

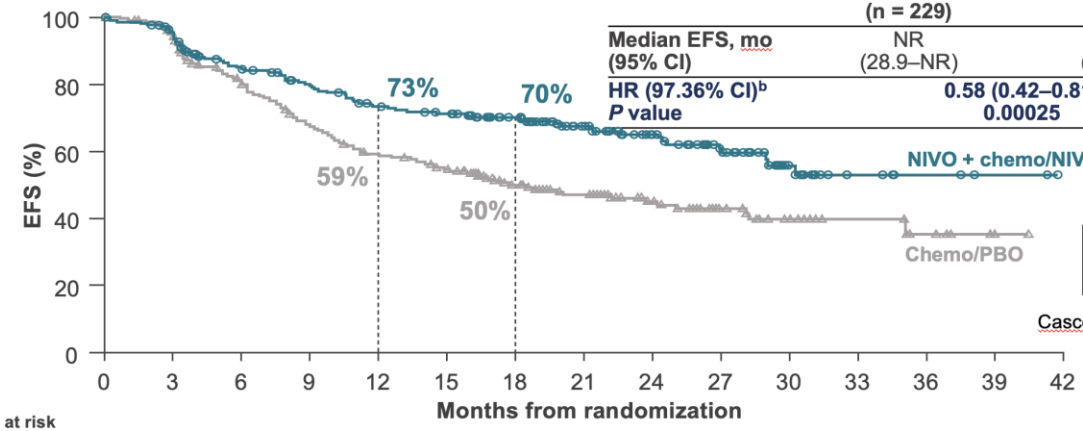
No. at risk										
397	330	236	172	117	72	42	11	0	0
400	294	183	124	74	38	24	9	1	0

18% pCR
30% mPR

Wakelee, ASCO 2023, NEJM 2023

CM77T Primary endpoint: EFS[a] per BICR with neoadjuvant NIVO + chemo/adjuvant NIVO vs chemo/PBO

	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)
Median EFS, mo (95% CI)	NR (28.9–NR)	18.4 (13.6–28.1)
HR (97.36% CI)[b]	0.58 (0.42–0.81)	
P value	0.00025	



25% pCR
35% MPR

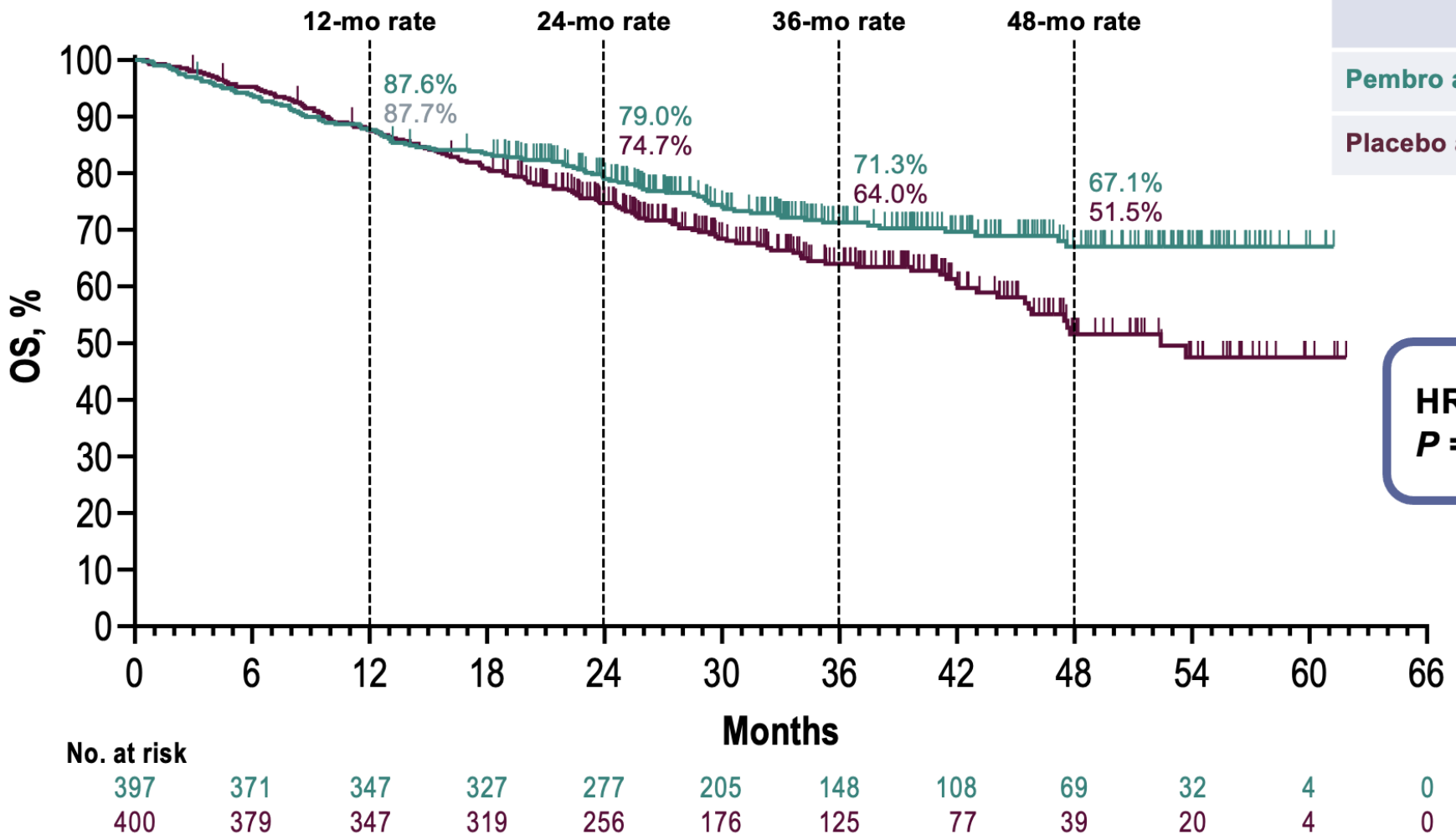
Cascone ESMO 2023

No. at risk															
NIVO + chemo/NIVO	229	208	173	157	141	134	115	89	69	46	20	7	4	2	0
Chemo/PBO	232	204	165	138	118	106	78	59	44	29	19	10	6	1	0

- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41–0.76

KN671 Overall Survival, IA2

Median Follow-Up: 36.6 months (range, 18.8-62.0)



	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

HR 0.72 (95% CI, 0.56-0.93)
***P* = 0.00517[a]**

Spicer ESMO 2023

FDA Approval OCT 2023

Neo-Adj risk of NO surgery

TRIAL	STAGES	% completing surgery
CM816	6% IB, 31% II, 63% III	84%
AEGEAN	29% II, 71% III	78%
NEOTORCH	Only III presented	82%
KN671	30% II, 70% III	82%
CM77T	35% II, 65% III	78%
RATIONALE-315	41% II, 58% III	84%

16-22% NO surgery

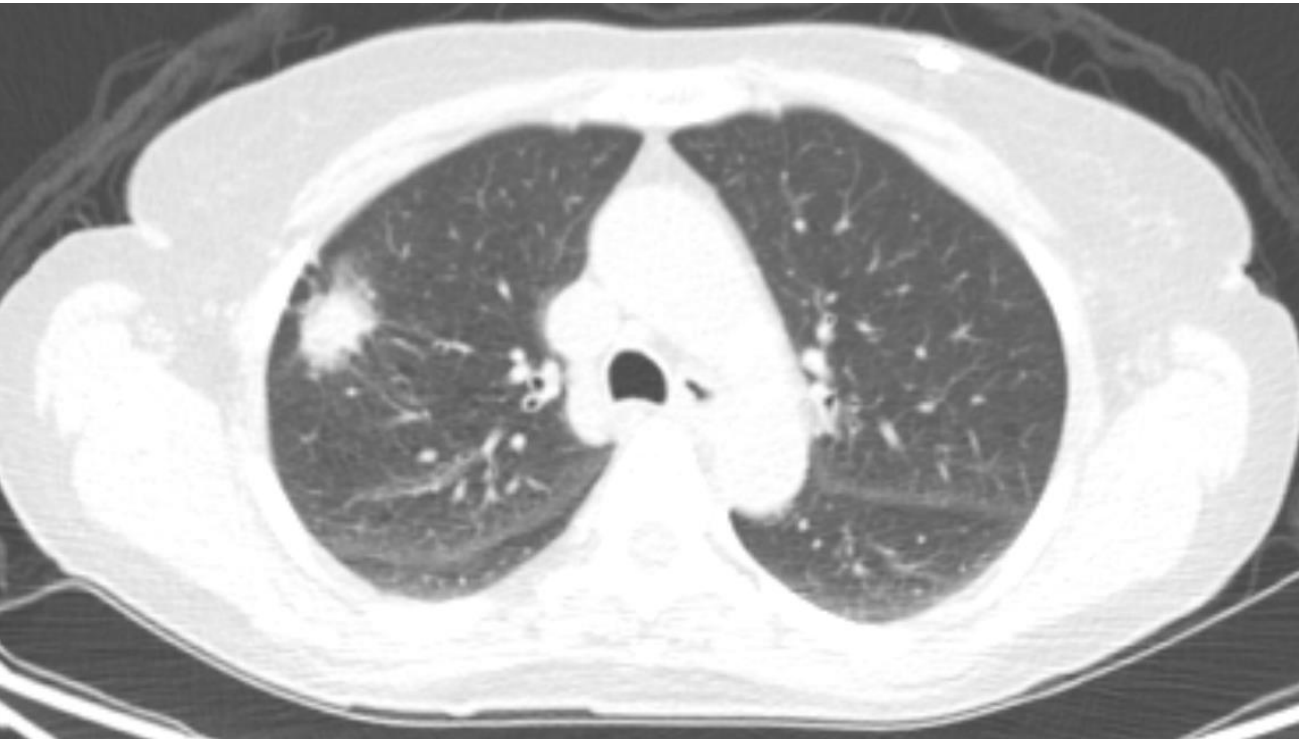
Case

AL is started on chemotherapy and nivolumab for 3 cycles

Treatment is tolerated well other than neutropenia

CT scan after 3 cycles shows minimal changes

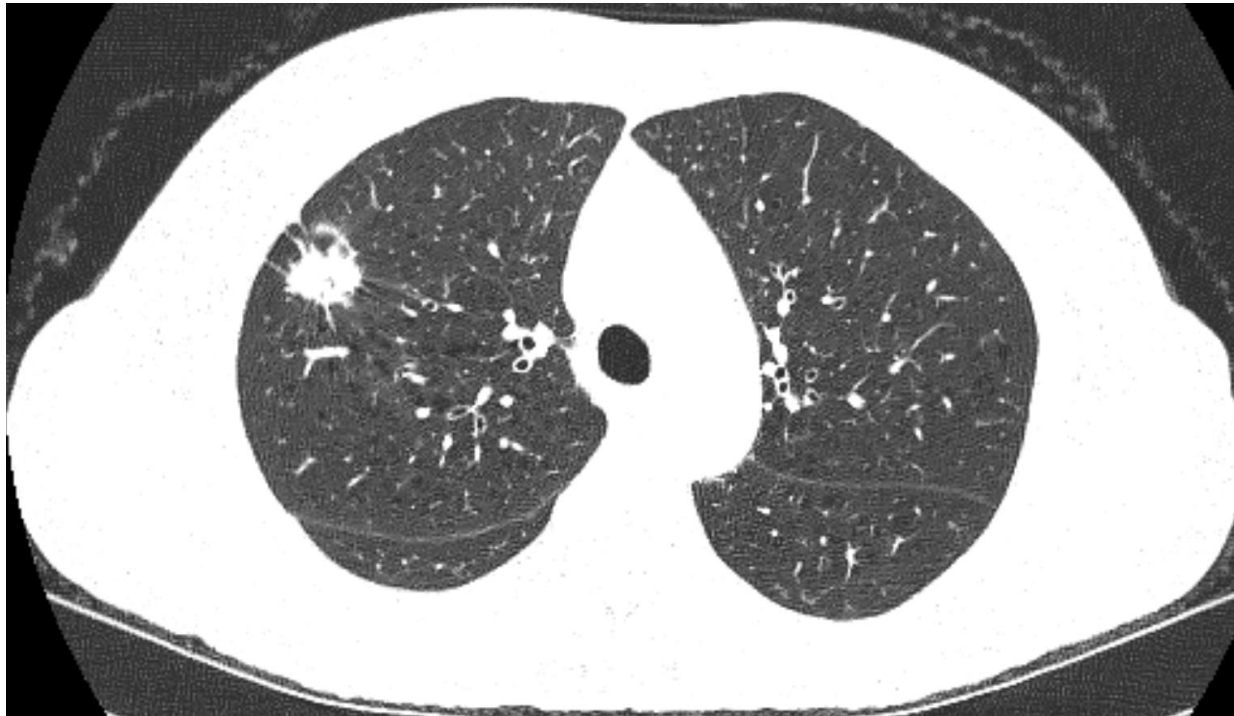
CT pre/post 3 cycles chemo +IO



Sept 2023

Lymph nodes: Similar borderline enlarged right hilar lymph node measuring 11 mm in short axis
Lung parenchyma: Moderate centrilobular emphysema. Slight interval decrease in size of a spiculated RUL nodule, now measuring approximately 21 x 19 mm

Dec 2023



Question

Would you proceed to surgery now?

- Yes
- No

Question

How would the findings at surgery influence your decision to pursue a pure neo-adjuvant (CM816) versus peri-operative (CM77T) approach?

- I would NOT give adjuvant nivolumab regardless of findings as I prefer the CM816 regimen
- I would pursue a peri-operative approach (CM77T) and give adjuvant nivolumab regardless of operative findings
- I would give adjuvant nivolumab (CM77T) UNLESS there was a pCR
- I would ONLY give adjuvant nivolumab (CM77T) if there was at least MPR achieved

Case/Question

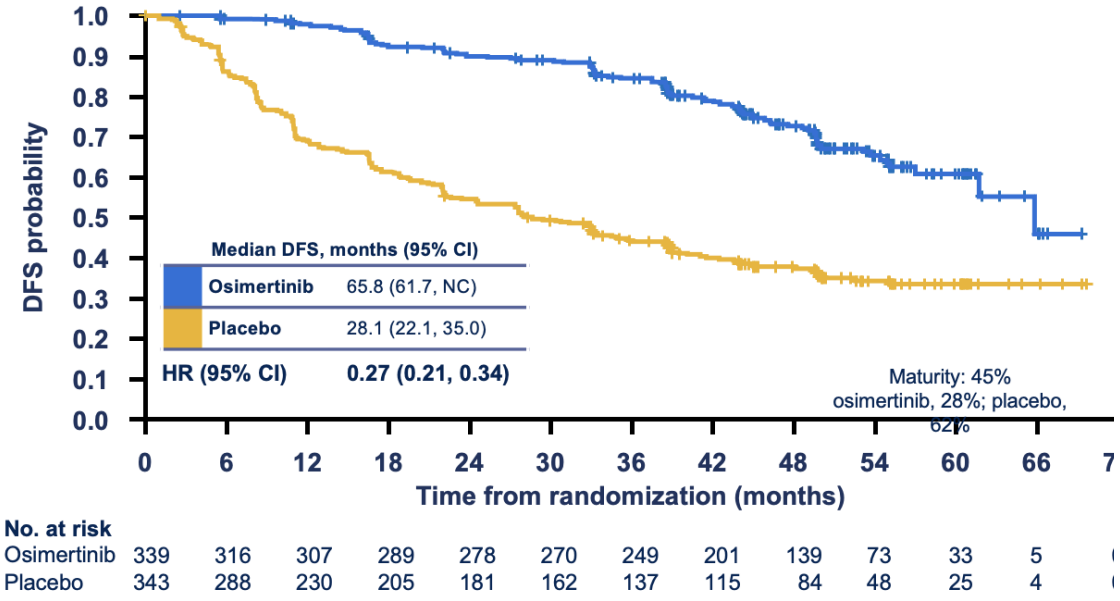
- What if her tumor has an EGFRdel19 mutation?
- Her tumor has a PD-L1 level of 85%

How would you proceed?

- Proceed to surgery and give adjuvant osimertinib
- Give neo-adjuvant osimertinib then surgery
- Give neo-adjuvant chemo-IO +/- adjuvant IO

Adjuvant targeted therapy
ADAURA DFS+ OS and ALINA DFS

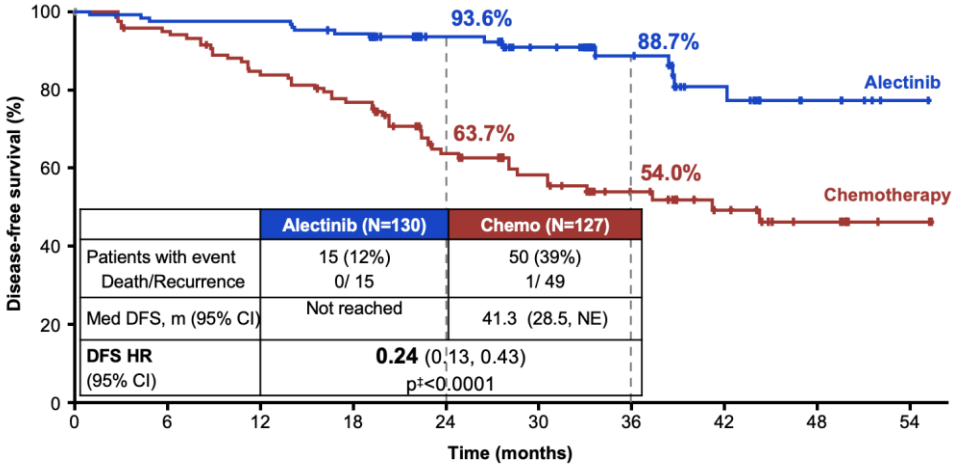
ADAURA DFS

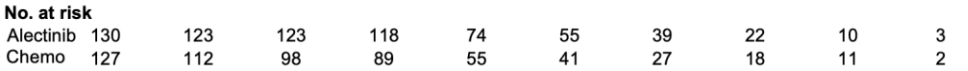


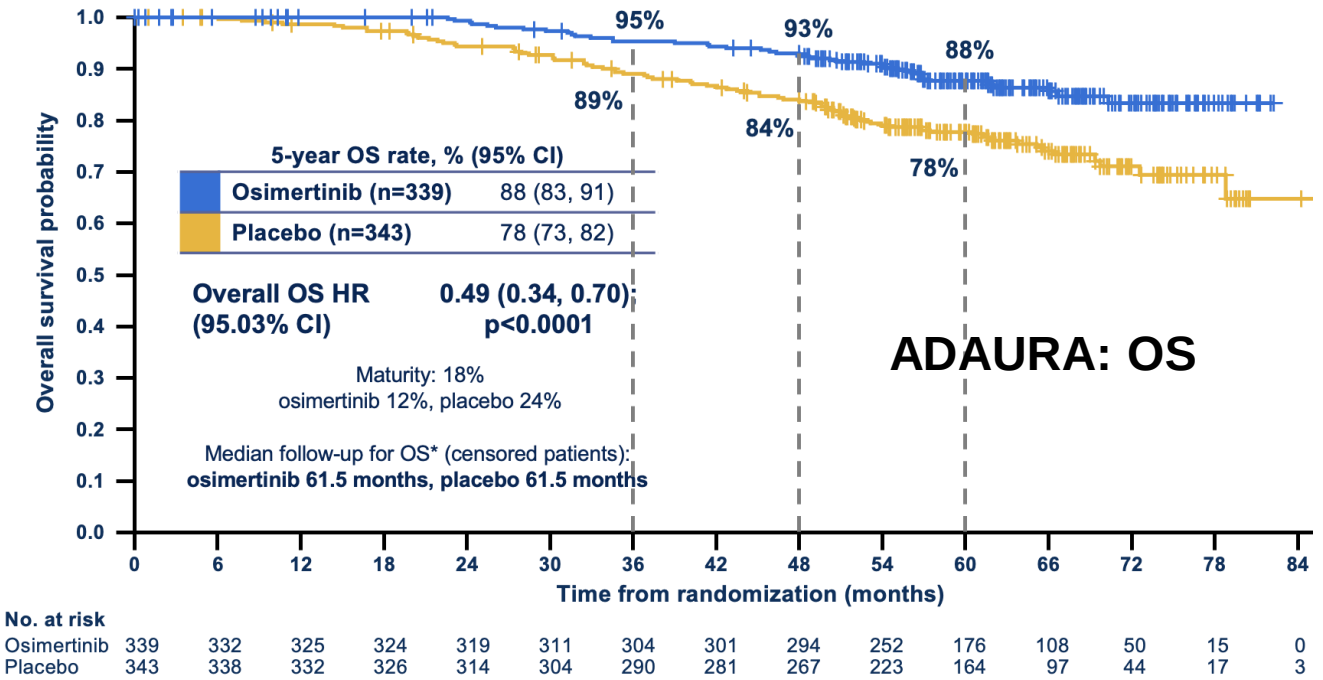
Herbst ASCO 2023, Tsuboi NEJM 2023

Solomon ESMO 2023

ALINA DFS
ALK+ Adj alectinib







Herbst ASCO2023, Tsuboi NEJM 2023

Key Clinical Takeaways

- It is important to complete staging prior to resection
- Molecular testing is critical prior to choosing a therapy (EGFR/ALK)
- PD-L1 testing is important to inform therapeutic strategy
- For stage II NSCLC without a driver mutation – either neo-adjuvant, peri-operative or adjuvant ICI therapy can be considered