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24th Multidisciplinary Management of Cancers: A Case-based Approach

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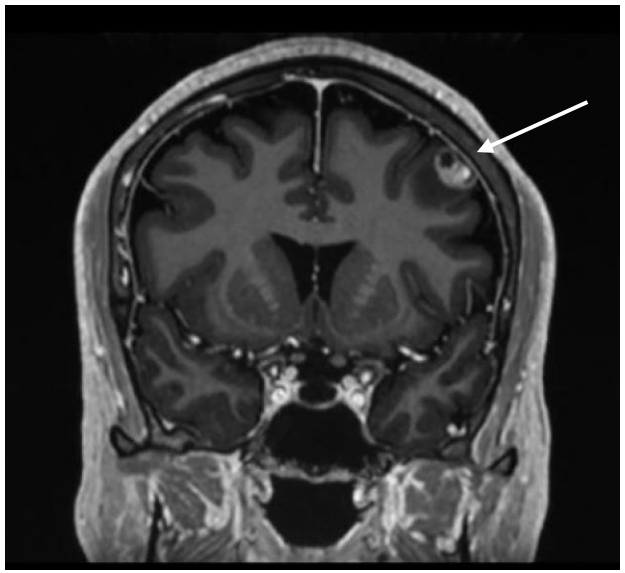
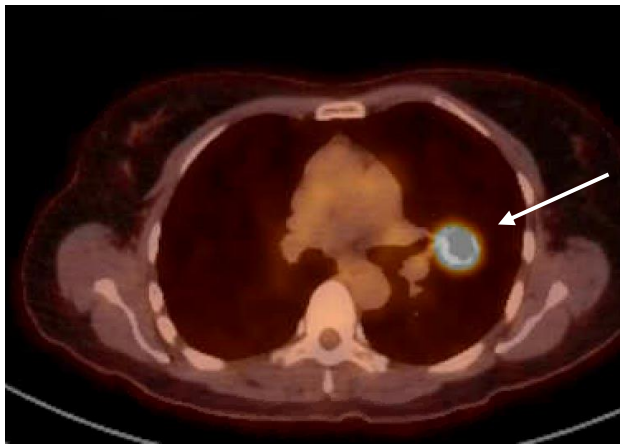
Case 1

50 yo woman, one pack year smoking history, presents w/ headache

- **Brain MRI:** 1.6 cm left frontal gyrus + 3 additional lesions 7-8 mm in size
- **CT CAP:** 3.5 cm left hilar mass
- **PET/CT:** hypermetabolic mass and left hilar node, no other metastatic disease
- **EBUS Biopsy:** left hilar node and mass positive for adenocarcinoma

Stage IVb (T2aN1M1b)





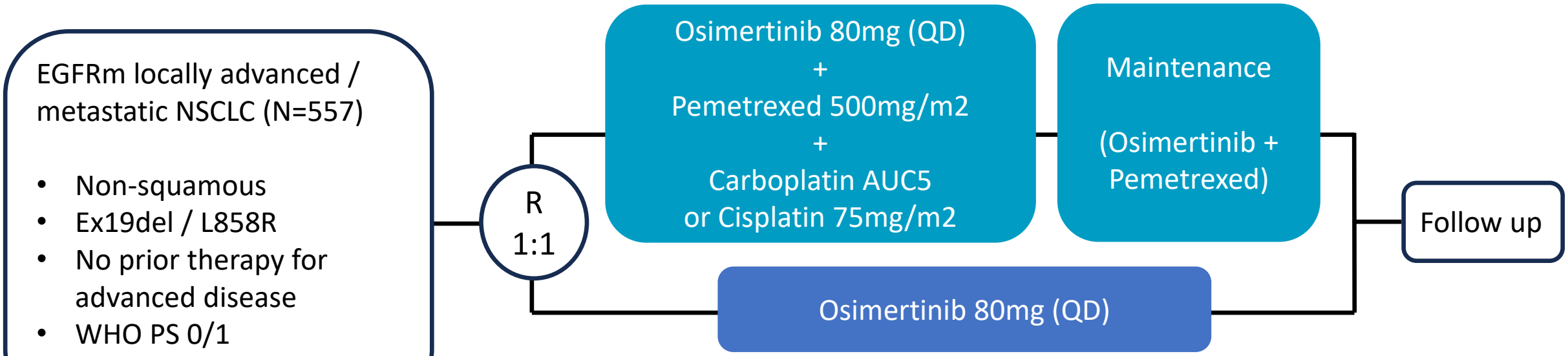
Case 1

- IHC/NGS: ***EGFR Exon19del+***, PD-L1 TPS 40%, *ALK/ROS1* negative

Question 1: In this patient with stage IVb disease and ECOG 1, what would you recommend?

1. Osimertinib plus chemotherapy and monitor the brain metastases
2. SBRT to the brain lesions, resect the primary, then osimertinib
3. SBRT to the brain lesions, resect the primary, then osimertinib plus chemotherapy
4. SBRT to the brain lesions, then osimertinib
5. SBRT to the brain lesions, then osimertinib plus chemotherapy

FLAURA2: Improved PFS when combining osimertinib + chemotherapy vs osimertinib alone

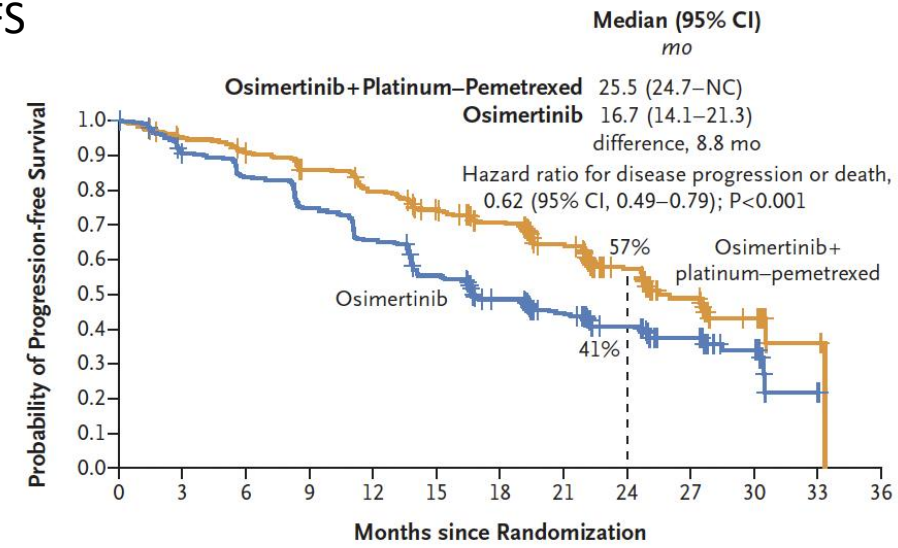


- Primary endpoint: PFS
- Secondary endpoint: OS, PFS2, ORR, HRQOL

Planchard et al, NEJM 2023; 389:1935-1948

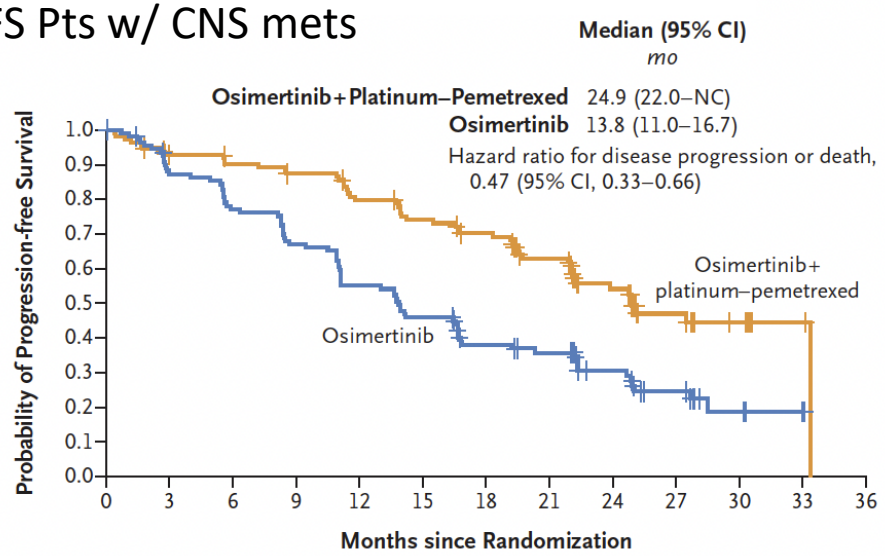
FLAURA2: Improved PFS when combining osimertinib + chemotherapy vs osimertinib alone

PFS

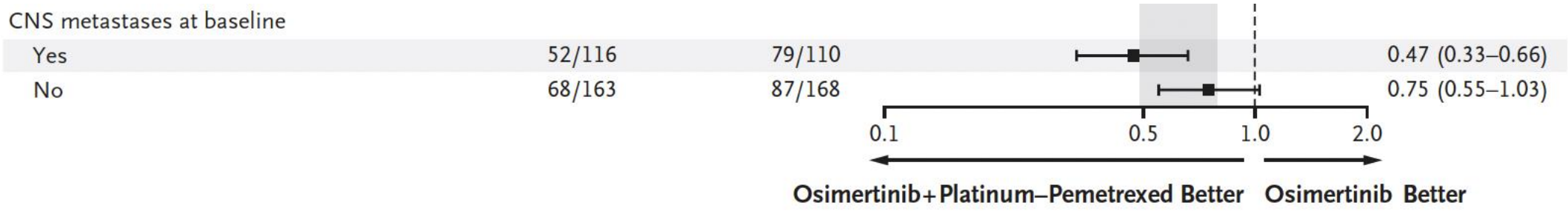


No. at Risk													
Osimertinib+ platinum–pemetrexed	279	254	241	225	207	187	165	133	84	42	21	3	0
Osimertinib	278	246	227	203	178	148	119	94	67	48	21	1	0

PFS Pts w/ CNS mets



No. at Risk													
Osimertinib+ platinum–pemetrexed	116	101	98	93	84	77	70	58	34	19	8	2	0
Osimertinib	110	95	84	73	60	50	37	32	21	13	5	1	0



Planchard et al, NEJM 2023; 389:1935-1948

Case 1

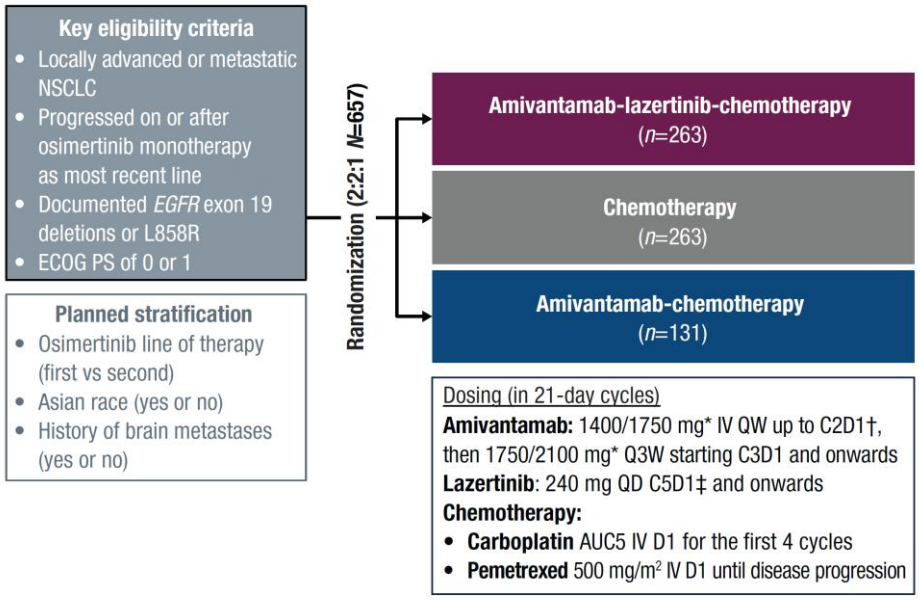
The patient undergoes SBRT to the brain lesions and resection of primary tumor. She starts on osimertinib monotherapy after surgery (before FLAURA2 results available). She remains on osimertinib monotherapy for 2 years without evidence of disease progression.

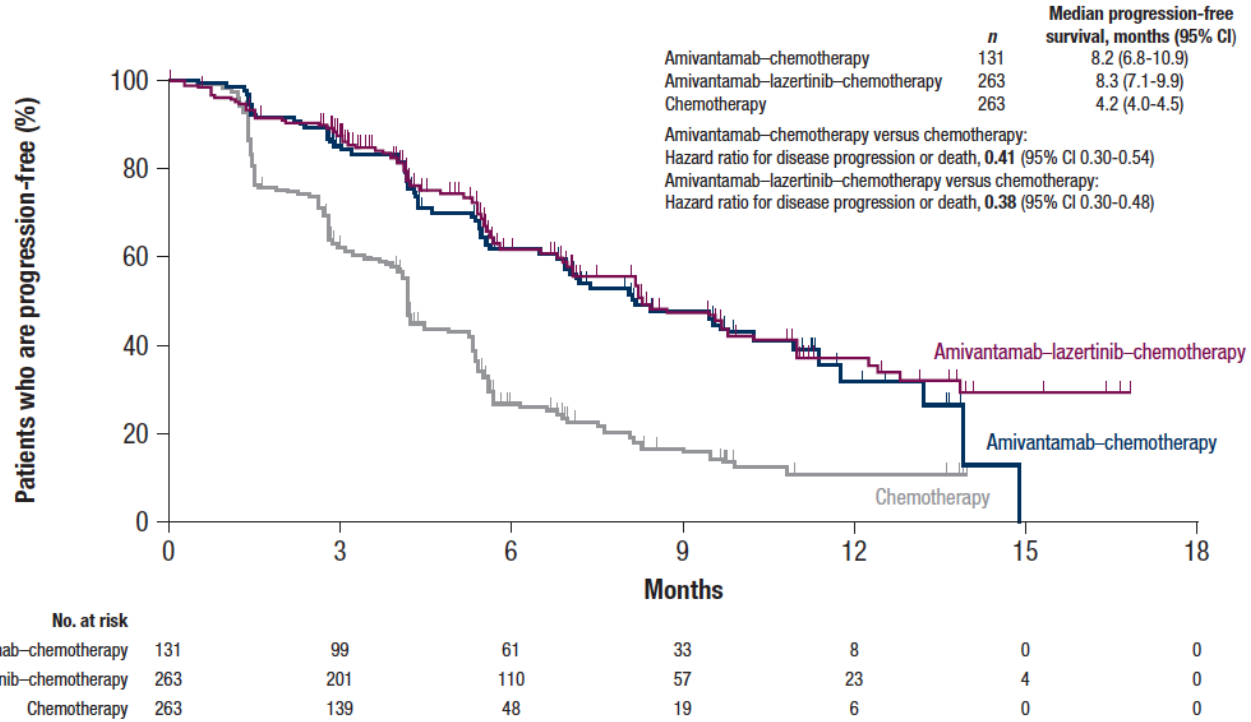
Scans subsequently show progression with one new metastasis in the liver, one in the contralateral lung, and one in the right third rib. ECOG is 1

Question 2: What would you recommend next?

1. Continue osimertinib, SBRT to sites of new disease
2. Molecular testing with liquid or tissue biopsy
3. Amivantamab + carboplatin + pemetrexed
4. Docetaxel + ramucirumab
5. Carboplatin + pemetrexed + pembrolizumab

MARIPOSA-2: Improved PFS w/ amivantamab + lazertinib + chemo vs chemo alone for *EGFR+* patients after progression on osimertinib



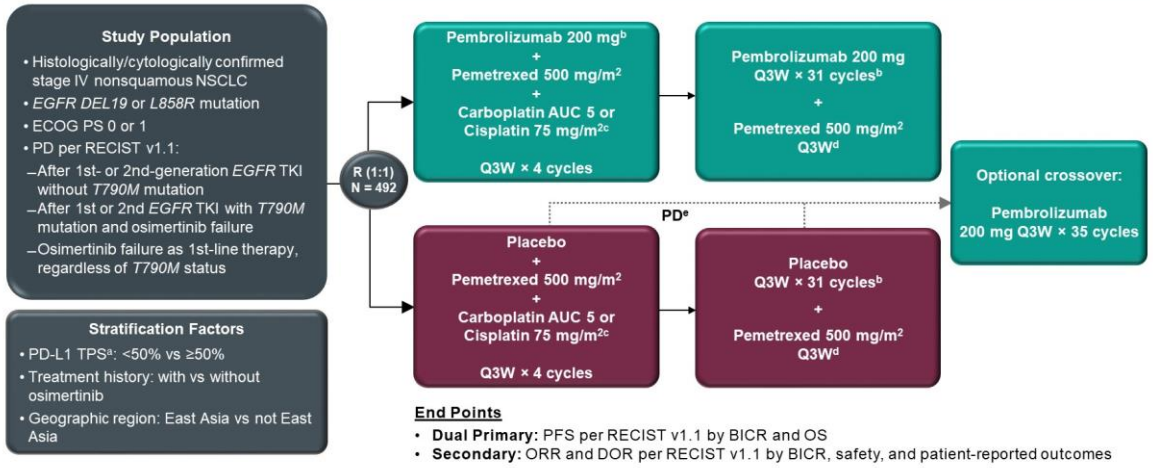


Passaro et al, Annals of Oncology 2023; 35:77-90

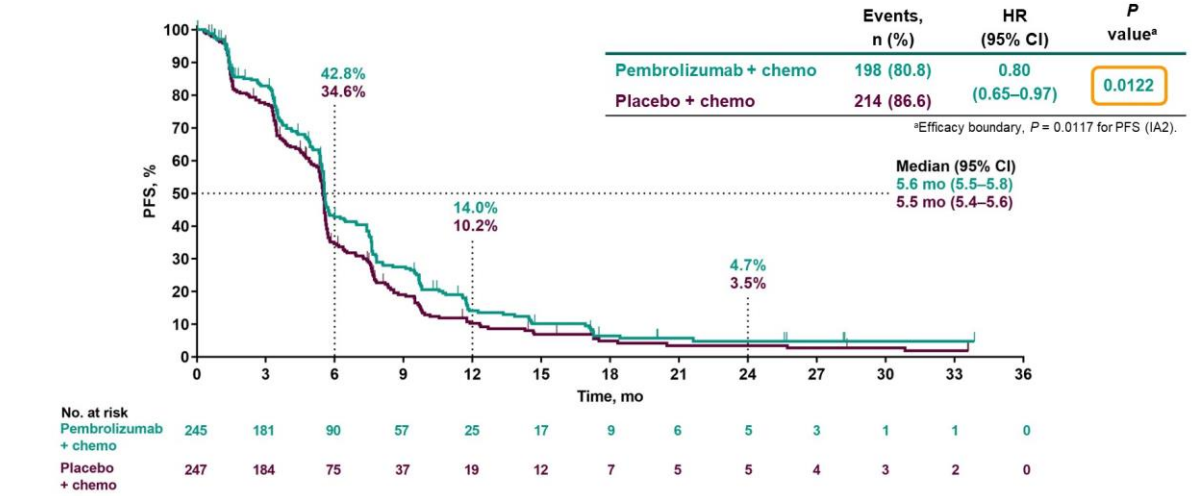
Keynote 789:

No difference in PFS or OS w/ addition of pembrolizumab to chemotherapy after osimertinib progression

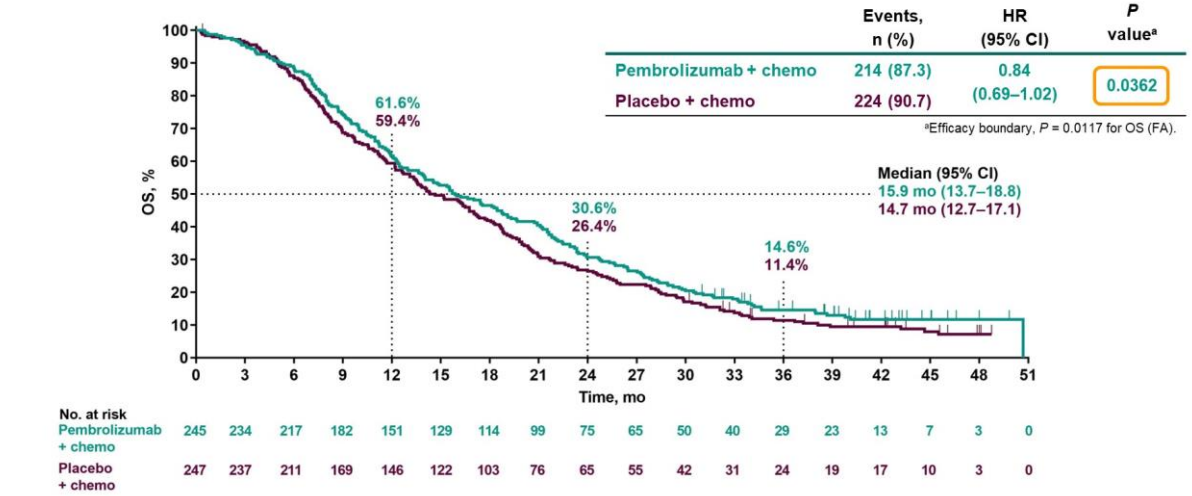
KEYNOTE-789: Phase 3 Randomized Study (NCT03515837)



Progression-Free Survival at IA2
(RECIST v1.1, BICR)



Overall Survival at FA



Yang et al, Abstract LBA9000, Presented at ASCO 2023

Case 1

The patient undergoes biopsy of the liver lesion which confirms adenocarcinoma, no new actionable mutations / resistance mechanisms. She is treated with carboplatin + pemetrexed + amivantamab with stable disease 6 months later.

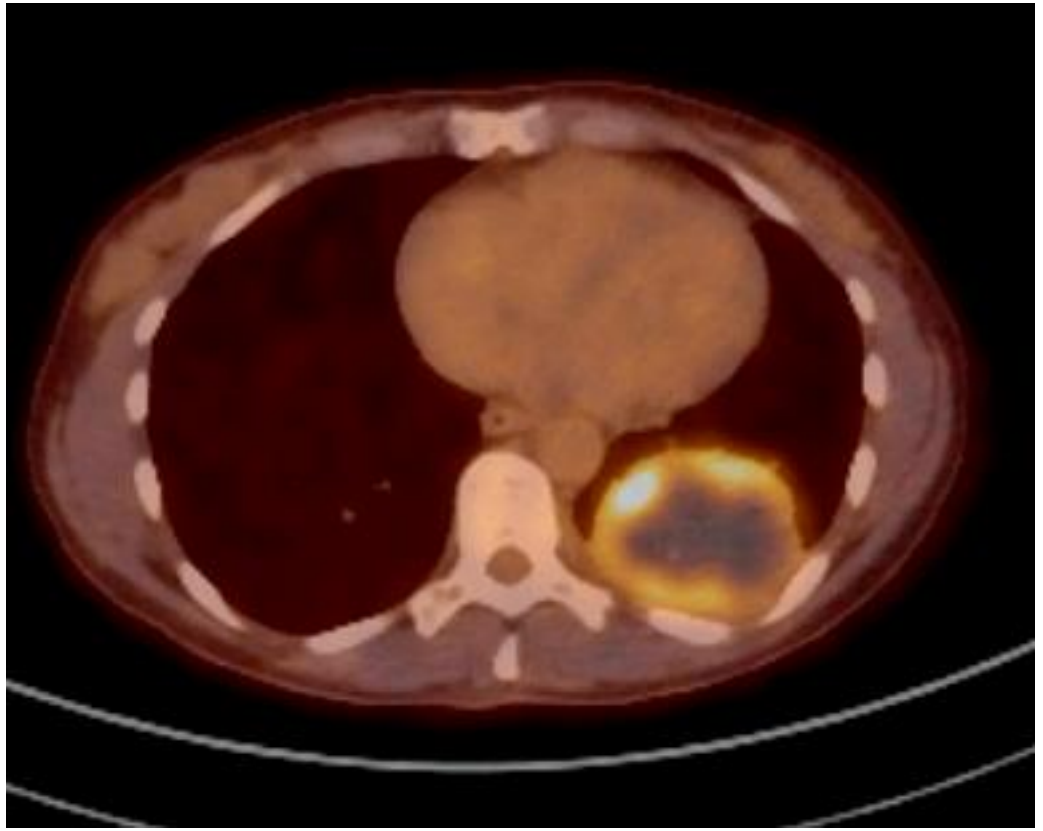
Take Home Messages

- **FLAURA2:** 1st line osimertinib + carbo/cis + pemetrexed in advanced *EGFR*-mutated (*L858R* or *Exon19del*) NSCLC improves PFS vs osimertinib alone, particularly if CNS metastases at presentation. Overall survival data immature.
- **MARIPOSA-2:** amivantamab +/- lazertinib + carbo + pemetrexed for *EGFR*-mutated NSCLC after progression on osimertinib improves PFS vs carbo + pemetrexed alone. Overall survival data immature.
- **KEYNOTE 789:** Adding pembro to carbo + pemetrexed for *EGFR*-mutated NSCLC after progression on osimertinib does NOT improve PFS or OS vs carbo + pemetrexed alone.
- Re-biopsy or plasma ctDNA analysis at the time of PD can be informative in identifying a treatable mechanism of resistance (e.g. MET amplification) or transformation to SCLC

Case 2

42 yo woman, no smoking history, presents w/ 3 mo of cough and SOB

- **CT CAP:** 6.5 cm LLL mass
- **Brain MRI:** no metastases
- **PET/CT:** hypermetabolic 6.5 cm mass and level 11 ipsilateral node, no distant metastatic disease
- **EBUS Biopsy:** LLL mass and (N1) node positive for adenocarcinoma



Stage IIIA (T3N1M0)

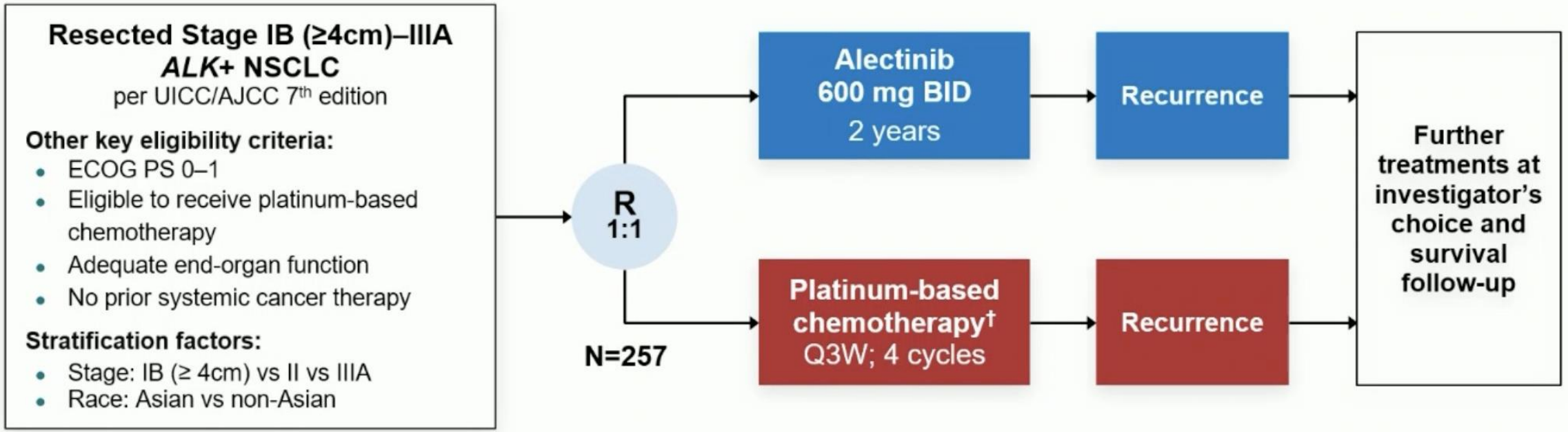
Case 2

- IHC/NGS: ***EML4-ALK* fusion** positive, PD-L1 TPS 90%, *EGFR* negative

Question 1: In this patient with stage IIIA disease and ECOG 0, what would you recommend?

1. Surgery then adjuvant chemotherapy
2. Surgery then adjuvant chemotherapy followed by atezolizumab
3. Surgery then adjuvant alectinib
4. Neoadjuvant chemotherapy + immunotherapy, then surgery +/- adjuvant immunotherapy
5. Chemoradiation then durvalumab

ALINA: Improved DFS w/ adjuvant alectinib (2yrs) for stage IB-IIIA *ALK+* disease vs platinum-based chemotherapy



Primary endpoint

- DFS per investigator,‡ tested hierarchically:
  - Stage II–IIIA → ITT (Stage IB–IIIA)

Other endpoints

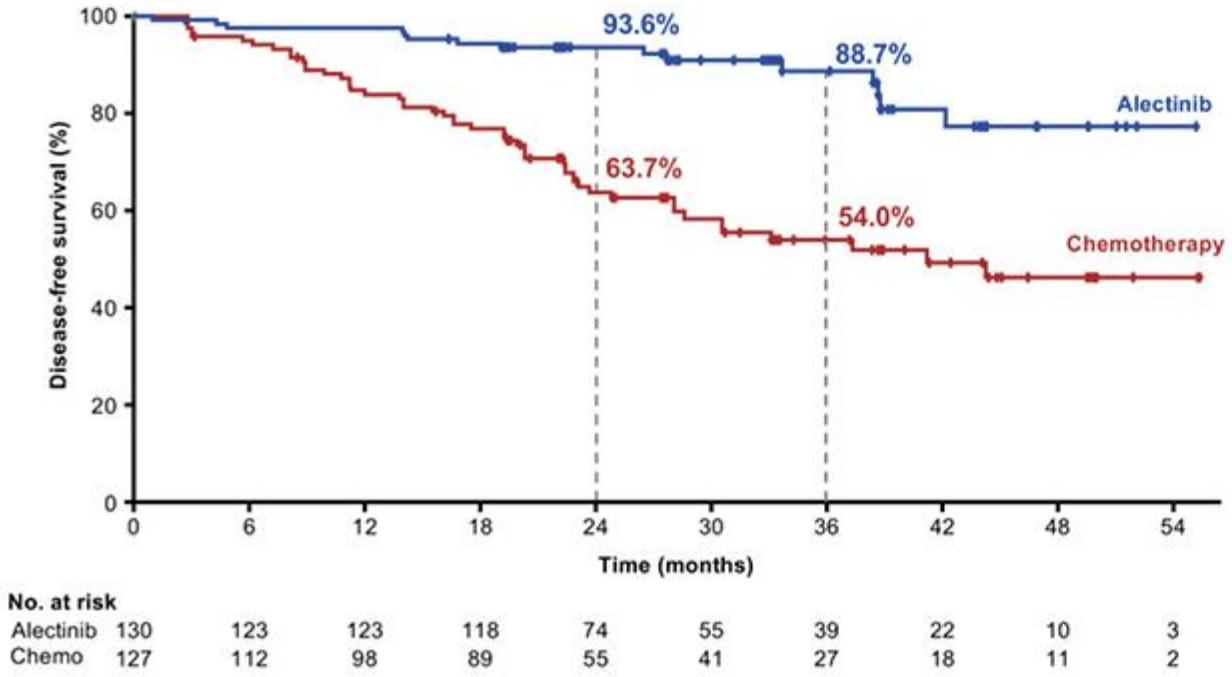
- CNS disease-free survival
- OS
- Safety

Disease assessments (including brain MRI)§ were conducted: at baseline, every 12 weeks for year 1–2, every 24 weeks for year 3–5, then annually

Solomon et al, Abstract LBA2, Presented at ESMO 2023

ALINA: Improved DFS w/ adjuvant alectinib x 2 yrs for stage IB-IIIA *ALK+* disease vs platinum-based chemotherapy

Disease-free survival: ITT (stage IB-IIIA)*



	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event Death Recurrence	15 (12%) 0 15	50 (39%) 1 49
Median DFS, months (95% CI)	Not reached	41.3 (28.5, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.43) p‡<0.0001	

At the data cutoff date, **OS data were immature** with only 6 (2.3%) OS events reported §

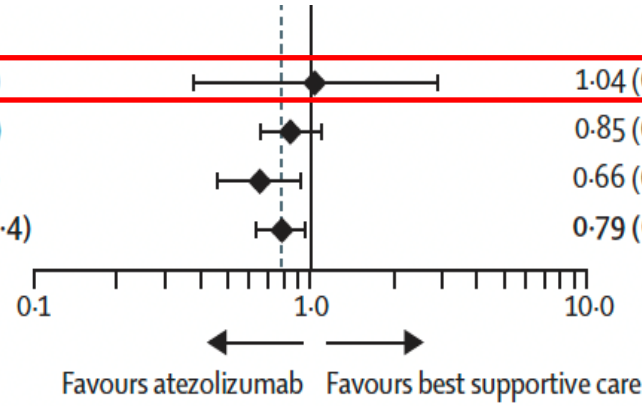
Median survival follow up: alectinib, 27.8 months; chemotherapy, 28.4 months

Solomon et al, Abstract LBA2, Presented at ESMO 2023

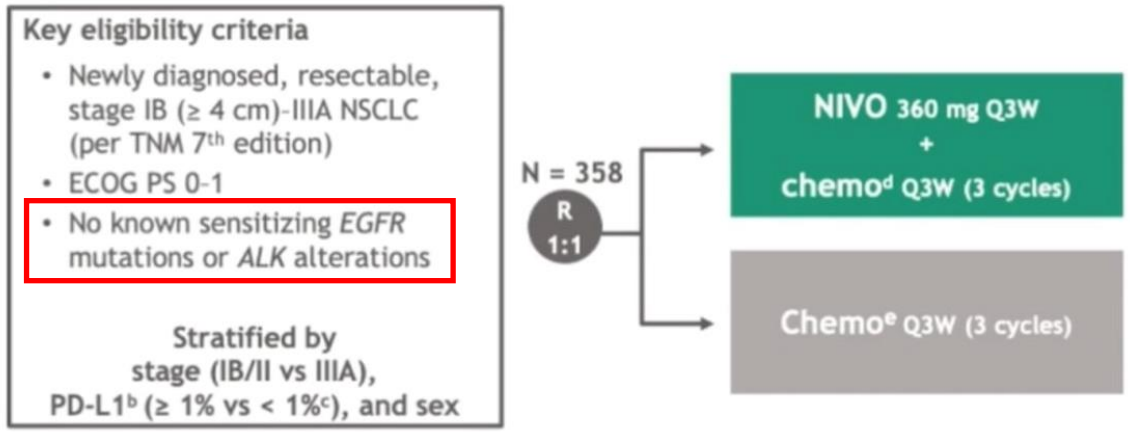
Checkpoint inhibitors likely not effective for *ALK* fusions

IMpower010 (neoadjuvant atezolizumab in early-stage NSCLC)

ALK rearrangement status					
Yes	14/31	30·5 (17·1–NE)	17/31	37·2 (19·5–NE)	1·04 (0·38–2·90)
No	251/507	36·1 (30·2–NE)	256/507	31·4 (24·7–NE)	0·85 (0·66–1·10)
Unknown	177/344	NE (36·1–NE)	167/344	37·3 (31·0–NE)	0·66 (0·46–0·93)
All patients	442/882	42·3 (36·0–NE)	440/882	35·3 (30·4–46·4)	0·79 (0·64–0·96)



CHECKMATE-816 (neoadjuvant nivolumab in early-stage NSCLC)



Felip et al, Lancet 2021; 398:1344-1357. Forde et al, NEJM 2022; 386:1973-1985

Case 2

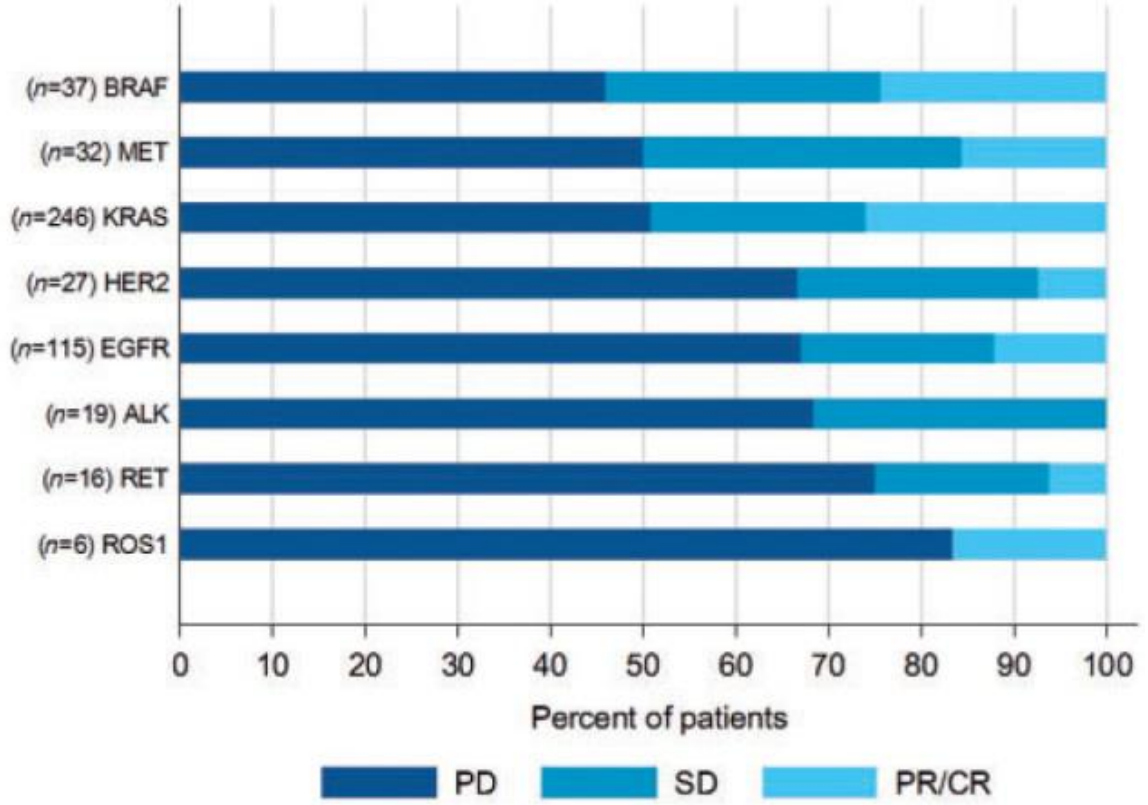
- IHC/NGS: ***ROS1*-fusion** positive, PD-L1 TPS 90%, *EGFR* mutation and *ALK* fusion negative, no other driver mutations

Question 2: If this patient w/ stage IIIA disease instead presented w/ the above molecular findings, what would your recommendation be?

1. Surgery then adjuvant chemotherapy
2. Surgery then adjuvant repotrectinib
3. Surgery then adjuvant entrectenib
4. Surgery then adjuvant chemotherapy followed by atezolizumab
5. Neoadjuvant chemotherapy + immunotherapy, then surgery +/- adjuvant immunotherapy

Checkpoint inhibitors likely have limited efficacy in ROS1 mutant NSCLC

- Retrospective analysis of patients w/ advanced NSCLC receiving ICI monotherapy in IMMUNOTARGET registry
- *ROS1* patients w/ 83% of patients w/ progressive disease, 17% w/ response (compare to *EGFR* 12%, *ALK* 0%)



PD, progressive disease; SD, stable disease; PR, partial response; CR, complete response

Mazieres et al, Annals of Oncology 2019; 30:1321-1328

Case 2

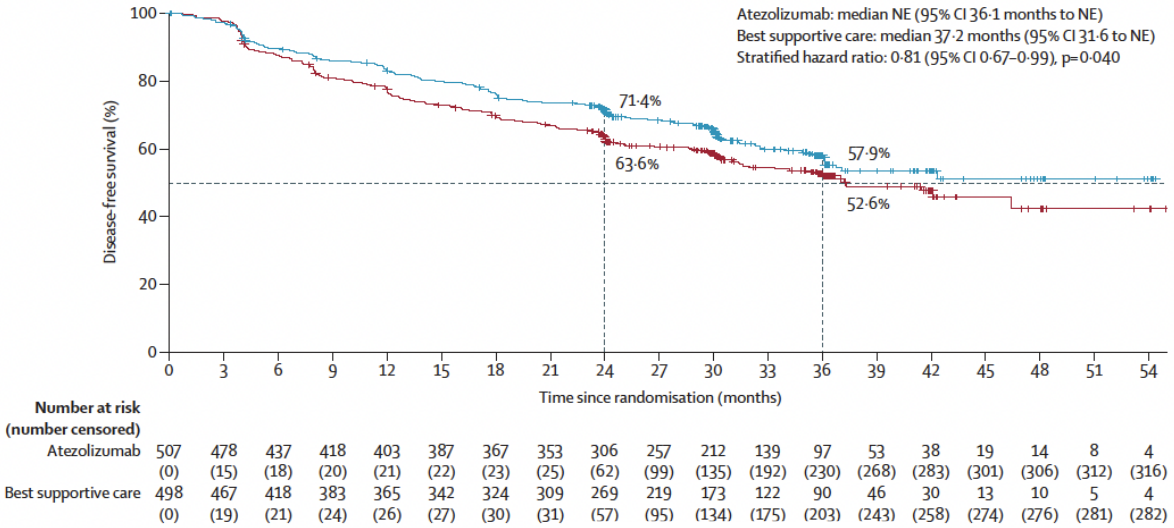
- IHC/NGS: PD-L1 TPS 90%, ***EGFR*** **negative, *ALK/ROS1* fusion negative**, no other driver mutations

Question 3: If this patient w/ stage IIIA disease instead presented w/ the above molecular findings, what would your recommendation be?

1. Surgery then adjuvant chemotherapy
2. Surgery then adjuvant chemotherapy followed by atezolizumab
3. Neoadjuvant chemotherapy + nivolumab then surgery
4. Neoadjuvant chemotherapy + pembrolizumab, then surgery followed by adjuvant pembrolizumab
5. Chemoradiation then durvalumab

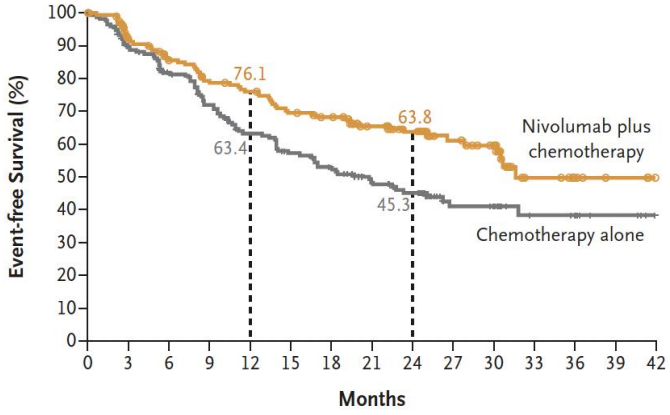
IMpower010: Improved DFS w/ adj chemo + atezo, stage IB-IIIA
CHECKMATE-816: Improved EFS w/ neoadj chemo + nivo, stage IIB-IIIA
KEYNOTE-671: Improved EFS w/ neoadj chemo + pembro and adj pembro, stage II-IIIB

010 (DFS)



Number at risk (number censored)																			
Atezolizumab	507	478	437	418	403	387	367	353	306	257	212	139	97	53	38	19	14	8	4
	(0)	(15)	(18)	(20)	(21)	(22)	(23)	(25)	(62)	(99)	(135)	(192)	(230)	(268)	(283)	(301)	(306)	(312)	(316)
Best supportive care	498	467	418	383	365	342	324	309	269	219	173	122	90	46	30	13	10	5	4
	(0)	(19)	(21)	(24)	(26)	(27)	(30)	(31)	(57)	(95)	(134)	(175)	(203)	(243)	(258)	(274)	(276)	(281)	(282)

816 (EFS)

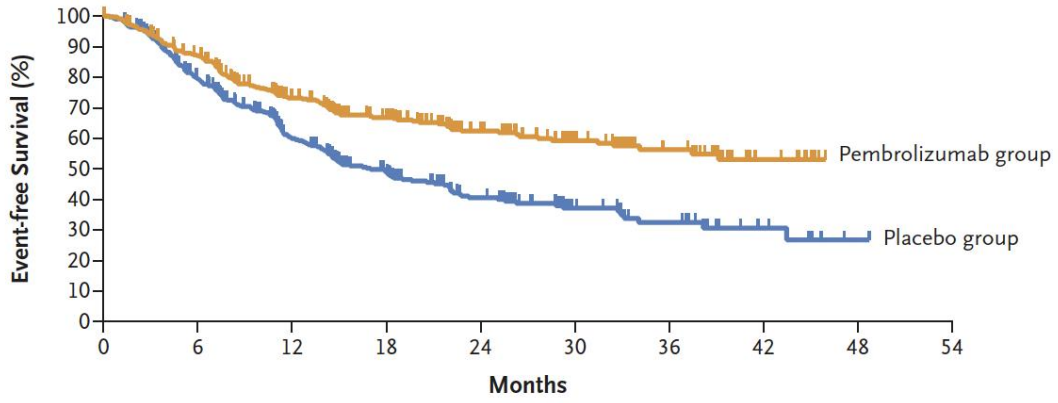


No. at Risk															
Nivolumab plus chemotherapy	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemotherapy alone	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

671 (EFS)



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

Felip et al, Lancet 2021; 398:1344-1357
Forde et al, NEJM 2022; 386:1973-1985
Wakelee et al, NEJM 2023; 389:491-503

Case 2

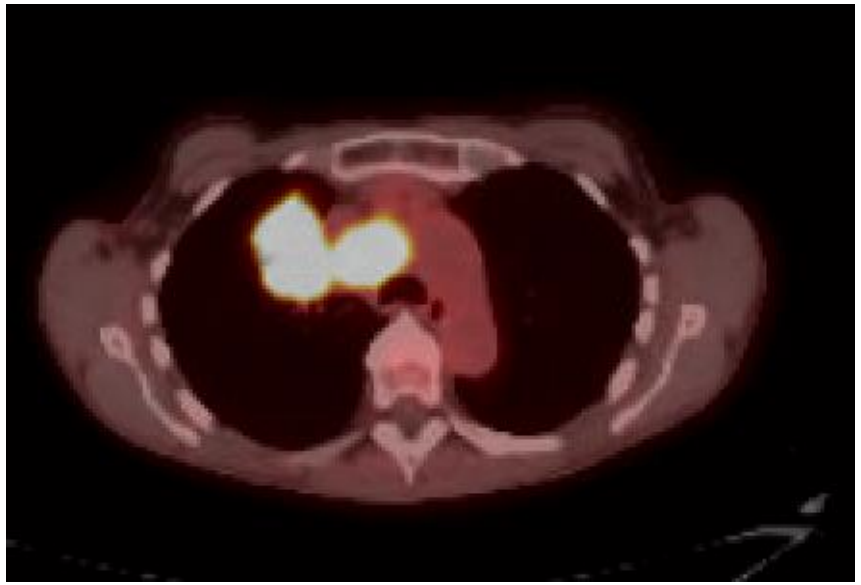
Take Home Messages

- Adjuvant alectinib improves DFS vs chemo in resectable stage IB-IIIA *ALK*+ disease
- Checkpoint inhibitors unlikely to benefit *ALK*+ and may not benefit *ROS1+* disease regardless of PD-L1 status
- No data yet on *ROS1* targeted agents in adjuvant treatment of *ROS1*+ early-stage NSCLC, though data for *EGFR* and *ALK* would suggest there could be a benefit
- In early-stage resectable PD-L1+ NSCLC, can use multiple perioperative IO regimens including atezolizumab, pembrolizumab, and nivolumab (refer back to trials for NSCLC stages included for each agent)

Case 3

75 yo woman, 15 pack year smoking history, presents w/ cough

- **CT CAP:** 5 cm RUL mass
- **Brain MRI:** no metastases
- **PET/CT:** hypermetabolic RUL mass and bilateral mediastinal lymph nodes
- **EBUS Biopsy:** level 4L node positive for adenocarcinoma



Stage IIIB (T3N3M0)

Case 3

- IHC/NGS: ***KRAS G12C* positive**, *KEAP1* and *STK11* mutations, PD-L1 TPS 30%, no other driver mutations

Question 1: In this patient with stage IIIB disease and ECOG of 1, what treatment course would you recommend?

1. Durvalumab followed by cisplatin + pemetrexed + radiation (CRT)
2. Concurrent durvalumab + CRT followed by durvalumab
3. CRT followed by durvalumab
4. CRT only
5. CRT followed by sotorasib

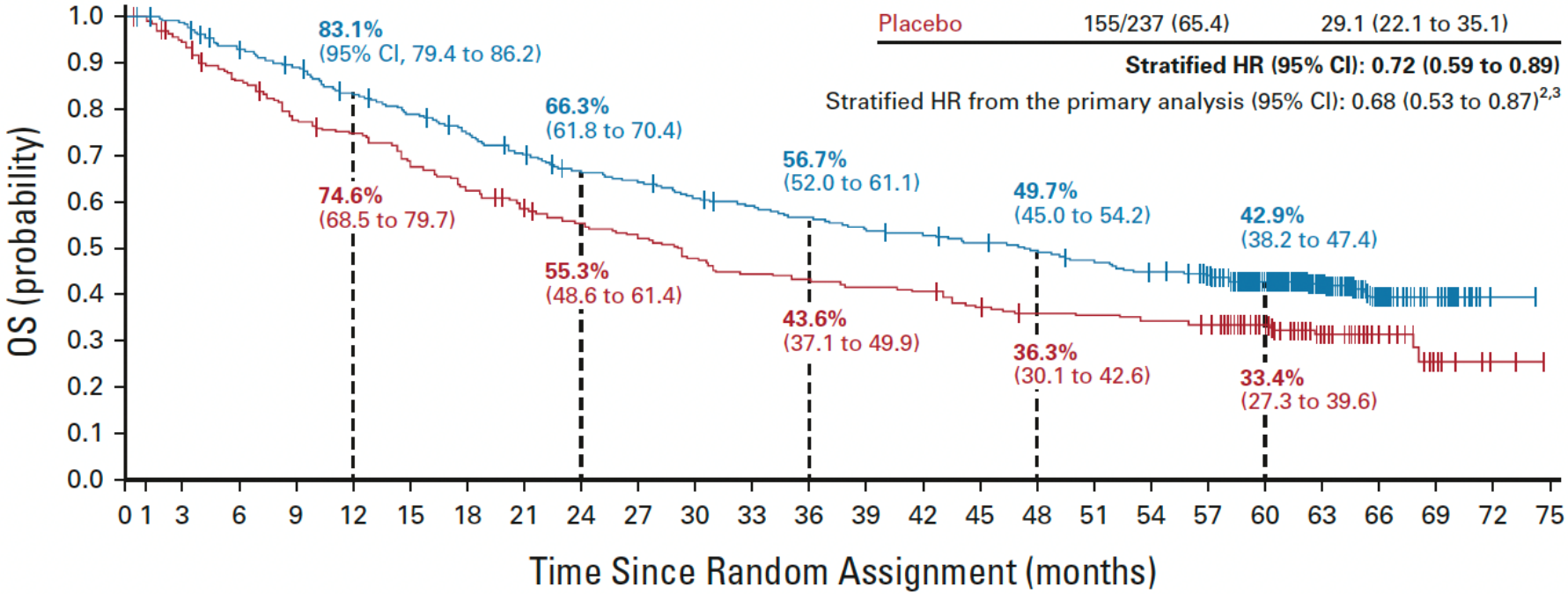
PACIFIC: Durvalumab after chemoradiation in stage III NSCLC prolongs OS and PFS

Overall Survival

Arm	No. of Events/ Total No. of Patients (%)	Median OS (95% CI), Months
Durvalumab	264/476 (55.5)	47.5 (38.1 to 52.9)
Placebo	155/237 (65.4)	29.1 (22.1 to 35.1)

Stratified HR (95% CI): 0.72 (0.59 to 0.89)

Stratified HR from the primary analysis (95% CI): 0.68 (0.53 to 0.87)[2,3]



No. at risk:

Durvalumab	476	464	431	414	385	364	343	319	298	289	273	264	252	241	236	227	218	207	196	183	134	91	40	18	2	0
Placebo	237	220	199	179	171	156	143	133	123	116	107	99	97	93	91	83	78	77	74	72	56	33	16	7	2	0

Spigel et al, JCO 2022; 40:1301-1311

IASLC 2021 Targeted Therapies of Lung Cancer Meeting

PACIFIC Trials

PACIFIC 2 Study Design:

Phase 3, randomized, double-blind, placebo-controlled, multicenter, global study[1,2]

Durvalumab + CRT followed by durvalumab versus placebo + CRT followed by placebo

Screening → **Treatment period** → **Follow-up**

Patient population
- Locally advanced, unresectable (Stage III) NSCLC
- WHO performance status 0 or 1

Stratification factors:
- Age (<65 vs ≥65 years)
- Stage (IIIA vs IIIB/C)

Randomize (2:1)

- Durvalumab 1500 mg IV q4w + SoC CRT[a] (Arm A) n=200 → Patients with CR, PR or SD → Durvalumab
- Placebo q4w + SoC CRT[a] (Arm B) n=100 → Patients with CR, PR or SD → Placebo

Primary endpoint
PFS using BICR assessments per RECIST v 1.1

Secondary endpoints
ORR, OS, OS24, DoR, DCR, TTDM, CR, PK, Health-related QoL, and Immunogenicity

Estimated Enrollment: 300
Enrollment Completed. Interim analysis expected in 2021
Estimated Study Completion: November, 2023

- Activated: 4/18
- Ex-US
- Treat until PD

- Upfront CRT & durva
- Dosing Interval/length
- PD-L1 Status

Jhanelle Gray MD

CRT + durvalumab followed by durvalumab did not achieve primary endpoint of PFS vs. CRT alone

AstraZeneca Press Release, 14 November, 2023

Case 3

- IHC/NGS: ***KRAS G12C* positive**, *KEAP1* and *STK11* mutation positive, PD-L1 TPS 30%, no other driver mutations

The patient completed 1 year of durvalumab consolidation without disease progression until 12 months post-treatment when they developed recurrence with multiple lesions in the liver, ribs, and adrenal glands. A biopsy of a liver lesion confirms the above molecular findings. ECOG is 1.

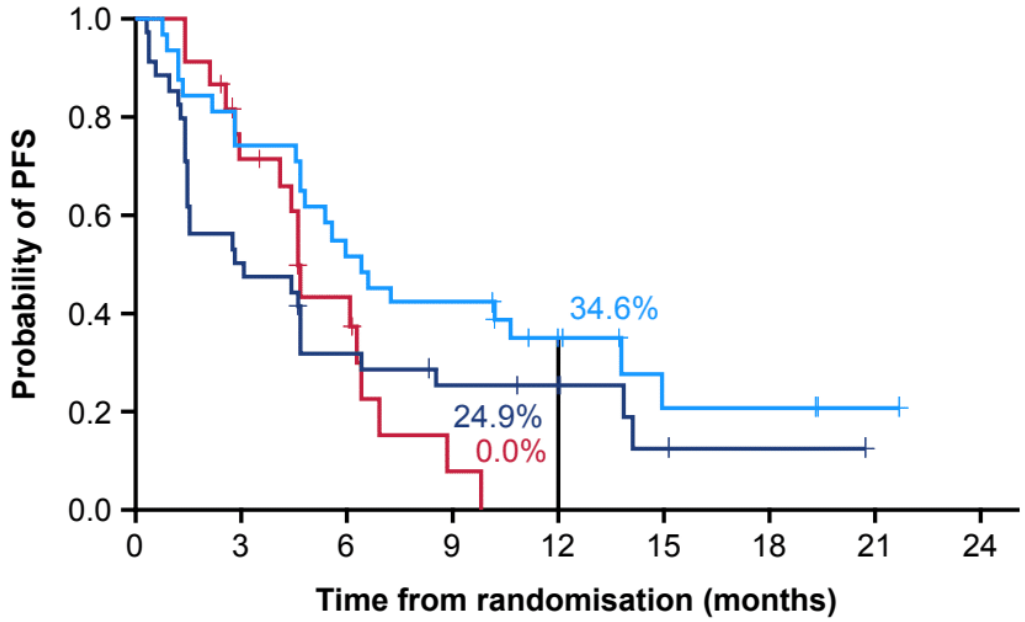
Question 2: What therapy do you recommend next?

1. Tremelimumab + durvalumab + carboplatin + pemetrexed
2. Carboplatin + pemetrexed + pembrolizumab
3. Carboplatin + pemetrexed + bevacizumab
4. Sotorasib + immunotherapy
5. Adagrasib
6. Sotorasib

KRAS G12C NSCLC can respond to anti-PD1/PD-L1 therapies, though co-mutation w/ *STK11* and/or *KEAP1* may promote resistance due to lack of T-cell infiltration

STK11m Subgroup

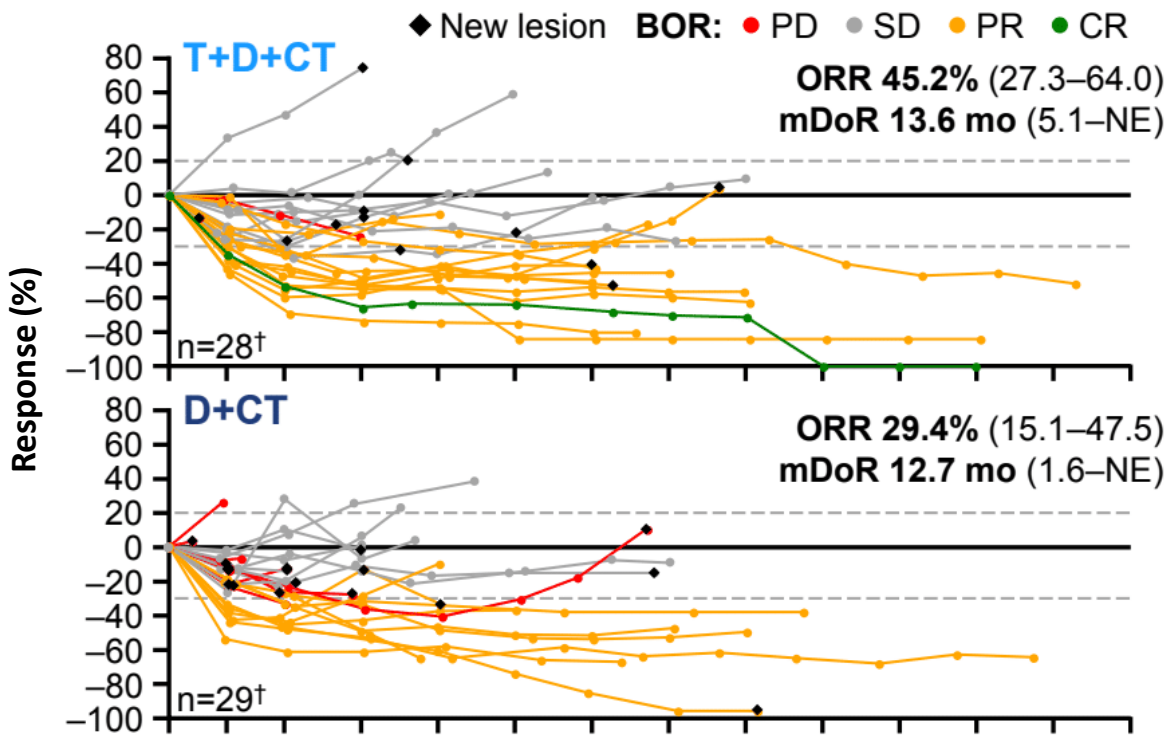
	T+D+CT	D+CT	CT
Events, n/N	22/31	27/34	17/22
mPFS, mo (95% CI)	**6.4** (4.7–13.8)	**2.9** (1.4–4.7)	**4.6** (2.9–6.4)
HR* (95% CI)	**0.47** (0.23–0.93)	**1.02** (0.55–1.93)	–



No. at risk									
T+D+CT	31	23	16	13	7	3	3	1	0
D+CT	34	17	10	7	5	2	1	0	0
CT	22	14	7	1	0	0	0	0	0

T = tremelimumab, D = durvalumab, CT = chemotherapy

Exploratory analysis: Adding CTLA4 inhibitor (tremelimumab) to anti-PD-L1 therapy (durvalumab) may overcome some of the resistance



Peters et al, Abstract OA15.04, Presented at IASLC WCLC 2022

CodeBreak 100/101: *KRAS G12C* inhibitor w/ pembrolizumab or atezolizumab shows potential for hepatotoxicity

Safety Summary: Lead-in versus Concurrent

	Sotorasib + Atezolizumab Lead-In (N = 10)	Sotorasib + Atezolizumab Concurrent (N = 10)	Sotorasib + Pembrolizumab Lead-In (N = 19)	Sotorasib + Pembrolizumab Concurrent (N = 19)
TRAE, any grade, n (%)	10 (100)	9 (90)	15 (79)	17 (89)
Grade 3	3 (30)	5 (50)	10 (53)	14 (74)
Grade 4*	0	1 (10)	0	1 (5)
TRAE leading to sotorasib and/or IO discontinuation, n (%)	1 (10)	5 (50)	6 (32)	10 (53)
Median duration of sotorasib, months (min, max)	6.5 (1, 18)	4.4 (1, 14)	2.8 (1, 15)	4.9 (2, 30)
Median duration of combination, months (min, max)‡	1.5 (0, 18)	2.5 (1, 14)	0.7 (1, 15)	2.3 (1, 9)
Hepatotoxicity grade ≥ 3, median onset, days (range)	50 (28, 93)	67 (36, 147)	73 (45, 127)	51 (29, 190)

- **Lead-in had lower incidence of Grade 3-4 TRAEs and TRAEs leading to discontinuation than concurrent**
- **Grade 3-4 hepatotoxicity first occurrence was outside DLT window† in 88% of patients; 97% of events resolved with corticosteroids, treatment modification, and/or discontinuation**
- **The incidence of hepatotoxicity TRAEs was similar in IO-naïve versus IO-pretreated patients**

Li et al, Abstract OA03.06, Presented at IASLC WCLC 2022

Case 3

- IHC/NGS: ***KRAS G12C* positive**, *KEAP1* and *STK11* mutation positive, PD-L1 TPS 30%, no other driver mutations

Now consider if the patient has progression during durvalumab consolidation and develops recurrent disease with multiple lesions in the liver, ribs, and adrenal glands. ECOG is 1.

Question 3: What therapy do you recommend next?

1. Tremelimumab + durvalumab + carboplatin + pemetrexed
2. Carboplatin + pemetrexed + pembrolizumab
3. Carboplatin + pemetrexed + bevacizumab
4. Sotorasib + immunotherapy
5. Adagrasib
6. Sotorasib

Case 3

Take Home Messages

- Durvalumab consolidation after CRT improves PFS and OS for locally-advanced NCSLC.
- Concurrent durvalumab + CRT has not shown a PFS benefit.
- 1st line therapy for advanced *KRAS G12C*-mutated NSCLC remains ICI +/- chemotherapy. *KRAS G12C* inhibitors reserved for 2nd line.
- *STK11/KEAP1* mutations, often co-mutated w/ *KRAS*, portend poor prognosis and worse response to ICIs. Exploratory analysis suggests that adding a CTLA4 inhibitor to PD-L1 inhibitor may improve outcomes although this has not been prospectively assessed.

Case 4

67 yo man, 10 pack year smoking history, presents w/ cough

- **CT CAP:** 5 cm LUL mass
- **Brain MRI:** No brain metastases
- **PET/CT:** hypermetabolic LUL mass bilateral mediastinal LNs, multiple bilateral pulmonary nodules, as well as several FDG–avid bone lesions
- **CT-guided biopsy:** LUL mass positive for squamous cell carcinoma

Stage IVB (T3N3M1c)

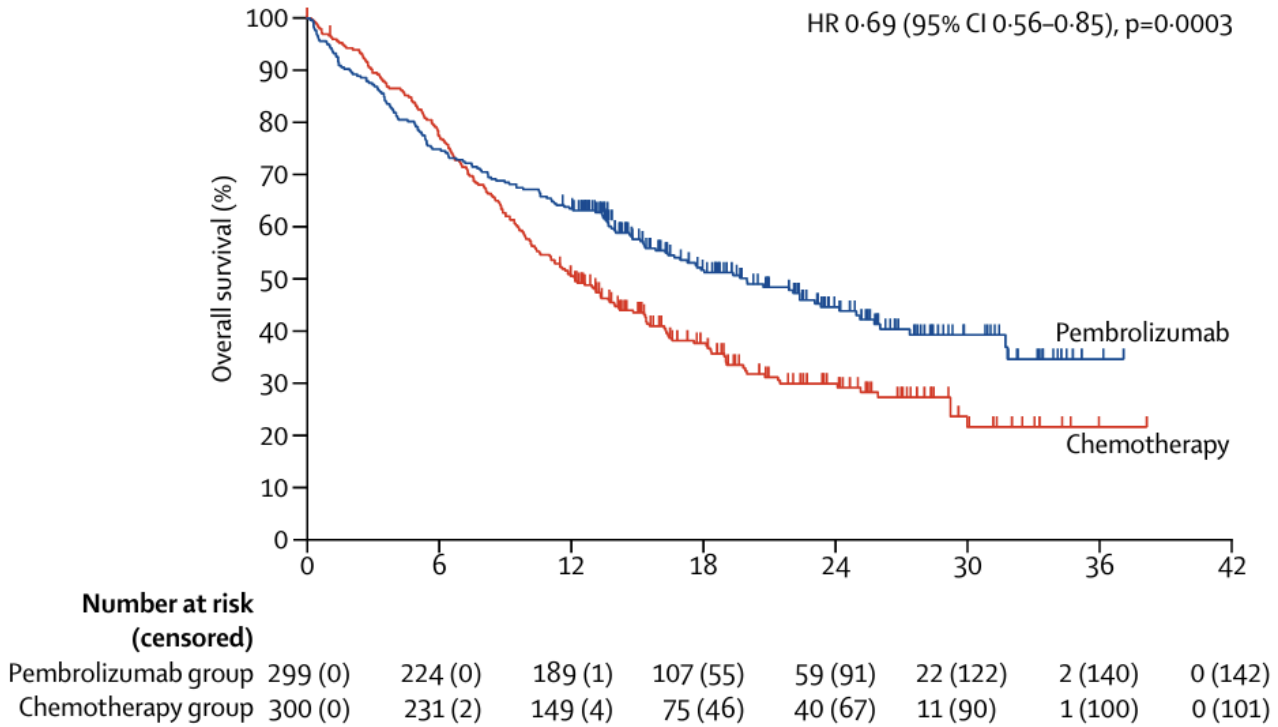
Case 4

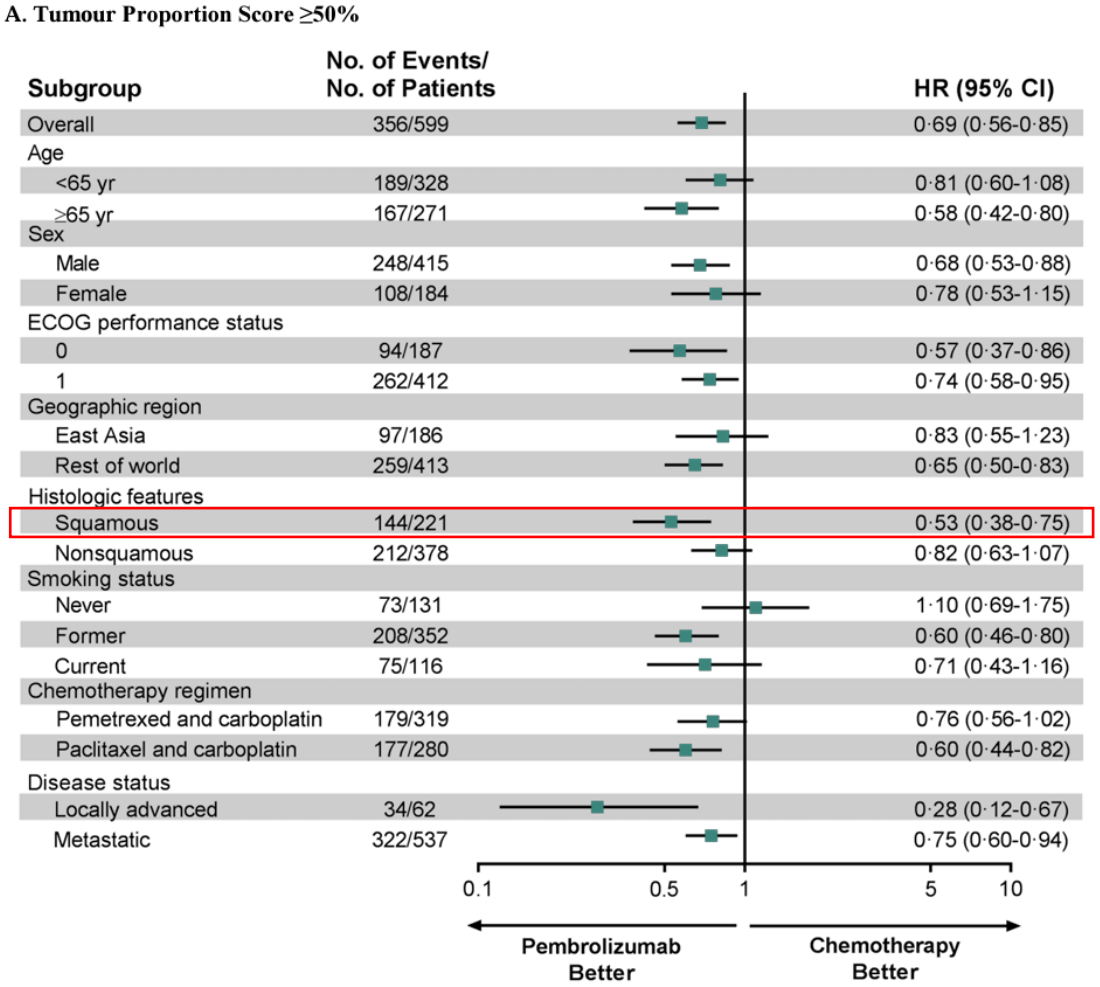
- IHC/NGS: **PD-L1 TPS 60%**, *EGFR* mutation and *ALK/ROS* fusion negative, no other driver mutations, *STK11*wt, *KEAP1*wt

Question 1: In this patient with stage IVB squamous cell lung cancer with PD-L1 TPS 60% and ECOG 1, what do you recommend as first line therapy?

1. Pembrolizumab or atezolizumab or cemiplimab single agent
2. Ipilimumab + nivolumab
3. Carboplatin + paclitaxel + bevacizumab + atezolizumab
4. Carboplatin + paclitaxel + pembrolizumab

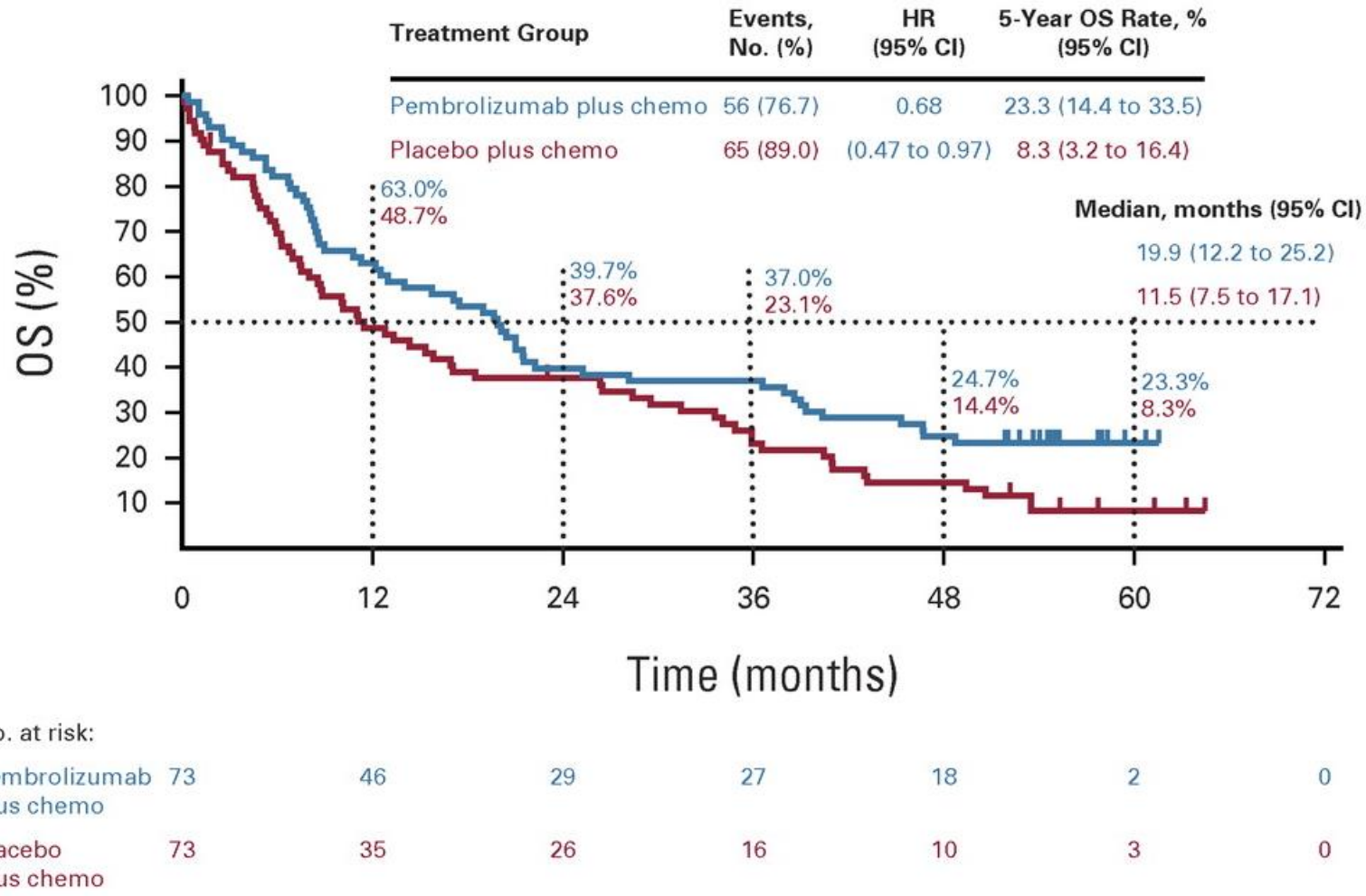
KEYNOTE-042: First line pembrolizumab improves OS vs chemotherapy among patients with PD-L1+ advanced NSCLC, benefit greatest if TPS ≥50%





Mok et al, Lancet 2019; 393:1819-1830

KEYNOTE-407: Five-year follow-up shows first line pembrolizumab plus chemo in squamous NSCLC improves OS over chemo alone

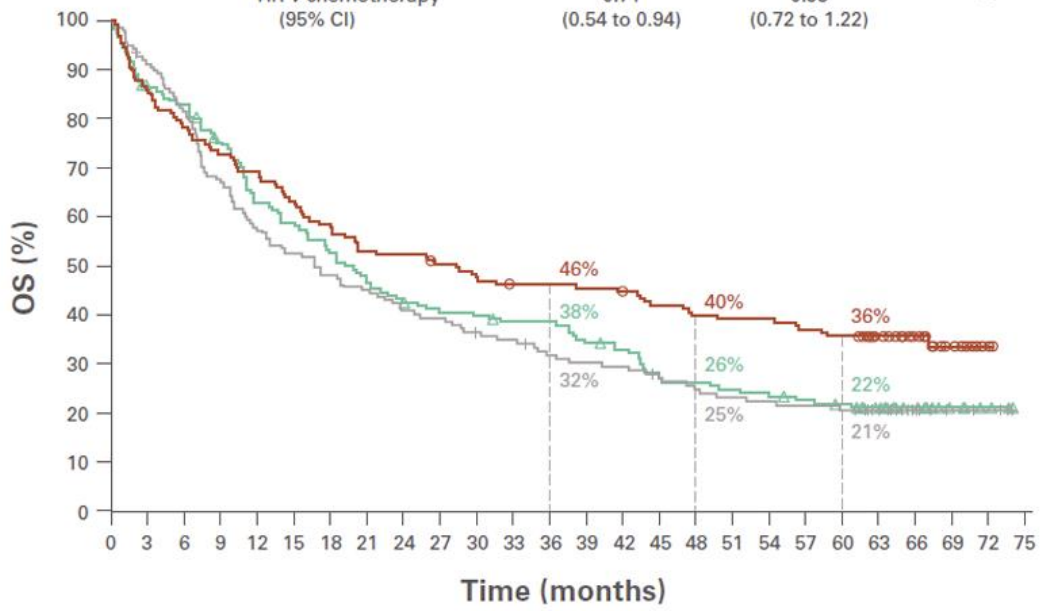


Novello et al, JCO 2023; 41:1999-2006

CheckMate 227: Five-Year follow-up shows first line nivolumab + ipilimumab improves OS vs nivolumab or chemo in mNSCLC, benefit greatest in non-squamous and if TPS ≥50%

PD-L1 ≥50% and nonsquamous tumor histology

	Nivolumab Plus Ipilimumab (n = 147)	Nivolumab (n = 154)	Chemotherapy (n = 137)
Median OS, mo (95% CI)	28.4 (18.0 to 44.2)	19.9 (15.1 to 25.2)	16.7 (11.4 to 23.7)
HR *v* chemotherapy (95% CI)	0.71 (0.54 to 0.94)	0.93 (0.72 to 1.22)	–

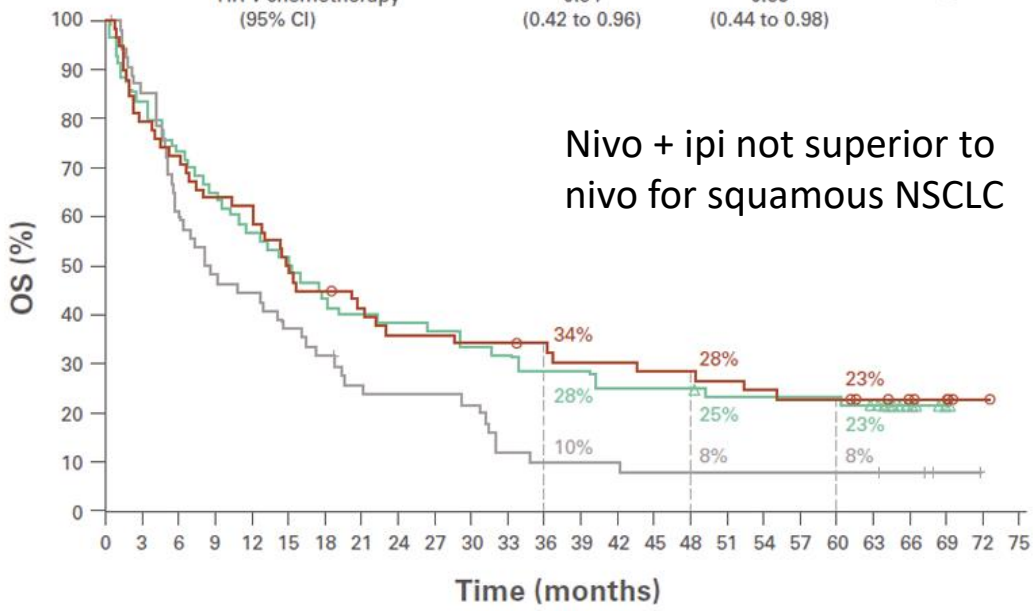


No. at risk:

Nivolumab plus ipilimumab	147	126	115	107	102	93	86	78	77	73	69	66	66	65	63	59	56	55	55	52	50	40	25	9	1	0
Nivolumab	154	131	125	112	93	87	78	68	64	59	58	55	55	49	45	37	36	34	32	30	28	22	12	6	3	0
Chemotherapy	137	123	110	90	77	71	65	61	55	53	48	46	41	39	38	34	31	29	28	27	26	19	9	3	2	0

PD-L1 ≥50% and squamous tumor histology

	Nivolumab Plus Ipilimumab (n = 58)	Nivolumab (n = 60)	Chemotherapy (n = 55)
Median OS, mo (95% CI)	14.9 (10.3 to 22.2)	15.2 (9.2 to 26.4)	8.3 (5.6 to 14.5)
HR *v* chemotherapy (95% CI)	0.64 (0.42 to 0.96)	0.65 (0.44 to 0.98)	–



Nivo + ipi not superior to nivo for squamous NSCLC

No. at risk:

Nivolumab plus ipilimumab	58	46	42	37	36	28	26	23	20	20	19	19	18	16	16	15	15	14	13	12	12	10	6	4	1	0
Nivolumab	60	50	44	39	34	31	26	24	23	22	20	19	17	17	15	15	15	13	13	13	13	11	5	1	0	0
Chemotherapy	55	46	32	26	24	20	17	13	12	12	11	6	5	5	5	4	4	4	4	4	4	4	3	1	0	0

Brahmer et al, JCO 2023; 41:1200-1212

Case 4

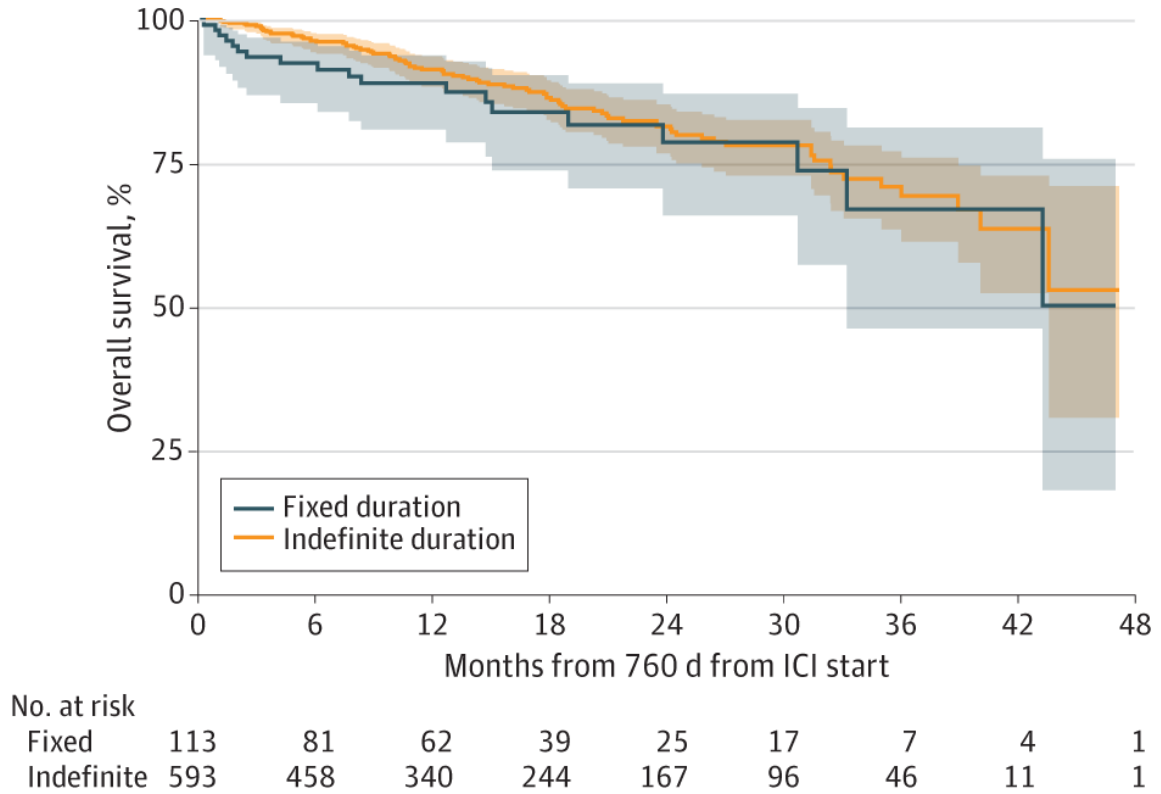
- IHC/NGS: PD-L1 TPS 60%, EGFR mutation and ALK/ROS fusion negative, no other driver mutations

The patient receives pembrolizumab monotherapy and has a complete response and completes 2 years of maintenance therapy.

Question 2: In this patient who has completed 2-years of maintenance pembrolizumab without evidence of disease progression, what is the best option?

1. Continue pembrolizumab indefinitely until disease progression or unacceptable AE
2. Stop pembrolizumab, surveillance only until disease progression
3. Stop pembrolizumab, start carboplatin + pemetrexed
4. Switch to nivolumab + ipilimumab
5. Perform plasma ctDNA analysis. If shows no ctDNA, stop pembrolizumab.

From: **Association Between Duration of Immunotherapy and Overall Survival in Advanced Non–Small Cell Lung Cancer**



Retrospective cohort study

Figure Legend:

Kaplan-Meier curve of overall survival from 2 years (760 days) from immune checkpoint inhibitor (ICI) treatment initiation in the fixed-duration cohort (stopped treatment at 2 years; 700-759 days of treatment) and indefinite-duration cohort (at least 760 days of treatment).

Sun et al, JAMA Oncol 2023; 9:1075-1082

Case 4

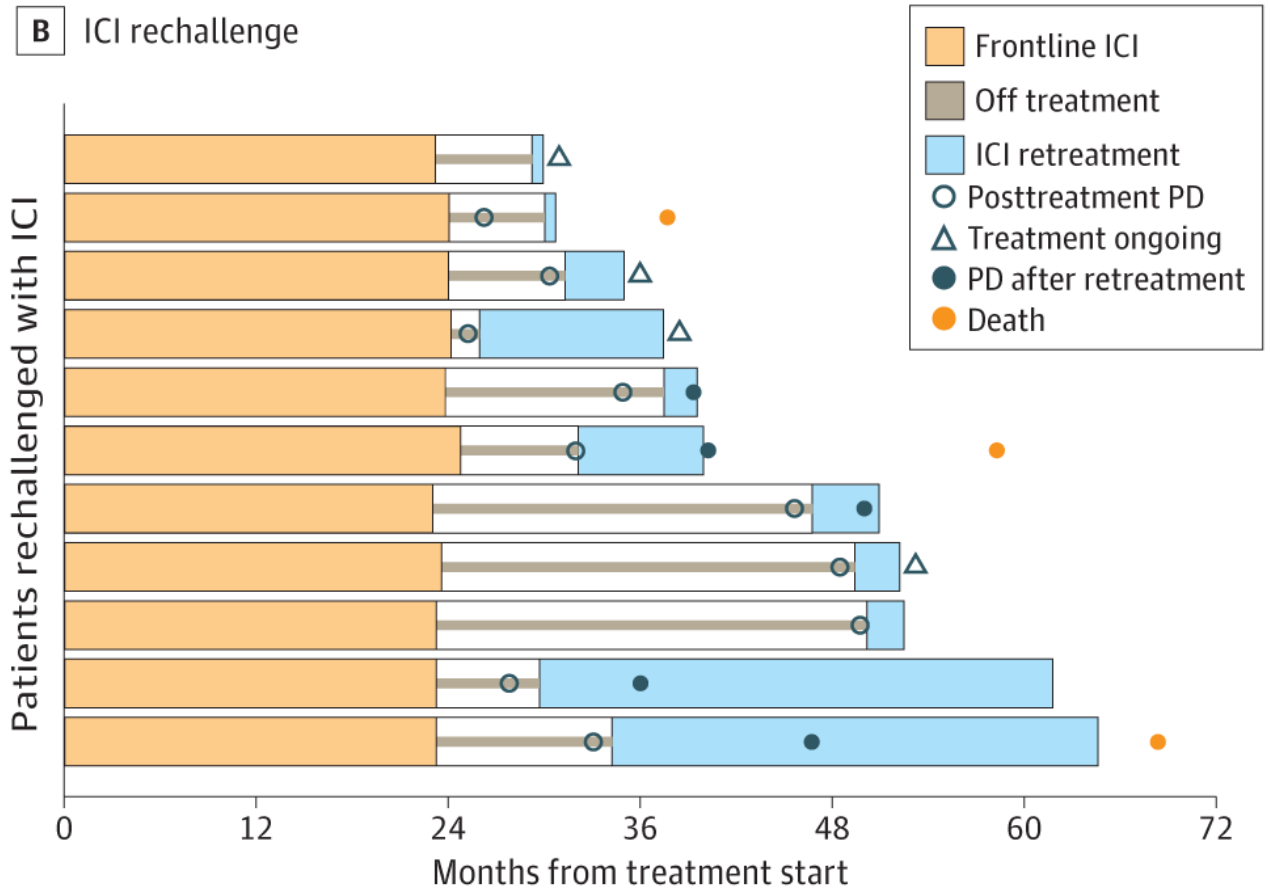
- IHC/NGS: PD-L1 TPS 60%, EGFR mutation and ALK/ROS fusion negative, no other driver mutations

The patient completes 2 years of maintenance pembrolizumab and discontinues therapy. At surveillance imaging in 1 year, multiple sites of disease are identified, and biopsy shows squamous cell lung cancer with **PD-L1 TPS of 1%**.

Question 3: What is the best course of treatment?

1. Pembrolizumab
2. Nivolumab
3. Nivolumab + ipilimumab
4. Carboplatin + nab-paclitaxel + pembrolizumab
5. Carboplatin + nab-paclitaxel

From: **Association Between Duration of Immunotherapy and Overall Survival in Advanced Non–Small Cell Lung Cancer**



Sun et al, JAMA Oncol 2023; 9:1075-1082

Case 4

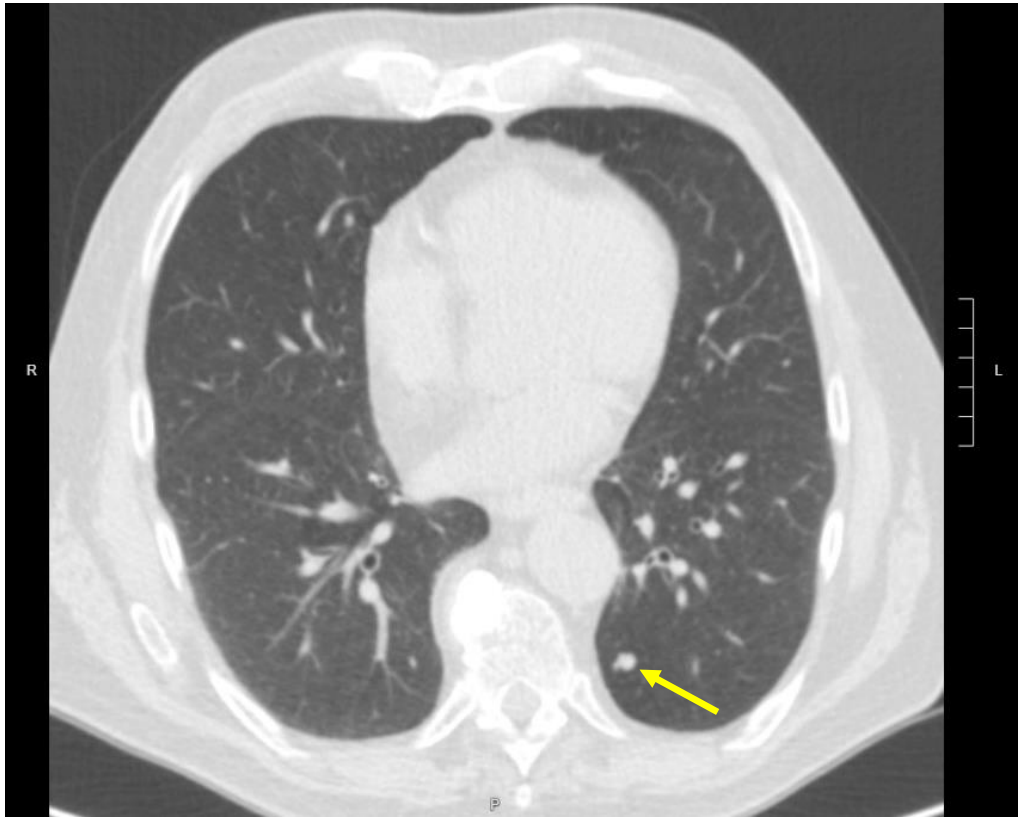
Take Home Messages

- ICI monotherapy is generally preferred to chemo + ICI in PD-L1 ≥50% given similar efficacy and less toxicity
- No OS advantage to continuing ICI beyond 2 years based on retrospective analysis
- Rechallenging with original ICI at disease progression off of therapy can be effective

Case 5

68 yo man, 40 pack year smoking history, presents after biopsy done for mass detected on screening CT chest

- **CT CAP:** 1.1 cm LLL mass
- **Brain MRI:** negative
- **PET/CT:** hypermetabolic LLL mass. No hilar or mediastinal hypermetabolic adenopathy. No metastatic disease.
- **CT-guided biopsy:** positive for **<u>small cell carcinoma</u>**



Stage I (T1N0M0)

Case 5

- IHC/NGS: TP53 (VAF 85%), PD-L1 TPS 50%, TMB 10

Question 1: In this patient with stage I SCLC and ECOG 0, what would you recommend as initial treatment?

1. Lobectomy w/ mediastinal LN dissection
2. Lobectomy w/ mediastinal LN dissection + adjuvant platinum/etoposide
3. SBRT only
4. SBRT + adjuvant platinum/etoposide and atezolizumab or durvalumab
5. Chemoradiation using platinum/etoposide followed by PCI

Case 5

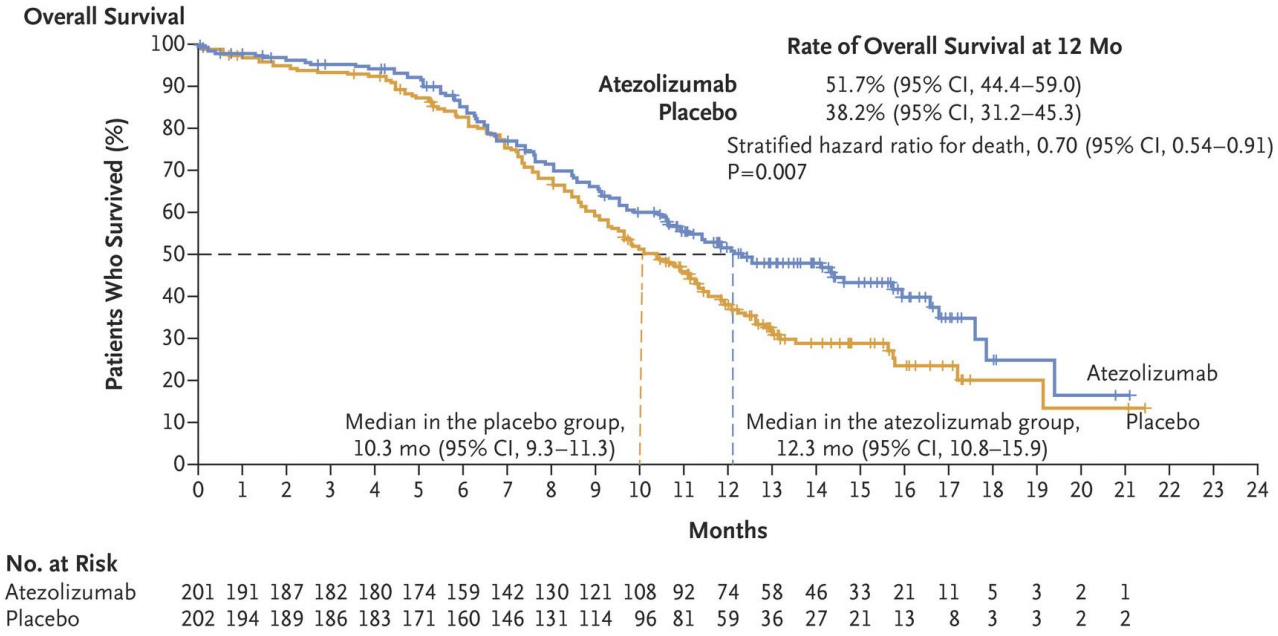
- IHC/NGS: TP53 (VAF 85%), PD-L1 TPS 50%, TMB 10

The patient undergoes surgical resection followed by adjuvant cisplatin + etoposide. He has recurrence of disease 12 months later with lesions in the lungs and liver. ECOG is 1.

Question 2: What treatment do you recommend?

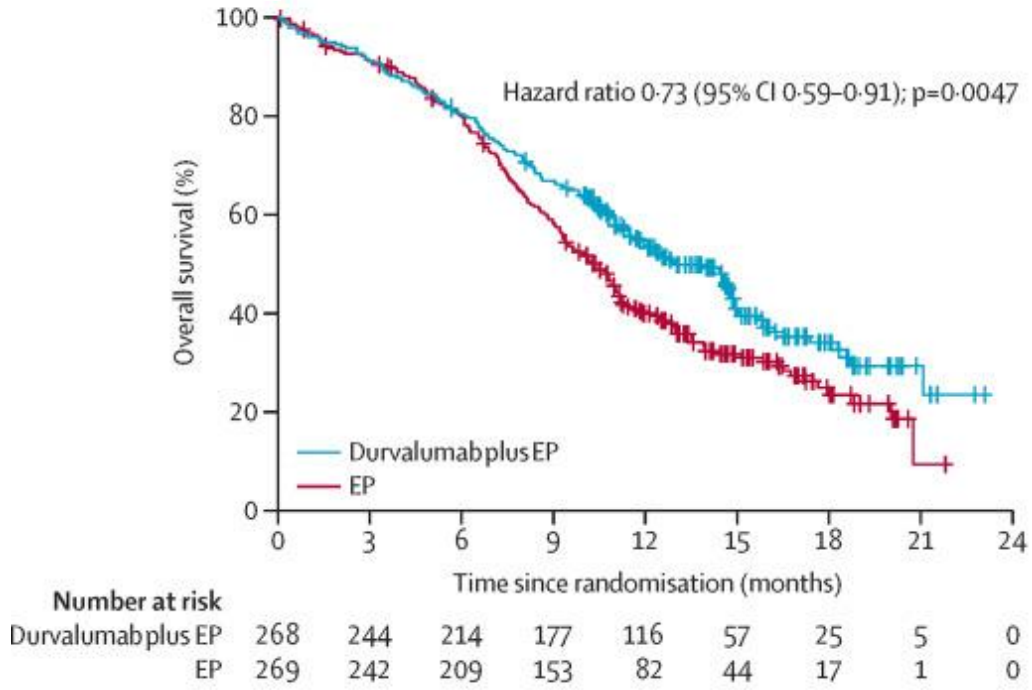
1. Carboplatin + etoposide + durvalumab
2. Cisplatin + etoposide + atezolizumab
3. Carboplatin + etoposide
4. Cisplatin + etoposide

IMpower133: First-Line atezolizumab plus chemotherapy in extensive-stage SCLC



Only carboplatin allowed

CASPIAN: Durvalumab plus platinum/etoposide versus platinum/etoposide in first-line treatment of extensive-stage SCLC



	Durvalumab plus EP events/patients (n)	EP events/patients (n)	Hazard ratio (95% CI)
All patients	155/268	181/269	0·73 (0·59–0·91)
Planned platinum			
Carboplatin	121/201	145/201	0·70 (0·55–0·89)
Cisplatin	34/67	36/68	0·88 (0·55–1·41)

Horn et al, N Engl J Med 2018; 379:2220-2229. Paz-Ares et al, Lancet 2019; 394:1929-1939

Case 5

Take Home Messages

- Although rare (~5% of cases), stage IIA or lower SCLC can be resected, and lobectomy is preferred if patient is a surgical candidate. Adjuvant therapy is still required.

- Atezolizumab + carbo + etoposide or durvalumab + cis/carbo + etoposide for ES-SCLC, carboplatin preferred