ATLANTA
LUNG CANCER SYMPOSIUM

Optimal Approach to Perioperative Management of Resectable NSCLC Without Driver Mutations

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DECLARATION OF INTERESTS

Clinical Trial Support to Institution: AstraZeneca; Bayer; BMS; Genentech/Roche; Gilead (via IIT) Helsinn; Merck; SeaGen; Xcovery
Advisory Board Participant: IOBiotech, Mirati, OncoC4, Beigene, GSK
CME talk and travel: Chugai
Unpaid Consultant Work: BMS; Genentech/Roche; Merck; AstraZeneca
Societies: IASLC (Past President); EcogAcrin (Executive Committee)

NEOADJUVANT Treatment:

Neoadjuvant alone

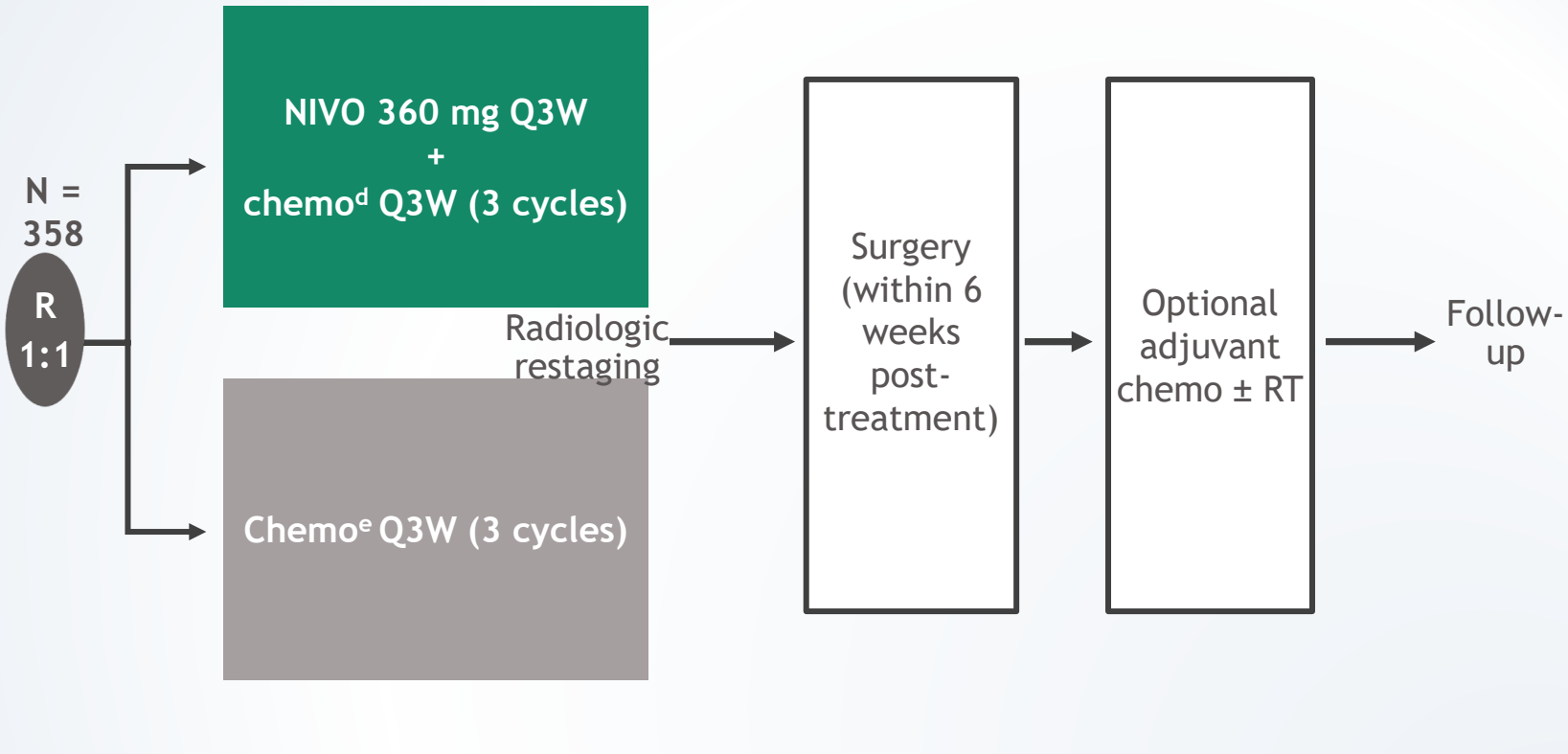
First Phase III: CheckMate816

37% stage IB/II; 63% Stage IIIA
50% PD-L1 >1%
No EGFR/ALK

Key eligibility criteria

- Newly diagnosed, resectable, stage IB (≥ 4 cm)–IIIA NSCLC (per TNM 7th edition)
- ECOG PS 0–1
- No known sensitizing *EGFR* mutations or *ALK* alterations

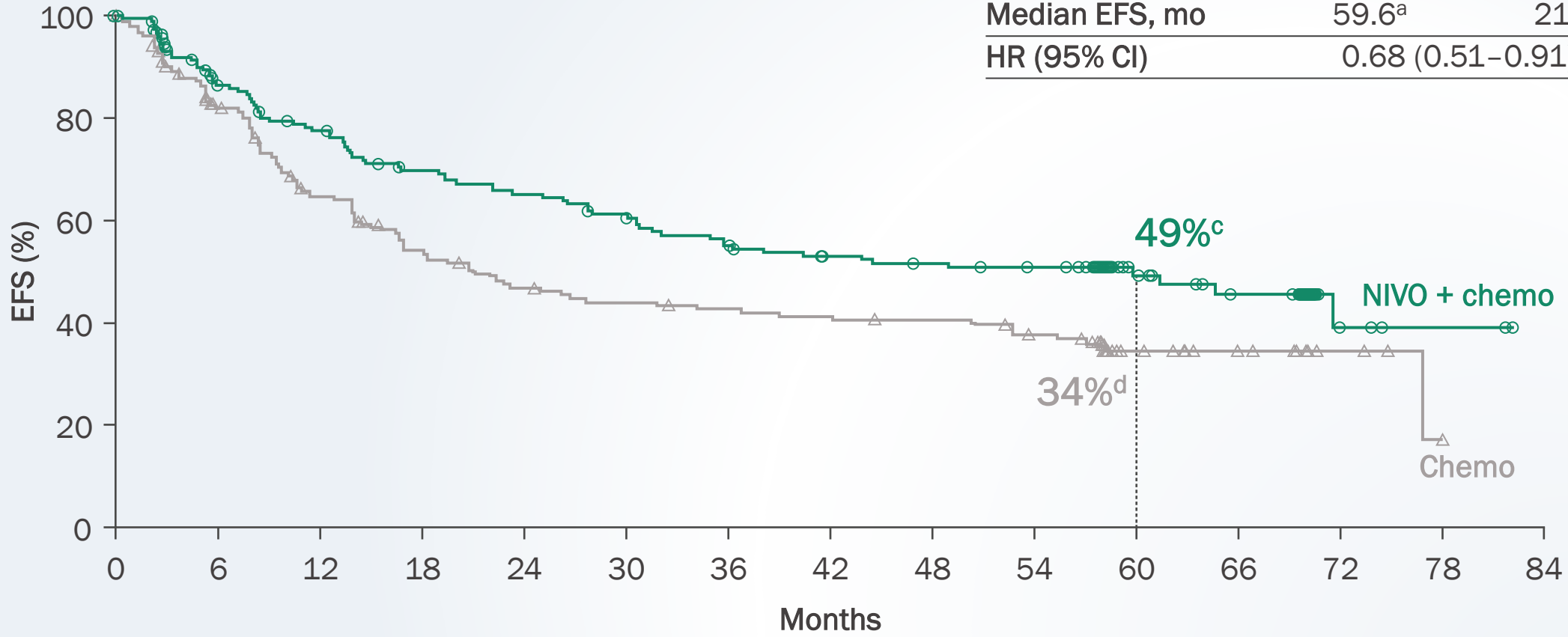
Stratified by stage (IB/II vs IIIA), PD-L1[b] (≥ 1% vs < 1%[c]), and sex



Spicer ASCO 2021 abstr: 8503, Forde NEJM

CM816 EFS: 5-year analysis

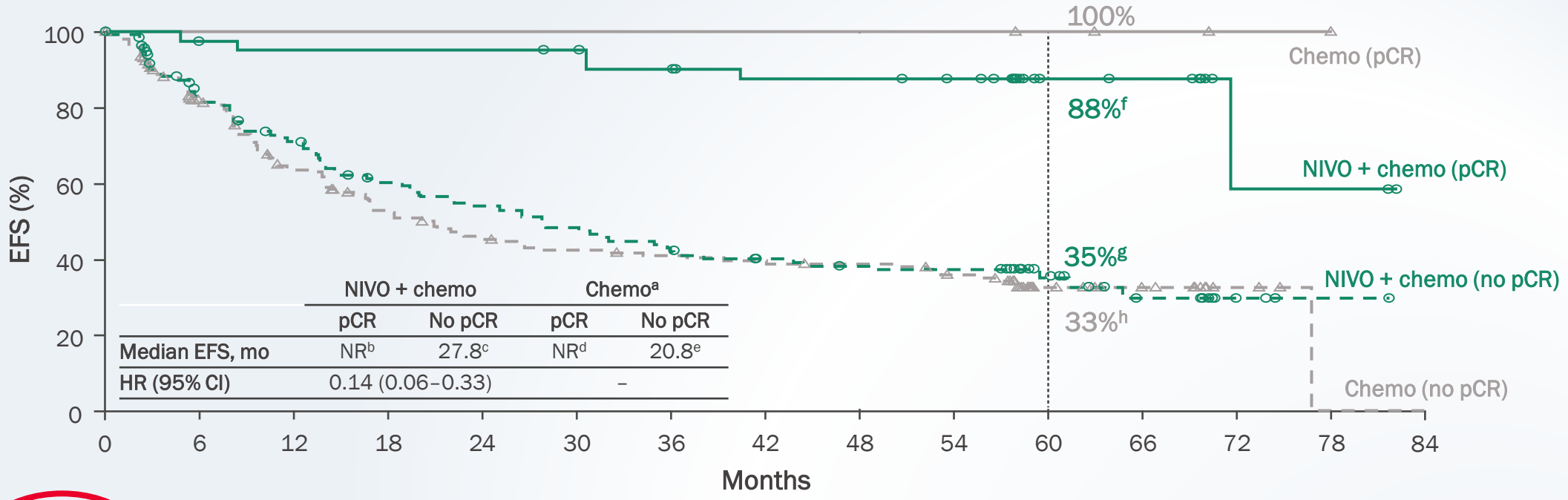
	NIVO + chemo (n = 179)	Chemo (n = 179)
Median EFS, mo	59.6[a]	21.1[b]
HR (95% CI)	0.68 (0.51–0.91)	



No. at risk

NIVO + chemo	179	137	121	106	99	92	82	74	71	68	31	23	5	3	0
Chemo	179	132	100	81	69	64	61	59	57	51	25	17	4	0	0

CM816 Exploratory analysis: EFS by pCR status



	NIVO + chemo		Chemo[a]	
	pCR	No pCR	pCR	No pCR
Median EFS, mo	NR[b]	27.8[c]	NR[d]	20.8[e]
HR (95% CI)	0.14 (0.06–0.33)		–	

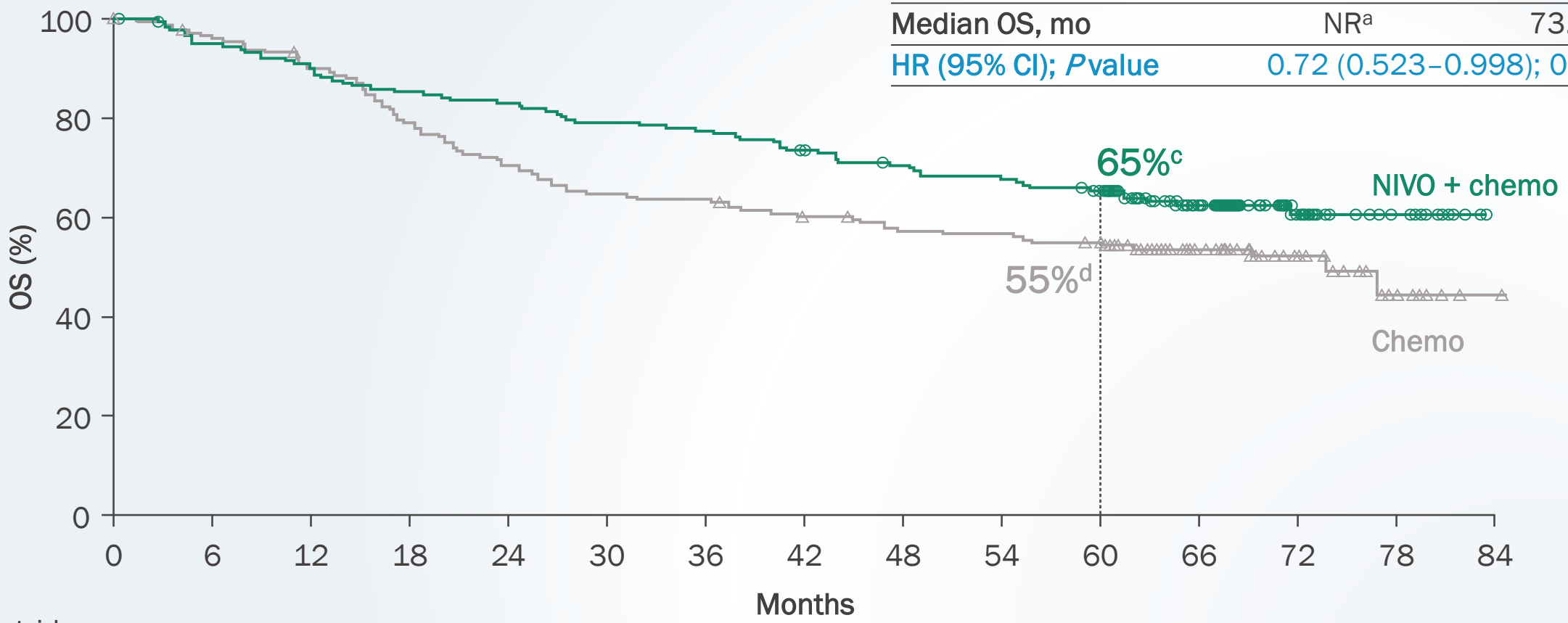
No. at risk															
pCR	43	41	40	40	40	39	36	33	33	31	14	13	2	2	0
pCR	4	4	4	4	4	4	4	4	4	4	3	2	1	0	0
No pCR	136	96	81	66	59	53	46	41	38	37	17	10	3	1	0
No pCR	175	128	96	77	65	60	57	55	53	47	22	15	3	0	0

In the NIVO + chemo arm:

- Among patients with pCR, 3 (7.0%) patients had disease recurrence or relapse[i]
- Among patients with no pCR, 57 (41.9%) patients had disease recurrence or relapse

CM816 Final analysis: OS with neoadjuvant NIVO + chemo vs chemo

	NIVO + chemo (n = 179)	Chemo (n = 179)
Median OS, mo	NR[a]	73.7[b]
HR (95% CI); *P* value	0.72 (0.523–0.998); 0.0479	



No. at risk

NIVO + chemo	179	168	159	151	147	140	137	129	122	117	111	67	29	9	0
Chemo	179	170	159	139	124	114	112	104	98	97	91	58	29	6	1

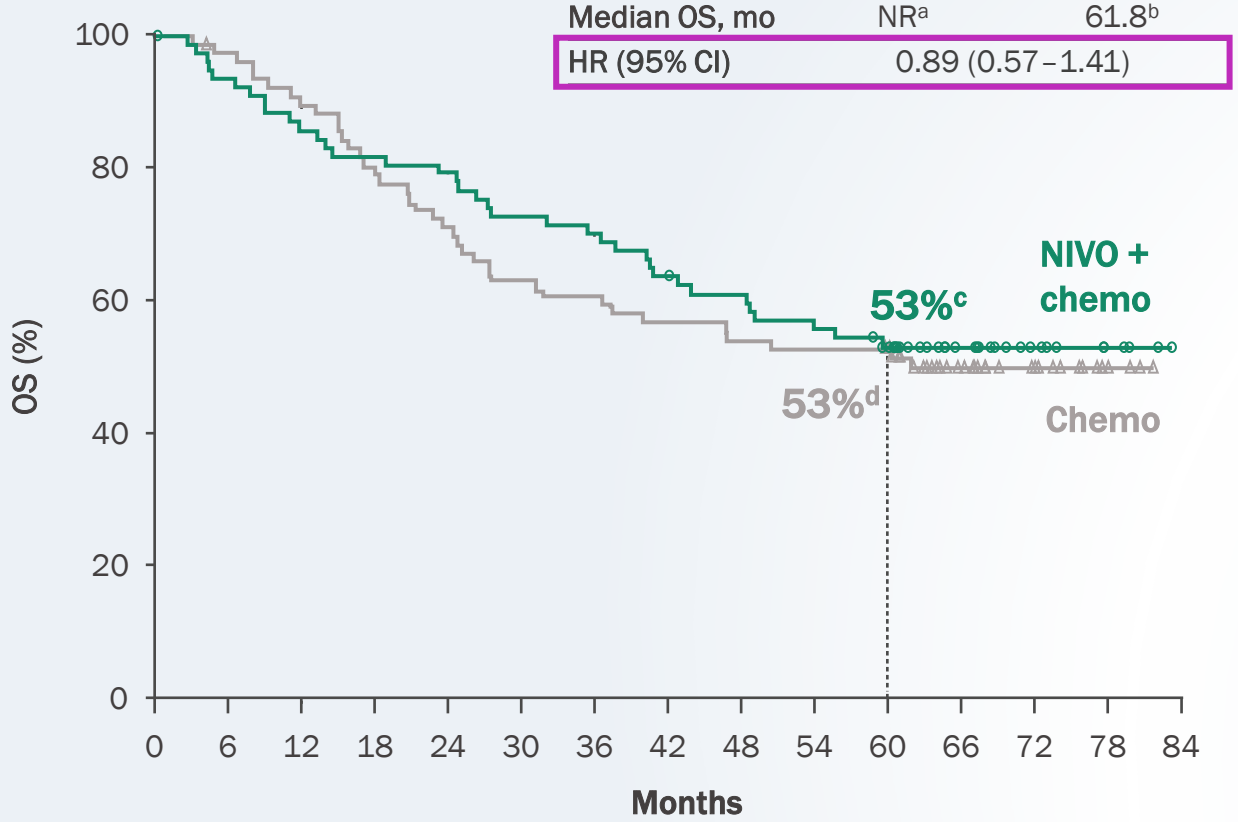
Minimum/median follow-up: 59.9/68.4 months.

[a-d]95% CI: [a]NR; [b]47.3–NR; [c]58–72; [d]47–62.

CM816 OS by tumor PD-L1 expression

PD-L1 < 1%

	NIVO + chemo (n = 78)	Chemo (n = 77)
Median OS, mo	NR[a]	61.8[b]
HR (95% CI)	0.89 (0.57–1.41)	

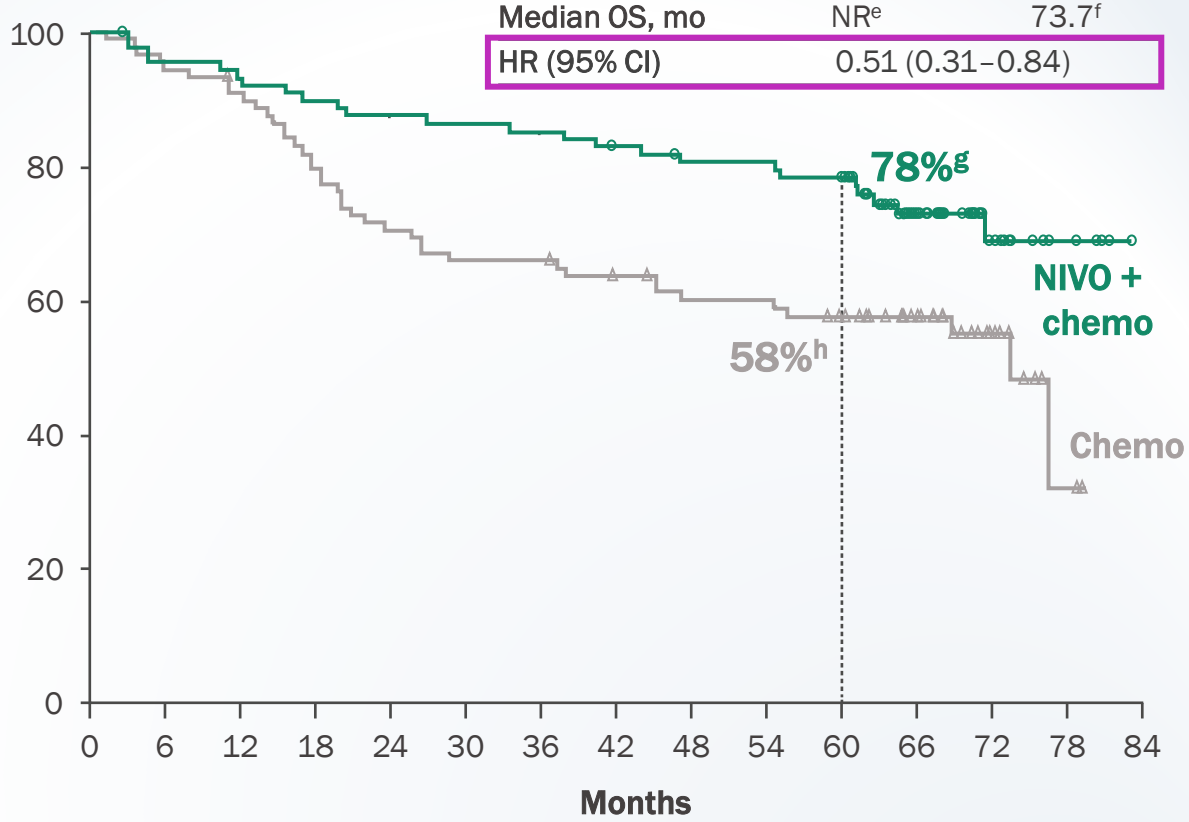


No. at risk

NIVO + chemo	78	72	66	63	61	56	54	49	46	42	38	23	12	4	0
Chemo	77	74	68	61	54	48	46	43	41	40	39	23	13	3	0

PD-L1 ≥ 1%

	NIVO + chemo (n = 89)	Chemo (n = 89)
Median OS, mo	NR[e]	73.7[f]
HR (95% CI)	0.51 (0.31–0.84)	



NIVO + chemo	89	84	82	79	77	76	75	72	69	69	67	40	16	5	0
Chemo	89	84	80	70	62	58	58	54	50	50	46	31	15	2	0

Neo-Adjuvant ICI Key Points

Only 3 cycles
All patients exposed to ICI
PD-L1 –important
Driver Mutations-excluded
OS benefit proven

What can Pure Adjuvant Do?

IMpower010
KN091 (Pearls)
BR.31

IMpower010 Study Design

12% stage 1, ~50% stage II, 40% stage III
55% PD-L1+; ~15% known driver mutation

Completely resected stage IB-IIIA[a] NSCLC

- Stage IB tumors ≥4 cm
- ECOG 0-1
- Lobectomy
- Tumor tissue for PD-L1 analysis

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

1-4 cycles

N=1280

R 1:1

No crossover

Atezolizumab 1200 mg q21d x 16 cycles or 1 year

BSC

N = 1005

Survival follow-up

Hierarchical statistical testing of endpoints

DFS in PD-L1 TC ≥1% stage II–IIIA population[b]

If positive:

DFS in all-randomized stage II–IIIA population[b]

If positive:

DFS in ITT population (stage IB-IIIA)[b]

If positive:

OS in ITT population[b]

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA and follow up is ongoing
- Endpoint was not formally tested

Stratification factors

- Sex | Stage | Histology | PD-L1 status

Key exploratory endpoints

- OS biomarker analyses

Key secondary endpoints

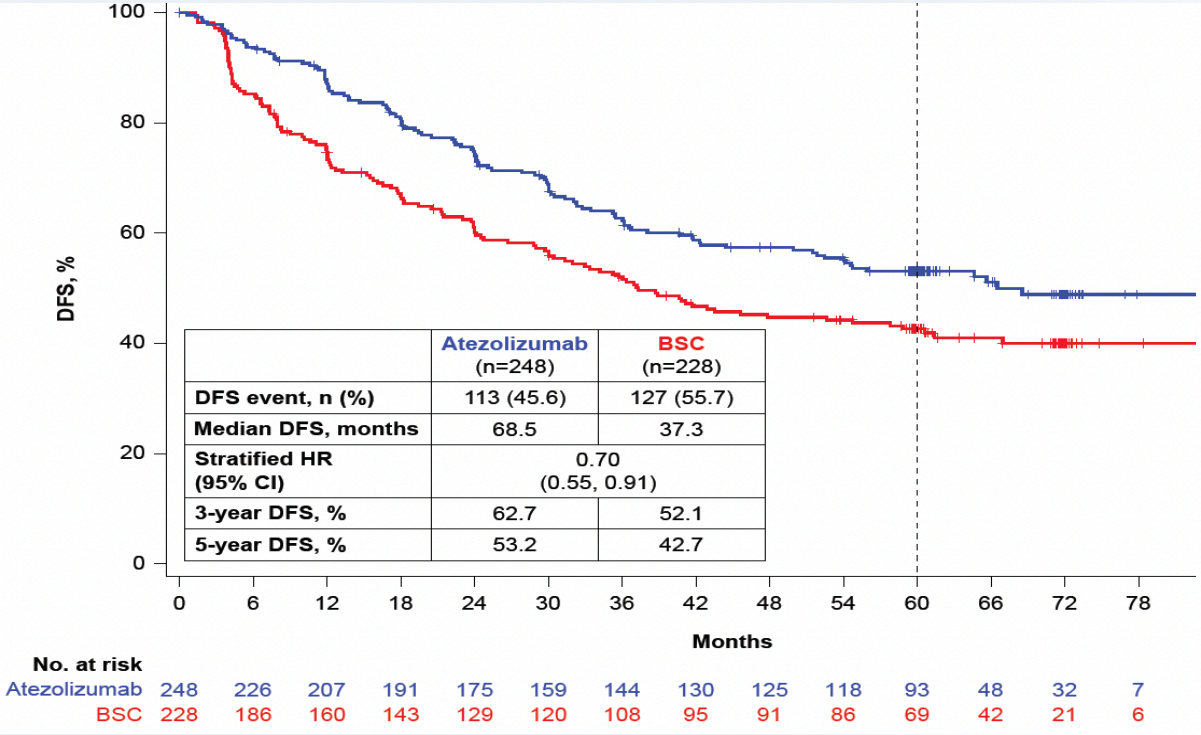
- OS in ITT | Safety | Exploratory OS biomarker analyses

Clinical cutoff: 18 April 2022. Both arms included observation and regular scans for disease recurrence on the same schedule. ECOG, Eastern Cooperative Oncology Group, q21d, every 21 days.
[a] Per UICC/AJCC staging system, 7th edition. [b] Two-sided α=0.05.

H. Wakelee ASCO 2021, abstr 8500:IMpower010 Interim Analysis; Felip Lancet 2021, Felip IASLC WCLC 2022

Adjuvant ICI: IMpower010 DFS+OS >60 Mo f/up

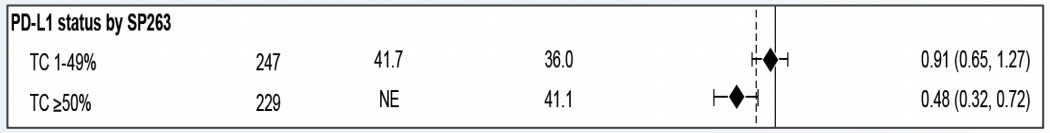
IMpower010 PD-L1 TC ≥1% stage II-IIIA population- DFS and OS

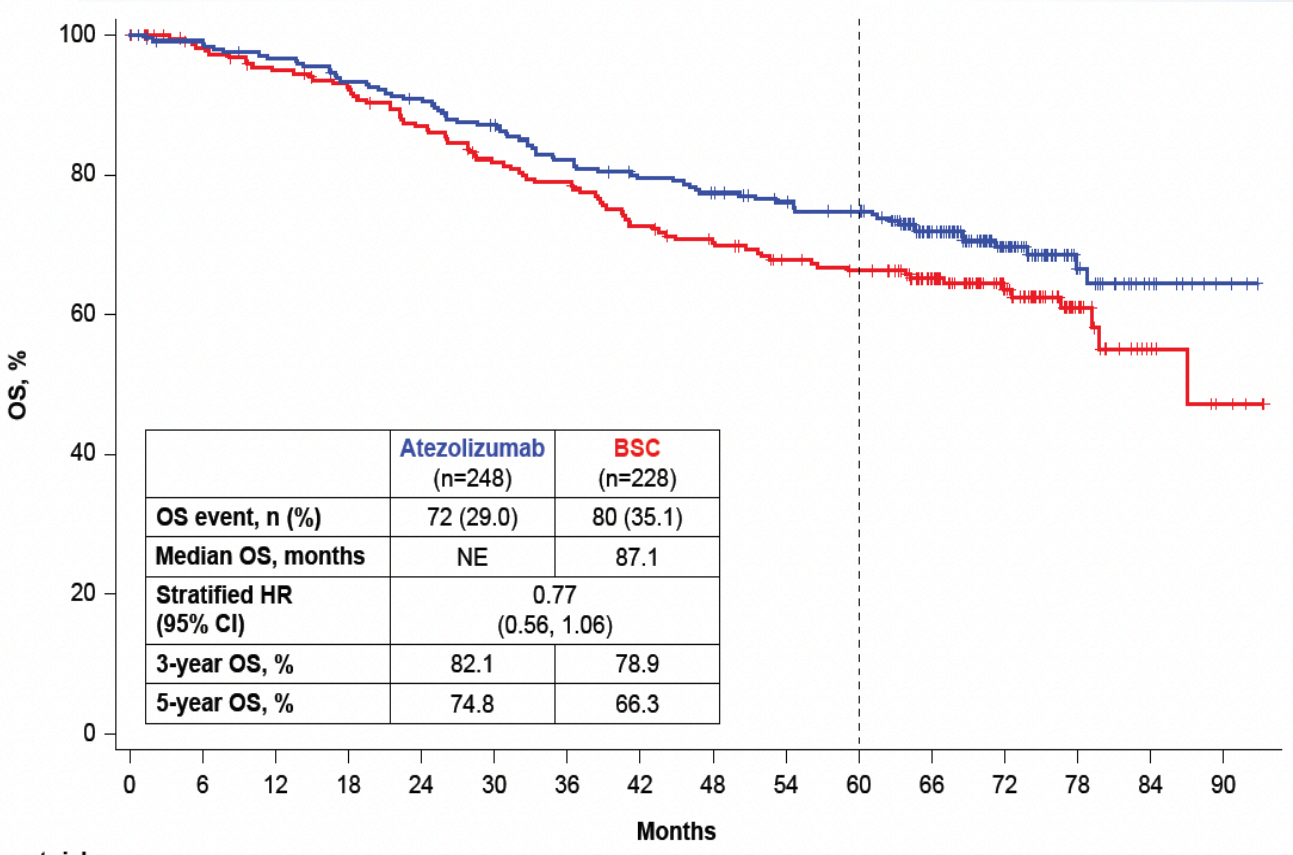


	Atezolizumab (n=248)	BSC (n=228)
DFS event, n (%)	113 (45.6)	127 (55.7)
Median DFS, months	68.5	37.3
Stratified HR (95% CI)	0.70 (0.55, 0.91)	
3-year DFS, %	62.7	52.1
5-year DFS, %	53.2	42.7

No. at risk

Atezolizumab	248	226	207	191	175	159	144	130	125	118	93	48	32	7
BSC	228	186	160	143	129	120	108	95	91	86	69	42	21	6





	Atezolizumab (n=248)	BSC (n=228)
OS event, n (%)	72 (29.0)	80 (35.1)
Median OS, months	NE	87.1
Stratified HR (95% CI)	0.77 (0.56, 1.06)	
3-year OS, %	82.1	78.9
5-year OS, %	74.8	66.3

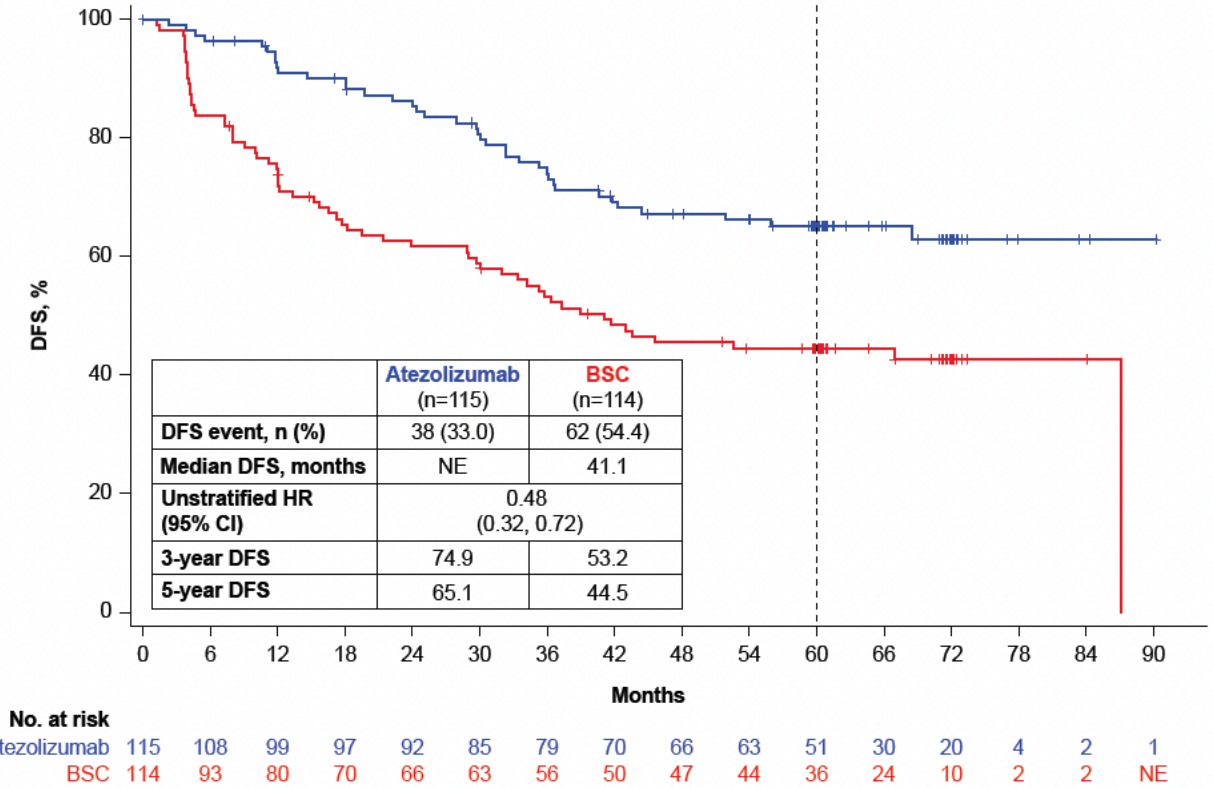
No. at risk

Atezolizumab	248	241	234	225	218	208	195	187	181	173	167	126	76	32	11	3
BSC	228	214	205	198	185	172	166	152	144	134	129	103	65	29	9	4

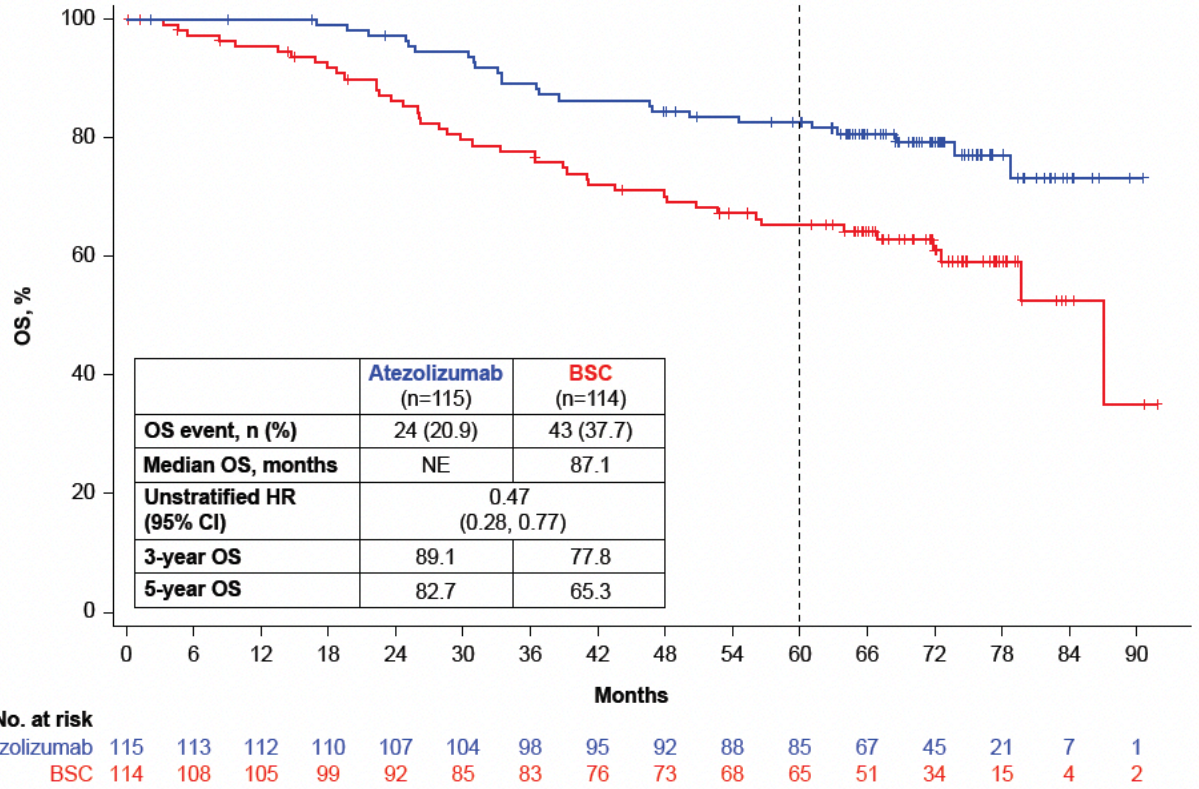
Wakelee ASCO 2021 abstr 8500; Felip Lancet 2021, Wakelee ASCO 2024

IMpower010: 5 yr Overall Survival- selected subsets

Figure 5. DFS and OS in the stage II-IIIA PD-L1 TC ≥50% population



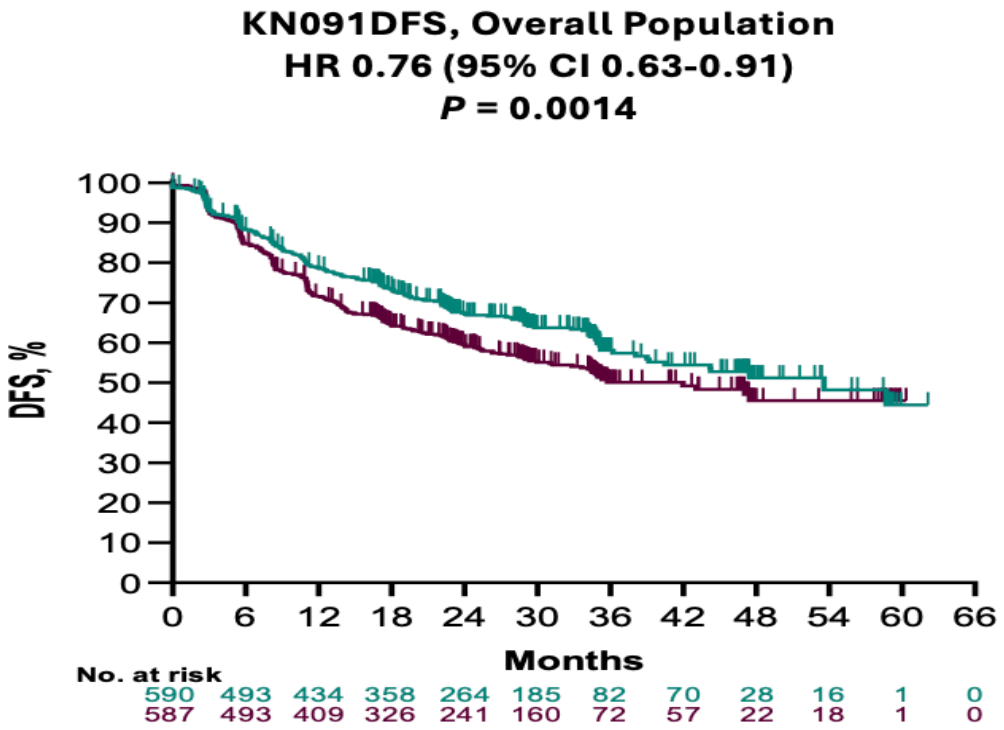
	Atezolizumab (n=115)	BSC (n=114)
DFS event, n (%)	38 (33.0)	62 (54.4)
Median DFS, months	NE	41.1
Unstratified HR (95% CI)	0.48 (0.32, 0.72)	
3-year DFS	74.9	53.2
5-year DFS	65.1	44.5



	Atezolizumab (n=115)	BSC (n=114)
OS event, n (%)	24 (20.9)	43 (37.7)
Median OS, months	NE	87.1
Unstratified HR (95% CI)	0.47 (0.28, 0.77)	
3-year OS	89.1	77.8
5-year OS	82.7	65.3

NO benefit in ITT or All randomized stage II-IIIA

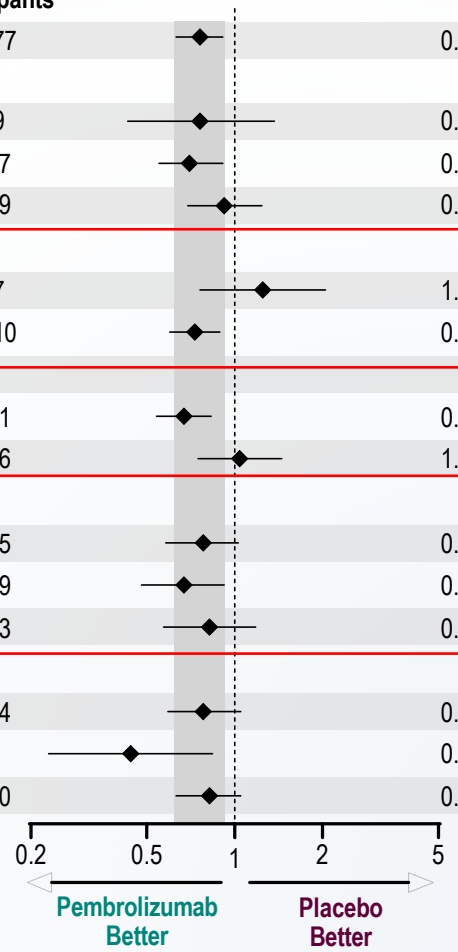
KN-091 (Adjuvant Pembro) Results: DFS in Subgroups



	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

Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	472/1177	0.76 (0.63-0.91)
Pathologic stage		
IB	46/169	0.76 (0.43-1.37)
II	246/667	0.70 (0.55-0.91)
IIIA	178/339	0.92 (0.69-1.24)
Received adjuvant chemotherapy		
No	64/167	1.25 (0.76-2.05)
Yes	408/1010	0.73 (0.60-0.89)
Histology		
Nonsquamous	330/761	0.67 (0.54-0.83)
Squamous	142/416	1.04 (0.75-1.45)
PD-L1 TPS		
<1%	195/465	0.78 (0.58-1.03)
1-49%	160/379	0.67 (0.48-0.92)
≥50%	117/333	0.82 (0.57-1.18)
***EGFR* mutation**		
No	186/434	0.78 (0.59-1.05)
Yes	40/73	0.44 (0.23-0.84)
Unknown	246/670	0.82 (0.63-1.05)

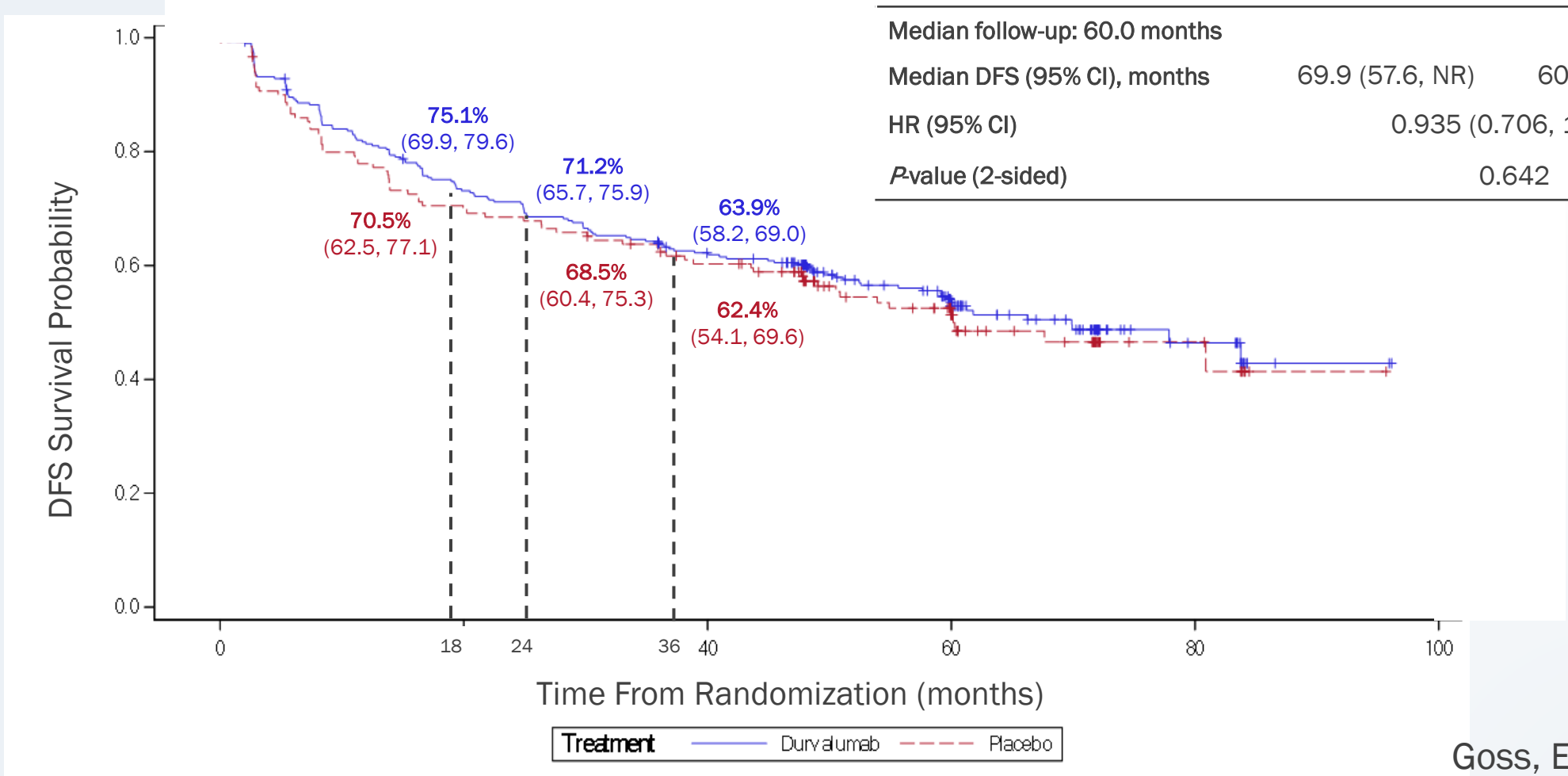


ed per RECIST v1.1 by investigator review.
September 20, 2021

CCTG BR.31 Primary Endpoint

DFS in PD-L1≥25% EGFR−/ALK−

	D arm n=316	PBO arm n=161
Median follow-up: 60.0 months		
Median DFS (95% CI), months	69.9 (57.6, NR)	60.2 (47.7, NR)
HR (95% CI)	0.935 (0.706, 1.247)	
P-value (2-sided)	0.642	



Durvalumab	316	287	273	258	248	240	228	219	216	208	202	198	190	183	179	177	149	125	119	117	86	65	62	58	39	21	19	18	7	2	2	2	1	0
Placebo	161	136	129	119	116	109	105	103	102	99	98	95	91	86	86	81	67	57	55	53	43	26	25	24	14	10	10	8	5	1	1	1	0	

Goss, ESMO2024

Adjuvant ICI

Everyone Gets Surgery (DFS endpoint)

Driver Mutations- Known for ALL

Maybe can limit to those who are MRD+ after Neo-adj?

Results are confusing across trials

Peri-Operative ICI
Neo-Adjuvant + Adjuvant

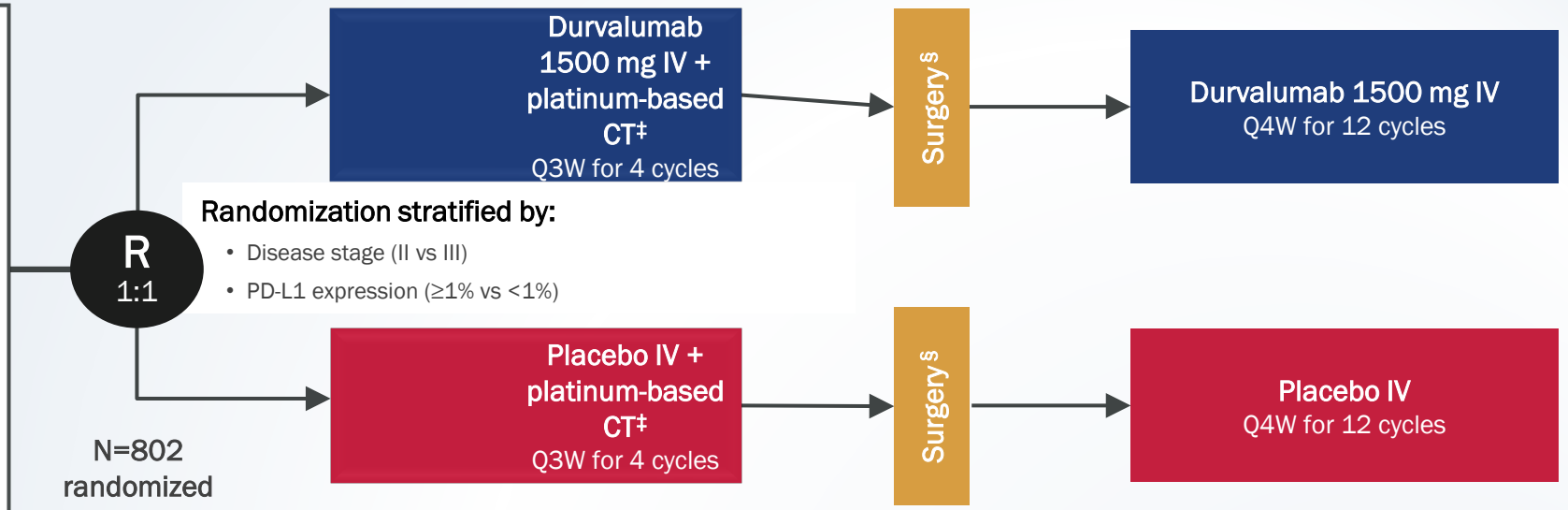
AEGEAN
NEOTORCH
KN671
CM77T
RATIONALE-315

AEGEAN: A Phase 3 Trial of Neoadjuvant Durvalumab + Chemotherapy Followed by Adjuvant Durvalumab in Patients with Resectable NSCLC

~30% stage II; ~ 1/3 each PD-L1 group (0, 1-49, 50+%); 6% known EGFRmut

Study population

- Treatment-naïve
- ECOG PS 0 or 1
- Resectable NSCLC* (**stage IIA–IIIB[N2]**; AJCC 8th ed)
- Lobectomy, sleeve resection, or bilobectomy as planned surgery*
- Confirmed PD-L1 status†
- No documented *EGFR/ALK* aberrations*



Endpoints: All efficacy analyses performed on a modified population that excludes patients with documented *EGFR/ALK* aberrations¶

Primary:

- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

Key secondary:

- MPR by central lab (per IASLC 2020[1])
- DFS using BICR (per RECIST v1.1)
- OS

*The protocol was amended while enrollment was ongoing to exclude (1) patients with tumors classified as T4 for any reason other than size; (2) patients with planned pneumonectomies; and (3) patients with documented *EGFR/ALK* aberrations. †Ventana SP263 immunohistochemistry assay. ‡Choice of CT regimen determined by histology and at the investigator's discretion. For non-squamous: cisplatin + pemetrexed or carboplatin + pemetrexed. For squamous: carboplatin + paclitaxel or cisplatin + gemcitabine (or carboplatin + gemcitabine for patients who have comorbidities or who are unable to tolerate cisplatin per the investigator's judgment). §Post-operative radiotherapy (PORT) was permitted where indicated per local guidance. ¶All efficacy analyses reported in this presentation were performed on the mITT population, which includes all randomized patients who did not have documented *EGFR/ALK* aberrations.

Heymach AACR 2023, NEJM2023

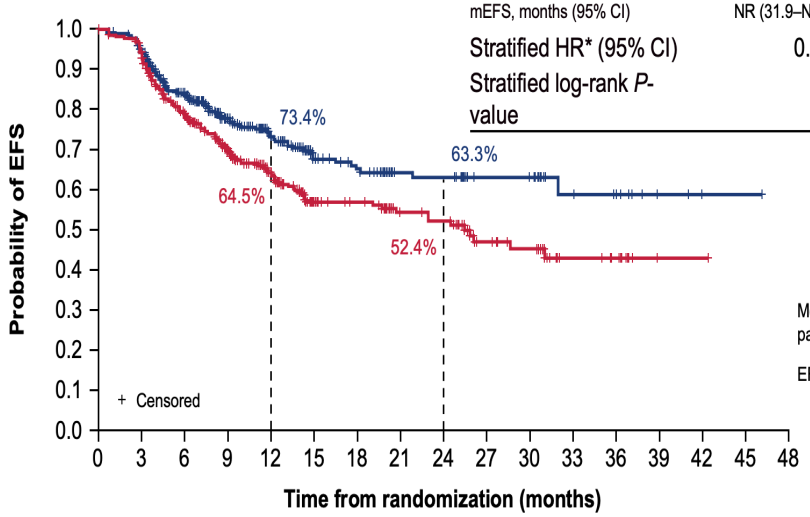
1Travis WD, et al. *J Thorac Oncol* 2020;15:709-40.

Peri-Operative ICI: 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	



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

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

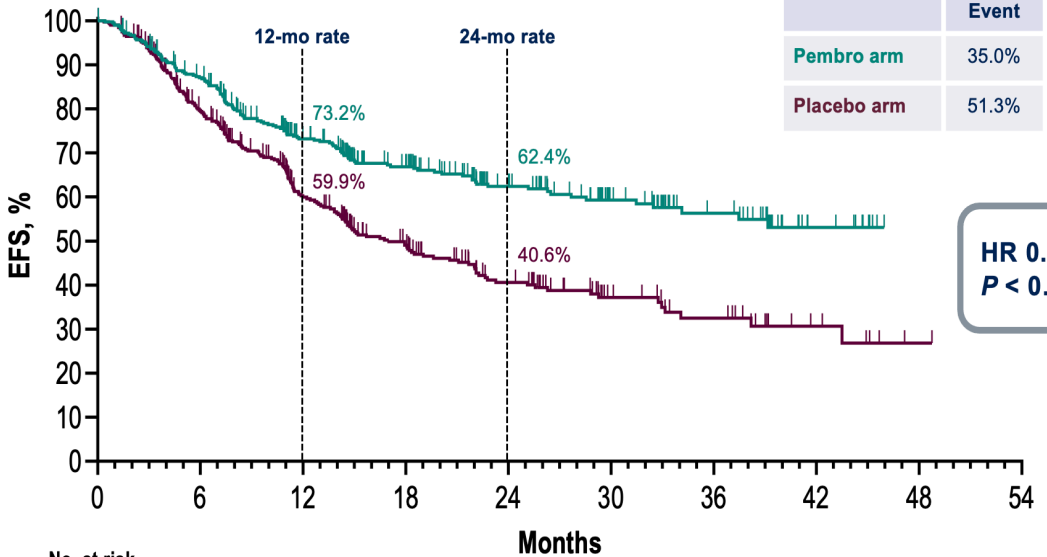
EFS maturity: 31.9%

17% pCR
33% mPR

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

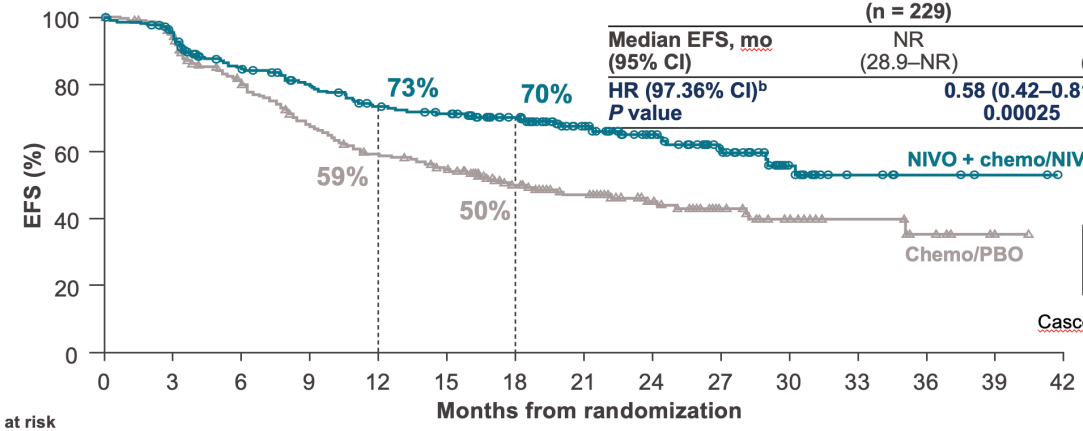
No. at risk										
397	330	236	172	117	72	42	11	0	0
400	294	183	124	74	38	24	9	1	0

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	



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

25% pCR
35% MPR

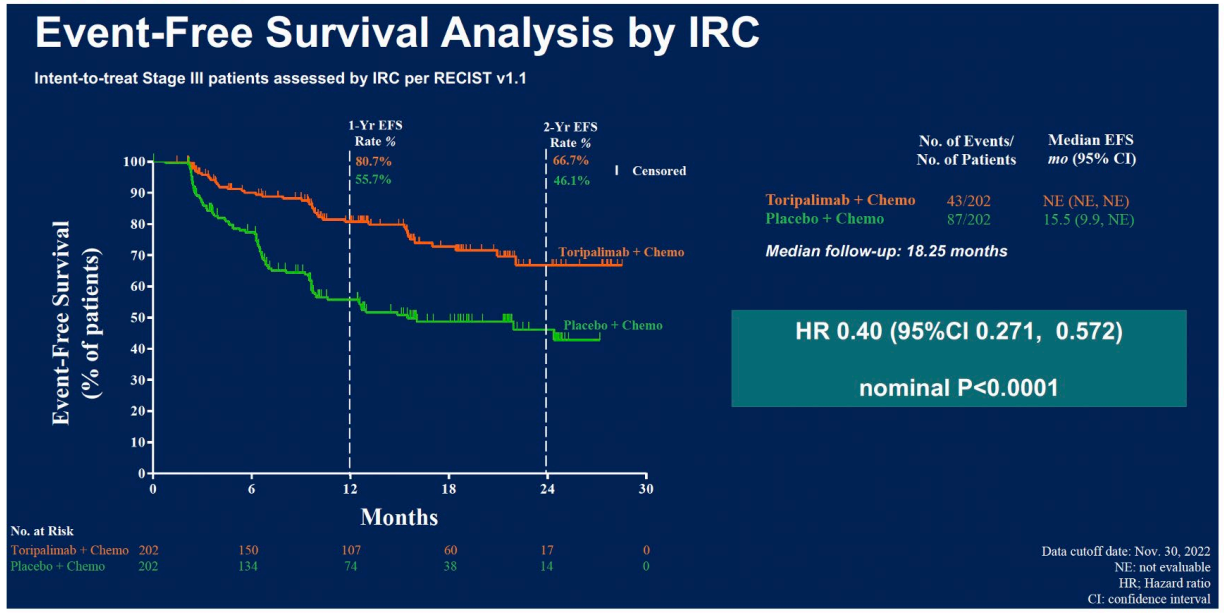
Cascone ESMO 2023

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

Peri-Operative ICI: EFS from NEOTORCH and RATIONALE-315

~25% pCR (stage III)

NEOTORCH

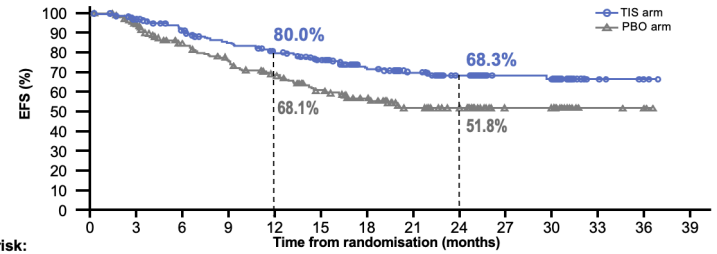


Lu, S ASCO Virtual Plenary April 20, 2023

RATIONALE 315 Event-Free Survival

Per BICR (ITT Analysis Set)

	Events (%)	Median (95% CI), months	HR (95% CI)	*P*-value
TIS arm	58 (25.7)	NR (NE, NE)	**0.56 (0.40, 0.79)**	0.0003
PBO arm	83 (36.6)	NR (16.6, NE)		



Number at risk:

TIS arm	226	196	176	160	146	127	105	84	67	37	35	10	3	0
PBO arm	227	187	149	129	113	95	77	57	42	24	23	4	2	0

- A statistically significant and clinically meaningful improvement in EFS (HR=0.56 [95% CI: 0.40, 0.79]; one-sided *P*=0.0003) was observed favouring perioperative TIS
- A clinically meaningful improvement in EFS per investigator (HR=0.55 [95% CI: 0.39, 0.77]) was also observed

Analysis occurred at the August 21, 2023, cut-off. EFS was defined as the time from randomisation until any of the following, whichever occurred first: disease progression precluding surgery, local or distant recurrence, or death due to any cause. The significance boundary of the EFS interim analysis was 0.0105 (calculated based on 141 actual EFS events).

Abbreviations: CI, confidence interval; BICR, blinded independent central review; EFS, event-free survival; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable; NR, not reached; PBO, placebo; TIS, tislelizumab.

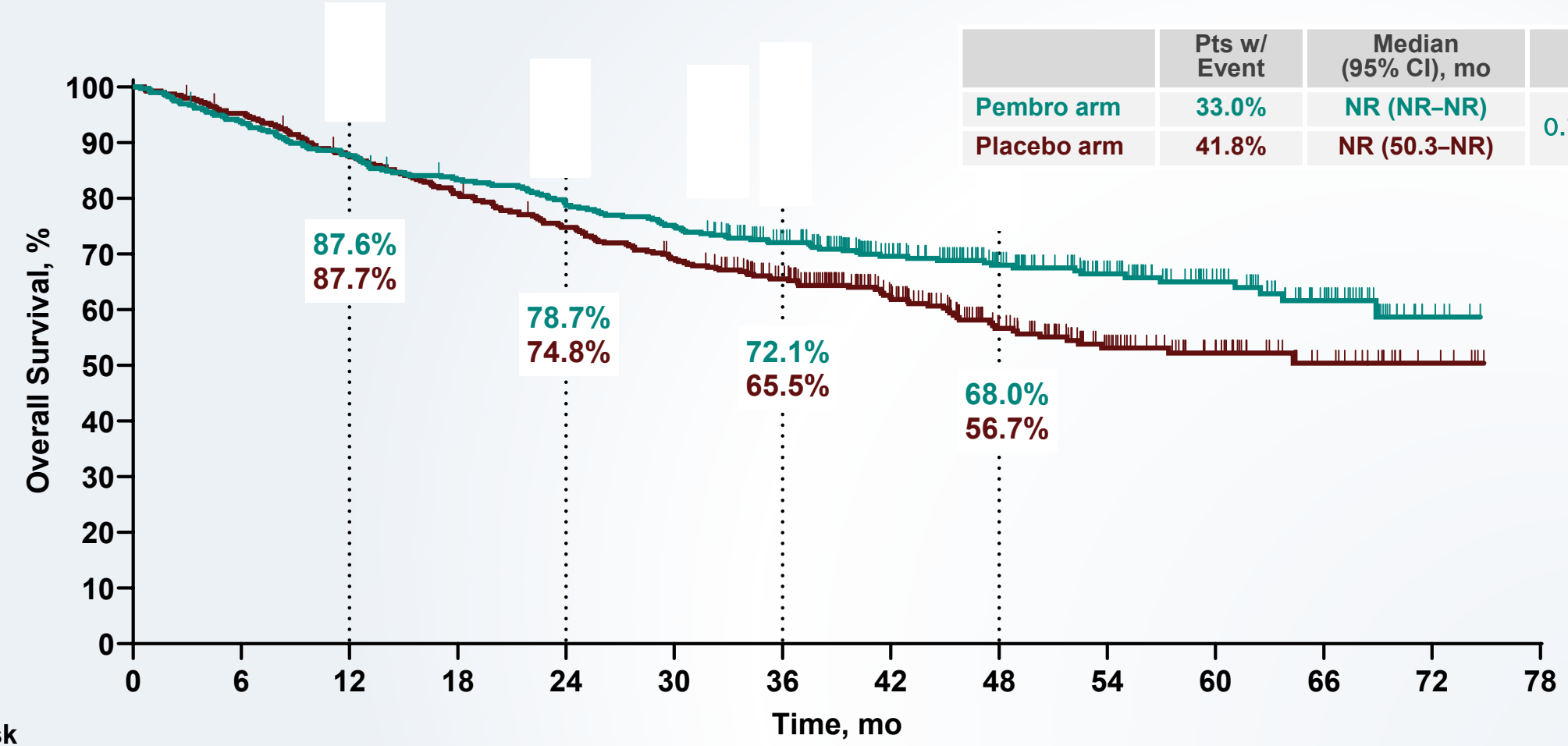
ESMO VIRTUAL PLENARY
WITH AACR EXPERT COMMENTARY

Dongsheng Yue

KN671 Overall Survival, IA3

Median Follow-Up: 41.1 (range, 0.4–75.3) months

	Pts w/ Event	Median (95% CI), mo	HR (95% CI)
Pembro arm	33.0%	NR (NR–NR)	0.73 (0.58–0.92)
Placebo arm	41.8%	NR (50.3–NR)	

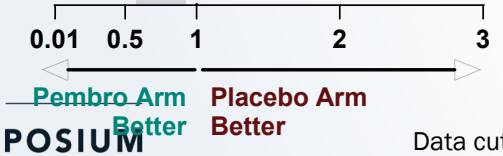


No. at risk													
Pembro arm	397	371	347	327	309	294	260	197	149	106	69	40	5	0
Placebo arm	400	379	347	320	294	270	236	170	114	72	46	22	6	0

Data cutoff date: August 19, 2024.

KN671 Overall Survival in Key Subgroups

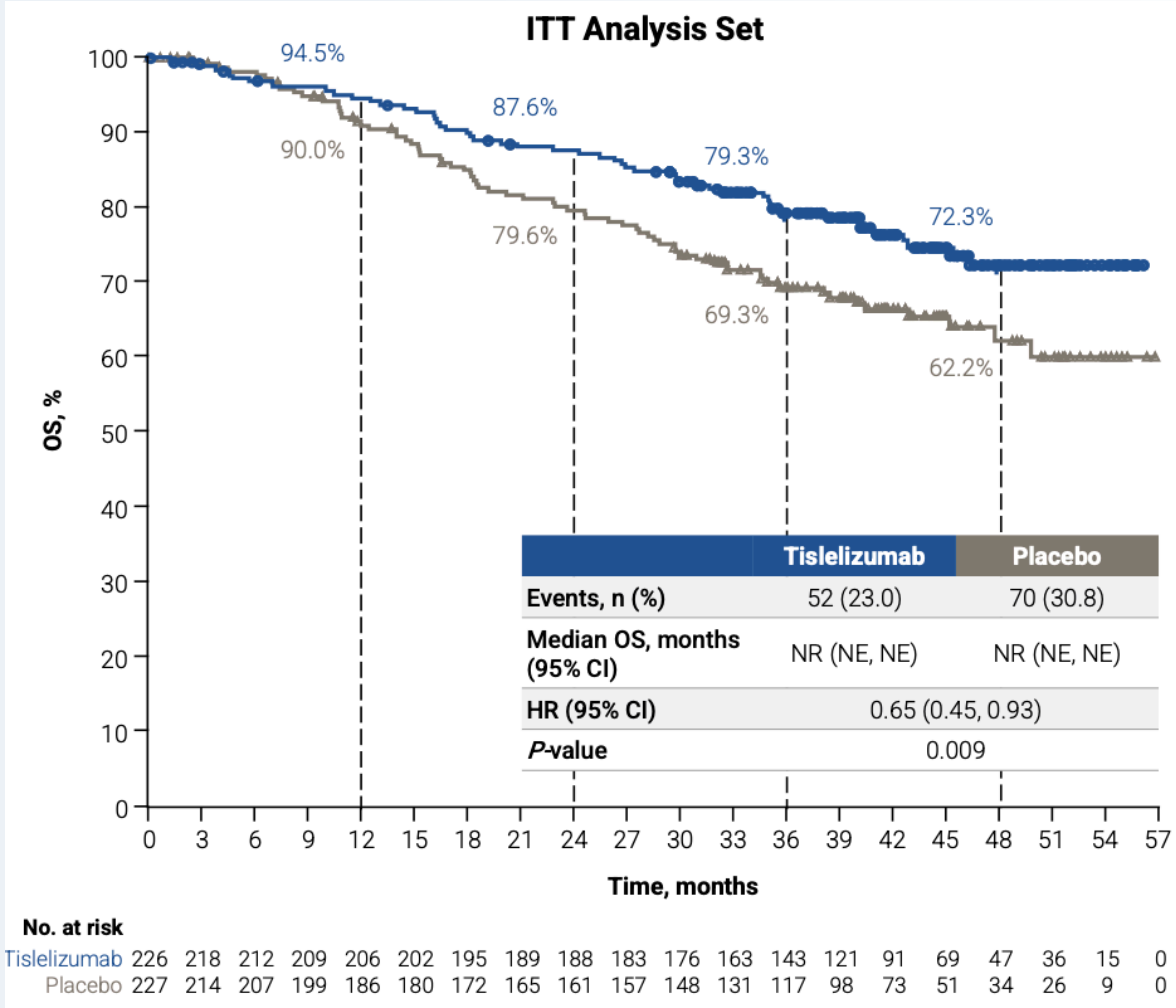
Subgroup	Events/patients: Pembro Arm	Events/patients: Placebo Arm	Hazard ratio (95% CI)
Overall	131/397	167/400	0.73 (0.58–0.92)
Age			
<65 y	63/221	96/214	0.56 (0.41–0.77)
≥65 y	68/176	71/186	1.01 (0.73–1.41)
Sex			
Male	105/279	130/284	0.75 (0.58–0.97)
Female	26/118	37/116	0.68 (0.41–1.13)
Race			
White	86/250	112/239	0.67 (0.50–0.89)
Others	38/134	47/145	0.86 (0.56–1.33)
Geographic region			
East Asia	35/123	38/121	0.91 (0.58–1.44)
Non-east Asia	96/274	129/279	0.69 (0.53–0.89)
Smoking status			
Never	12/54	10/47	1.08 (0.47–2.50)
Former	85/247	103/250	0.80 (0.60–1.06)
Current	34/96	54/103	0.58 (0.38–0.89)
ECOG			
0	79/253	91/246	0.79 (0.58–1.07)
1	52/144	76/154	0.67 (0.47–0.96)



Subgroup	Events/patients: Pembro Arm	Events/patients: Placebo Arm	Hazard ratio (95% CI)
Overall	131/397	167/400	0.73 (0.58–0.92)
Histology			
Squamous	67/171	90/173	0.69 (0.51–0.95)
Nonsquamous	64/226	77/227	0.79 (0.57–1.10)
Clinical stage			
II	29/118	42/121	0.69 (0.43–1.11)
III	102/279	125/279	0.75 (0.58–0.97)
PD-L1 TPS			
≥50%	27/132	44/134	0.57 (0.35–0.92)
1–49%	42/127	52/115	0.68 (0.45–1.02)
≥1%	69/259	96/249	0.63 (0.47–0.86)
<1%	62/138	71/151	0.93 (0.66–1.31)
EGFR activiating mutaion status			
Yes	1/14	5/19	0.23 (0.03–1.94)
No	27/111	40/124	0.70 (0.43–1.14)
Unknown/missing	103/272	122/257	0.75 (0.58–0.98)
ALK translocation status			
No	28/104	46/132	0.72 (0.45–1.15)
Unknown/missing	102/281	120/259	0.74 (0.57–0.96)

Data cutoff date: August 19, 2024, Majem ESMO I-O 2024.

PERIOPERATIVE TISLELIZUMAB FOR RESECTABLE NON-SMALL CELL LUNG CANCER: FINAL ANALYSIS OF RATIONALE-315



Yue DS, et al. WCLC 2025. Abstract MO04.08

38.5 mo f/up

Neo-Adjuvant risk of NO surgery

16-22% 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%

Peri-Operative ICI

5 trials with consistent EFS benefit

OS proven in KN671, RATIONALE315

PD-L1 – very important in all trials
Driver Mutations- excluded or ? benefit
Stage – Benefit across stages

However, increased toxicity risk (more therapy)

Increased costs (more therapy)

AND 20% risk no surgery

Some Key Remaining Questions

- Who Should Still Go to Surgery First?
- What Does the Adjuvant ICI Component Add to Neo-Adjuvant?
- What is the Optimal Duration of ICI or Adj Targeted Therapy?
- How Does ctDNA Analysis Help?
- What are Future Steps?

Some Key Remaining Questions

- **Who Should Still Go to Surgery First?**

  - All stage I?
  - Which stage II?
  - How to determine who is at most risk of NOT getting surgery if systemic therapy is started first?

Some Key Remaining Questions

- Who Should still Go to Surgery First?

- **What Does the Adjuvant ICI Component Add to Neo-Adjuvant?**

  We need to do the trials to answer the question!

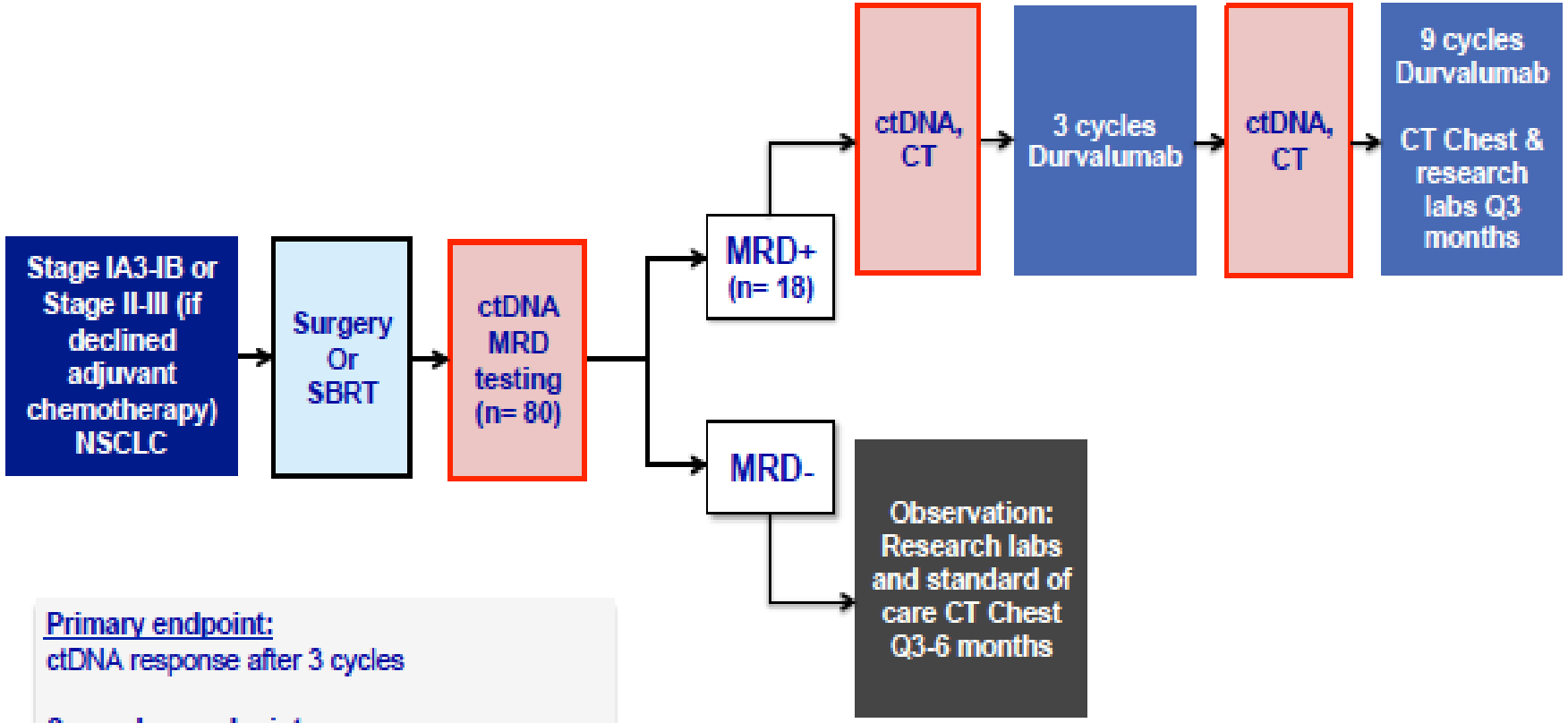
  CM816 (neo-adj) vs CM77T (neo-adj + Adj) nivolumab comparison was flawed in comparing all on CM816 who had surgery vs those on CM77T who had surgery AND got at least 1 dose of adjuvant therapy

  But we know those who do not get Adj on a peri-operative regimen trial tend to do poorly (ie there are reasons they did not proceed to adjuvant)

Key Remaining Questions

- Who Should still Go to Surgery First?
- What Does the Adjuvant ICI Component Add to Neo-Adjuvant?
- **What is the Optimal Duration of ICI or Adj Targeted Therapy?**
- We are not sure of these answers even in metastatic NSCLC
- Perhaps ctDNA will help guide

Adjuvant Durvalumab for early-stage NSCLC patients with ctDNA Minimal Residual Disease



Primary endpoint:
ctDNA response after 3 cycles

Secondary endpoints:
- DFS, OS
- Safety

M. Diehn and J. Neal / Stanford

Key Remaining Questions

- Who Should still Go to Surgery First?
- What Does the Adjuvant ICI Component Add to Neo-Adjuvant?
- What is the Optimal Duration of ICI or Adj Targeted Therapy?
- How Does ctDNA Analysis Help?
- What are Future Steps? – Novel Drugs, Contribution of Components Trials

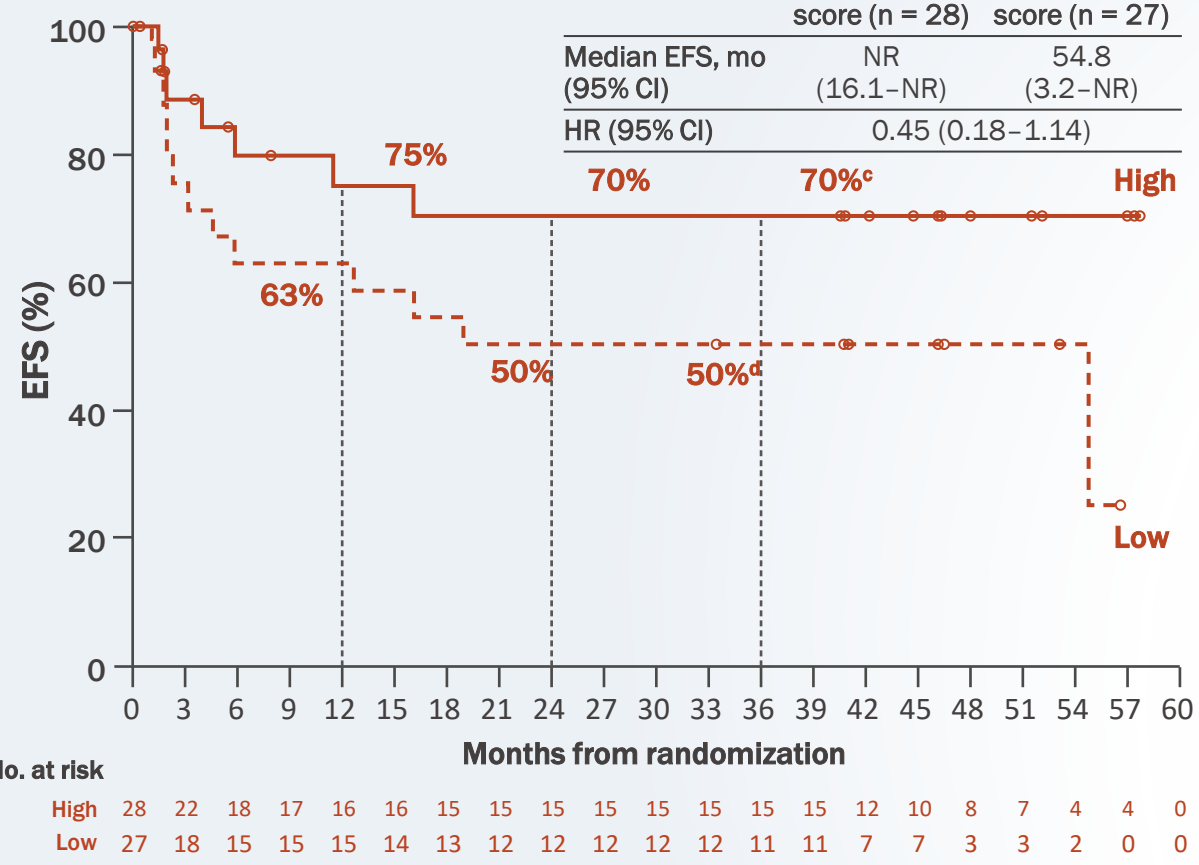
Novel Agents in Early Stage NSCLC

CM816:Baseline 4-gene inflammatory signature score[a] and EFS[b]

Maybe we can Choose who will benefit from the CTLA4 additional therapy?

[a]The 4-gene inflammatory signature comprised *CD8A*, *STAT1*, *LAG3*, and *CD274* (encoding PD-L1)[1]

NIVO + IPI

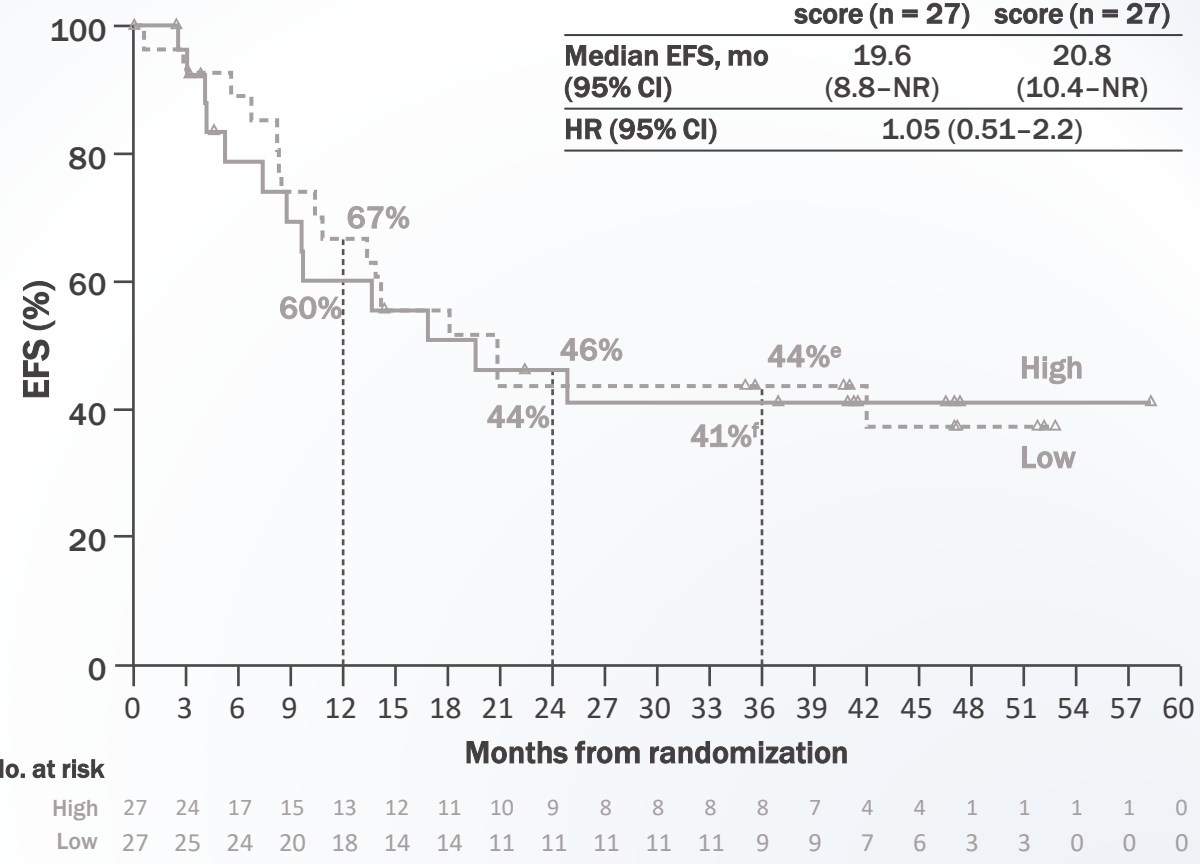


	High 4-gene inflammatory score (n = 28)	Low 4-gene inflammatory score (n = 27)
Median EFS, mo (95% CI)	NR (16.1–NR)	54.8 (3.2–NR)
HR (95% CI)	0.45 (0.18–1.14)	

No. at risk

High	28	22	18	17	16	16	15	15	15	15	15	15	15	15	12	10	8	7	4	4	0
Low	27	18	15	15	15	14	13	12	12	12	12	12	11	11	7	7	3	3	2	0	0

Chemo



	High 4-gene inflammatory score (n = 27)	Low 4-gene inflammatory score (n = 27)
Median EFS, mo (95% CI)	19.6 (8.8–NR)	20.8 (10.4–NR)
HR (95% CI)	1.05 (0.51–2.2)	

No. at risk

High	27	24	17	15	13	12	11	10	9	8	8	8	8	7	4	4	1	1	1	1	0
Low	27	25	24	20	18	14	14	11	11	11	11	11	9	9	7	6	3	3	0	0	0

NEOCOAST-2: Study of Neoadjuvant and Adjuvant Treatment in Resectable NSCLC

MEDI5752 Volrustomig - PD-1/CTLA-4 Bispecific
Dato-DXd – Trop-2 ADC
AZD0171- MAb to Leukemia inhibitory factor (LIF)

A Phase 2, Open-label, Randomized, Multicenter, Multi-arm Platform Study of Neoadjuvant and Adjuvant Treatment in Patients With Resectable, Early-stage (II to IIIB) Non-small Cell Lung Cancer Versus Surgery Alone

Study Design

Patients with resectable, early-stage NSCLC (N≈350)[a]

- Stage IIA to IIIB NSCLC
- Squamous and non-squamous histology
- No actionable genomic alterations
- ECOG PS 0 or 1
- Mandatory tumor sample required

Stratification by PD-L1 expression (<1% vs ≥1%)[2]

Randomization

Neoadjuvant treatment

- **Arm 1: Durvalumab + oleclumab +** platinum doublet CT[b,c]
- **Arm 2: Durvalumab + Monalizumab +** platinum doublet CT[b,c]
- **Arm 3: Volrustomig (MEDI5752) +** platinum doublet CT[b]
- **Arm 4: Dato-DXd + Durvalumab +** single agent platinum CT[b]
- **Arm 5: AZD0171 + Durvalumab +** platinum doublet CT[b]

Surgery[i]

Adjuvant treatment

- **Arm 1: Durvalumab + oleclumab[f]**
- **Arm 2: Durvalumab + monalizumab[f]**
- **Arm 3: Volrustomig (MEDI5752)**
- **Arm 4: Durvalumab**
- **Arm 5: AZD0171 + Durvalumab**

Safety and efficacy follow-up[2]

Locations: North America, Europe, Asia
ClinicalTrials.gov Identifier: NCT05061550

Primary endpoints

- pCR[g]
- Safety and tolerability

Secondary endpoints

- EFS[h]
- DFS[h]
- Number of participants with surgical resection[d,h]
- MPR[h]
- ORR[h]
- OS[h]
- Baseline PD-L1 expression[j]
- Changes in ctDNA[k]

[a]Estimated enrollment, [b]Based on tumor histology and investigator discretion: paclitaxel/carboplatin, cisplatin/pemetrexed, or carboplatin/pemetrexed, [c]Patients received treatment (Q3W) x4 cycles, [d]Planned surgery to be performed will be lobectomy, sleeve resection, or bilobectomy, [e]Unless progression of disease (PD) or any withdrawal criteria are met, [f]Q4wx12 cycles. Patients will receive adjuvant therapy starting within 10 weeks after surgery, for 12 cycles or until disease progression per RECIST v1.1 (except for patients receiving PORT, which must be started within 8 weeks after surgery, adjuvant therapy must be given within 3 weeks from the end of PORT), [g]As determined by central BIPR and described by IASLC 2020, [h]Assessed by Investigator, [i]Feasibility to surgery is defined as having the planned surgical resection within 40 days from the end of the last dose of neoadjuvant study drugs, [j]The baseline PD-L1 expression in participants treated with neoadjuvant and adjuvant treatment, and associations with clinical endpoints will be investigated, [k]During neoadjuvant treatment in participants with evaluable ctDNA and associations with clinical endpoints will be evaluated.

1. ClinicalTrials.gov. NCT05061550. http://clinicaltrials.gov/ct2/show/ NCT05061550. Accessed April 20, 2023. **2.** Cascone T et al. Poster presented at: AACR Meeting; April 8-13, 2022; New Orleans, LA. Poster CT124. **3.** Guisier F et al. Poster presented at: ASCO; June 2-6, 2023; Chicago, IL. Poster TPS8604.

Conclusions

1) Neo-Adjuvant, Adjuvant or Peri-operative PD-(L)1 ICI – are all Standard of Care options for early NSCLC (w/o driver mutation or contraindication)
2) Accurately STAGE and discuss at Multidisciplinary Tumor Board
   TEST for EGFR, ALK, PD-L1 (and others)
   Adjuvant targeted therapy SOC for EGFR/ALK+ NSCLC
3) Stage III - Neo-Adjuvant/Peri-Operative ICI SOC for all operable stage III
4) Stage I/II - more controversial - surgery first/ adj approaches can be an option
5) More work needed on biomarkers of response and comparative trials!
6) The additional benefit of Adjuvant is possible after Neo-Adjuvant therapy
7) ctDNA will be critical for optimal management
7) Novel Agents Needed!
8) Many remaining questions including Who should go to surgery first?

EXCITING TIMES FOR EARLY STAGE NSCLC