ERKEN EVRE AKCİĞER KANSERİ YÖNETİMİNDE GÜNCEL GELİŞMELER

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Erken Evre KHDAKda Güncel Pratiğe Yansıyan Çalışmalar

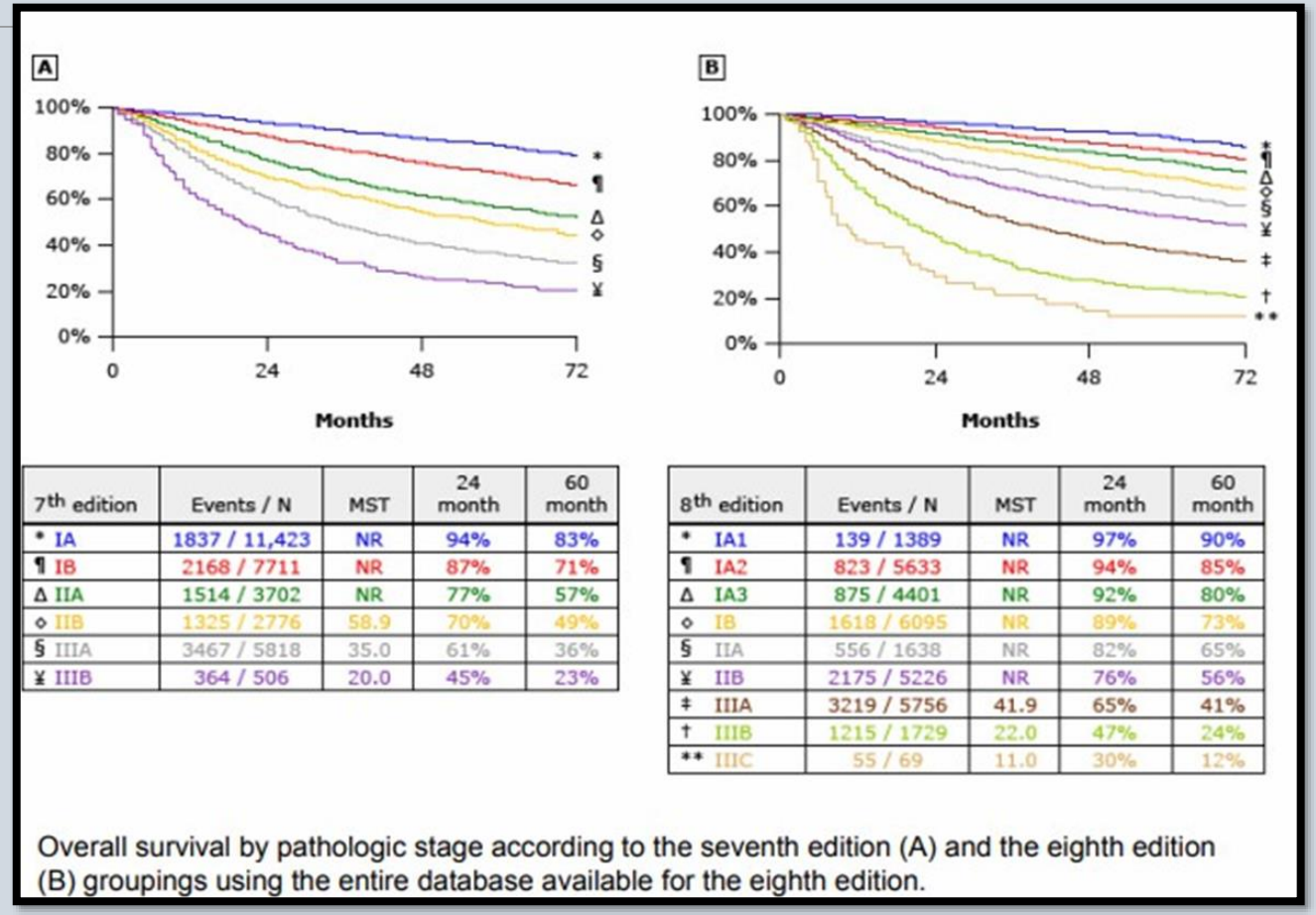
Adjuvan	• Adjuvan Kemoterapi • IMpower 010 / PEARLS • ADAURA / ALINA
İzole Neoadjuvan	• Checkmate 816
Perioperatif	• Checkmate 77T • AEGEAN • Keynote 671

- Tek başına cerrahi rezeksiyon ile erken evre akciğer kanserlerinde kür şansı az, 5 yıllık rekürenssiz sağkalım oranı genellikle düşüktür
- Rekürensler genelde uzak metastazlar şeklinde izlenir

Sites of Recurrence Following Complete Surgical Resection

Recurrence	Histology, %	
	Adenocarcinoma/Large Cell	Squamous Cell
Regional	17	24
Distant	79	71
Regional and distant	4	5

Mountain CF, McMurtrey MJ, Frazier OH. Current results of surgical treatment for lung cancer. Cancer Bull 1980;32:105–108



7th edition	Events / N	MST	24 month	60 month
* IA	1837 / 11,423	NR	94%	83%
¶ IB	2168 / 7711	NR	87%	71%
Δ IIA	1514 / 3702	NR	77%	57%
◇ IIB	1325 / 2776	58.9	70%	49%
§ IIIA	3467 / 5818	35.0	61%	36%
¥ IIIB	364 / 506	20.0	45%	23%

8th edition	Events / N	MST	24 month	60 month
* IA1	139 / 1389	NR	97%	90%
¶ IA2	823 / 5633	NR	94%	85%
Δ IA3	875 / 4401	NR	92%	80%
◇ IB	1618 / 6095	NR	89%	73%
§ IIA	556 / 1638	NR	82%	65%
¥ IIB	2175 / 5226	NR	76%	56%
‡ IIIA	3219 / 5756	41.9	65%	41%
† IIIB	1215 / 1729	22.0	47%	24%
** IIIC	55 / 69	11.0	30%	12%

Overall survival by pathologic stage according to the seventh edition (A) and the eighth edition (B) groupings using the entire database available for the eighth edition.

Pratik değiştirenler

Trials	No. Patients	Stage	Chemotherapy	Overall Survival				Ref.
				5-Year Survival, %		Hazard Ratio (95% CI)	P Value	
				Chemotherapy	Control			
IALT	1867	I-III	Cis/Vinca	44.5	40.4	0.86 (0.76-0.98)	< .03	3
JBR.10	482	IB-II	Cis/Vino	69	54	0.69 (0.52-0.91)	.04	5
ANITA	840	IB-IIIA	Cis/Vino	51.2	42.6	0.80 (0.66-0.96)	.02	6
LACE meta-analysis	4584	I-IIIA	Cisplatin-based	48.8	43.5	0.89 (0.82-0.96)	.004	10

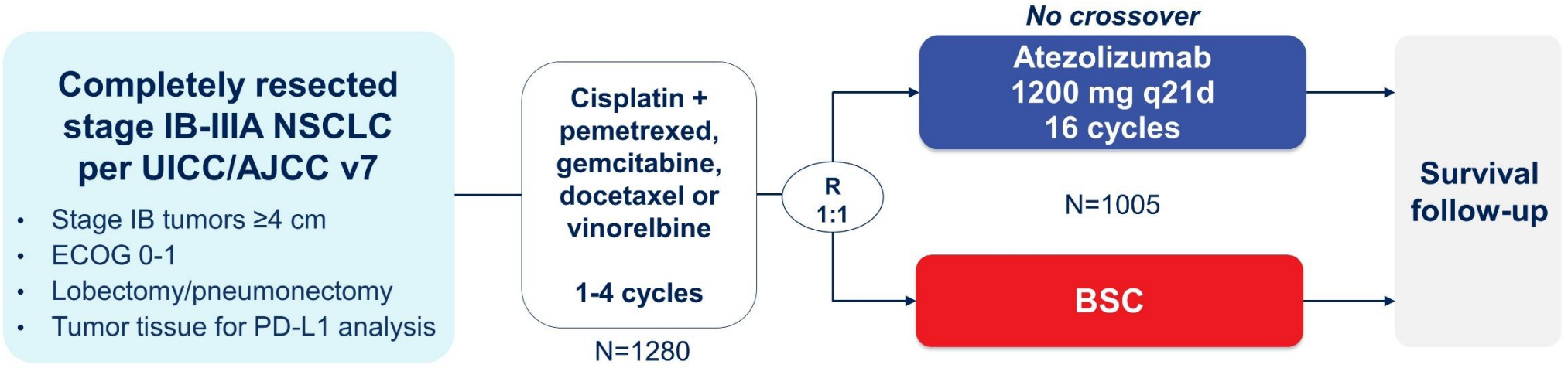
Abbreviations: ANITA = Adjuvant Navelbine International Trialist Association; CI = confidence interval; Cis = cisplatin; IALT = International Adjuvant Lung Cancer Trial; LACE = Lung Adjuvant Cisplatin Evaluation; Ref. = reference; Vinca = Vinca Alkaloid; Vino = vinorelbine.

Hedefe Yönelim - İmmunoterapi

Trials	Drug	No. Patients	Stage	Primary Endpoint	NCT Number	Ref.
PEARLS	Pembrolizumab	1380	IB-IIIA	DFS	NCT02504372	49
BR31	Durvalumab	1360	IB-IIIA	DFS	NCT02273375	50
IMpower010	Atezolizumab	1127	IB-IIIA	DFS	NCT02486718	51
ANVIL	Nivolumab	714	IB-IIIA	OS/DFS	NCT02595944	52

Abbreviations: DFS = disease-free survival; NCT = National Clinical Trials; OS = overall survival; Ref. = reference.

IMpower010: study design



Stratification factors

- Male/female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Both arms included observation and regular scans for disease recurrence on the same schedule.
ECOG, Eastern Cooperative Oncology Group; IC, tumor-infiltrating immune cells; ITT, intent to treat; TC, tumor cells. [a] Per SP142 assay.

Presented By: Dr. Heather A. Wakelee
IMpower010 Interim Analysis
https://bit.ly/33t6JJP

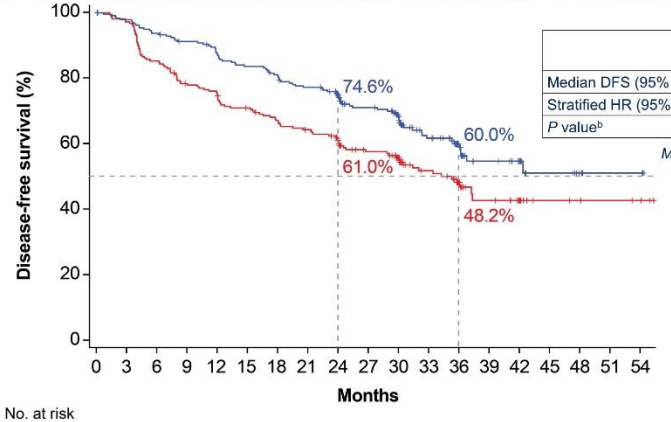
Table S1: **Overview of chemotherapy cycles by treatment arm**

	PD-L1 TC≥1% (SP263) (stage II-IIIA)		**All Randomised (stage II-IIIA)**		**ITT (stage IB-IIIA)**	
No. of cycles	**Atezolizumab (n = 248)**	**BSC (n = 228)**	**Atezolizumab (n = 442)**	**BSC (n = 440)**	**Atezolizumab (n = 507)**	**BSC (n = 498)**
1	1 (<1%)	11 (5%)	6 (1%)	14 (3%)	7 (1%)	14 (3%)
2	8 (3%)	11 (5%)	18 (4%)	19 (4%)	22 (4%)	22 (4%)
3	28 (11%)	18 (7.9%)	40 (9%)	35 (8%)	42 (8%)	39 (8%)
4	211 (85%)	188 (83%)	378 (86%)	372(85%)	436 (86%)	423 (85%)

Data are n (%).

BSC, best supportive care; ITT, intent-to-treat.

IMpower010: DFS in the PD-L1 TC ≥1%[a] stage II-IIIA population (primary endpoint)



	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]	

Median follow-up: 32.8 mo (range, 0.1-57.5)

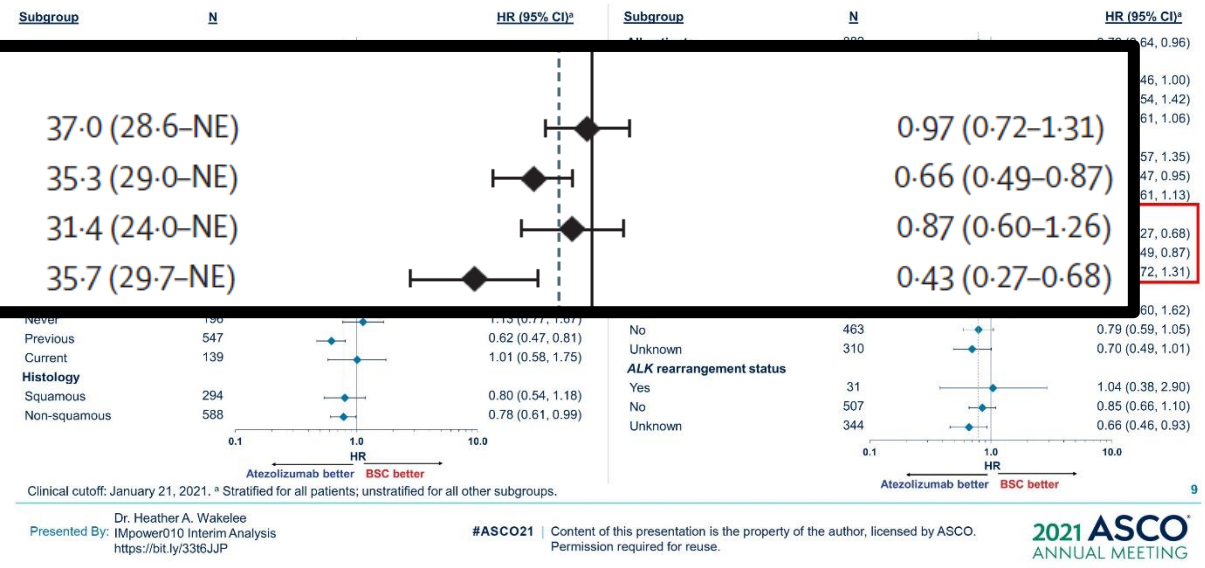
No. at risk

Clinical cutoff: Jan

Presented By: Dr IM ht

PD-L1 status by SP263					
TC <1%	181/383	36·1 (30·2–NE)	202/383	37·0 (28·6–NE)	0·97 (0·72–1·31)
TC ≥1%	248/476	NE (36·1–NE)	228/476	35·3 (29·0–NE)	0·66 (0·49–0·87)
TC 1–49%	133/247	32·8 (29·4–NE)	114/247	31·4 (24·0–NE)	0·87 (0·60–1·26)
TC ≥50%	115/229	NE (42·3–NE)	114/229	35·7 (29·7–NE)	0·43 (0·27–0·68)

IMpower010: DFS in key subgroups of the all-randomized stage II-IIIA population



Clinical cutoff: January 21, 2021. [a] Stratified for all patients; unstratified for all other subgroups.

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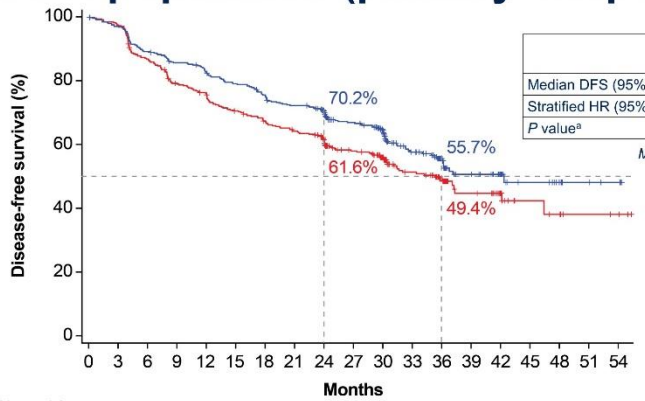
IMp... stage II-IIIA population (primary endpoint)



	Atezolizumab (n=442)	BSC (n=440)
Median DFS (95% CI), mo	42.3 (36.0, NE)	35.3 (30.4, 46.4)
Stratified HR (95% CI)	0.79 (0.64, 0.96)	
P value[a]	0.02[b]	

Median follow-up: 32.2 mo (range, 0-57.5)

No. at risk

Atezolizumab 442 418 384 367 352 337 319 305 269 225 185 120 84 48 34 16 11 5 3

BSC 440 412 366 331 314 292 277 263 230 182 146 102 71 35 22 10 8 4 3

Clinical cutoff: January 21, 2021. [a] Stratified log-rank. [b] Crossed the significance boundary for DFS.

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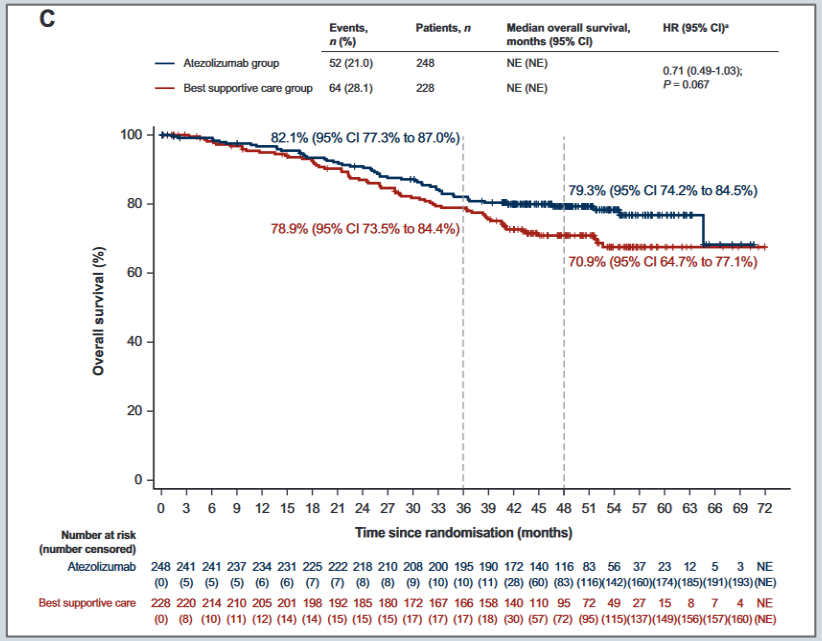
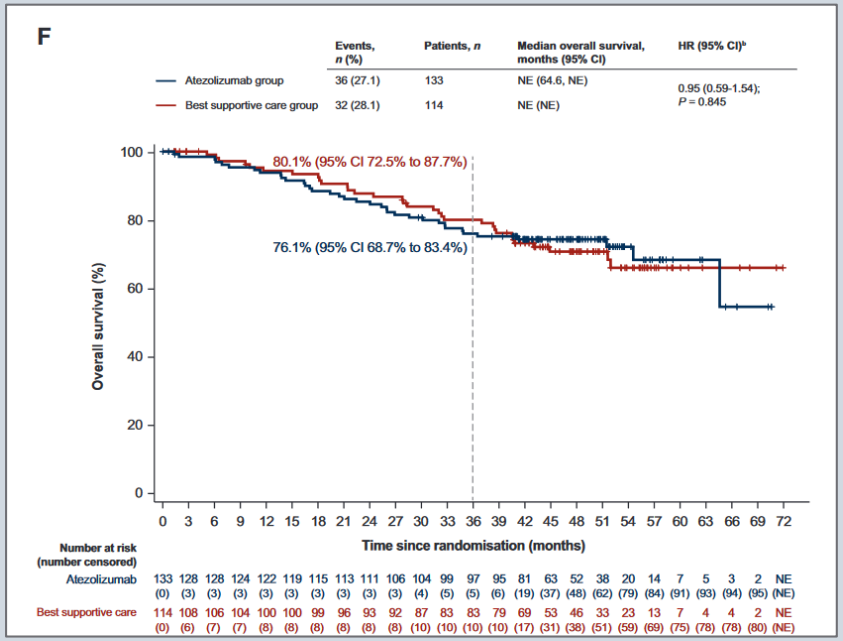
Genel Sağkalım

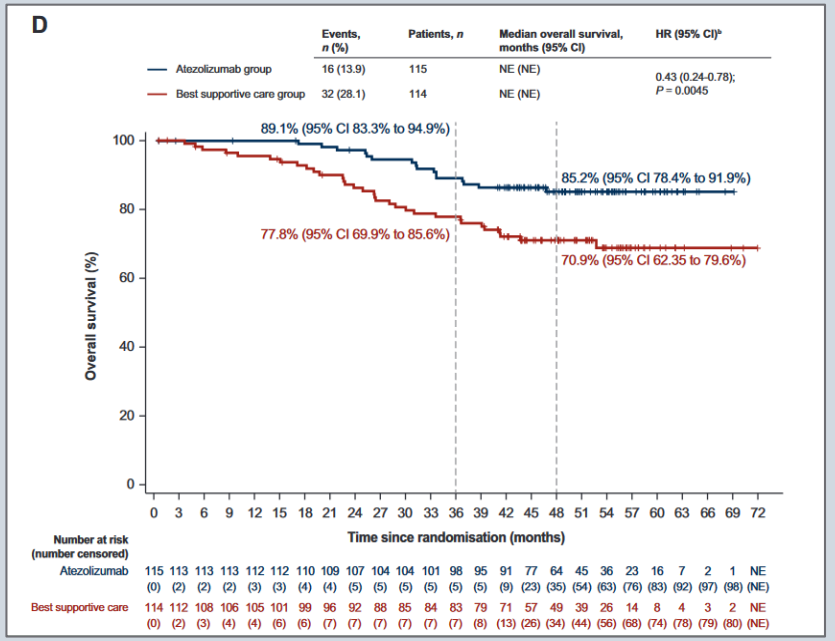
EVRE 2 – 3A
PD-L1 > %1

EVRE 2 – 3A
PD-L1 % 1- 49

EVRE 2 – 3A
PD-L1 > % 50

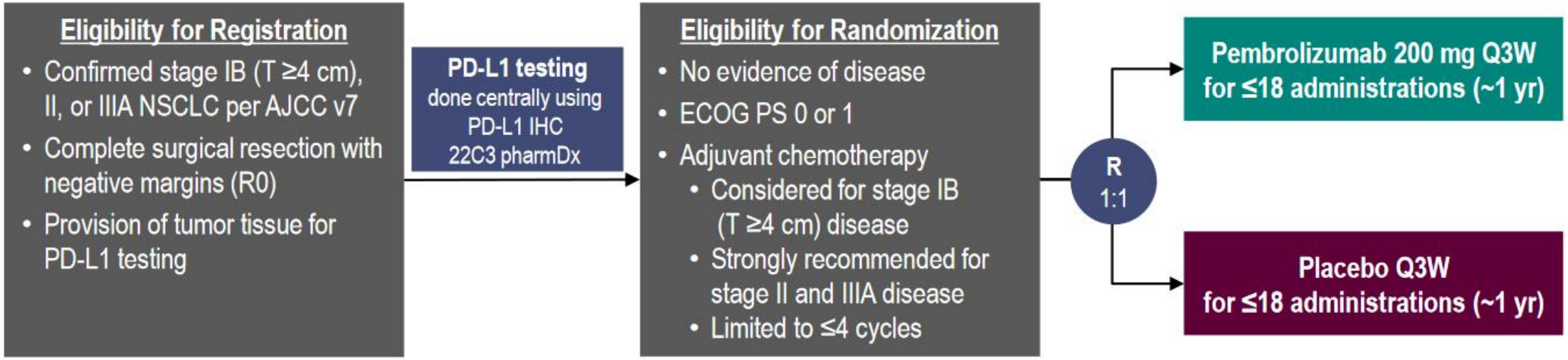






PEARLS/KEYNOTE-091 Study Design

Randomized, Triple-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (IB vs II vs IIIA)
- PD-L1 TPS (<1% vs 1-49% vs ≥50%)
- Receipt of adjuvant chemotherapy (yes vs no)
- Geographic region (Asia vs Eastern Europe vs Western Europe vs rest of world)

Dual Primary End Points

- DFS in the overall population
- DFS in the PD-L1 TPS ≥50% population

Secondary End Points

- DFS in the PD-L1 TPS ≥1% population
- OS in the overall, PD-L1 TPS ≥50%, and PD-L1 TPS ≥1% populations
- Lung cancer-specific survival in the overall population
- Safety

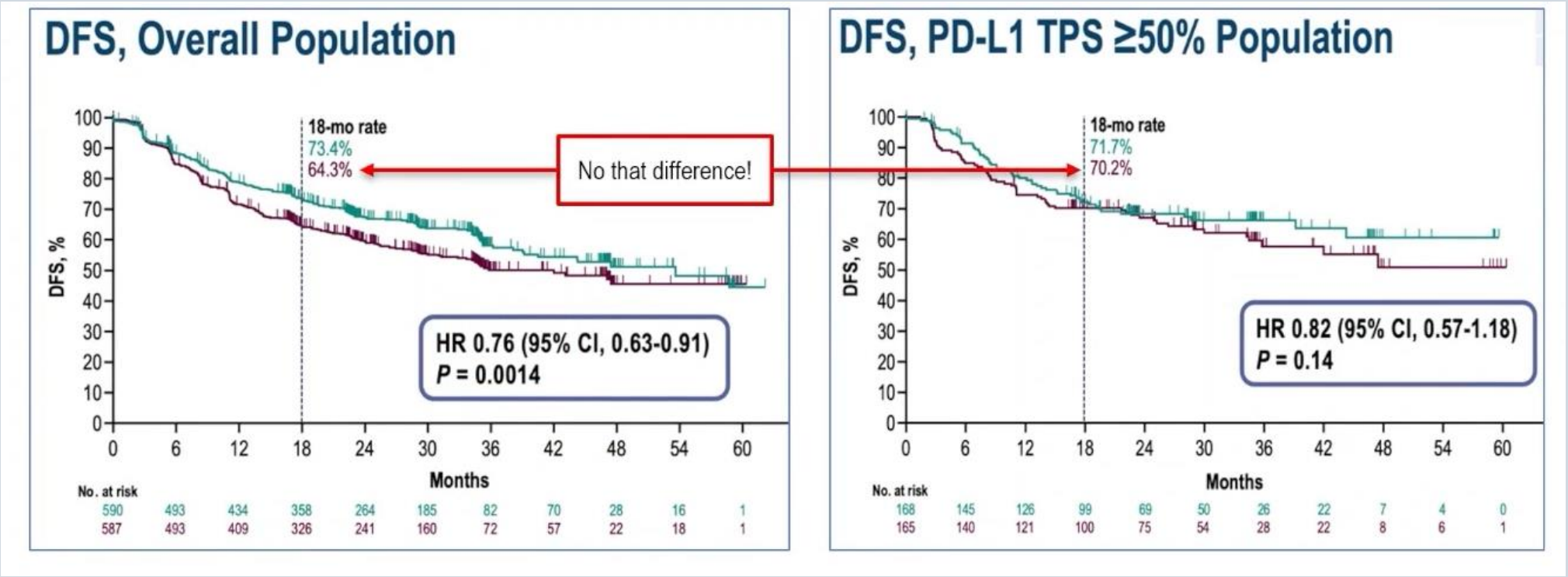
ClinicalTrials.gov number, NCT02504372.

Baseline Characteristics, Overall Population

	Pembrolizumab (N = 590)	Placebo (N = 587)
Age, median (range)	65 y (31-87)	65 y (37-85)
Male	401 (68.0%)	403 (68.7%)
Geographic region		
Asia	106 (18.0%)	105 (17.9%)
Eastern Europe	116 (19.7%)	113 (19.3%)
Western Europe	303 (51.4%)	301 (51.3%)
Rest of world	65 (11.0%)	68 (11.6%)
ECOG PS 1	210 (35.6%)	244 (41.6%)
Current/former smoker	503 (85.3%)	521 (88.8%)
***EGFR* mutation**[a]	39 (6.6%)	34 (5.8%)
***ALK* translocation**[b]	7 (1.2%)	7 (1.2%)
Nonsquamous histology	398 (67.5%)	363 (61.8%)
Pathologic stage[c]		
IB	84 (14.2%)	85 (14.5%)
II	329 (55.8%)	338 (57.6%)
IIIA	177 (30.0%)	162 (27.6%)
Received adjuvant chemotherapy		
Yes	506 (85.8%)	504 (85.9%)
No	84 (14.2%)	83 (14.1%)
PD-L1 TPS		
<1%	233 (39.5%)	232 (39.5%)
1-49%	189 (32.0%)	190 (32.4%)
≥50%	168 (28.5%)	165 (28.1%)

[a] *EGFR* status unknown for 333 (56.4%) in pembro arm and 337 (57.4%) in placebo arm.
[b] *ALK* status unknown for 357 (60.5%) in pembro arm and 390 (66.4%) in placebo arm.
[c] 2 (0.3%) participants in the placebo group had stage IV disease.

Data cutoff date: September 20, 2021


DFS, Overall Population
18-mo rate
73.4%
64.3%
No that difference!
HR 0.76 (95% CI, 0.63-0.91)
P = 0.0014
DFS, %
Months
No. at risk
590 493 434 358 264 185 82 70 28 16 1
587 493 409 326 241 160 72 57 22 18 1
DFS, PD-L1 TPS ≥50% Population
18-mo rate
71.7%
70.2%
HR 0.82 (95% CI, 0.57-1.18)
P = 0.14
DFS, %
Months
No. at risk
168 145 126 99 69 50 26 22 7 4 0
165 140 121 100 75 54 28 22 8 6 1

DFS in Key Subgroups, Overall Population

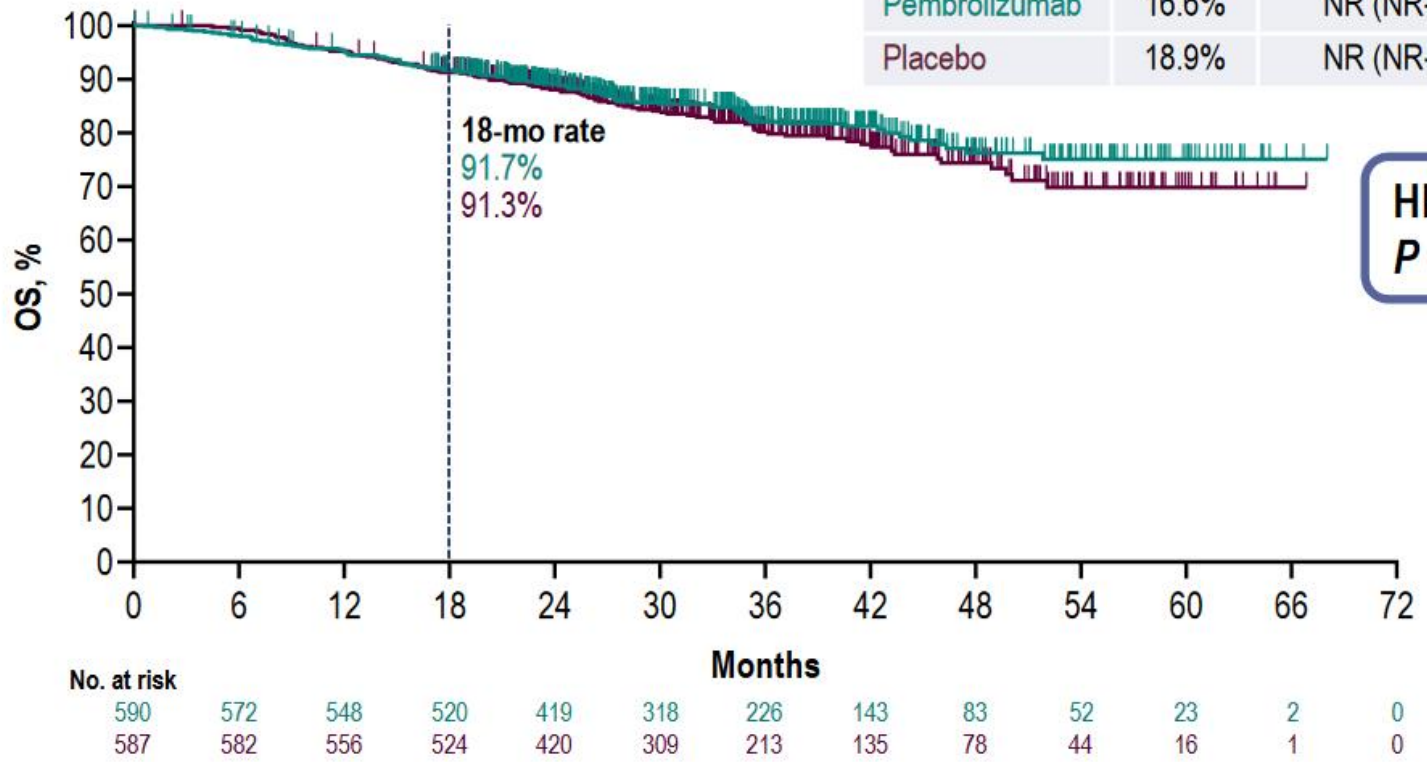
Subgroup	No. Events/ No. Participants	Hazard Ratio (95% CI)
Overall	472/1177	0.76 (0.63-0.91)
Age		
<65 years	213/558	0.73 (0.56-0.96)
≥65 years	259/619	0.84 (0.66-1.07)
Sex		
Female	158/373	0.73 (0.54-1.00)
Male	314/804	0.81 (0.65-1.01)
Geographic region		
Asia	96/211	0.74 (0.49-1.10)
Eastern Europe	90/229	0.84 (0.56-1.27)
Western Europe	245/604	0.77 (0.60-1.00)
Rest of world	41/133	0.74 (0.40-1.39)
ECOG performance status		
0	288/723	0.78 (0.62-0.99)
1	184/454	0.79 (0.59-1.06)
Smoking status		
Current	53/165	0.42 (0.23-0.77)
Former	340/859	0.84 (0.68-1.04)
Never	79/153	0.72 (0.47-1.13)

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)

Response assessed per RECIST v1.1 by investigator review.
Data cutoff date: September 20, 2021

OS, Overall Population

	Pts w/ Event	Median, mo (95% CI)
Pembrolizumab	16.6%	NR (NR-NR)
Placebo	18.9%	NR (NR-NR)



HR 0.87 (95% CI, 0.67-1.15)
***P* = 0.17**

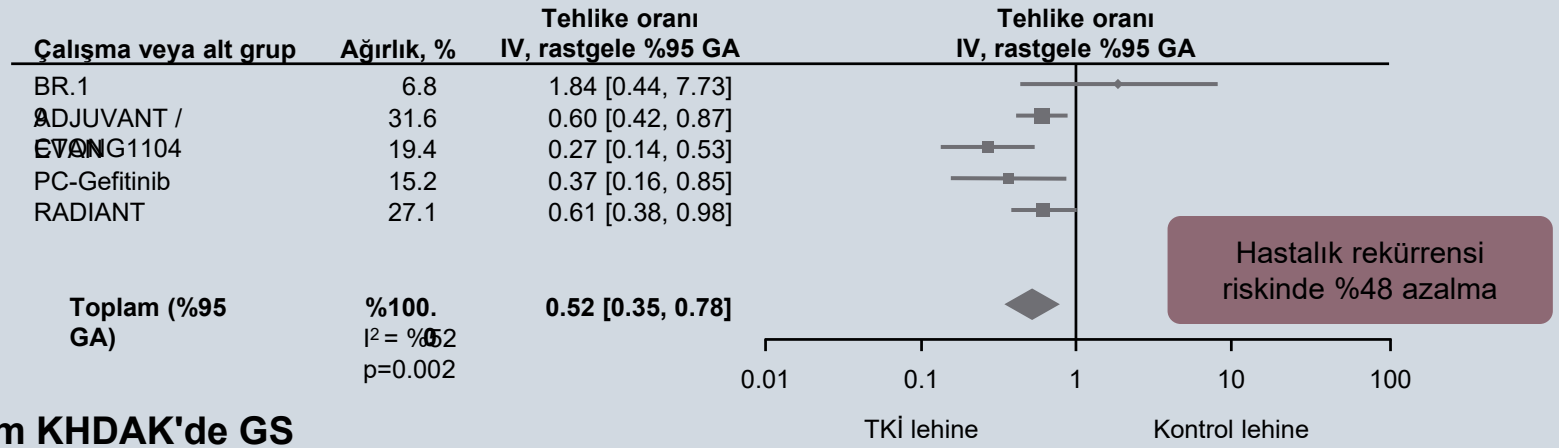
ESMO VIRTUAL PLENARY

Data cutoff date: September 20, 2021

*EGFR*m KHDAK'de Adjuvan EGFR-TKİ'ler için Randomize Çalışmalardan Elde Edilen Güncel Kanıtlar: Daha İyi DFS, Ancak Şimdiye Kadar GS Yararı Yok

6 randomize çalışmanın meta analizi (n=1860; *EGFR*m ile n=599)

_EGFR_m KHDAK'de DFS



_EGFR_m KHDAK'de GS

HR 0.64 (%95 GA 0.22, 1.89)

Hastalık rekürrensi riskinde azalma, adjuvan EGFR-TKİ tedavisinin zamanlaması/sıralamasına göre farklılık göstermiştir:

- Kemoterapiye kıyasla adjuvan EGFR-TKİ: %57
- Adjuvan kemoterapi sonrası (verilmişse) EGFR-TKİ: %38

GS verileri olgunlaşmamıştır ve daha uzun süreli takip gereklidir.

GA = güven aralığı; DFS = hastalıksız sağkalım; *EGFR*m = epidermal büyüme faktörü reseptörü mutasyonu pozitif; EGFR-TKİ = epidermal büyüme faktörü reseptörü tirozin kinaz inhibitörü; HR = tehlike oranı; KHDAK = küçük hücreli dışı akciğer kanseri; GS = genel sağkalım.

Raphael J et al. *Am J Clin Oncol*. 2019;42:440-445.

ADAURA Phase III study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
≥18 years (Japan / Taiwan: ≥20)
WHO performance status 0 / 1
Confirmed primary non-squamous NSCLC Ex19del / L858R‡
Brain imaging, if not completed pre-operatively
Complete resection with negative margins§
Maximum interval between surgery and randomization:
- 10 weeks without adjuvant chemotherapy
- 26 weeks with adjuvant chemotherapy

Stratification by:
Stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
Race (Asian vs non-Asian)

Randomization 1:1 (N=682)

Osimertinib 80 mg, once daily

Placebo, once daily

Planned treatment duration: 3 years

Treatment continued until:
- Disease recurrence
- Treatment completion
- Discontinuation criterion met

Follow-up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

Endpoints
- **Primary endpoint:** DFS by investigator assessment in stage II–IIIA patients
- **Key secondary endpoints:** DFS in the overall population (stage IB–IIIA), landmark DFS rates, OS, safety, health-related quality of life

*At the time of recruitment, staging was determined by the AJCC / UICC Staging Manual 7th edition. Patients with stage IB disease were not eligible in Japan. †Pre-operative, post-operative, or planned radiotherapy was not allowed. ‡Centrally confirmed in tissue. §Patients received a CT scan after resection and within 28 days prior to treatment.

PRESENTED BY: Roy S. Herbst

AJCC, American Joint Committee on Cancer; CT, computerized tomography; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OS, overall survival; UICC, Union for International Cancer Control; WHO, World Health Organization

Baseline characteristics: overall population (stage IB / II / IIIA)[1]

Characteristics, %	Osimertinib (n=339)	Placebo (n=343)
Sex: male / female	32 / 68	28 / 72
Age: median (range), years	64 (30–86)	62 (31–82)
Smoking history:* yes / no	32 / 68	25 / 75
Race: Asian / non-Asian	64 / 36	64 / 36
WHO PS: 0 / 1	64 / 36	64 / 36
AJCC / UICC staging at diagnosis (7th edition): IB / II / IIIA	32 / 34 / 35	32 / 34 / 34
Histology: adenocarcinoma / other	96 / 4	97 / 3
EGFR mutation at randomization:† Ex19del / L858R	55 / 45	55 / 45
Adjuvant chemotherapy: yes / no	60 / 40	60 / 40

only 26% of patients with stage IB disease received chemotherapy compared with 71% with stage II disease and 80% with stage IIIA disease.

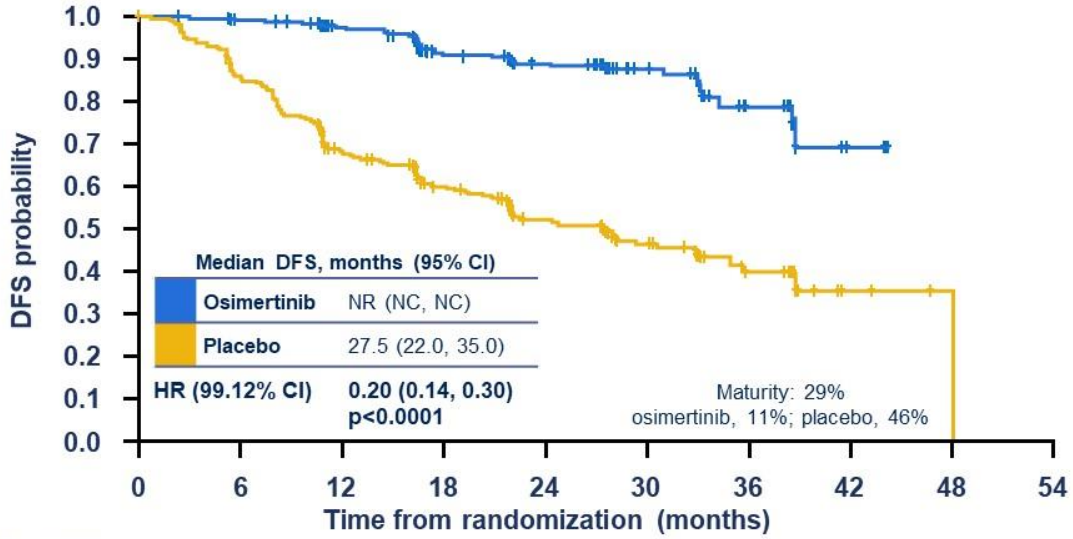
Data cut-off: January 17, 2020.
8%), placebo n=257 (75%). †Central test.
al. N Engl J Med 2020;383:1711–1723.

Adjuvant osimertinib has significantly improved DFS

- Adjuvant osimertinib demonstrated highly statistically significant[1,2] and clinically meaningful improvement in DFS in completely resected EGFRm NSCLC vs placebo in both the primary (stage II–IIIA) and overall (IB–IIIA) populations, along with a tolerable safety profile[1–4]

ADAURA primary DFS analysis[1,2] (stage IB–IIIA)*

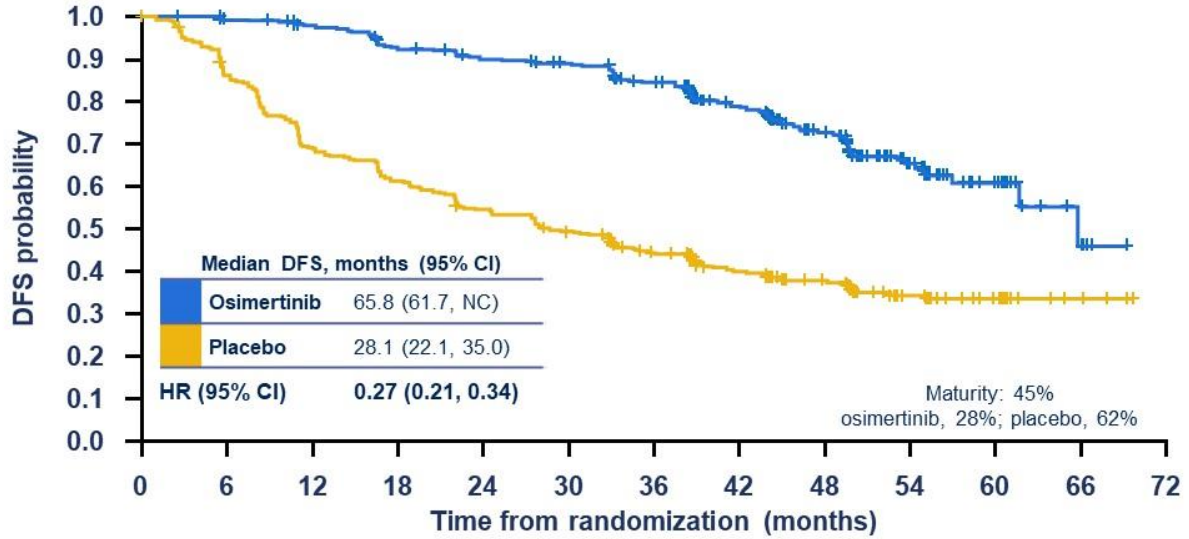
NEJM October 2020



No. at risk										
Osimertinib	339	313	272	208	138	74	27	5	0	-
Placebo	343	287	207	148	88	53	20	3	1	0

ADAURA updated DFS analysis[3,4] (stage IB–IIIA)†

JCO January 2023



No. at risk													
Osimertinib	339	316	307	289	278	270	249	201	139	73	33	5	0
Placebo	343	288	230	205	181	162	137	115	84	48	25	4	0

*Data cut-off: January 17, 2020. †Data cut-off: April 11, 2022.

1. Wu et al. N Engl J Med 2020;383:1711–1723; 2. Herbst et al. J Clin Oncol 2020;38(Suppl 18): abstract / oral LBA5; 3. Herbst et al. J Clin Oncol 2023;41:1830–1840; 4. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47.

PRESENTED BY: Roy S. Herbst

CI, confidence interval; DFS, disease-free survival; EGFRm, epidermal growth factor receptor-mutated; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

Adjuvant osimertinib has significantly improved CNS DFS

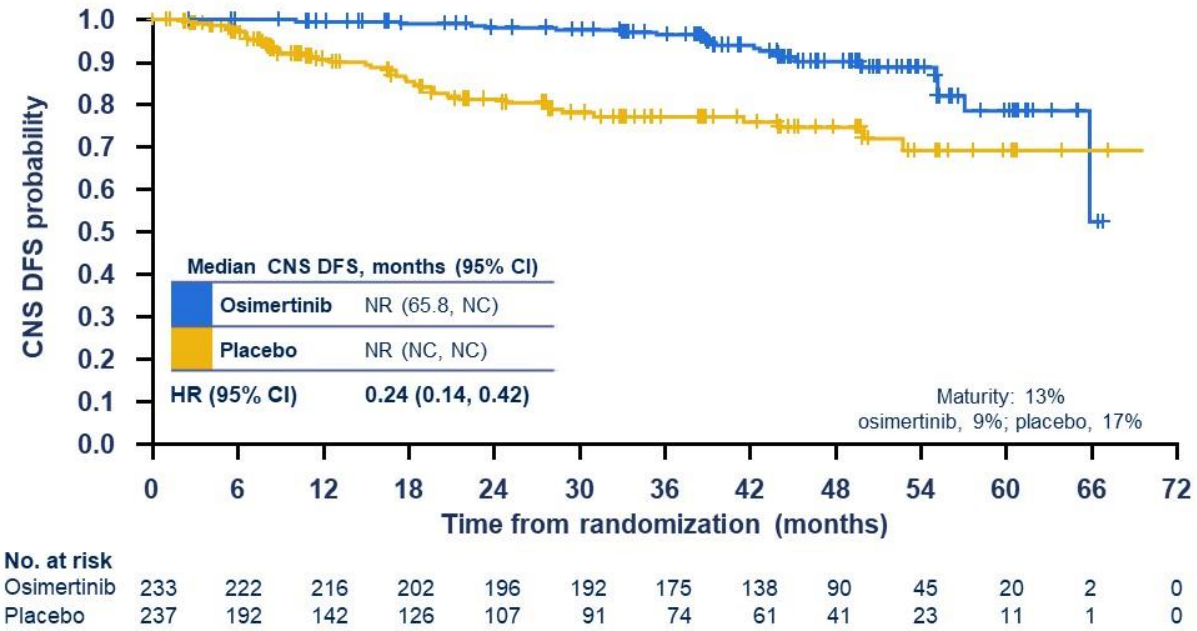
- CNS metastases are a poor prognostic factor among patients with NSCLC, and are associated with deterioration in quality of life[1]

Improved CNS efficacy with osimertinib treatment

- Osimertinib has shown greater penetration of the blood-brain barrier and higher exposure in the brain compared with other EGFR-TKIs[2–4]
- Adjuvant osimertinib demonstrated CNS DFS* benefit vs placebo in both the stage II–IIIA and IB–IIIA populations[5,6]

ADAURA updated CNS DFS analysis[5,6] (stage II–IIIA)

JCO January 2023



No. at risk													
Osimertinib	233	222	216	202	196	192	175	138	90	45	20	2	0
Placebo	237	192	142	126	107	91	74	61	41	23	11	1	0

Data cut-off: April 11, 2022.

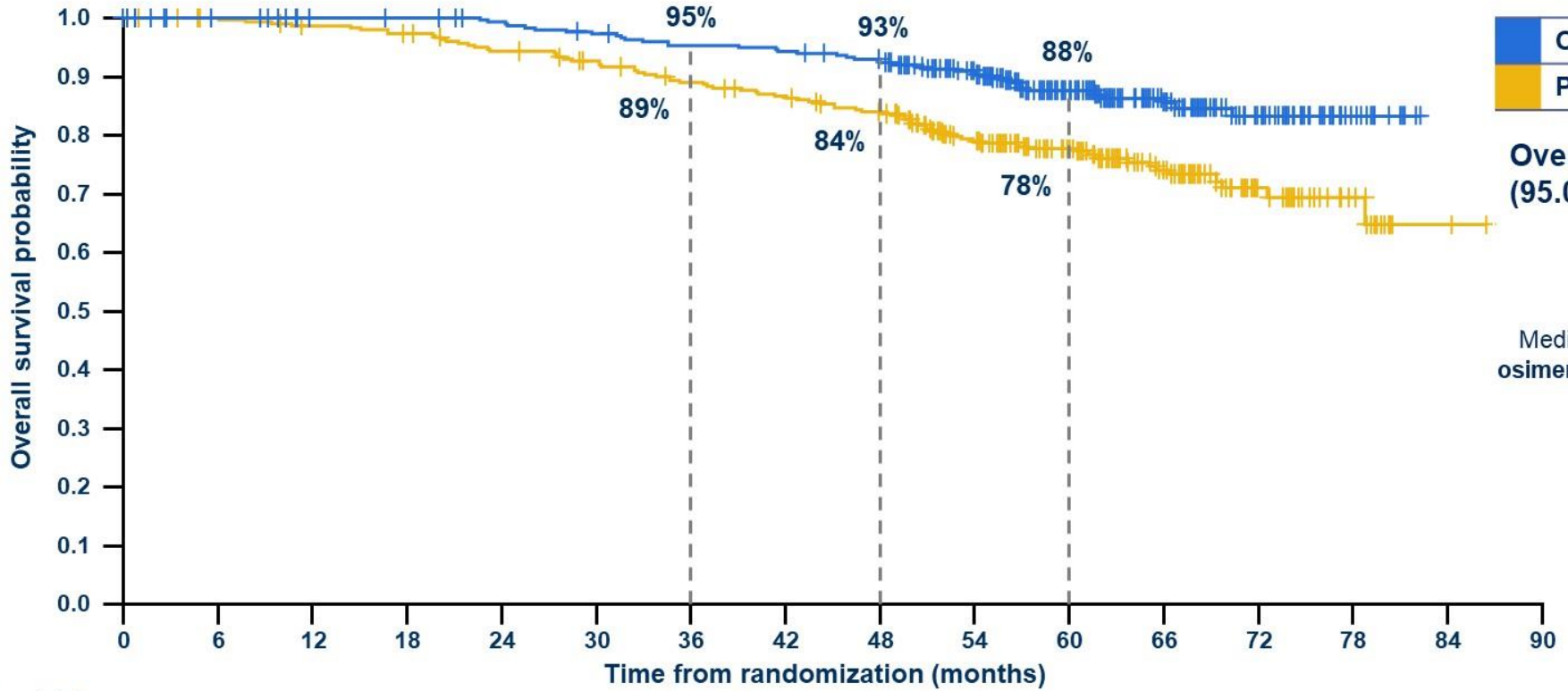
*CNS DFS events were defined as CNS disease recurrence or death by any cause.

1. Peters et al. Cancer Treat Rev 2016;45:139–162; 2. Colclough et al. Eur J Cancer 2016;69:S28; 3. Ballard et al. Clin Cancer Res 2016;22:5130–5140; 4. Vishwanathan et al. Cancer Res 2018; 78:CT013; 5. Herbst et al. J Clin Oncol 2023;41:1830–1840; 6. Tsuboi et al. Ann Oncol 2022;33(Suppl 7): abstract / oral LBA47.

CI, confidence interval; CNS, central nervous system; DFS, disease-free survival; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; EGFR-TKI, EGFR-tyrosine kinase inhibitor; HR, hazard ratio; NC, not calculable; NR, not reached; NSCLC, non-small cell lung cancer

Overall survival: patients with stage IB / II / IIIA disease

- Adjuvant osimertinib demonstrated a statistically and clinically significant improvement in OS vs placebo in the overall population of stage IB–IIIA disease



No. at risk																
Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	-
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

5-year OS rate, % (95% CI)	
Osimertinib (n=339)	88 (83, 91)
Placebo (n=343)	78 (73, 82)

Overall OS HR (95.03% CI) **0.49 (0.34, 0.70); p<0.0001**

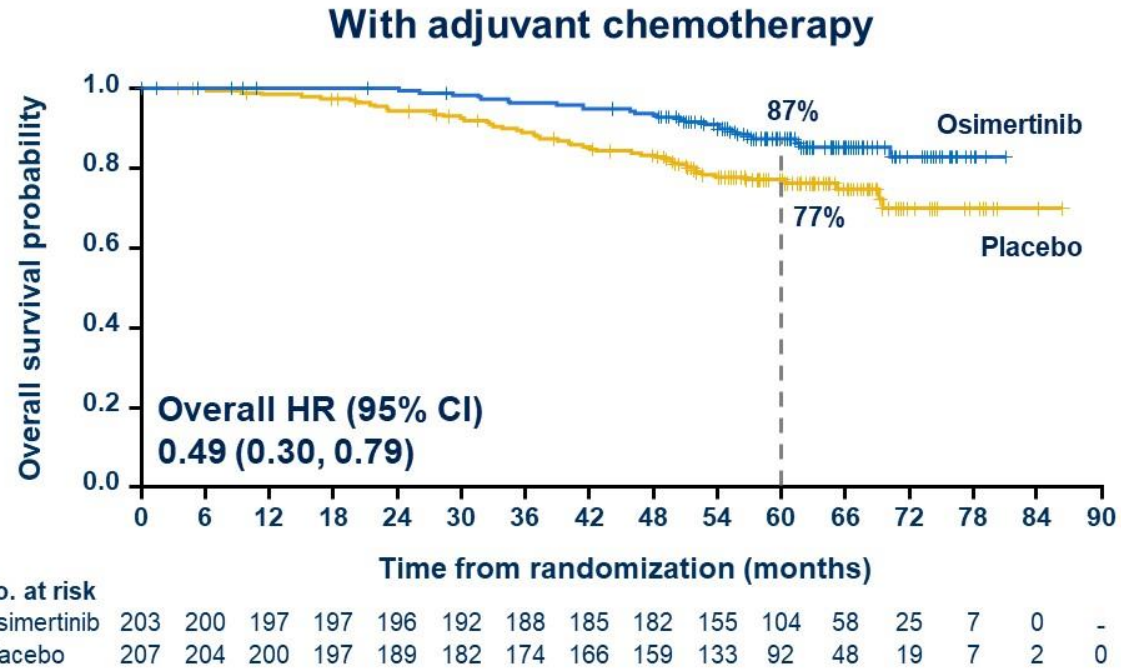
Maturity: 18%
osimertinib 12%, placebo 24%

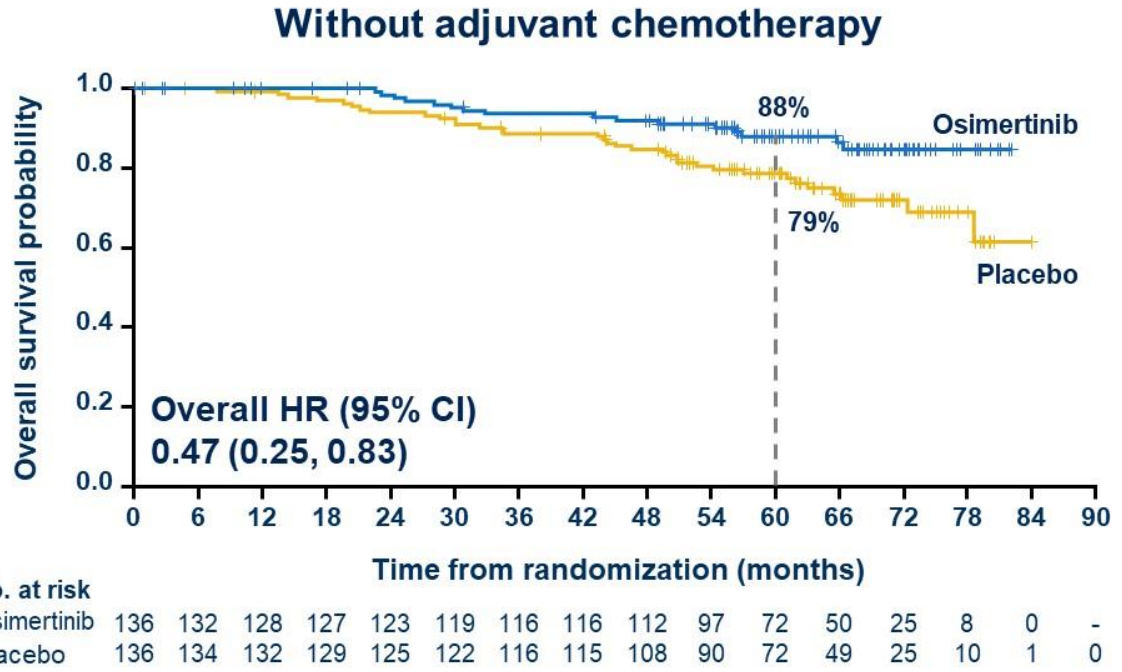
Median follow-up for OS* (censored patients):
osimertinib 61.5 months, placebo 61.5 months

Data cut-off: January 27, 2023.
Tick marks indicate censored data. Alpha allocation of 0.0497. *Median follow-up for OS (all patients): osimertinib 60.4 months, placebo 59.4 months.

CI, confidence interval; HR, hazard ratio; OS, overall survival

OS in patients with and without adjuvant chemotherapy: patients with stage IB / II / IIIA disease



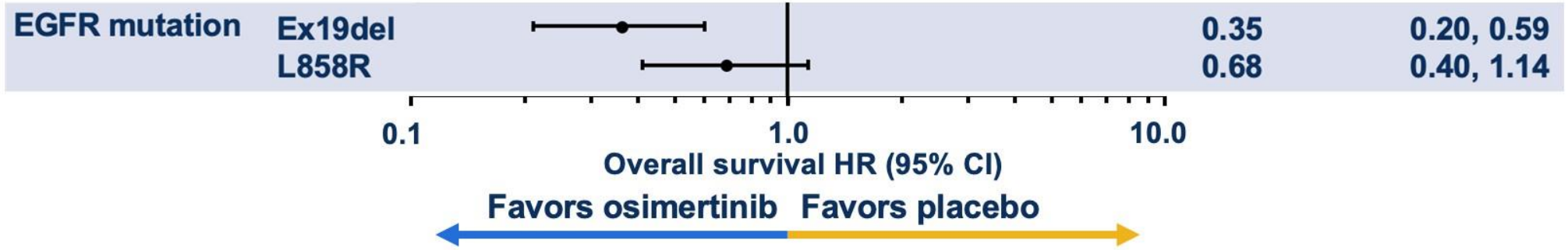


Data cut-off: January 27, 2023.
Overall population: stage IB / II / IIIA. Tick marks indicate censored data.
Use of adjuvant chemotherapy before randomization was allowed but not mandatory; decided by the physician and patient before enrollment.

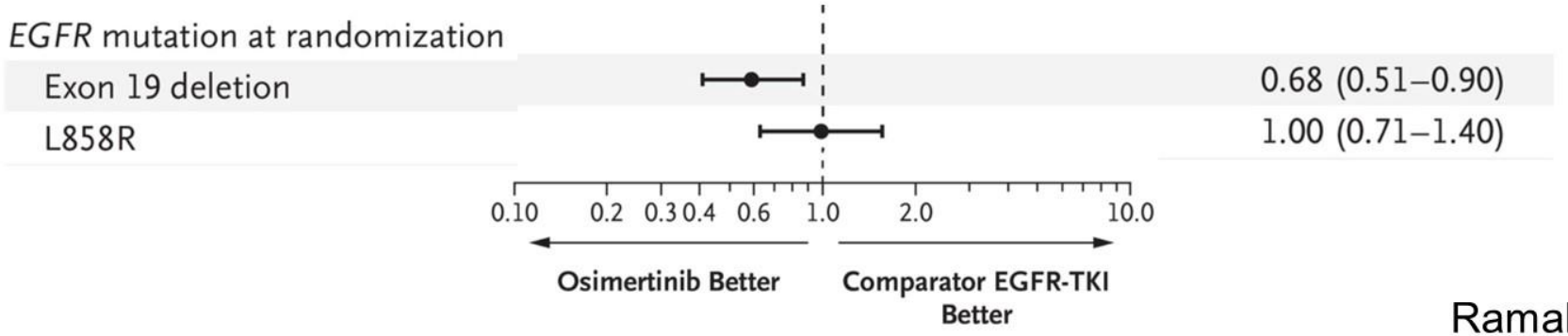
CI, confidence interval; HR, hazard ratio; OS, overall survival

Benefit in *EGFR* Exon 19del vs L858R mutations

ADAURA – overall survival

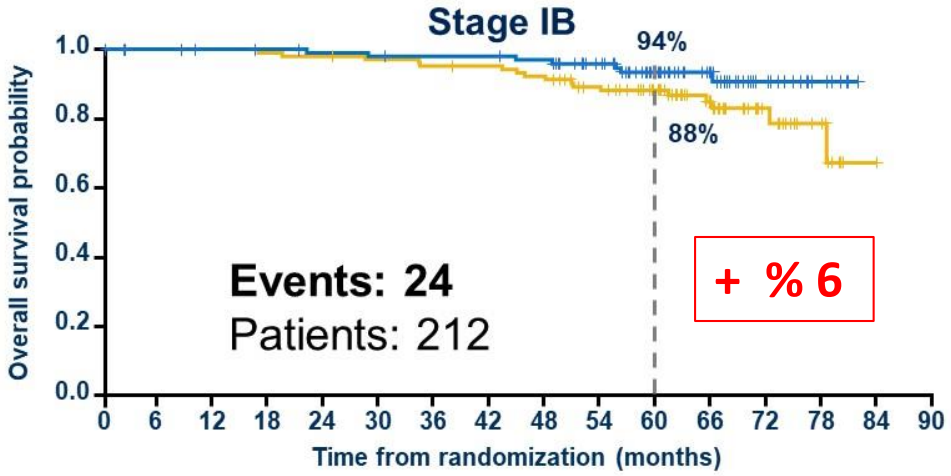


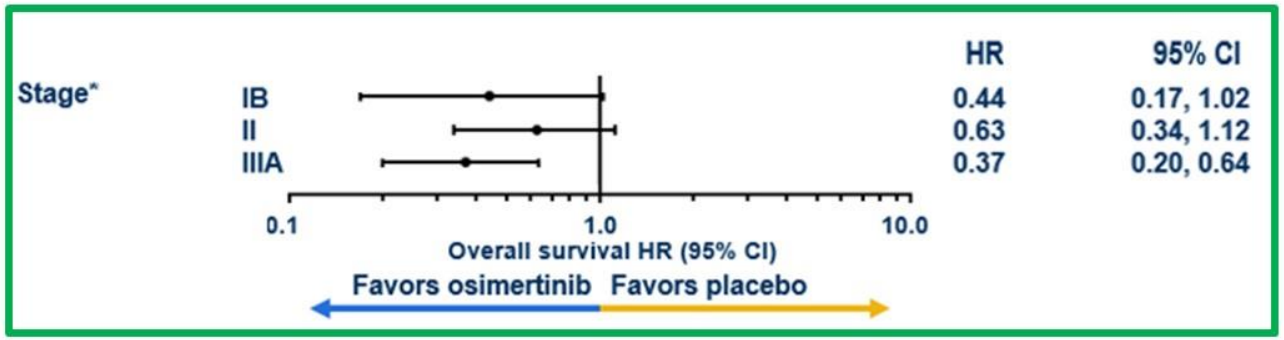
FLAURA Overall Survival – Firstline Osimertinib vs Gefitinib or Erlotinib in Advanced Disease

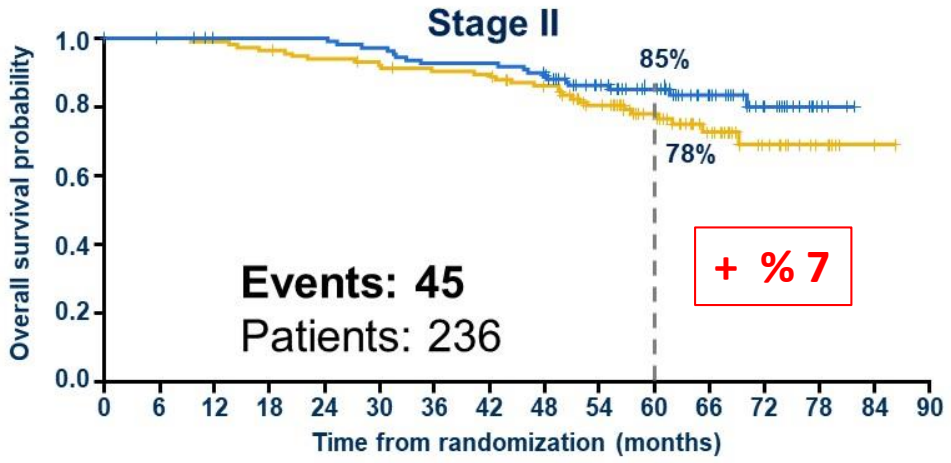


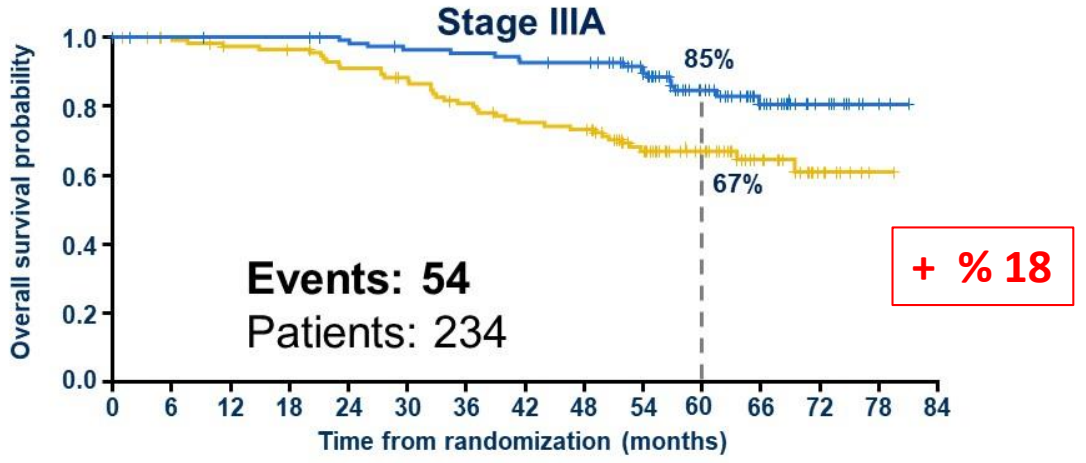
Ramalingam NEJM 2020

Benefit seen across stages







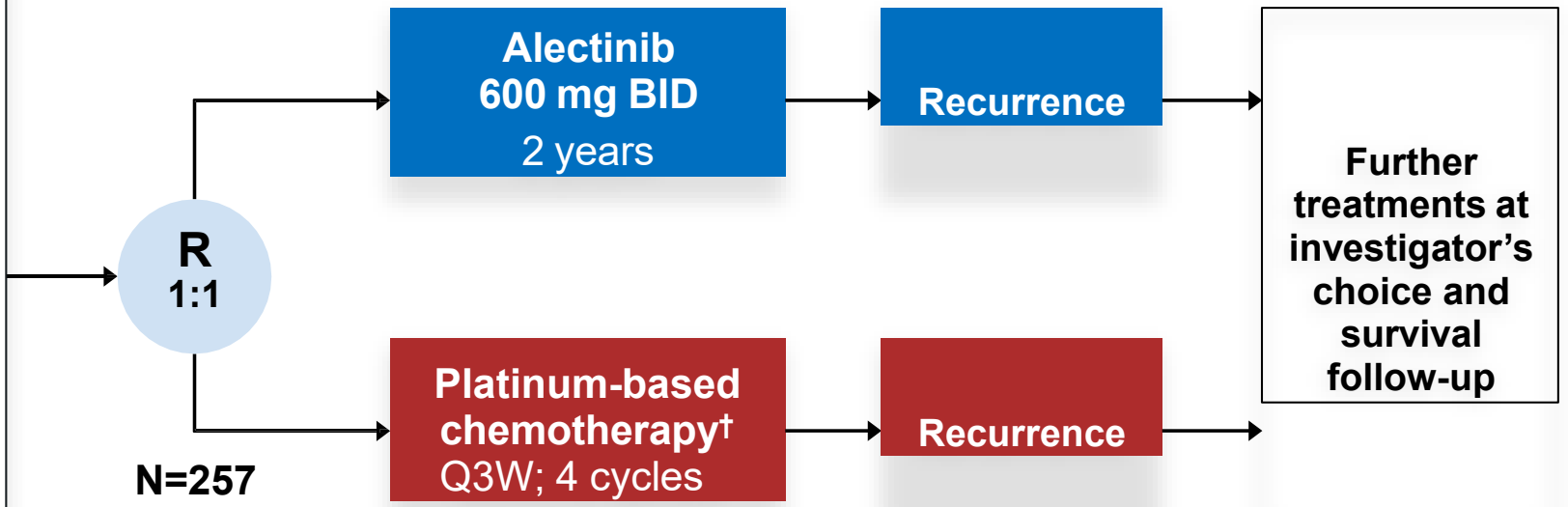


ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian



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

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Data cut-off: 26 June 2023; CNS, central nervous system; DFS, disease-free survival; ITT, intention to treat
*Superiority trial; †Cisplatin + pemetrexed, cisplatin + vinorelbine or cisplatin + gemcitabine; cisplatin could be switched to carboplatin in case of intolerability; ‡DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first; §Assessment by CT scan where MRI not available; NCT03456076

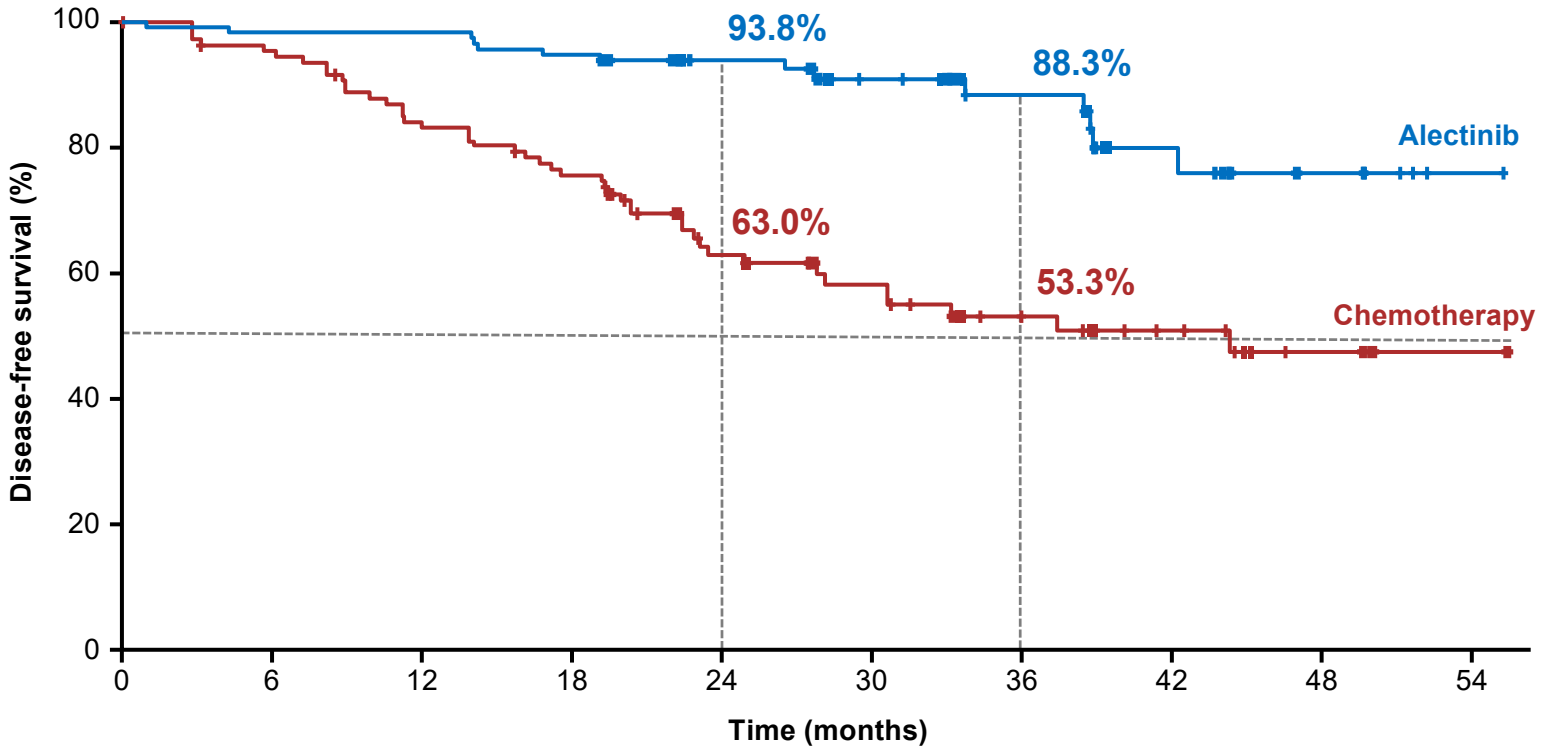
Patient demographics and baseline characteristics (ITT)

Characteristic	Alectinib (n=130)	Chemotherapy (n=127)
Median age <65 / ≥65 years, %	54 years 79 / 21	57 years 73 / 27
Sex: female / male, %	58 / 42	46 / 54
Smoking status: never / former / current, %	65 / 32 / 4	55 / 43 / 2
Race: Asian / non-Asian, %	55 / 45	56 / 44
ECOG PS: 0 / 1, %	55 / 45	51 / 49
Stage at diagnosis*: IB / II / IIIA, %	11 / 36 / 53	9 / 35 / 55
Nodal status: N0 / N1 / N2, %	16 / 35 / 49	14 / 34 / 52
Histology: squamous / non-squamous, %	5 / 95	2 / 98
Surgical procedure: Lobectomy / Other‡, %	97 / 3	92 / 8

Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; ‡Pneumonectomy (alectinib arm, 2%; chemotherapy arm, 3%), bilobectomy (2%; 4%), sleeve lobectomy (0; 1%)

Disease-free survival: stage II–IIIA*



No. at risk

Alectinib	116	111	111	107	67	49	35	21	10	3
Chemo	115	102	88	79	48	35	23	17	10	2

	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

Median survival follow up: alectinib, 27.9 months; chemotherapy, 27.8 months

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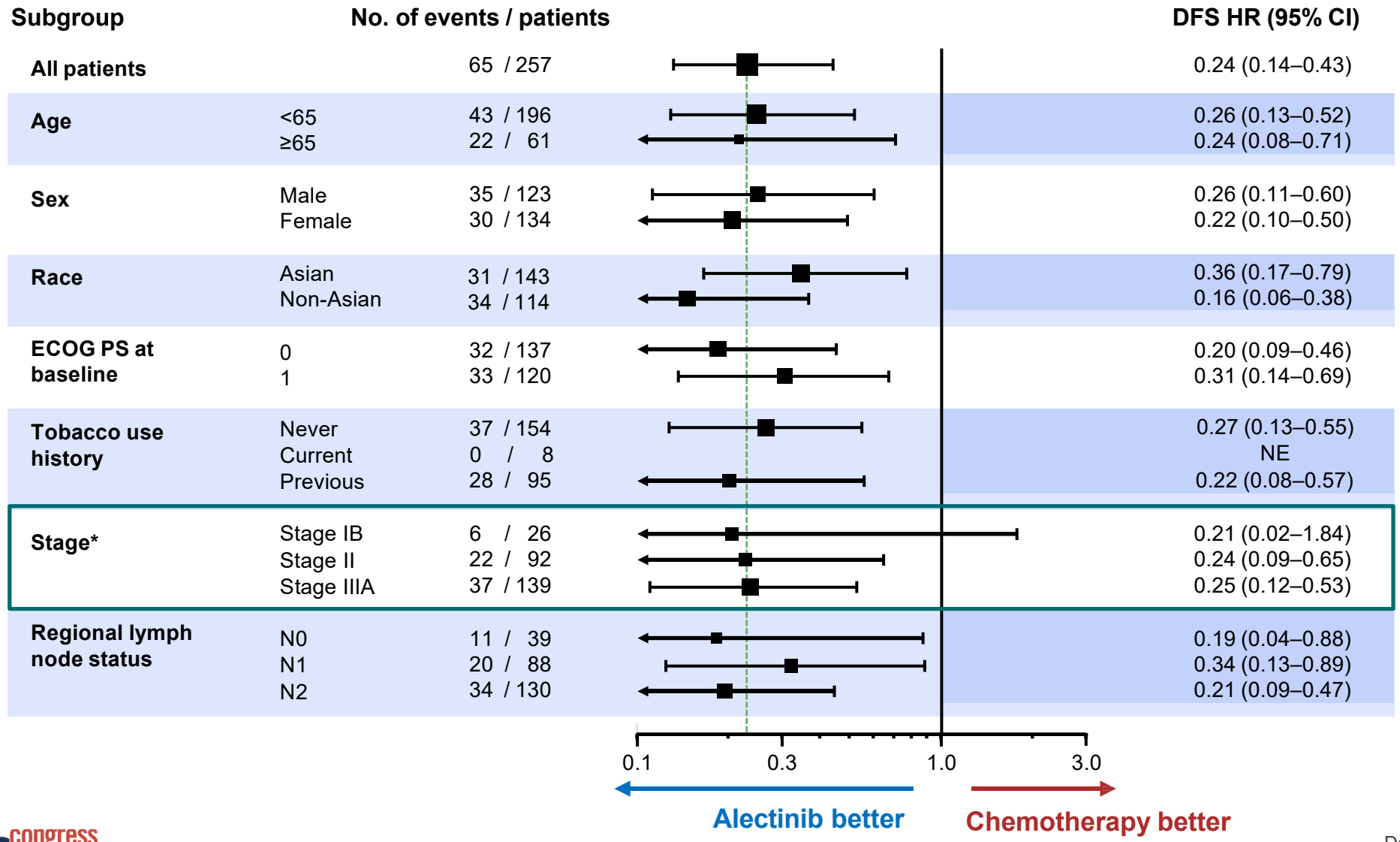
Data cut-off: 26 June 2023; Time from last patient in to data cut off was ~18 months

*Per UICC/AJCC 7th edition; †Stratified log rank; DFS defined as the time from randomisation to the first documented recurrence of disease or new primary NSCLC as determined by the investigator, or death from any cause, whichever occurs first

Disease-free survival subgroup analysis (ITT)

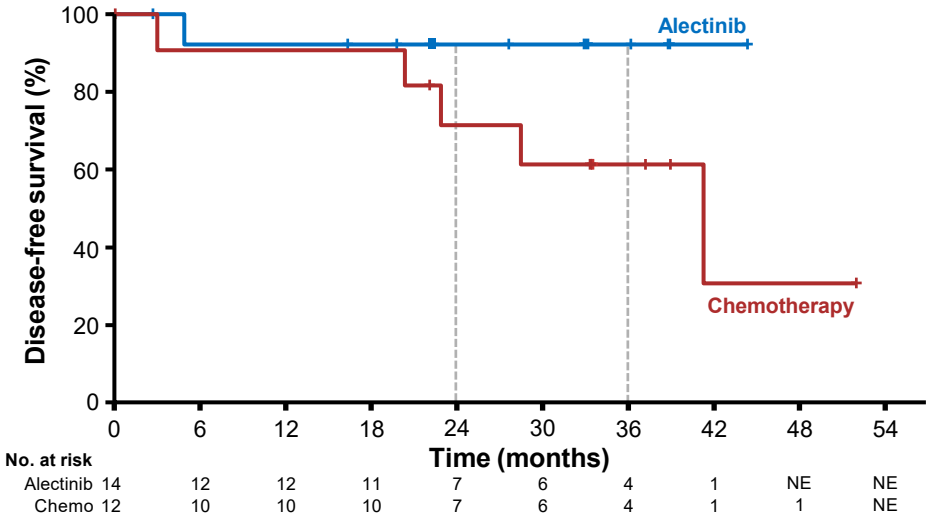


Data cut-off: 26 June 2023

Arrows indicate lower bound of the CI<0.1; *Per UICC/AJCC 7th edition

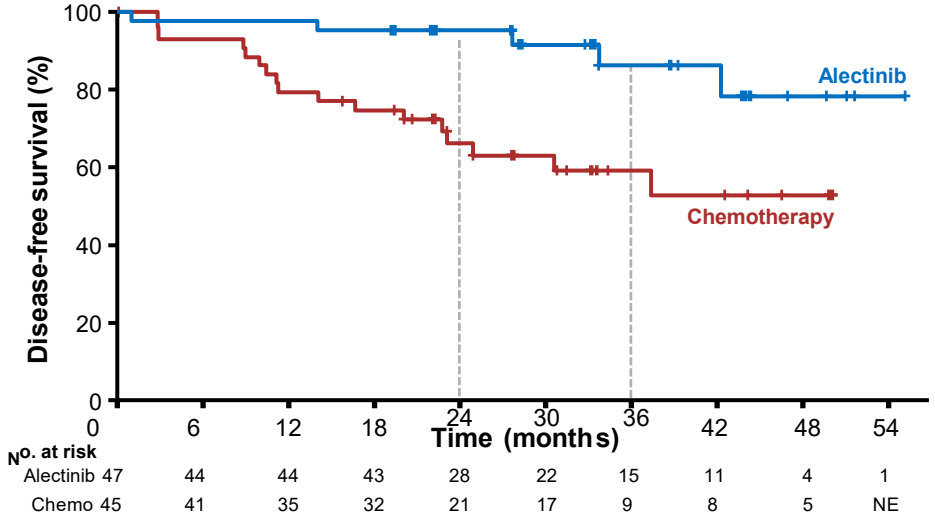
Disease-free survival by stage*

Stage IB

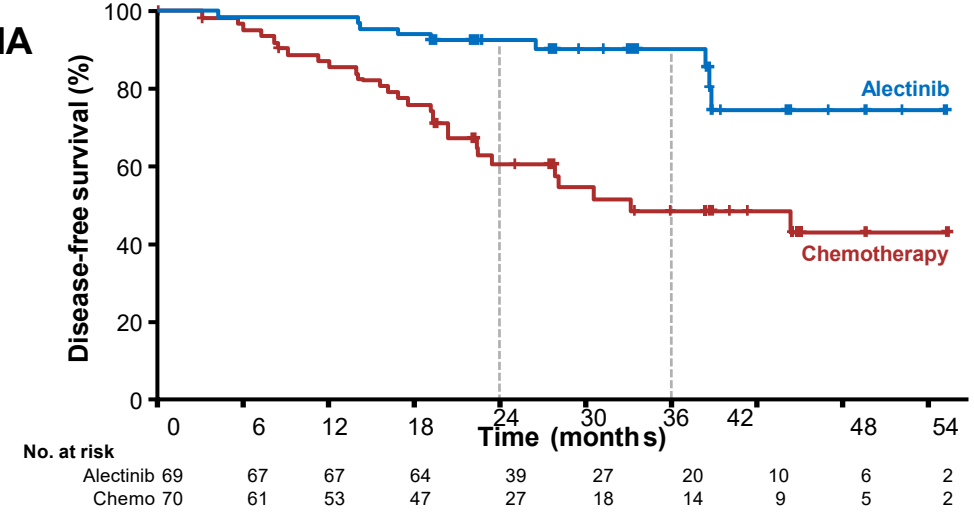


2-year DFS rate, % (95% CI)	Stage IB (n=26)	Stage II (n=92)	Stage IIIA (n=139)
Alectinib	92.3 (77.8, 100.0)	95.6 (89.5, 100.0)	92.7 (86.4, 98.9)
Chemotherapy	71.6 (44.2, 99.0)	66.3 (51.7, 81.0)	60.7 (47.9, 73.5)
HR† (95% CI)	0.21 (0.02, 1.84)	0.24 (0.09, 0.65)	0.25 (0.12, 0.53)

Stage II



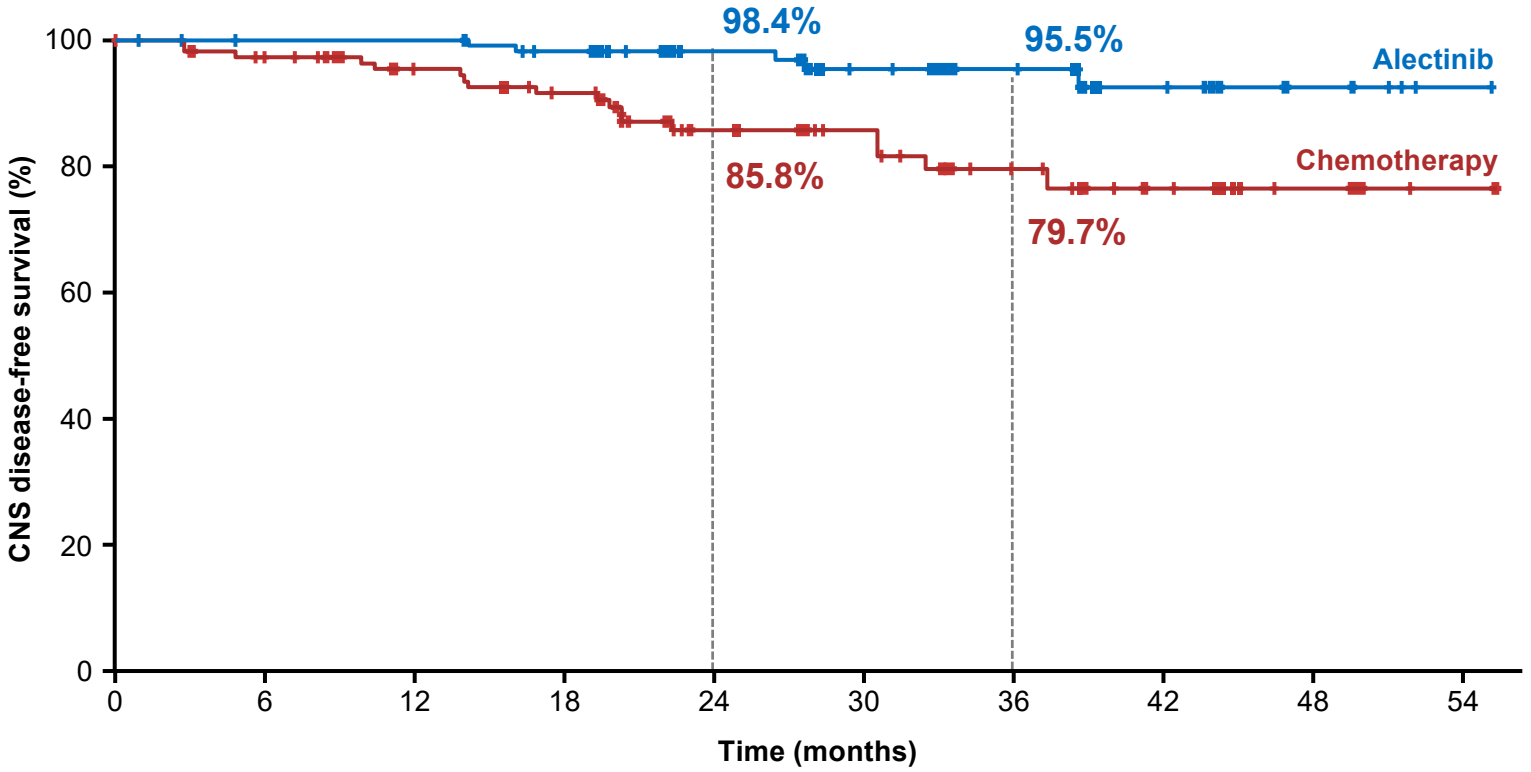
Stage IIIA



Data cut-off: 26 June 2023

*Per UICC/AJCC 7th edition; †Unstratified analysis

CNS disease-free survival in the ITT population



No. at risk

Alectinib	130	124	124	118	74	55	39	22	10	3
Chemo	127	113	98	90	57	43	27	18	11	2

	Alectinib (N=130)	Chemotherapy (N=127)
Patients with event	5	18
Death	1	4
Brain recurrence	4	14
CNS-DFS HR* (95% CI)	**0.22** (0.08, 0.58)	

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

Data cut-off: 26 June 2023

*Stratified analysis with race and stage as stratification factors

CNS-DFS defined as time from randomisation to the first documented recurrence of disease in the CNS or death from any cause

Post-recurrence subsequent therapy

Number of patients with disease recurrence, n (%)	Alectinib (n=15)	Chemotherapy (n=49)
Patients with any subsequent therapy	13 (87)	43 (88)
Systemic therapy	13 (87)	38 (78)
ALK TKI	7 (47)	37 (76)
Alectinib	4 (27)	29 (59)
Brigatinib	4 (27)	4 (8)
Crizotinib	0	4 (8)
Lorlatinib	0	2 (4)
Ceritinib	0	1 (2)
Chemotherapy	6 (40)	2 (4)
Immunotherapy	1 (7)	1 (2)
Other anti-cancer therapy	1 (7)	1 (2)
Radiotherapy	5 (33)	9 (18)
Surgery	1 (7)	3 (6)

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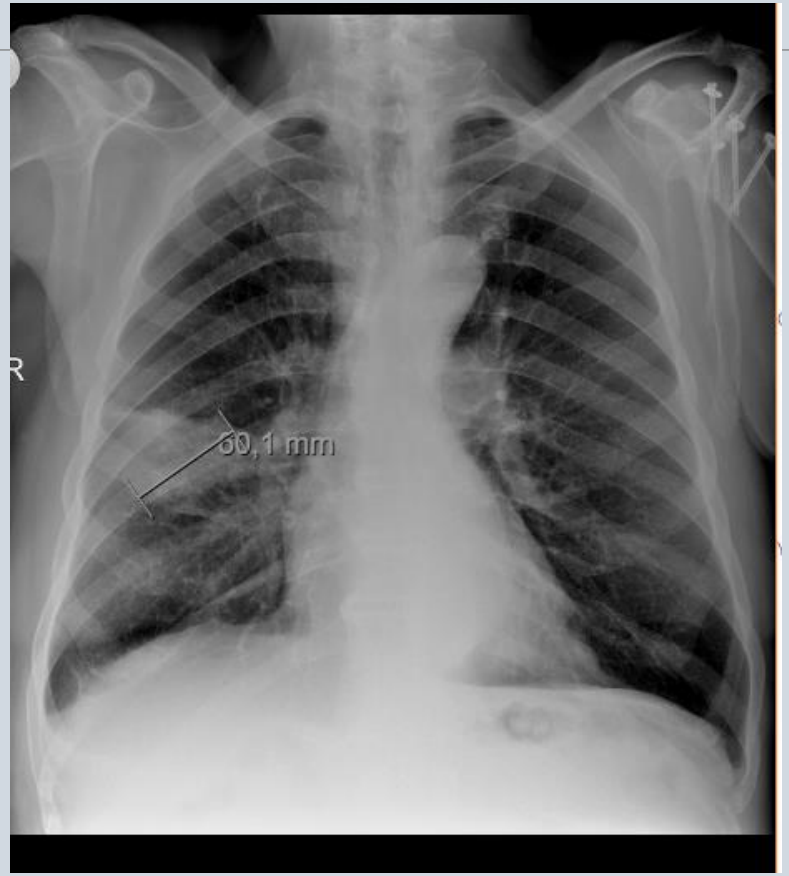
Data cut-off: 26 June 2023

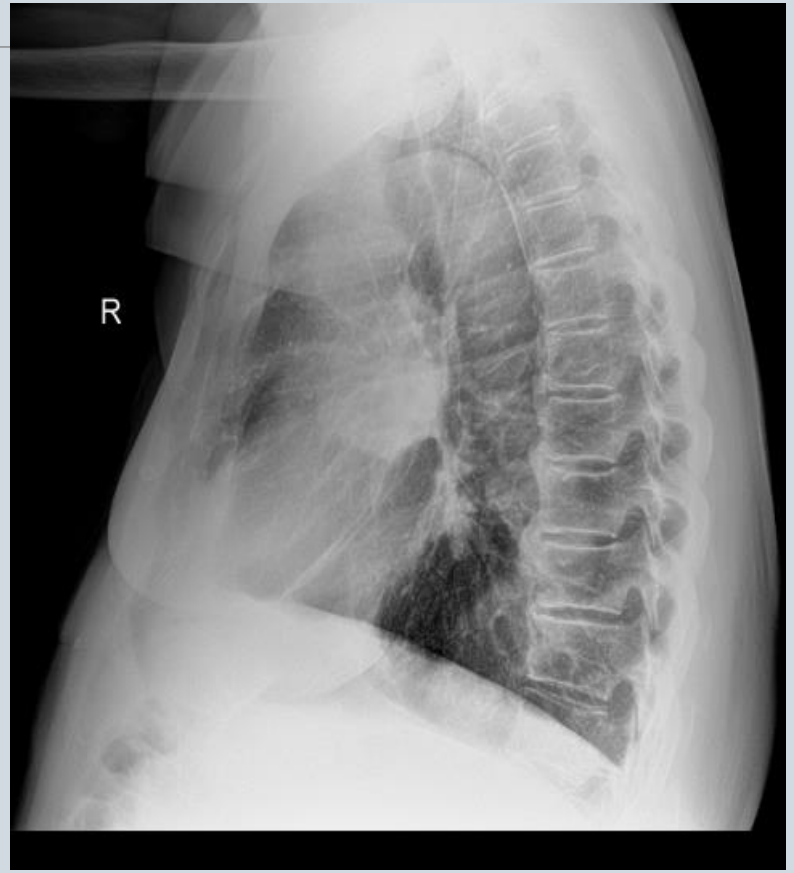
Includes any subsequent therapy reported on or after date of earliest contributing event to disease recurrence; Patients may have received more than one subsequent anticancer therapy

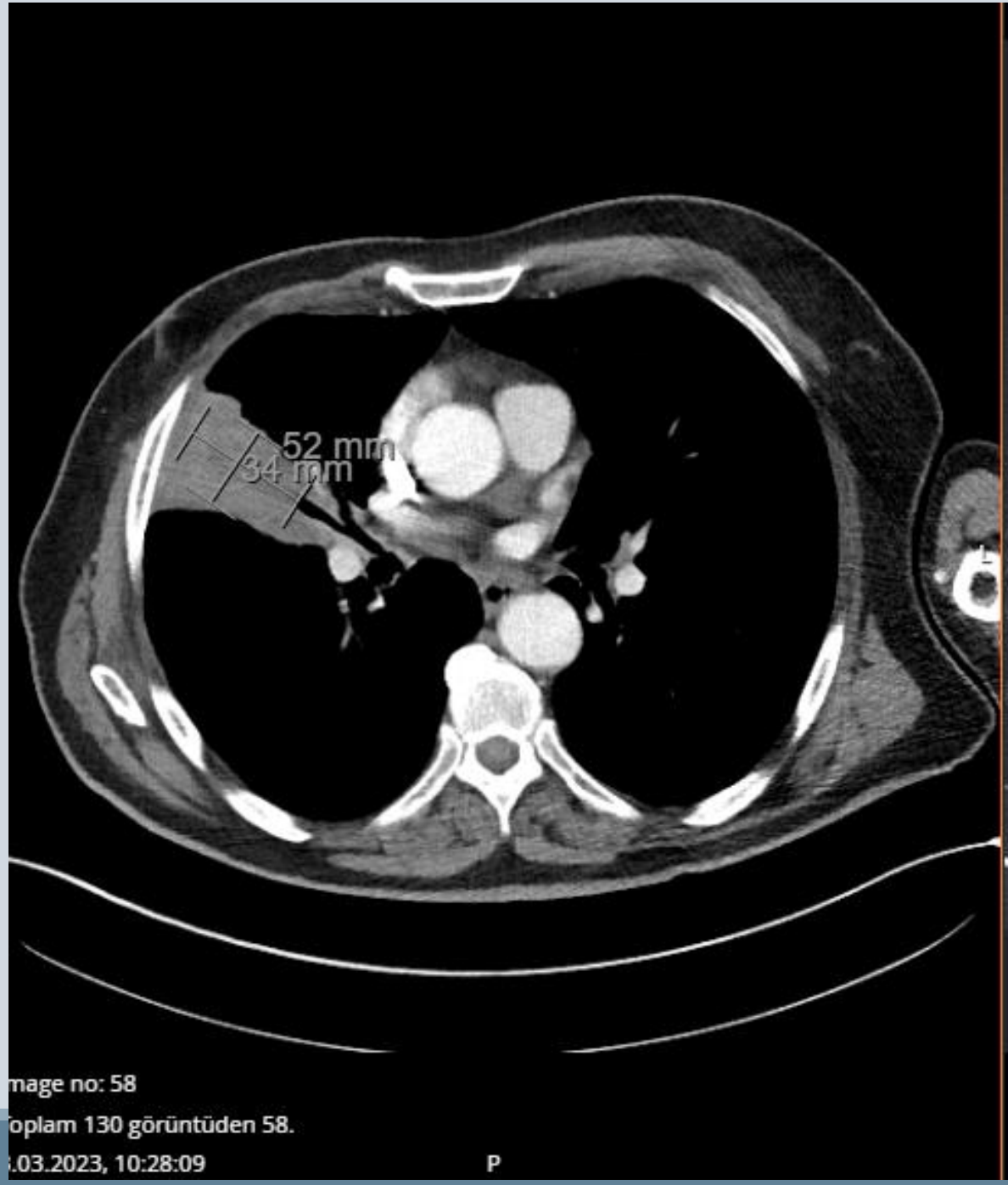
VAKA 1 : HT, 71 yaş Erkek hasta

Mart 2023

- Kilo kaybı, 1 aydır öksürük
- HT öyküsü
- **FM:** Sağ akciğer orta zonda krepitasyon
- 50 p/y sigara, HT
- **Lab:** Anemi, CRP artışı
- Post obst pnomoni ile yatış



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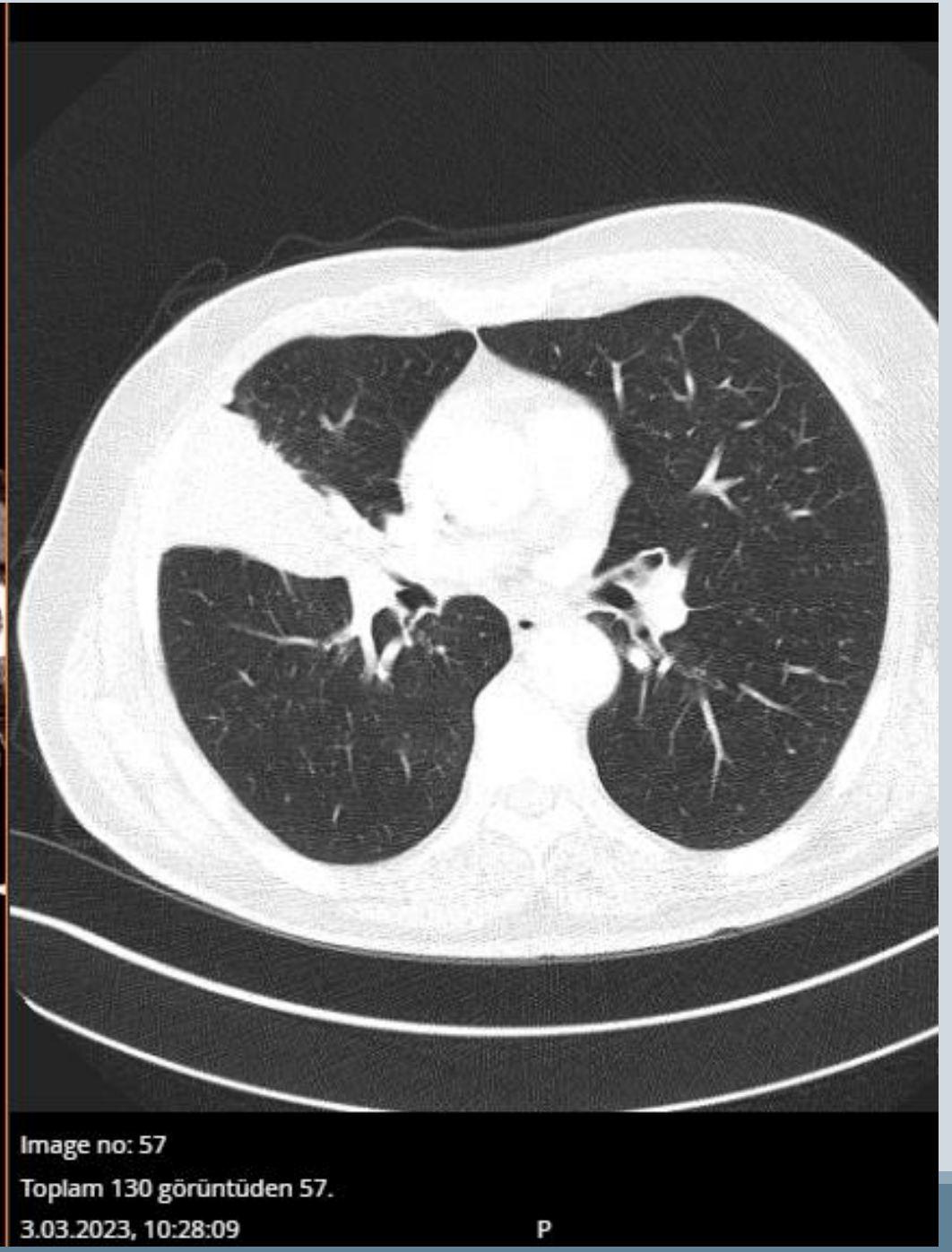
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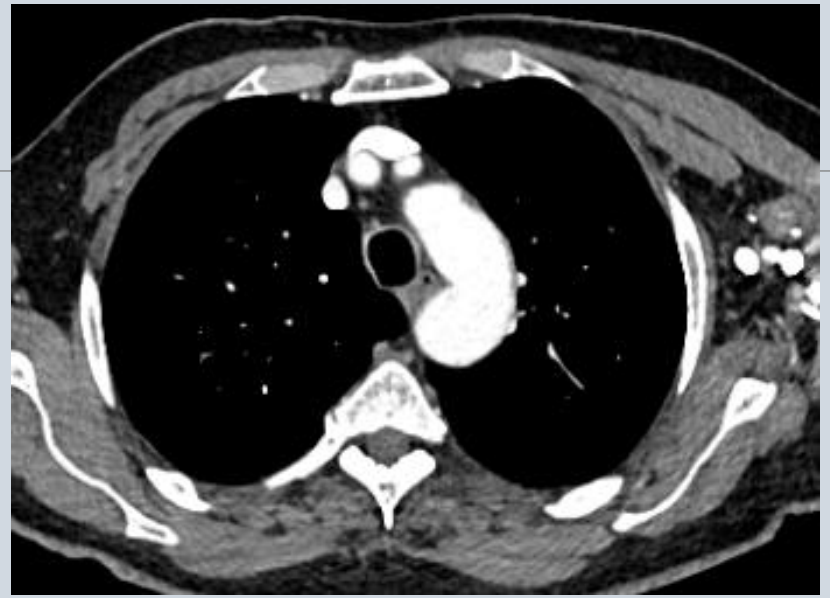
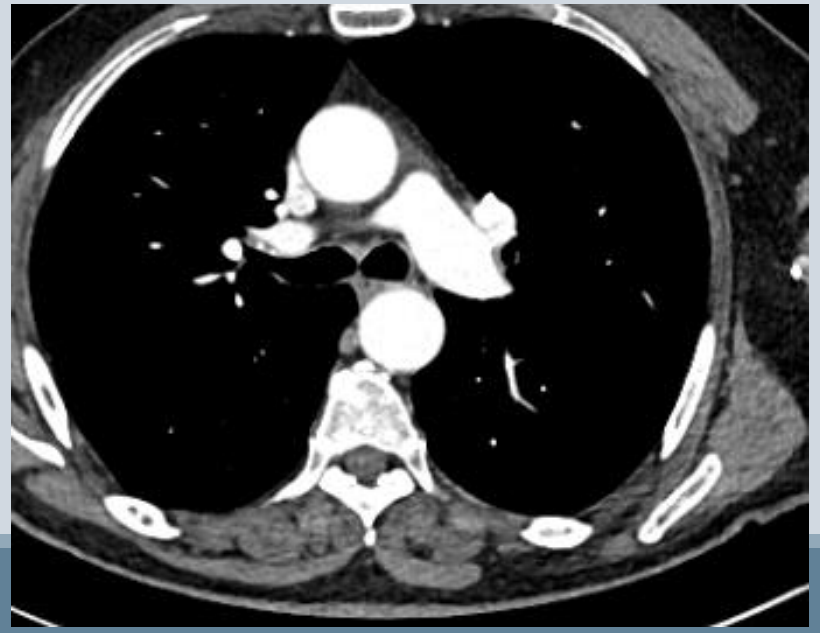
Bronkoskopi

- PATOLOJİK TANI
  1. Sağ akciğer üst lob, orta lob atelektezik alan, transbronşial, İİAB:
  - Mukoid zeminde, olağan ve reaktif bronş epitel hücreleri, kan elemanları izlendi

  2. Sağ akciğer ana bronş distali tümör alanı, forceps biyopsi:
  Kırıntı halinde dokuda, olağan respiratuvar epitel ve epitel altında hafif fibrozis varlığı
  - Küçük hücreli dışı karsinom hücreleri





ROBOTİK AKCİĞER REZEKSİYONU VE MEDİASTİNAL LENF NODU DİSSEKSİYONU

Sağ akciğer, orta lobektomi + alt lob superior segmentektomi + üst lob posterior segment kısmi rezeksiyonu, mediastinal lenf nodu disseksiyonu:
ADENOKARSİNOM
- Tümör lokalizasyonu: ana kitle orta lobda olup, üst lob anterior segmente uzanmaktadır.
- Tümör boyutu: 8,6x6x4,8 cm
- Histolojik tip: adenokarsinom
    - Tümör alanlarının % 70 kadarı papiller, % 20 kadarı mikropapiller, % 10 kadarı lepidik ve % 10 kadarı asiner alanlardan oluşmaktadır.
- Histolojik derece: G3 - az diferansiye
- Visseral plevra invazyonu: mevcut
- Lenfovasküler invazyon: mevcut
- Cerrahi sınırlar: Negatif
- Lenf nodları: 0/24
Peribronşial 2R 4R 7 9 11

Patolojik evre: pT4 pN0 pMx
- Diğer bulgular: Çevre akciğerde atelektazi alanları ve amfizematöz değişiklikler

İmmünohistokimyasal bulgular:
Tümör alanlarında;
TTF1: pozitif
Napsin A: pozitif
p40: negatif

HT, 71 yaş Erkek hasta

Nisan-Haziran 2023

- Paklitaksel-Karboplatin X4
- Sitopeni nedeniyle 1 kez erteleme
- Son kürde Febril nötropeni

Moleküler Sonuçlar

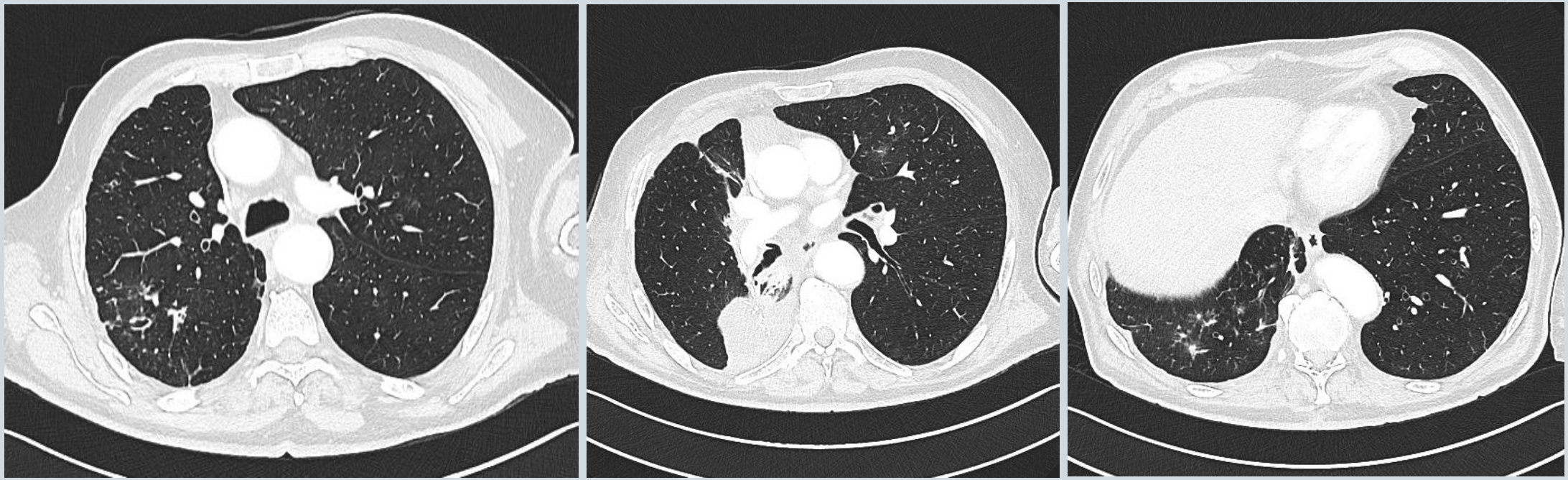
PDL-1 %20

EGFR Exon 19 del

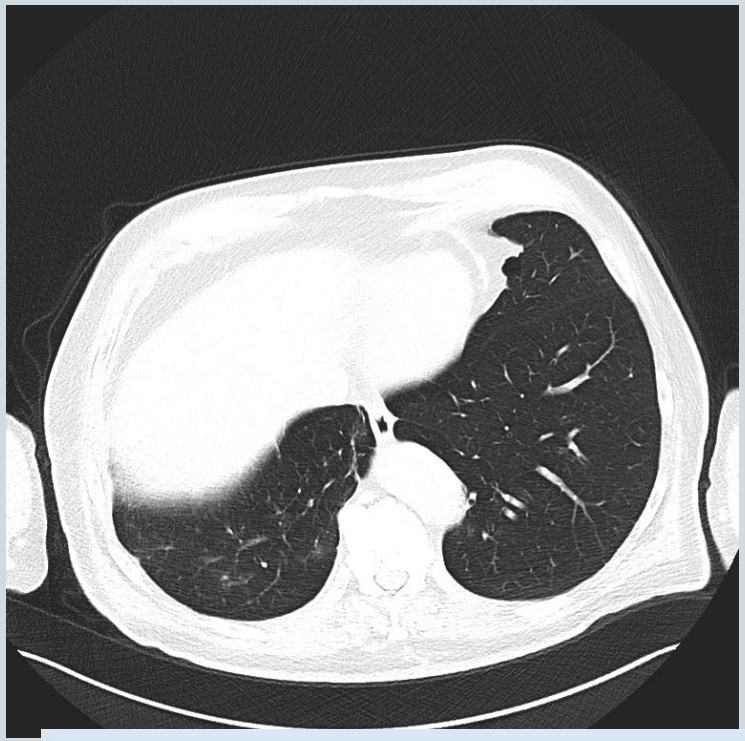
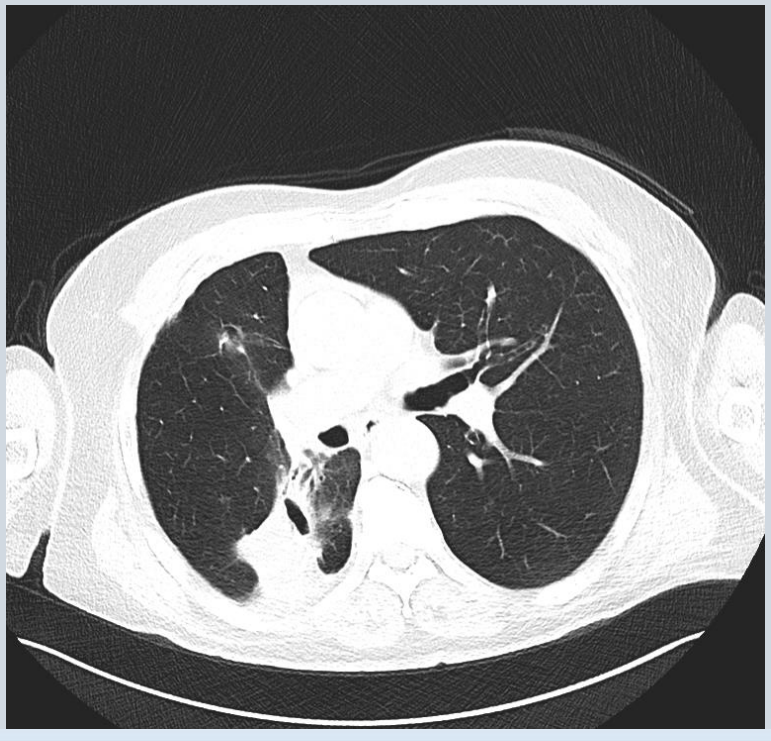
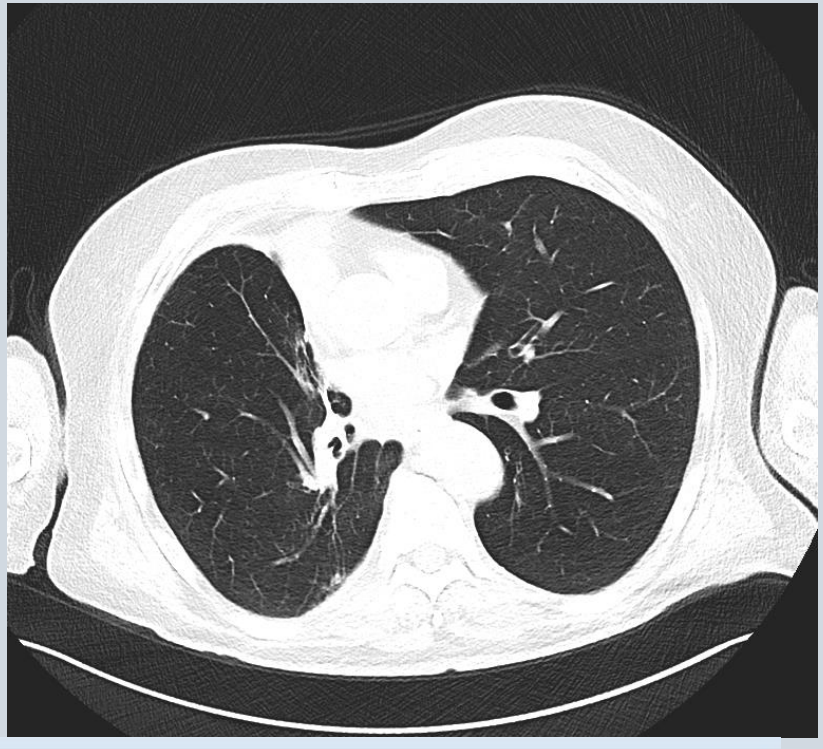
ALK Negatif

Temmuz 2023

- Osimertinib 80 mg başlandı



TORAKS BT Klinik Öykü: Akciğer Ca tanılı 70 yaşında erkekTeknik:Çok dedektör sıralı BT cihazıyla transvers planda volümetrik spiral tarama yapılmış ve elde edilen verilerden sagital ve koronal planda reformat görüntüler elde edilmiştir.Kontrast Madde: 1 adet 350/100 cc Omnipol kullanıldı.Bulgular: Sağ orta lobektomi, üst lob posterior segment ve alt lob süperior segment rezeksiyonlarına ait postop değişimler mevcuttur. Sağ akciğer ve sağ hemitoraks volümü azalmıştır. Sağda 4. kosta lateral ve anterior bölümü rezekedir. Orta lob bronş güdüğü tabiidir. Sağ akciğerde perihiler bölgede ve alt lob bazal bazal segmentler boyunca devamlılığı izlenen dilate bronşların eşlik ettiği parankimal ve bronşial distorsiyonların da izlendiğ dens konsolidasyon görünümü mevcuttur. Metalik süturlar komşuluğunda loküle hava seçilmektedir. Muhtemel fissür içerisinde loküle karakterlidir. Sağ hemitoraksta kostal plevral yüzeylerde orta ve alt bölümde özellikle lateral duvarda düzensizlikler ve kalınlaşmalar vardır. Miniml plevral efüzyon izlenmiştir. Desendan aorta ektazik ve kıvrımlıdır. Pulmoner trunkus ve her iki pulmoner arter lümen genişliği ve kontrast dolumu doğaldır. Mediastende; sağ alt paratrakeal kalsifikasyon barındıran lenf nodları görülmüştür. Patolojik boyut ve morfolojide lenf nodu ayırt edilmemiştir. Minimal perikardiyal efüzyon mevcuttur. Her iki akciğerde sentrilobüler amfizeme ait değişiklikler vardır. Sağ akciğer üst lob posteriorda apikal ve posterior segmentlerde kalsifikasyonlar barındıran lineer plöroparankimal sekel dansiteler izlenmiştir. Sağ akciğerde üst lob anterior, apikal-posterior segmentlerde, alt lobda özellikle lateral ve posterobazal segmentte, solda üst lobda ve sol akciğer alt lob laterobazal segmentte sentrilobüler nodüller, dallanan tübüler yapılar yer yer fokal buzlu cam dansitesinde alanlar görülmektedir. Farklı morfolojik özelliklere sahip parankim bulguları mevcuttur. Kümeleşmiş milimetrik nodüller vardır. Sol akciğer alt lob laterobazal segmentte periferik yerleşimli 6 mm boyutlarında subplevral nodül mevcuttur. Batından geçen kesitlerde sürrenal glandlarda kitle lezyonu ayırt edilmemiştir. Her iki böbrekte değişik boyutlarda büyüğü sağ böbrekte üst pol posterolateralde ekzofitik komponenti belirgin 52 mm boyutlarında, sol böbrekte ise 55 mm boyutlarında hipodens kistik lezyonlar vardır. Safra kesesinde kalküller izlenmiştir. Dejeneratif omurga bulguları vardır. Sonuç: -- Sağ akciğerde ve hemitoraksta postop. değişiklikler -- Sağ akciğerde perihiler bölgede ve alt loba uyan lokalizasyonda paramediastinal akciğer parankiminde dilate kıvrımlı bronşların ve parankimde yapısal distorsiyonların eşlik ettiği dens konsolidasyon ve operasyon lojunda muhtemel fissür içerisinde kalan loküle hava -- Sağda minimal plevral efüzyon -- Her iki akciğer parankiminde öncelikle enfeksiyon düşündüren bulgular. İmmün tedavi öyküsü olan hastada tüm bulguların enfeksiyon ile uyumlu olabileceği düşünülmüştür. Ancak radyolojik morfolojik farklılıklar multipl etken varlığı söz konusu olabilir. Klinik-laboratuvar bulguları ile birlikte değerlendirme önerilir. Çekim Tarihi : 01-09-2023 12:28:58

TORAKS BT Klinik Öykü:Opere akciğer kanseri tanılı 71 yaşında erkekTeknik:Çok dedektör sıralı BT cihazıyla transvers planda volümetrik spiral tarama yapılmış ve elde edilen verilerden sagital ve koronal planda reformat görüntüler elde edilmiştir.Kontrast Madde:1 adet 350/100 cc Opaxol kullanıldı.Bulgular:Sağ orta lobektomi, üst lob posterior segment ve alt lob süperior segment rezeksiyonlarına ait postop değişimler mevcuttur. Sağ akciğer ve sağ hemitoraks volümü azalmıştır. Sağda 4. kosta lateral ve anterior bölümü rezekedir. Orta lob bronş güdüğü tabiidir. Sağ akciğerde perihiler bölgede ve alt lob bazal bazal segmentler boyunca devamlılığı izlenen dilate bronşların eşlik ettiği parankimal ve bronşial distorsiyonların da izlendiğ dens konsolidasyon görünümü mevcuttur. Metalik süturlar komşuluğunda loküle hava seçilmektedir. Muhtemel fissür içerisinde loküle karakterlidir. Sağ hemitoraksta kostal plevral yüzeylerde orta ve alt bölümde özellikle lateral duvarda düzensizlikler ve kalınlaşmalar vardır. Miniml plevral efüzyon izlenmiştir. Desendan aorta ektazik ve kıvrımlıdır. Pulmoner trunkus ve her iki pulmoner arter lümen genişliği ve kontrast dolumu doğaldır. Mediastende; sağ alt paratrakeal kalsifikasyon barındıran lenf nodları görülmüştür. Patolojik boyut ve morfolojide lenf nodu ayırt edilmemiştir. Minimal perikardiyal efüzyon mevcuttur. Her iki akciğerde sentrilobüler amfizeme ait değişiklikler vardır. Sağ akciğer üst lob posteriorda apikal ve posterior segmentlerde kalsifikasyonlar barındıran lineer plöroparankimal sekel dansiteler izlenmiştir. Sağ akciğerde üst lob anterior, apikal-posterior segmentlerde, alt lobda özellikle lateral ve posterobazal segmentte, solda üst lobda ve sol akciğer alt lob laterobazal segmentte sentrilobüler nodüller, dallanan tübüler yapılar yer yer fokal buzlu cam dansitesinde alanlar görülmektedir. Sol akciğer alt lob laterobazal segmentte periferik yerleşimli 6 mm boyutlarında subplevral nodül mevcuttur. Batından geçen kesitlerde sürrenal glandlarda kitle lezyonu ayırt edilmemiştir. Her iki böbrekte değişik boyutlarda büyüğü sol böbrekte ise 5 cm boyutlarında hipodens kistik lezyonlar vardır. Sol böbrekte büyüğü orta kalisiyel sisteme uyan 5 mm boyutlarında olan her iki böbrekte multipl kalküller vardır. Safra kesesinde kalküller izlenmiştir. Dejeneratif omurga bulguları vardır. Sonuç: --Aralık 2023 tarihli BT ler ile mukayese edildiğinde mevcut bulgularda farklılık ve ek bulgu izlenmedi. İstem Tarihi : 11-03 -2024 10:48:00

Erken Evre KHDAKda Güncel Pratiğe Yansıyan Çalışmalar

Adjuvan	• Adjuvan Kemoterapi • IMpower 010 / PEARLS • ADAURA / ALINA
İzole Neoadjuvan	• Checkmate 816
Perioperatif	• Checkmate 77T • AEGEAN • Keynote 671

Neoadjuvan Tedavi Rasyoneli

- Mikrometastazların erken kontrolü

- Rezektabilitede artış, down staging

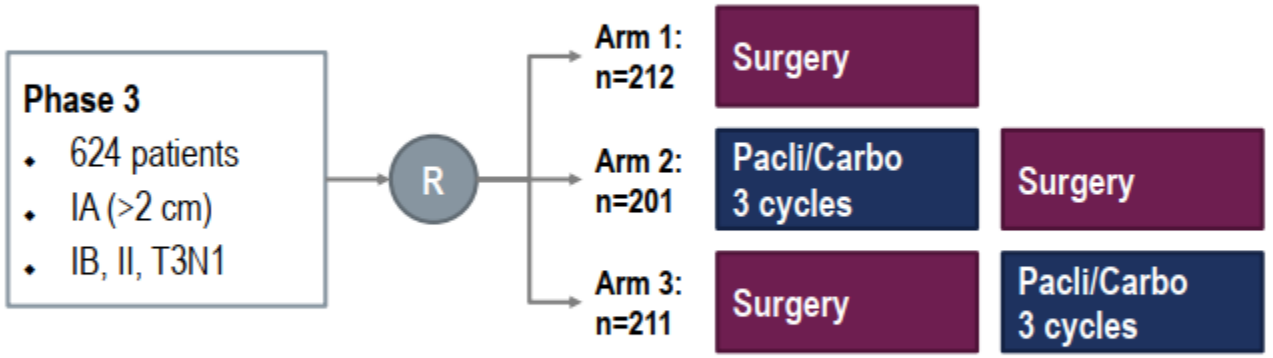
- Cerrahi sürecinde morbiditede azalma

- Patolojik cevabın gözlenebilmesi, in vivo tedavi etkinliğinin bilinebilmesi

- Olası genel sağkalım faydası

ADJUVANT OR NEOADJUVANT?

NATCH Study



Paclitaxel 200 mg/m² + carboplatin AUC 6 q3w

Main objective: PFS at 5-year chemotherapy *vs.* surgery

COMPLIANCE

Trials	At least 1 cycle	2 cycles	3 cycles	4 cycles
ALPI	90%	ND	69%	NA
IALT	92%	ND	ND	ND
ANITA	90%	72%	61%	50%
JBR10	95.5%	64%	55%	45%
NATCH adj	66%	ND	61%	NA
Depierre	98%	90%	NA	NA
NATCH neoadj	97%	ND	90%	NA
Gilligan	96%	89%	96%	NA
SWOG 9900	ND	ND	79%	NA

Neoadjuvan Rasyoneli

İmmunoterapi Rasyoneli

- Mikrometastazların erken kontrolü

- Rezektabilitede artış, down staging

- Cerrahi sürecinde morbiditede azalma

- Patolojik cevabın gözlenebilmesi, in vivo tedavi etk

- Olası genel sağkalım faydası

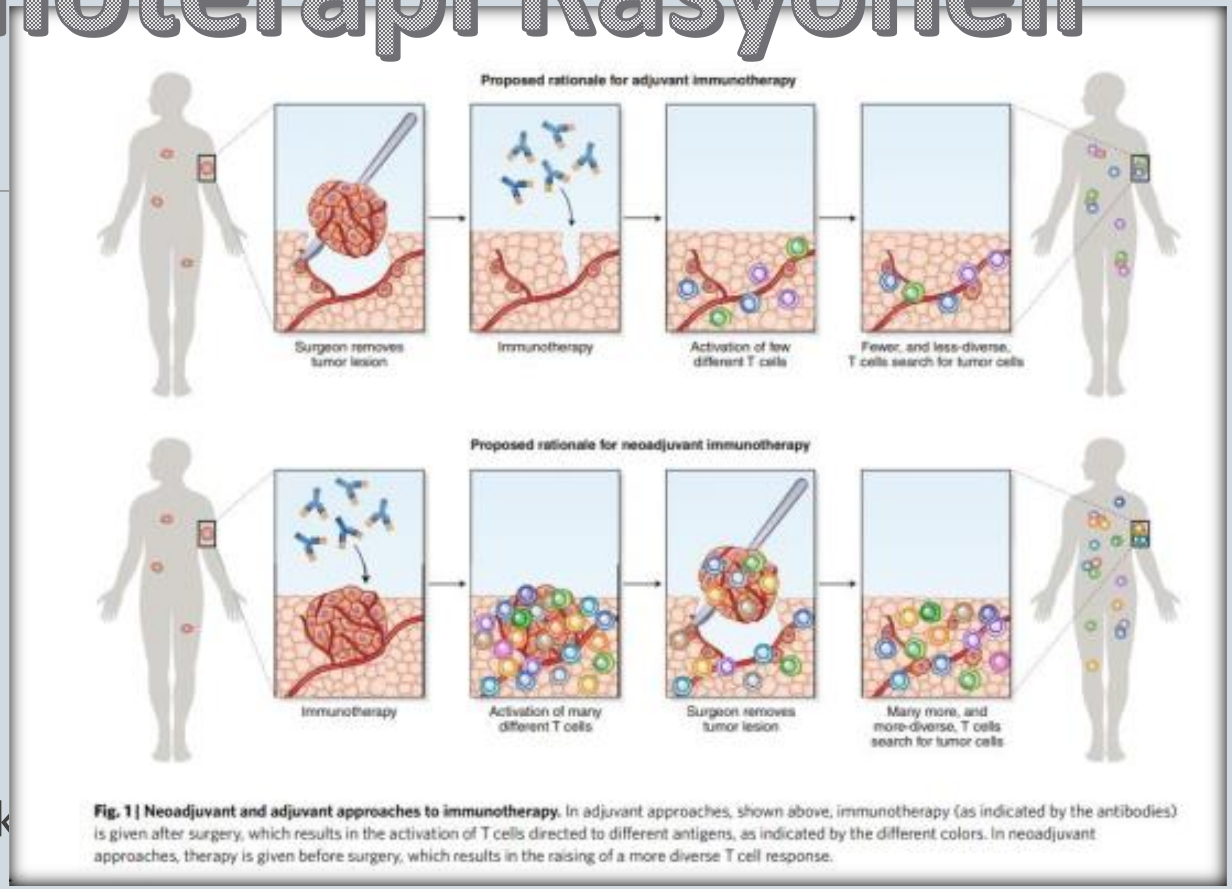


Fig. 1 | Neoadjuvant and adjuvant approaches to immunotherapy. In adjuvant approaches, shown above, immunotherapy (as indicated by the antibodies) is given after surgery, which results in the activation of T cells directed to different antigens, as indicated by the different colors. In neoadjuvant approaches, therapy is given before surgery, which results in the raising of a more diverse T cell response.

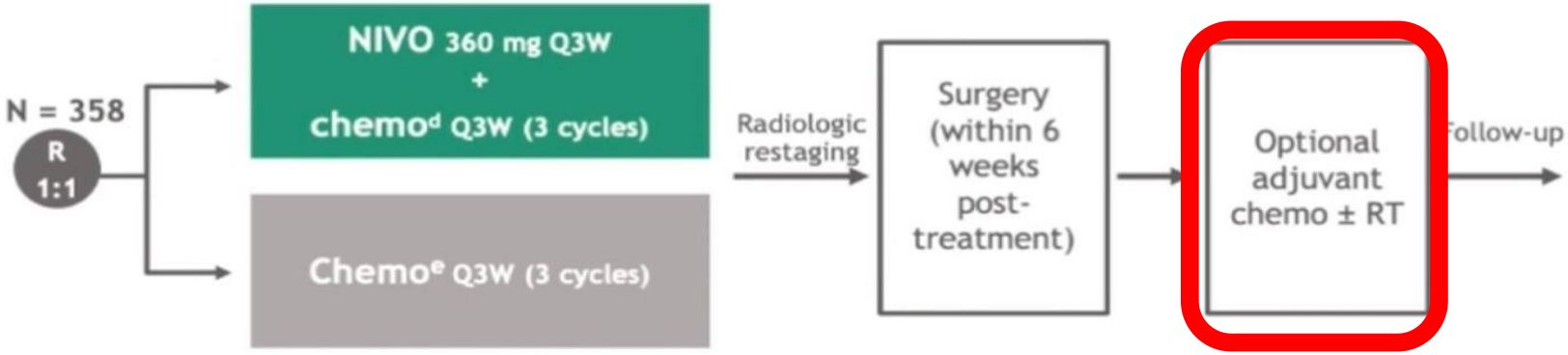
İmmun Tanıma!!

CheckMate 816 study design[a,1]

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



Primary endpoints
- pCR by BIPR
- EFS by BICR

Key secondary endpoints
- MPR by BIPR
- OS
- Time to death or distant metastases

Key exploratory endpoints included
- ORR by BICR
- **Feasibility of surgery; peri- and post-operative surgery-related AEs**

Database lock: September 16, 2020; minimum follow-up: 7.6 months for NIVO + chemo and chemo arms.

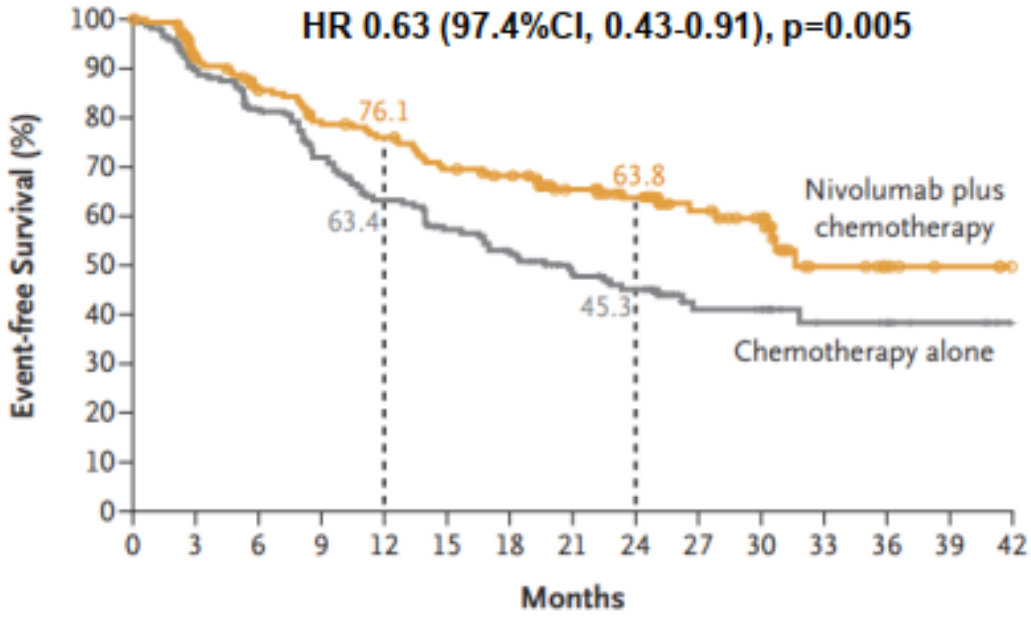
[a]NCT02998528; this study included an exploratory arm: NIVO 3 mg/kg Q2W (3 cycles) + ipilimumab 1 mg/kg (cycle 1 only). Data from this arm are not included in this presentation; [b]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako); [c]Included patients with PD-L1 expression status not evaluable and indeterminate; [d]NSQ: pemetrexed + cisplatin or paclitaxel + carboplatin; SQ: gemcitabine + cisplatin or paclitaxel + carboplatin; [e]Vinorelbine + cisplatin, docetaxel + cisplatin, gemcitabine + cisplatin (SQ only), pemetrexed + cisplatin (NSQ only), or paclitaxel + carboplatin.

1. Forde PM, et al. Oral presentation at the AACR Annual Meeting; April 8-10, 2021; virtual. Abstract 5218.

CheckMate 816: Neoadjuvant Nivolumab + Chemotherapy

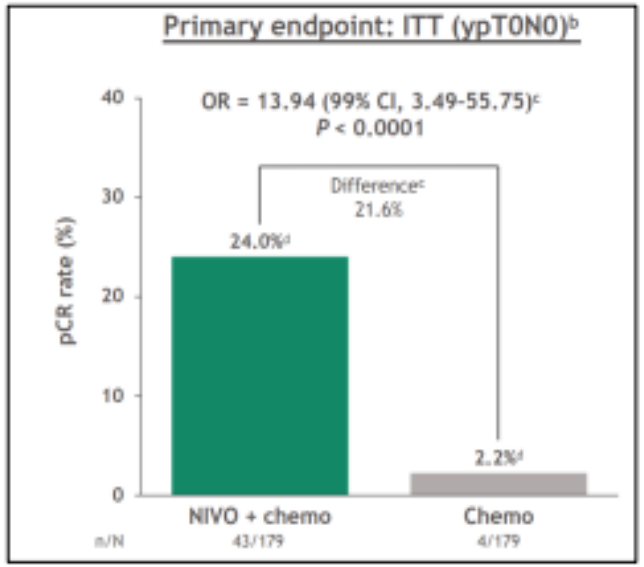
Event Free Survival

31.6m vs 20.8m
HR 0.63 (97.4%CI, 0.43-0.91), p=0.005



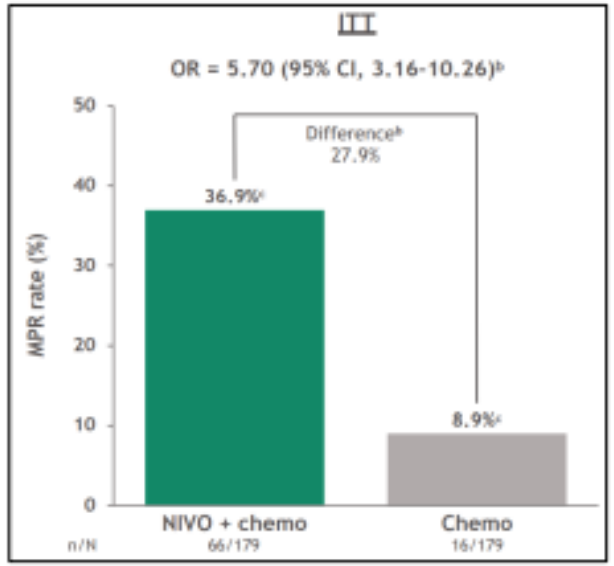
pCR

24% vs 2.2%



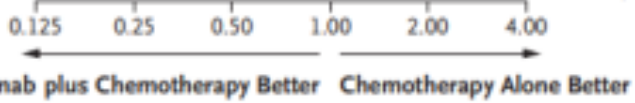
MPR

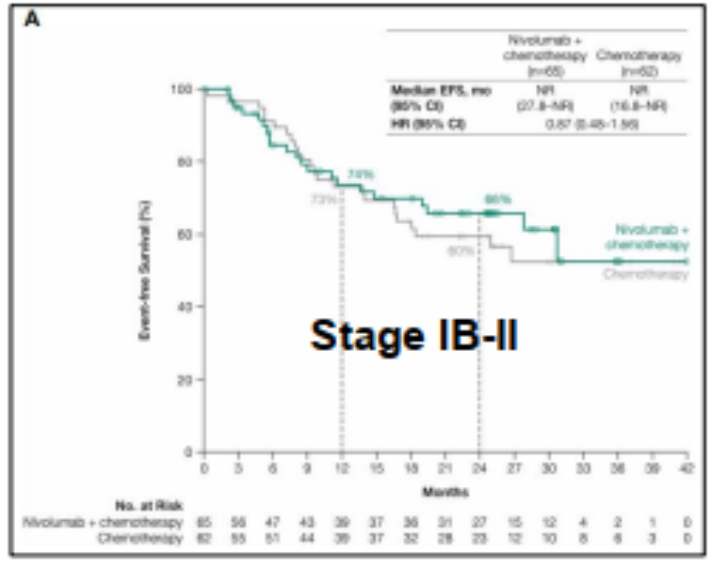
36.9% vs 8.9%

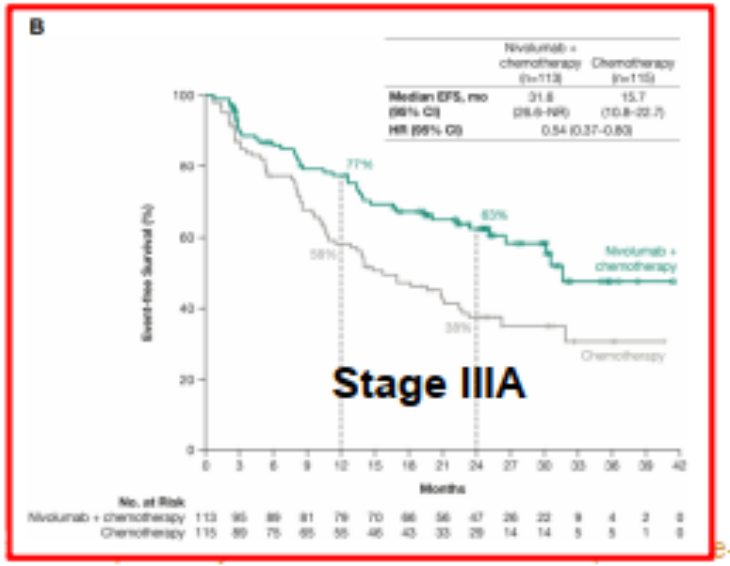


Evre 3A hastalık

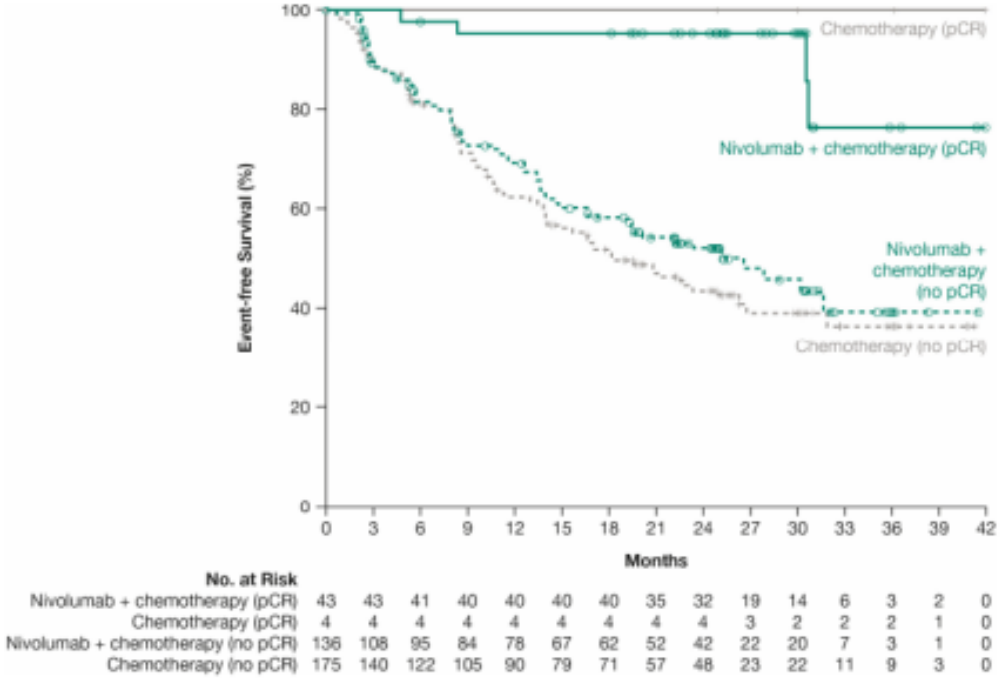
Disease stage at baseline					
IB or II	127	NR (27.8–NR)	NR (16.8–NR)		0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)		0.54 (0.37–0.80)
Histologic type of tumor					
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)		0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)		0.50 (0.32–0.79)
Smoking status					
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)		0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)		0.33 (0.13–0.87)
PD-L1 expression level					
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)		0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)		0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)		0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)		0.24 (0.10–0.61)
TMB					
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)		0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)		0.69 (0.33–1.46)
Type of platinum therapy					
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)		0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)		0.31 (0.14–0.67)







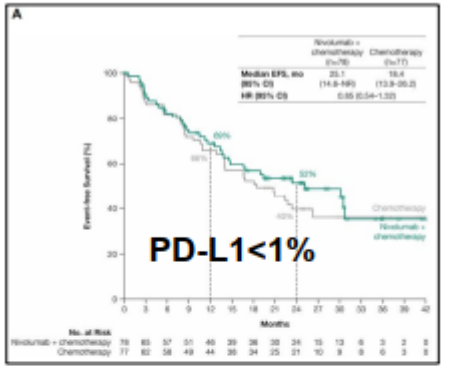
CheckMate 816: EFS by Pathologic CR

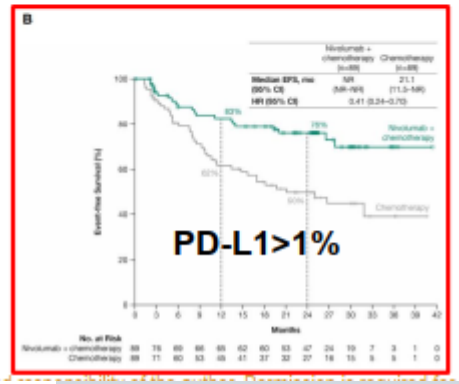


Pathologic CR

24% vs 2.2%

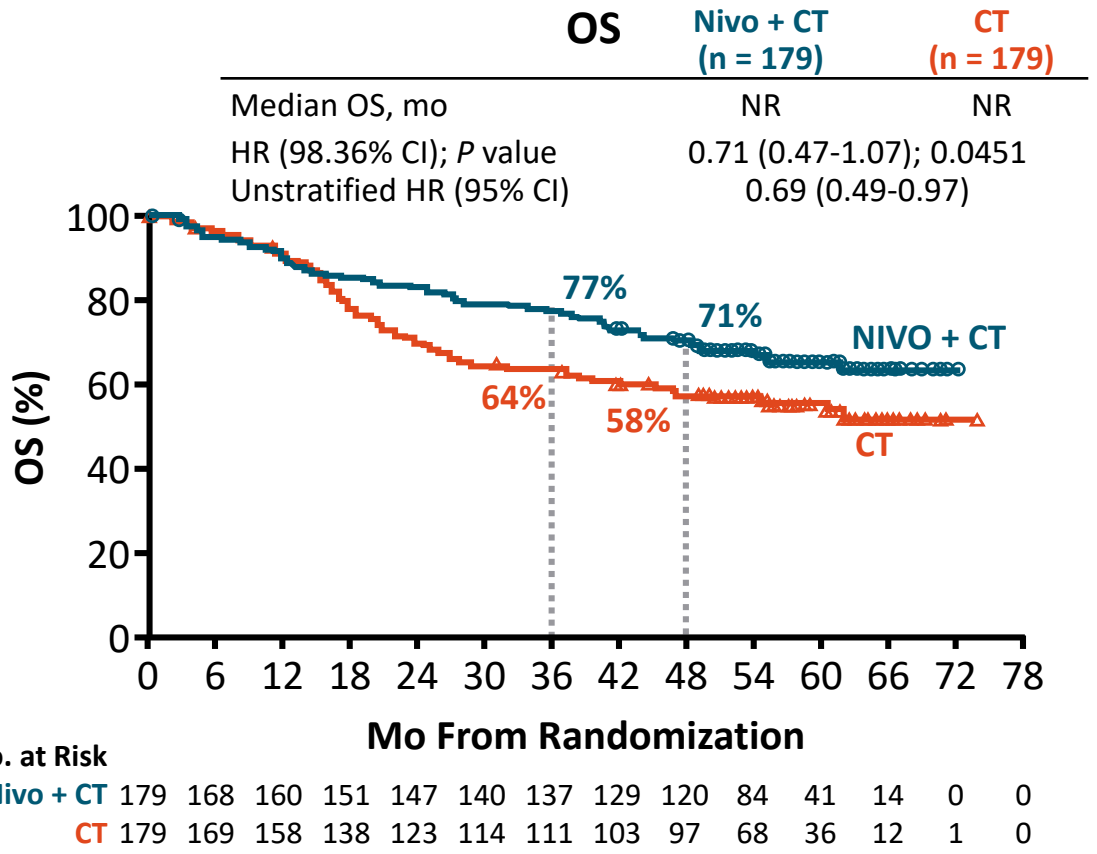
	Nivolumab + chemotherapy		Chemotherapy	
	pCR (n=43)	No pCR (n=136)	pCR (n=4)	No pCR (n=175)
Median EFS, mo (95% CI)	NR (30.6–NR)	26.6 (16.6–NR)	NR (NR–NR)	18.4 (13.9–26.2)
HR (95% CI)*	0.13 (0.05–0.37)		Not computed†	

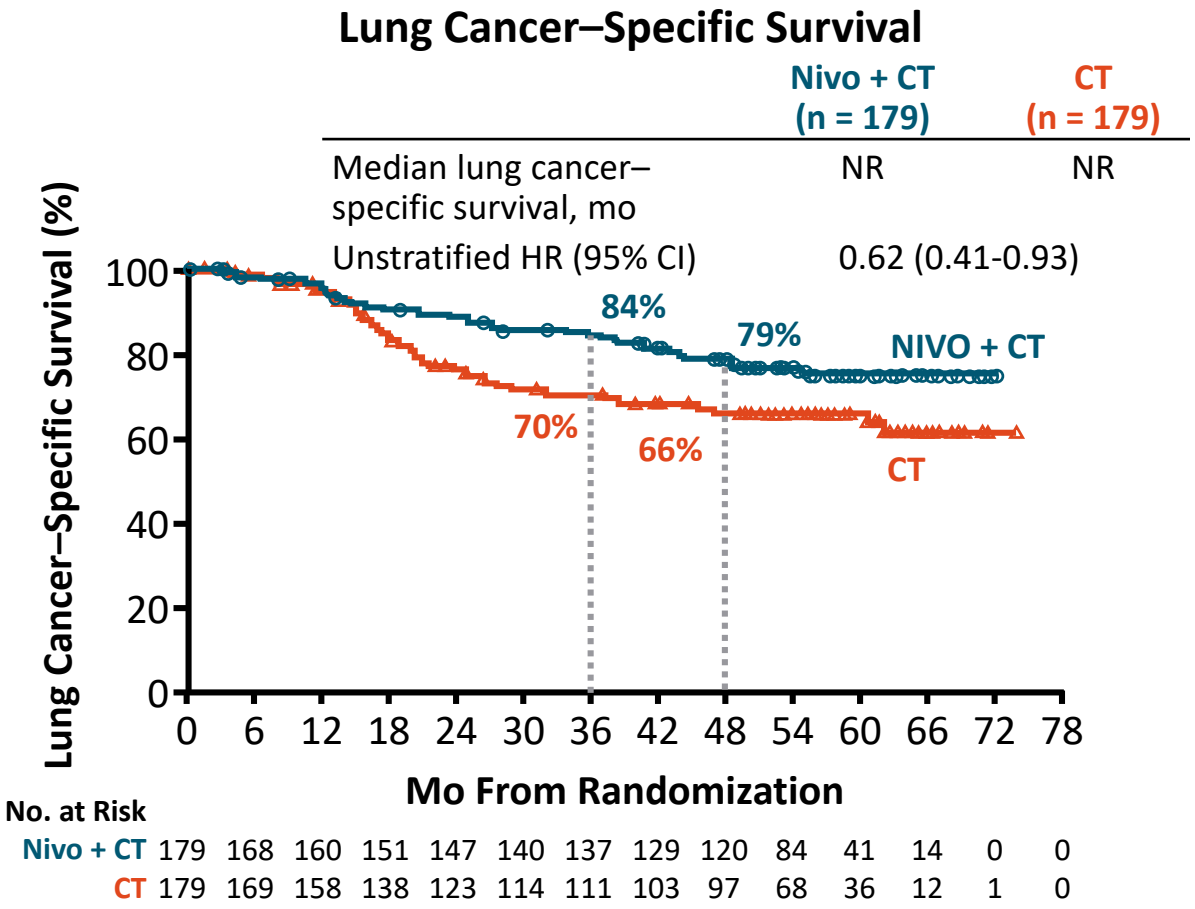




Phase III CheckMate 816: 4-Yr OS

- Patients who received Nivo + CT and had pCR continued to have improved OS vs those who did not (HR: 0.08; 95% CI: 0.02-0.34; **4-yr OS rates: 95% vs 63%**)





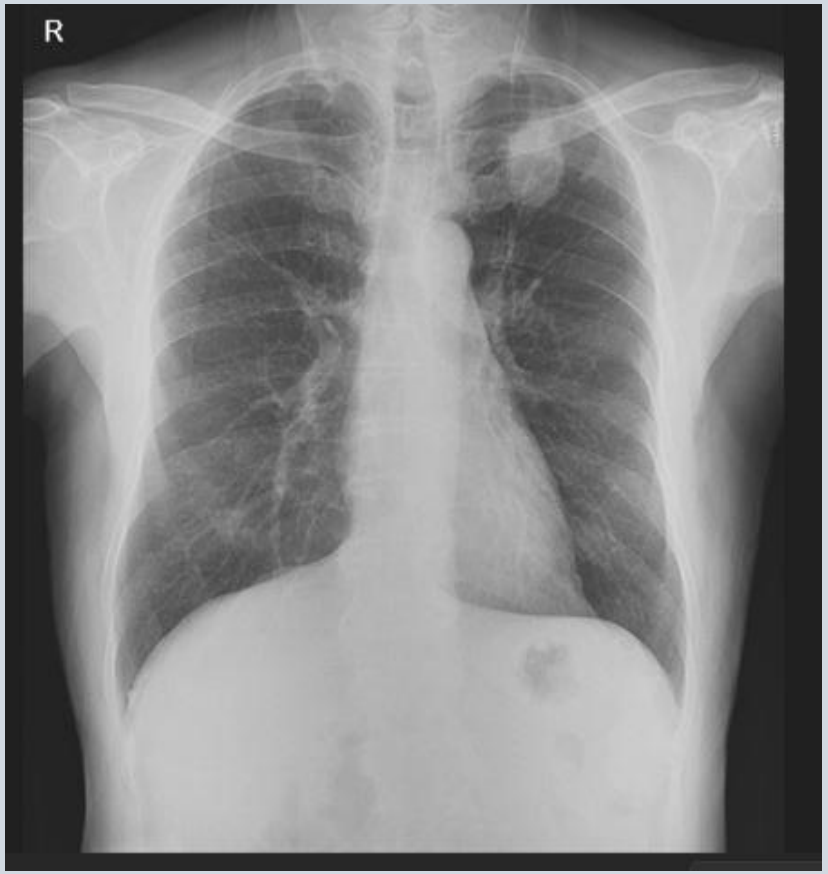
Spicer. ASCO 2024. Abstr LBA8010.

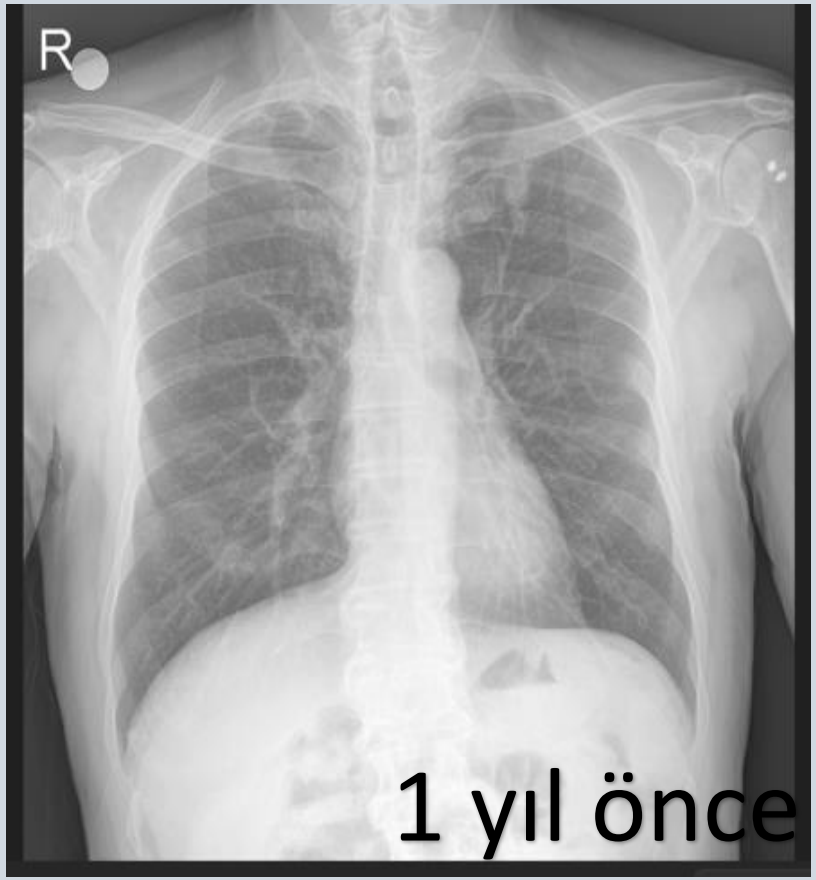
VAKA 2 : İG, 67 yaş Erkek hasta

Nisan 2024

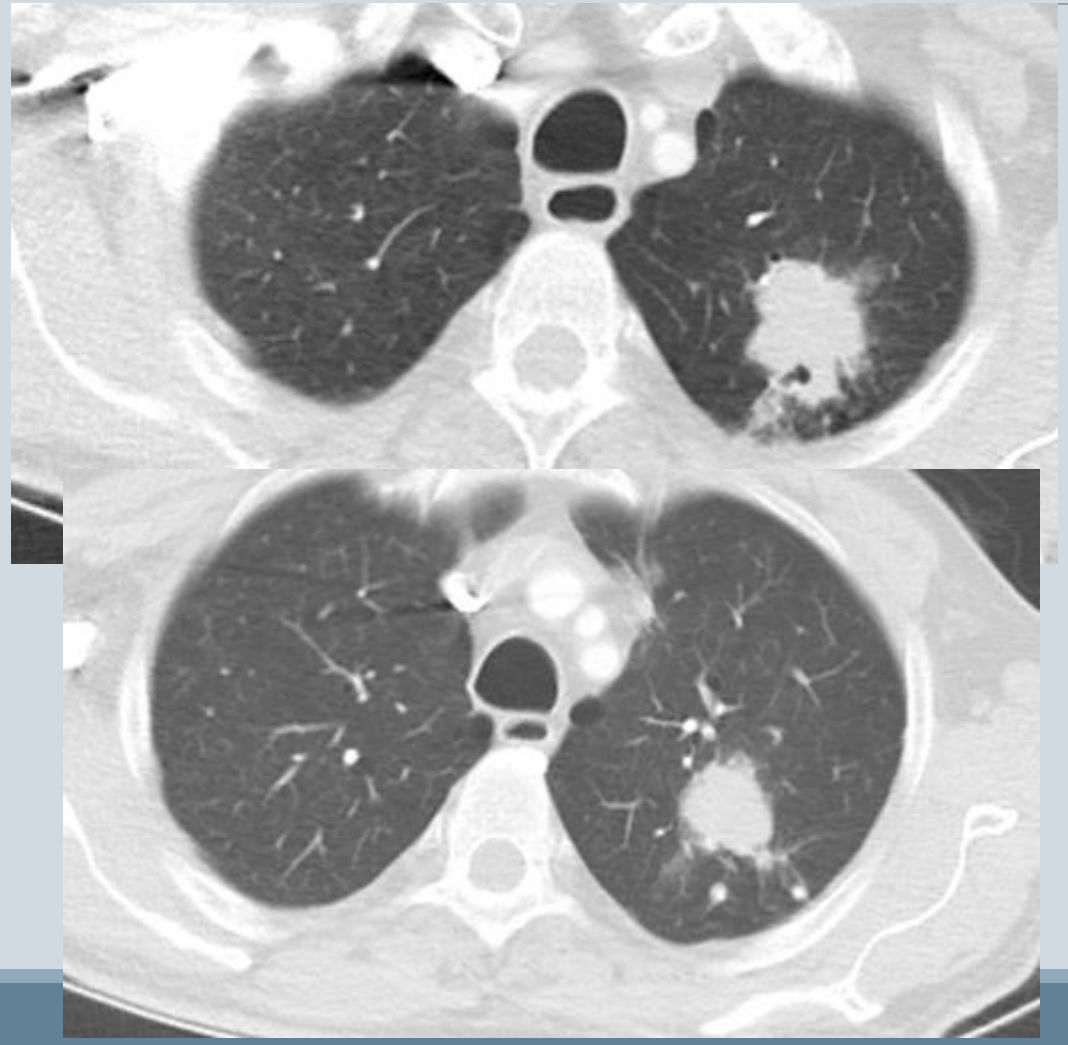
- Şikayet: Ses kısıklığı
- 100 p/y sigara
- HT, DM, BPH
- Beloc, Lustral, Nootropil, Protonex, Candexil, Glifix, Urorec
- **FM:** Ssde değişim yok, Lap yok
- **Lab:** KCFT/BFT N

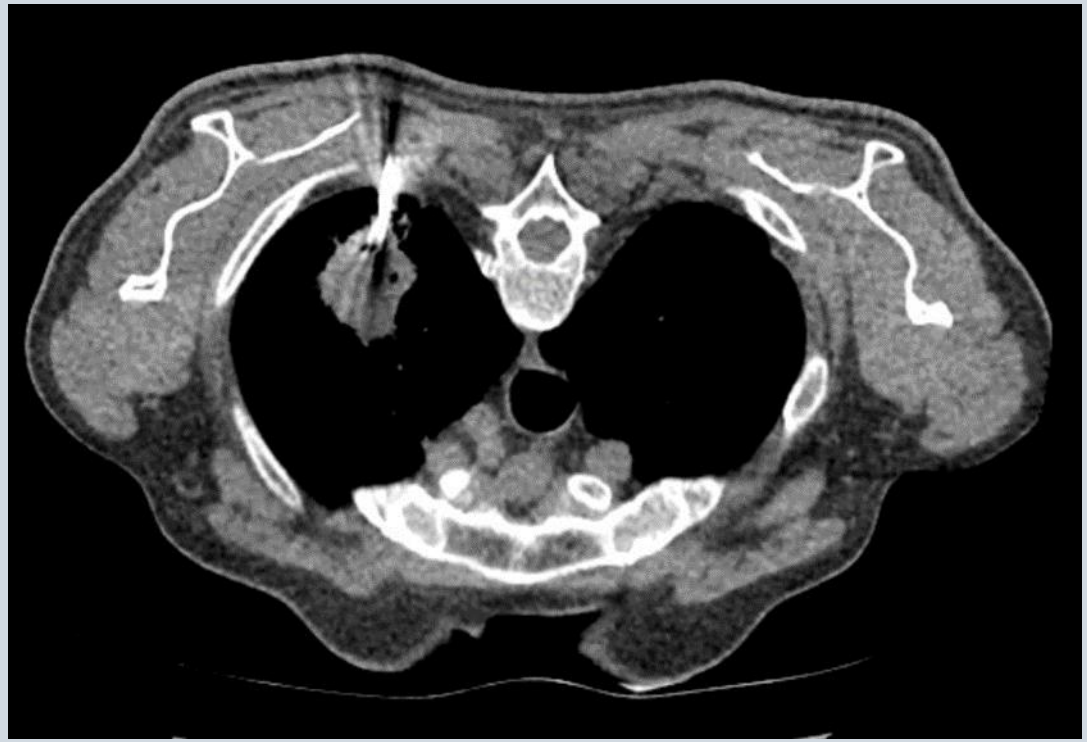
HbsAg neg; Anti HbcIgG poz;Anti Hbs 79





BALIKESİR EDREMİT DEVLET HASTANESİ - 30/04/2024 Tarihli Toraks BT
Sol akciğer üst lob apiko posterior segmentde düzensiz sınırlı 3.8 cm çapında malign görünümde kitle lezyonu izlenmektedir.

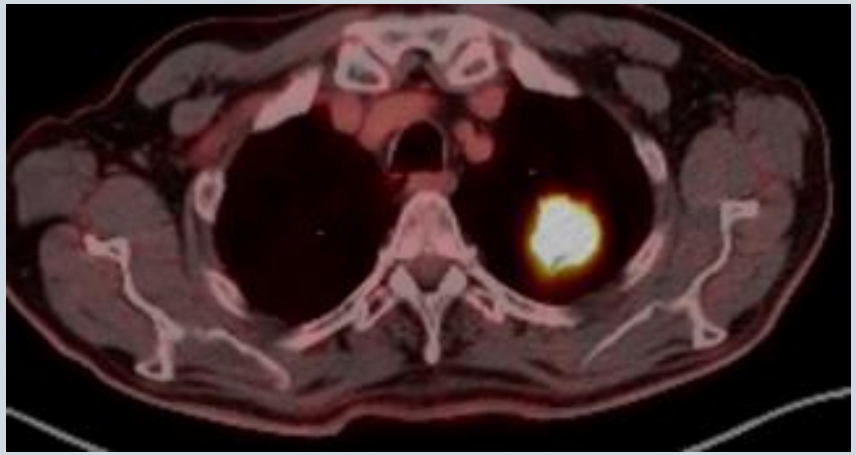


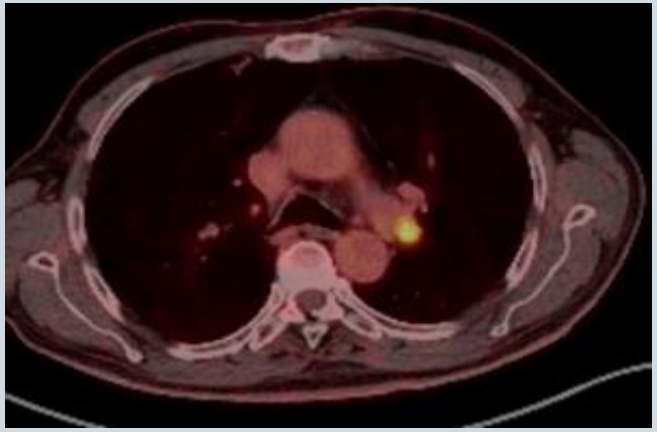


TTİAB ve EBUS (Dış Merkez) : Skuamoz Hücreli Karsinom

11L: SIVI BAZLI SİTOLOJİ + HÜCRE BLOĞU:; HİPOSELLÜLER ASPİRAT;; - LENFOİD ZEMİNE AİT SEYREK HÜCRESEL ELEMANLAR

Tedavi önerisi için Ek tetkik?





PET-CT (09.05.2024)
Sol hiler/bronkopulmoner alanda SUV 11 LN
Sol akciğer üst lob 45*38 SUV 20 lezyon

Hastanızın KONTRASTLI KRANİAL MRG incelemesinde:Hastaya Gadovist 7.5 ml. FLK. kullanılmıştır.

Her iki lateral ventrikül dilate olup sol lateral ventrikül sağa göre asimetrik dilatedir.

Sol periatrial beyaz cevherde sekel T2 FLAIR sinyal artışı izlenmiştir. Dural sinüsler açıktır.Kavernöz sinüsler simetrik ve açıktır.Pontoserebellar açı sisternaları simetrik, normal genişliktedir.Sellar, parasellar yapılar normaldir.Orbital yapılar normaldir.Kranioservikal bileşke normaldir.

Diffüzyon kısıtlaması gösteren lezyon saptanmadı.

Postkontrast seride patolojik kontrastlanma izlenmedi.

MİKROSKOBİ BULGULARI
Kesitlerde belirgin iltihabi lenfo stromal reaksiyon ile birlikte solid adacıklar halinde karsinom hücreleri izlenmiştir. Tümör oluşturan hücreler iri- hiperkromatik veziküler çekirdekli orta genişlikte şeffaf yada eozinofilik sitoplazmalı hücrelerdir.

PATOLOJİK TANI
Hücre Bloğu :
SKUAMÖZ HÜCRELİ KARSİNOM

YORUM
1) EGFR Mutasyon Analizi Sonucu:
-EGFR mutasyonu saptanmamıştır.

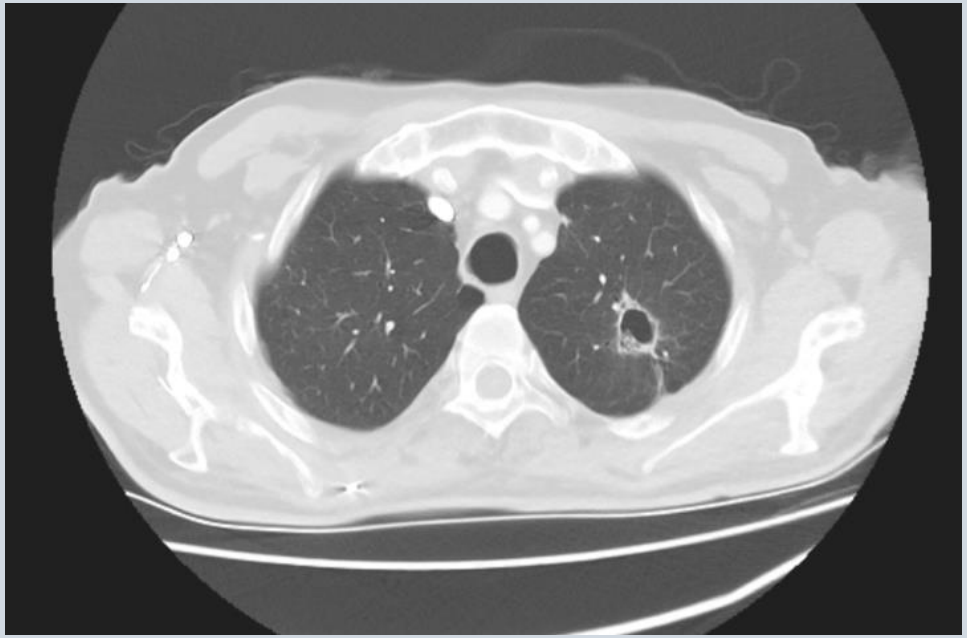
2) ALK Rearanjmanı Testi Sonucu:
-ALK rearanjmanı mevcut değildir.

3) ROS1 Rearanjmanı Testi Sonucu:
-ROS1 rearanjmanı mevcut değildir.

4) PD-L1 İmmünhistokimyasal Test Sonucu:
- PD-L1 ekspresyon derecesi : %20
PD-L1 ekspresyonu mevcuttur. Düşük Pozitif

Paklitaksel 200 mg/m2; Karboplatin AUC 5; Nivolumab 360 mg başlandı

20.07.2024: ESKİ TETKİKİNDE 33,5X30,5 MM BOYUTUNDA ÖLÇÜLEN DÜZENSİZ SINIRLI ETRAFINDA SİLİK BUZLU CAM DANSİTESİNDE ALANLARIN İZLENDİĞİ YUMUŞAK DOKU DANSİTESİNDE KİTLE LEZYON GÜNCEL TETKİKİNDE BOYUTU REGRESE GÖRÜNÜMDE OLUP KAVİTERLEŞMİŞTİR. SOLİD KOMPONENTİ BELİRGİN AZALMIŞ OLUP BOYUTU 22X26,5 MM BOYUTUNDA İZLENMİŞTİR.



2 kür sonra

4 Kür sonrası
Sol Üst Lobektomi + Lenfadenektomi

Fikse Fikzasyonun tipi: Formol
Büyüklük (3 boyut-cm): 18x14x5 cm
Rezeksiyon tipi: Lobektomi
Plevranın özellikleri:
Fibrozis: (+)
Fibrin: (+)
Visseral plevra tutulumu:
Paryetal plevra tutulumu:
Tümörün özellikleri:
Büyüklük (3 boyut-mm): 30x20x20 mm
Lob ve segment lokalizasyonu: Sol-üst
Bronşla ilişki: Bronşla ilişkisiz Periferik
Kanama: Görüldü
Nekroz: Görüldü
Kavitasyon: Görüldü
Büyük damar invazyonu: Görülmedi
Pulmoner arter cerrahi sınır: Tümör görülmedi.
Pulmoner ven cerrahi sınır: Tümör görülmedi.
İnterlober fissüre yayılım: Tümör görülmedi (6 cm)
Plevraya yayılım: Görülmedi
Bronş rezeksiyon hattına uzaklık (mm): 4 cm
Plevraya uzaklık (mm): 1 cm
Çevre akciğer: Kanamalı
PaCS,BCS,VCS,ÇA,TÇ,PL,T5,LG5,P5/V

NOT: Akciğerde izlenen tümör yatağının tamamı örneklendi. Kesitlerde tümör içi ve çevresinde multinükleer yabancı cisim tipi dev hücreler içeren, yer yer histiyositlerden zengin, geniş alanda foliküler tipte interstisyel inflamasyon, kolesterol kleftleri ve fibrozis izlendi. Canlı tümör oranı %80 saptandı.

TANI:
I-AKCİĞER, SOL ÜST, LOBEKTOMİ: SKUAMÖZ HÜCRELİ KARSİNOM, ORTA DERECEDE DİFERANSİE, NONKERATİNİZE, TÜMÖR İÇİ VE ÇEVRESİNDE TEDAVİYE SEKONDER REGRESYON BULGULARI (BAKINIZ NOT).
LENF NODU, 12 NO?LU İSTASYON, 5 ADET: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).
LENF NODU, 14 NO?LU İSTASYON, 1 ADET: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).
LENF NODLARI, MEDİASTİNAL DİSEKSİYON:
II-5 NO?LU İSTASYON, 1 ADET: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).
III-6 NO?LU İSTASYON, 1 ADET: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).
IV-7 NO?LU İSTASYON, 1 ADET: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).
V-9 NO?LU İSTASYON, 1 ADET: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).
VI-10 NO?LU İSTASYON, 2 ADET: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).
VII-11 NO?LU İSTASYON, 2 PARÇA: SİNÜZAL HİSTİYOSİTOZ, ANTRAKOZ (METASTAZ GÖRÜLMEDİ).

Adjuvan İT önerildi,
ancak maliyet nedenli devam edilemedi

Erken Evre KHDAKda Güncel Pratiğe Yansıyan Çalışmalar

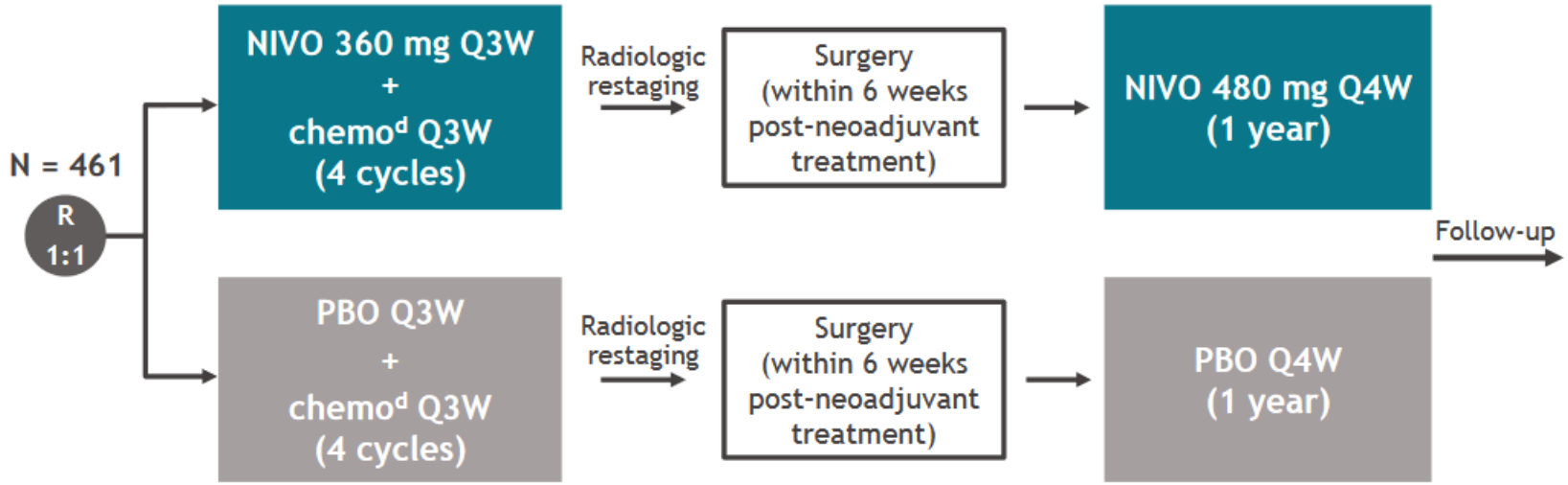
Adjuvan	• Adjuvan Kemoterapi • IMpower 010 / PEARLS • ADAURA / ALINA
İzole Neoadjuvan	• Checkmate 816
Perioperatif	• Checkmate 77T • AEGEAN • Keynote 671

CheckMate 77T[a] study design

Key eligibility criteria

- Resectable, stage IIA (> 4 cm)-IIIB (N2) NSCLC (per AJCC 8th edition)
- No prior systemic anti-cancer treatment
- ECOG PS 0-1
- No *EGFR* mutation/known *ALK* alterations[b]

Stratified by histology (NSQ vs SQ) disease stage (II vs III), and tumor PD-L1[c] (≥ 1% vs < 1% vs not evaluable/indeterminate)



Follow-up, median (range): 25.4 (15.7-44.2) months

Primary endpoint
- EFS by BICR

Secondary endpoints
- pCR[e] by BIPR
- MPR[e] by BIPR
- OS
- Safety

Exploratory analyses
- EFS by pCR/MPR
- EFS by adjuvant treatment

Database lock date: September 6, 2023.

[a]NCT04025879. [b]*EGFR* testing was mandatory in all patients with NSQ histology. *ALK* testing was done in patients with a history of *ALK* alterations. *EGFR*/*ALK* testing done using US FDA/local health authority-approved assays. [c]Determined by the PD-L1 IHC 28-8 pharmDx assay (Dako). [d]NSQ: cisplatin + pemetrexed, carboplatin + pemetrexed, or carboplatin + paclitaxel; SQ: cisplatin + docetaxel or carboplatin + paclitaxel. [e]Assessed per immune-related pathologic response criteria.[1] BICR, blinded independent central review; BIPR, blinded independent pathological review.

1. Cottrell TR, et al. *Ann Oncol* 2018:29:1853-1860.

Baseline patient characteristics

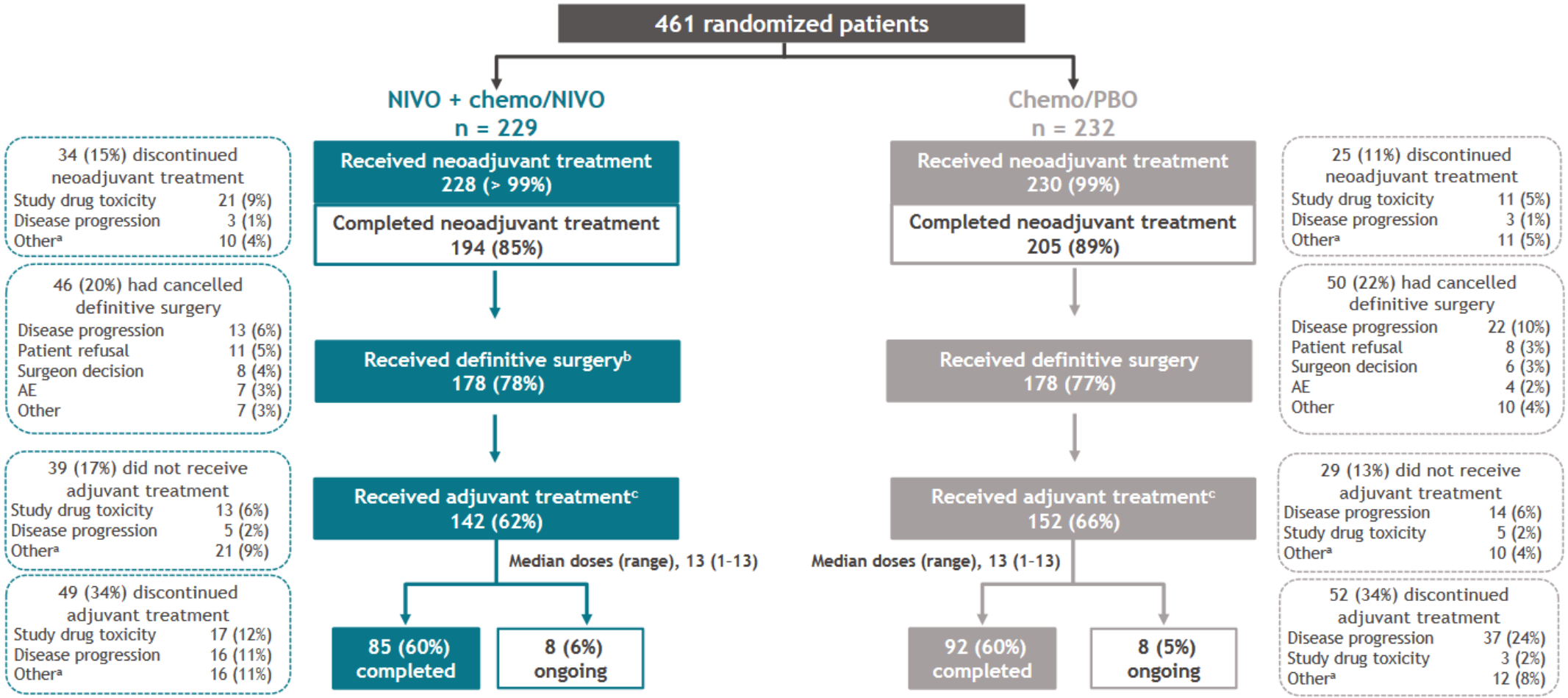
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)[a]
Median age, years (range)	66 (37-83)	66 (35-86)
Male, n (%)	167 (73)	160 (69)
Geographic region, n (%)		
North America	23 (10)	21 (9)
Europe	123 (54)	127 (55)
Asia	65 (28)	50 (22)
Rest of the world[b]	18 (8)	34 (15)
ECOG PS, n (%)		
0	147 (64)	141 (61)
1	82 (36)	91 (39)
Disease stage,[c] n (%)		
IIA-B[d]	81 (35)	81 (35)
IIIA-B[e]	146 (64)	149 (64)
Histology, n (%)		
Squamous	116 (51)	118 (51)
Non-squamous	113 (49)	114 (49)

	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)[a]
Smoking status, n (%)		
Current/former	212 (93)	205 (88)
Never	17 (7)	27 (12)
Tumor PD-L1 expression,[f] n (%)		
Not evaluable	8 (4)	11 (5)
< 1%	93 (41)	93 (40)
≥ 1%	128 (56)	128 (55)
1-49%	83 (36)	76 (33)
≥ 50%	45 (20)	52 (22)
Platinum therapy type, n (%)		
Cisplatin	55 (24)	42 (18)
Carboplatin	167 (73)	180 (78)

- PD-L1 1-49% subgroup mostly consisted of patients with low tumor PD-L1 expression level; median tumor PD-L1 expression in this subgroup was 10% across both treatment arms

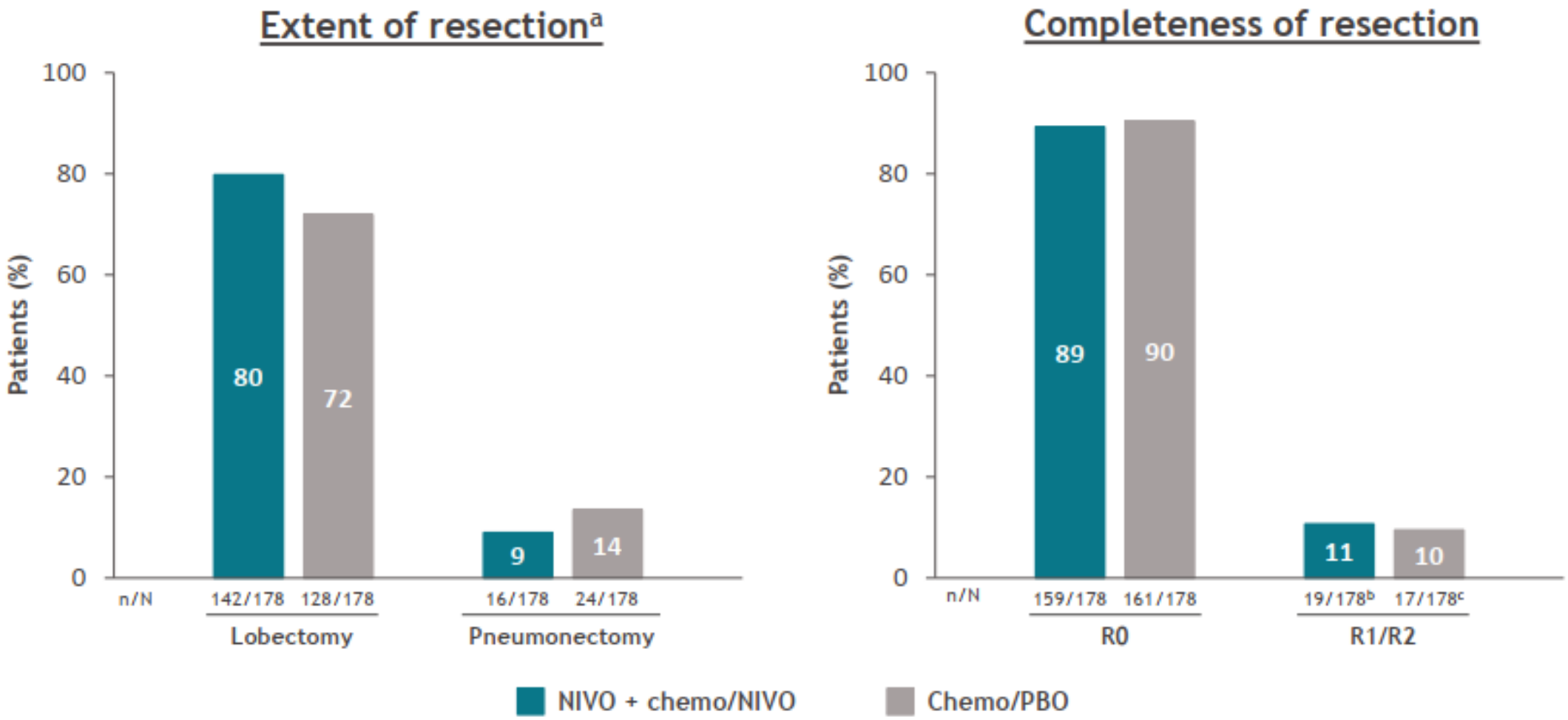
Percentages may not total 100 due to rounding. [a]1 (< 1%) patient with squamous histology had a reported *EGFR* mutation; this was tested locally and could not be confirmed due to site closure. [b]Includes only Argentina, Australia, Brazil, and Mexico. [c]Disease stage (per AJCC 8th edition) as reported in case report forms. 2 (1%) patients in the NIVO + chemo/NIVO arm had stage IIIC disease, and 2 (1%) patients in the chemo/PBO arm had stage IV disease. [d]Stage IIA was reported in 15 (7%) patients in the NIVO + chemo/NIVO arm and 18 (8%) patients in the chemo/PBO arm; stage IIB disease was reported in 66 (29%) and 63 (27%) patients, respectively. [e]Stage IIIA was reported in 103 (45%) patients in the NIVO + chemo/NIVO arm and 114 (49%) patients in the chemo/PBO arm; stage IIIB disease was reported in 43 (19%) and 35 (15%) patients, respectively. [f]Determined using the PD-L1 IHC 28-8 pharmDx assay (Dako).

Treatment and surgery summary

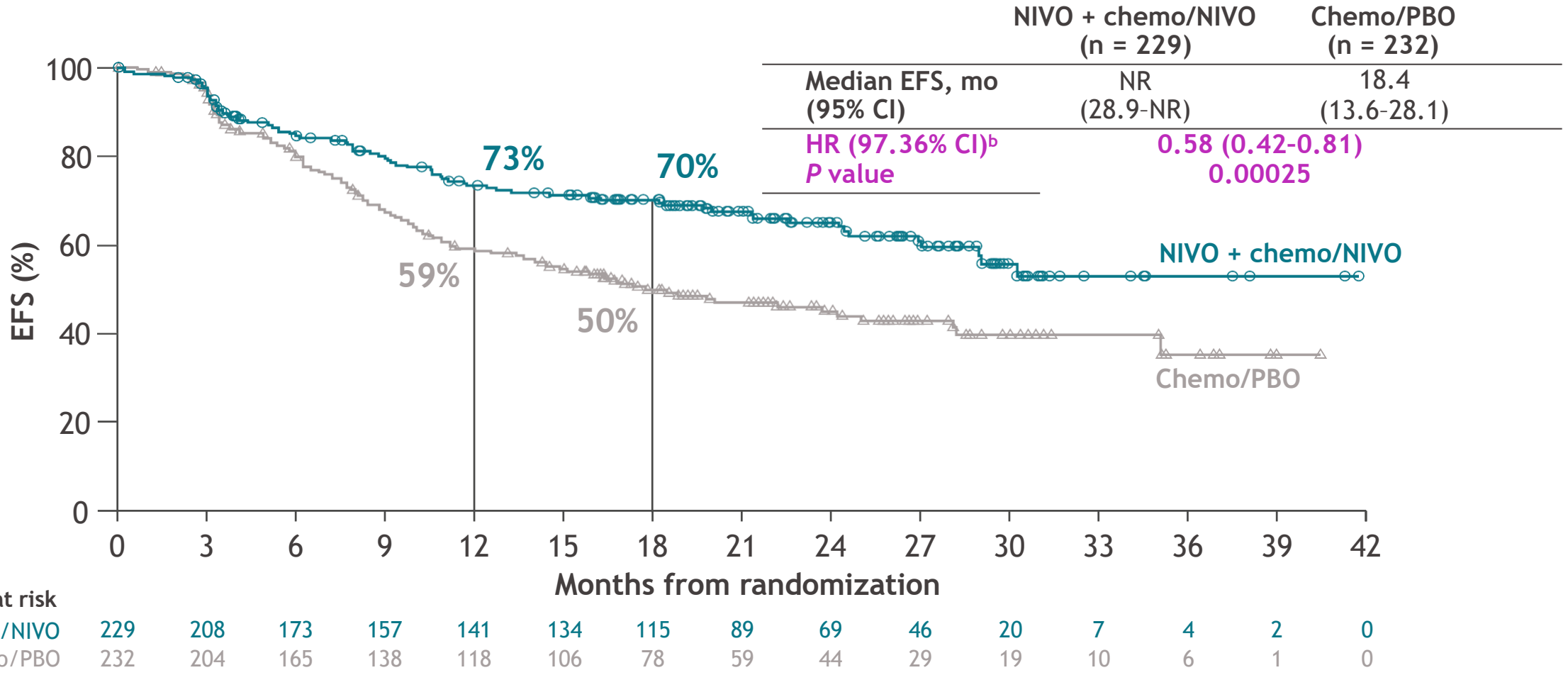


All percentages calculated from patients who received neoadjuvant study treatment except for discontinuation of adjuvant treatment. [a]Included AE unrelated to study treatment, patient request, withdrawn consent, and no longer meeting study criteria. [b]Surgery status was not reported in 2 (1%) patients in the NIVO + chemo/NIVO arm. [c]3 patients in each arm did not receive surgery but received adjuvant treatment.

Surgical outcomes



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



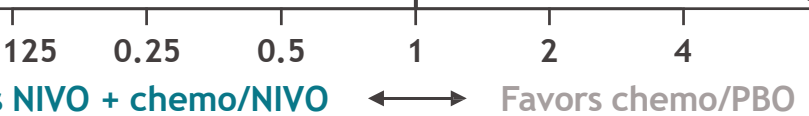
- EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

Median follow-up (range): 25.4 months (15.7-44.2).

[a]Time from randomization to any disease progression precluding surgery, abandoned surgery due to unresectability or disease progression, disease progression/recurrence after surgery, progression in patients without surgery, or death due to any cause. Patients who received subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [b]Unstratified HR (95% CI), 0.59 (0.44–0.79).

EFS analysis by key subgroups

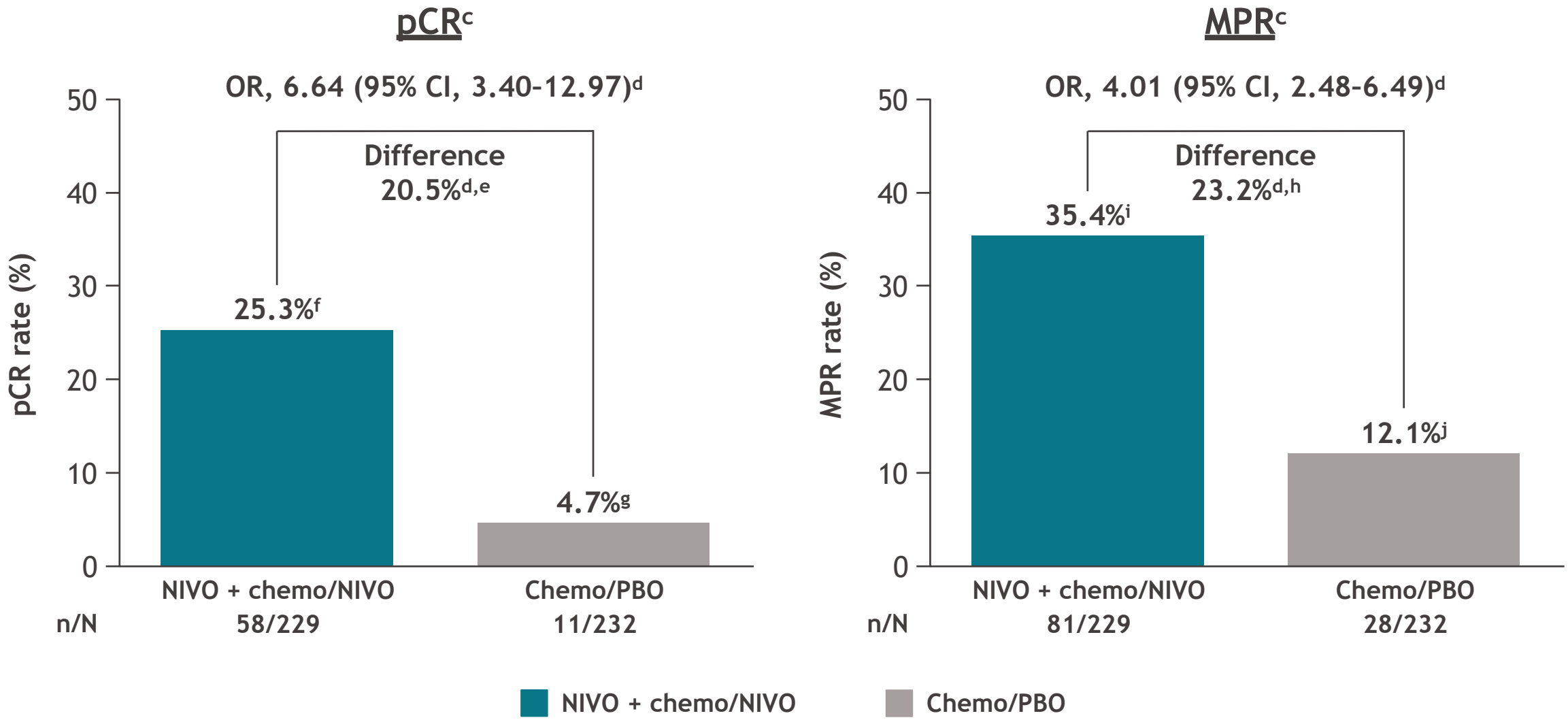
	Median EFS,[a] mo		Unstratified HR (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)	
Overall (N = 461)	NR	18.4	0.59 (0.44-0.79)
< 65 years (n = 202)	NR	16.7	0.55 (0.36-0.85)
≥ 65 years (n = 259)	NR	20.1	0.61 (0.41-0.91)
Male (n = 327)	NR	16.7	0.53 (0.37-0.75)
Female (n = 134)	30.2	18.8	0.71 (0.41-1.20)
North America (n = 44)	30.2	9.4	0.59 (0.25-1.38)
Europe (n = 250)	NR	23.7	0.61 (0.40-0.92)
Asia (n = 115)	NR	13.9	0.47 (0.26-0.86)
ECOG PS 0 (n = 288)	NR	20.1	0.57 (0.39-0.83)
ECOG PS 1 (n = 173)	29.0	17.3	0.61 (0.39-0.97)
Stage II (n = 162)	NR	NR	0.81 (0.46-1.43)
Stage III (n = 297)	30.2	13.4	0.51 (0.36-0.72)
N0 (n = 167)[b]	NR	NR	0.80 (0.48-1.32)
N1 (n = 108)[b]	NR	28.1	0.58 (0.29-1.16)
N2 (n = 182)[b,c]	30.2	10.0	0.46 (0.30-0.70)
Single-station (n = 112)	30.2	10.0	0.49 (0.29-0.84)
Multi-station (n = 69)	NR	10.0	0.43 (0.21-0.88)
Squamous (n = 234)	NR	17.0	0.46 (0.30-0.72)
Non-squamous (n = 227)	28.9	18.4	0.72 (0.49-1.07)
Current/former smoker (n = 417)	NR	17.0	0.54 (0.40-0.74)
Never smoker (n = 44)	19.7	25.0	1.32 (0.54-3.20)
PD-L1 < 1% (n = 186)[d]	29.0	19.8	0.73 (0.47-1.15)
PD-L1 ≥ 1% (n = 256)[d]	NR	15.8	0.52 (0.35-0.78)
PD-L1 1-49% (n = 159)[e]	30.2	28.1	0.76 (0.46-1.25)
PD-L1 ≥ 50% (n = 97)	NR	8.0	0.26 (0.12-0.55)
Cisplatin (n = 97)	27.0	15.8	0.61 (0.35-1.08)
Carboplatin (n = 347)	NR	17.3	0.53 (0.37-0.75)



Median follow-up (range): 25.4 months (15.7-44.2).

[a]Per BICR. [b]Nodal status was N3 in 4 patients. [c]N2 subcategory was not reported in 1 patient.Baseline characteristics were similar across treatment arms in the N2 nodal status subgroup, which comprised ~40% of patients. [d]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients. [e]Most patients in this subgroup had low PD-L1 expression (median 10% across both arms).

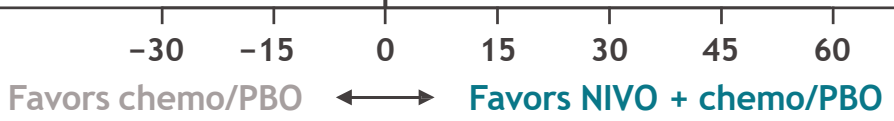
pCR[a] and MPR[b] per BIPR



[a]0% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [b]≤ 10% residual viable tumor cells post-surgery in both primary tumor (lung) and sampled lymph nodes per immune-related pathologic response criteria. [c]Patients who did not undergo surgery or received alternative anti-cancer treatment prior to surgery were classified as non-responders. [d]Calculated using the stratified Cochran–Mantel–Haenszel method. [e–j]95% CI: [e]14.3–26.6; [f]19.8–31.5; [g]2.4–8.3; [h]15.8–30.6; [i]29.2–41.9; [j]8.2–17.0. BIPR, blinded independent pathological review.

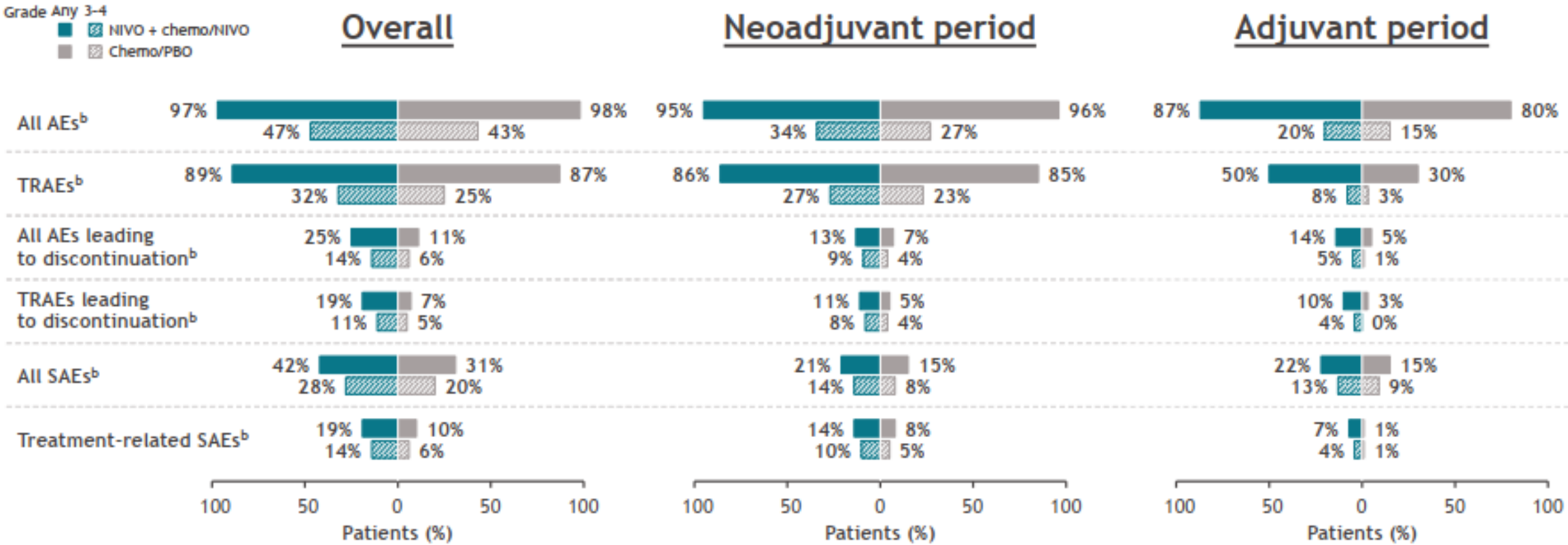
pCR analysis by key subgroups

	pCR rate,[a] %		Unweighted difference, % (95% CI)
	NIVO + chemo/NIVO (n = 229)	Chemo/PBO (n = 232)	
Overall (N = 461)	25.3	4.7	20.6 (14.3-26.9)
< 65 years (n = 202)	25.5	4.0	21.5 (12.0-31.0)
≥ 65 years (n = 259)	25.2	5.3	19.9 (11.4-28.5)
Male (n = 327)	26.9	5.0	21.9 (14.3-29.5)
Female (n = 134)	21.0	4.2	16.8 (5.7-28.8)
North America (n = 44)	13.0	0	13.0 (−4.6 to 32.1)
Europe (n = 250)	22.0	5.5	16.4 (8.0-25.0)
Asia (n = 115)	36.9	2.0	34.9 (21.3-47.2)
ECOG PS 0 (n = 288)	25.9	5.0	20.9 (12.8-28.9)
ECOG PS 1 (n = 173)	24.4	4.4	20.0 (9.8-30.6)
Stage II (n = 162)	29.6	3.7	25.9 (14.9-36.9)
Stage III (n = 299)[b]	23.0	5.3	17.7 (10.0-25.5)
Squamous (n = 234)	28.4	5.9	22.5 (13.1-31.8)
Non-squamous (n = 227)	22.1	3.5	18.6 (10.2-27.4)
Current/former smoker (n = 417)	25.9	4.9	21.1 (14.4-27.7)
Never smoker (n = 44)	17.6	3.7	13.9 (−4.6 to 37.5)
PD-L1 < 1% (n = 186)[c]	12.9	4.3	8.6 (0.4-17.3)
PD-L1 ≥ 1% (n = 256)[c]	35.2	4.7	30.5 (21.2-39.4)
PD-L1 1-49% (n = 159)	26.5	3.9	22.6 (11.7-33.3)
PD-L1 ≥ 50% (n = 97)	51.1	5.8	45.3 (28.1-59.8)
Cisplatin (n = 97)	29.1	4.8	24.3 (9.2-37.8)
Carboplatin (n = 347)	24.6	5.0	19.6 (12.3-27.0)



[a]Per BIPR. [b]Included 2 patients with stage IV disease. [c]Tumor PD-L1 expression was not evaluable/indeterminate in 19 patients.

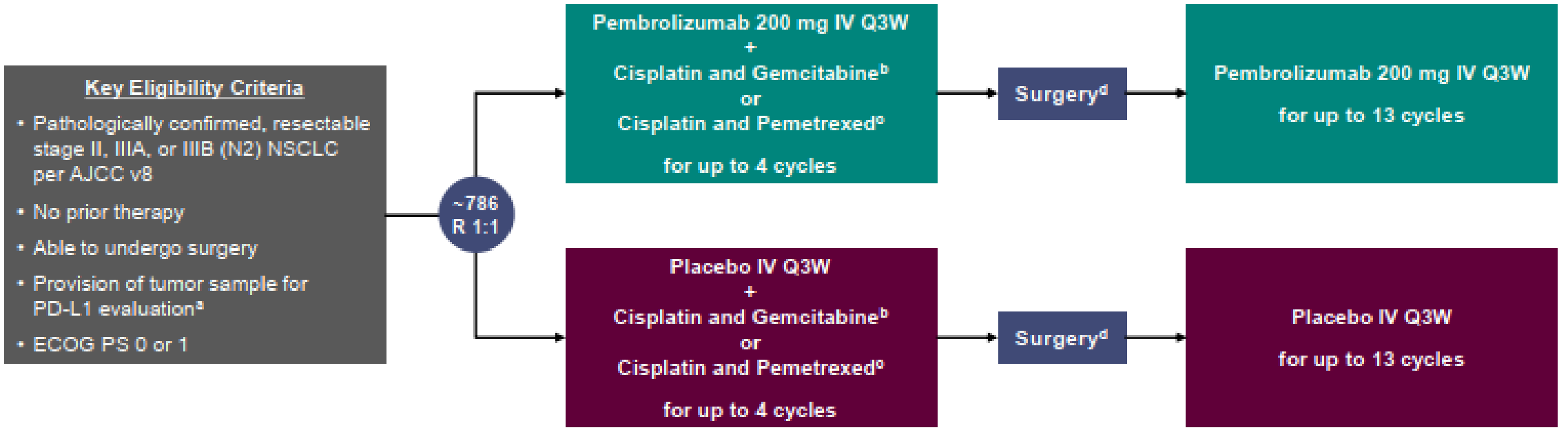
Safety summary[a] across study phases



- Any-grade surgery-related AEs occurred in 73 (41%) and 69 (39%) patients in the NIVO + chemo/NIVO and chemo/PBO arms, respectively; 21 (12%) patients in each arm experienced grade 3-4 events[c]
- Treatment-related deaths occurred in 2 (1%) patients in the NIVO + chemo/NIVO arm (1 due to grade 5[d] pneumonitis and 1 due to grade 4 pneumonitis, both occurring after completion of neoadjuvant treatment)

KEYNOTE-671 Study Design

Randomized, Double-Blind, Phase 3 Trial



Stratification Factors

- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review and safety

Baseline Characteristics, IA2

	Pembro Arm (N = 397)	Placebo Arm (N = 400)
Median age (range), years	63 (26-83)	64 (35-81)
Male	279 (70.3%)	284 (71.0%)
Race		
American Indian or Alaska Native	1 (0.3%)	0
Asian	124 (31.2%)	125 (31.3%)
Black or African American	6 (1.5%)	10 (2.5%)
Multiple	3 (0.8%)	10 (2.5%)
White	250 (63.0%)	239 (59.8%)
Missing data	13 (3.3%)	16 (4.0%)
Geographic region		
East Asia	123 (31.0%)	121 (30.3%)
Not east Asia	274 (69.0%)	279 (69.8%)
ECOG PS		
0	253 (63.7%)	246 (61.5%)
1	144 (36.3%)	154 (38.5%)
Histology		
Nonsquamous	226 (59.6%)	227 (56.8%)
Squamous	171 (43.1%)	173 (43.3%)

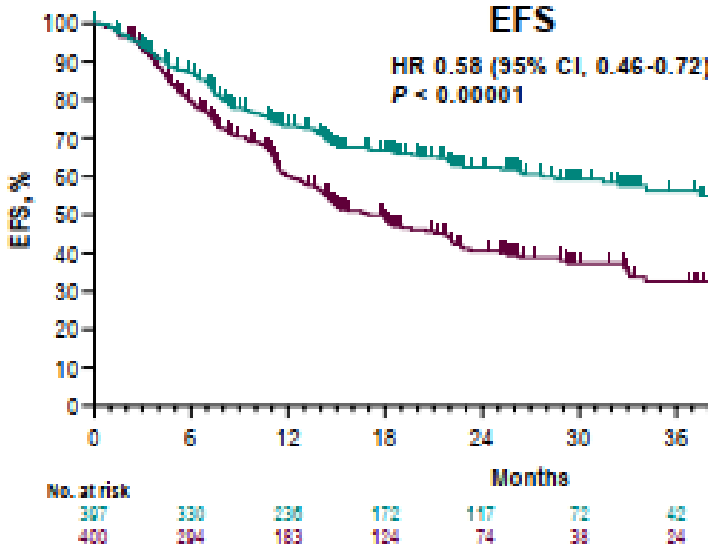
	Pembro Arm (N = 397)	Placebo Arm (N = 400)
Smoking status		
Current	96 (24.2%)	103 (25.8%)
Former	247 (62.2%)	250 (62.5%)
Never	54 (13.6%)	47 (11.8%)
Clinical stage[a]		
II	118 (29.7%)	121 (30.3%)
IIIA	217 (54.7%)	224 (56.0%)
IIIB	62 (15.6%)	55 (13.8%)
N status[a]		
cN0	148 (37.3%)	142 (35.5%)
cN1	81 (20.4%)	71 (17.8%)
cN2	168 (42.3%)	187 (46.8%)
PD-L1 TPS		
≥50%	132 (33.2%)	134 (33.5%)
1-49%	127 (32.0%)	115 (28.8%)
<1%	138 (34.8%)	151 (37.8%)
Known *EGFR* mutation[b]	14 (3.5%)	19 (4.8%)
Known *ALK* translocation[b]	12 (3.0%)	9 (2.3%)

[a] As determined by imaging and biopsy. [b] *EGFR* mutation and *ALK* translocation status were tested locally per investigator dis[illegible]tion. *EGFR* status was unknown in 272 (68.5%) participants in the pembro arm and 257 (64.3%) in the placebo arm; *ALK* status was unknown in 281 (70.8%) and 259 (64.8%), respectively. Data cutoff date fo[illegible]ly 10, 2023.

KEYNOTE-671 Results: Interim Analysis 1

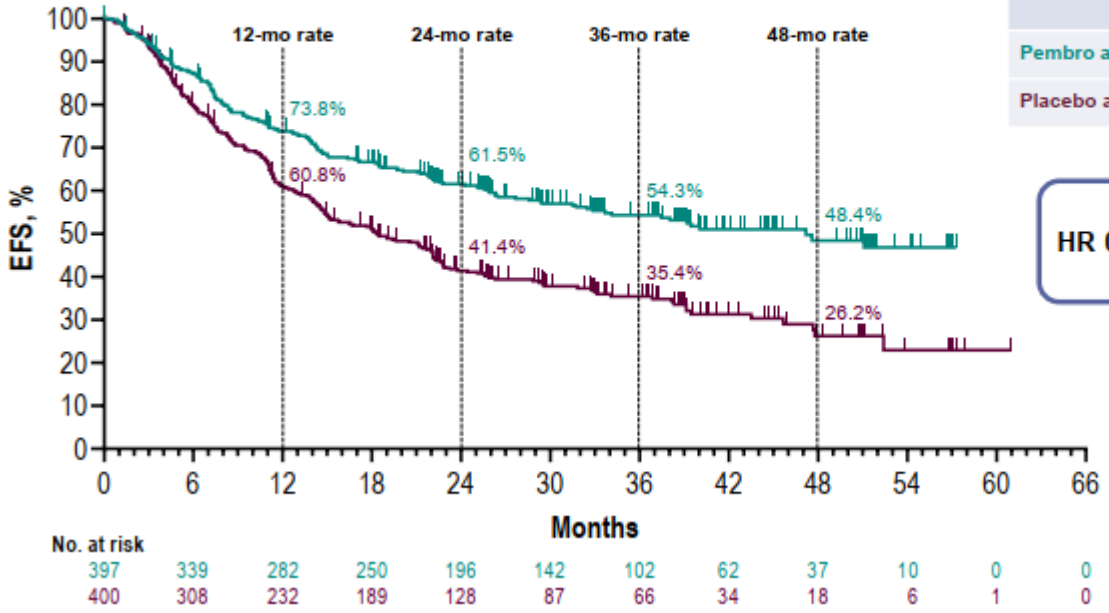
Median Follow-Up[a]: 25.2 months (range, 7.5-50.6)

- Neoadjuvant pembrolizumab + chemotherapy followed by surgery and adjuvant pembrolizumab significantly improved EFS, mPR, and pCR compared with neoadjuvant chemotherapy and surgery alone
- AE profile was as expected based on the known profiles of the individual treatment components



Event-Free Survival, IA2

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

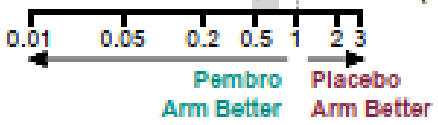


	Pts w/ Event	Median (95% CI), mo
Pembro arm	43.8%	47.2 (32.9-NR)
Placebo arm	62.0%	18.3 (14.8-22.1)

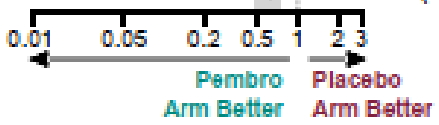
HR 0.59 (95% CI, 0.48-0.72)

Event-Free Survival in Subgroups, IA2

Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
Age			
<65 y	88/221	136/214	0.51 (0.39-0.67)
≥65 y	86/176	112/186	0.70 (0.52-0.92)
Sex			
Female	47/118	70/116	0.52 (0.36-0.75)
Male	127/279	178/284	0.62 (0.49-0.78)
Race			
White	109/250	151/239	0.56 (0.44-0.72)
All others	57/134	85/145	0.63 (0.45-0.88)
Geographic region			
East Asia	51/123	70/121	0.63 (0.44-0.91)
Not east Asia	123/274	178/279	0.57 (0.45-0.72)
Smoking status			
Current	44/96	68/103	0.53 (0.36-0.77)
Former	105/247	155/250	0.59 (0.46-0.75)
Never	25/54	25/47	0.77 (0.44-1.35)
Histology			
Nonsquamous	102/226	131/227	0.66 (0.51-0.86)
Squamous	72/171	117/173	0.51 (0.38-0.69)

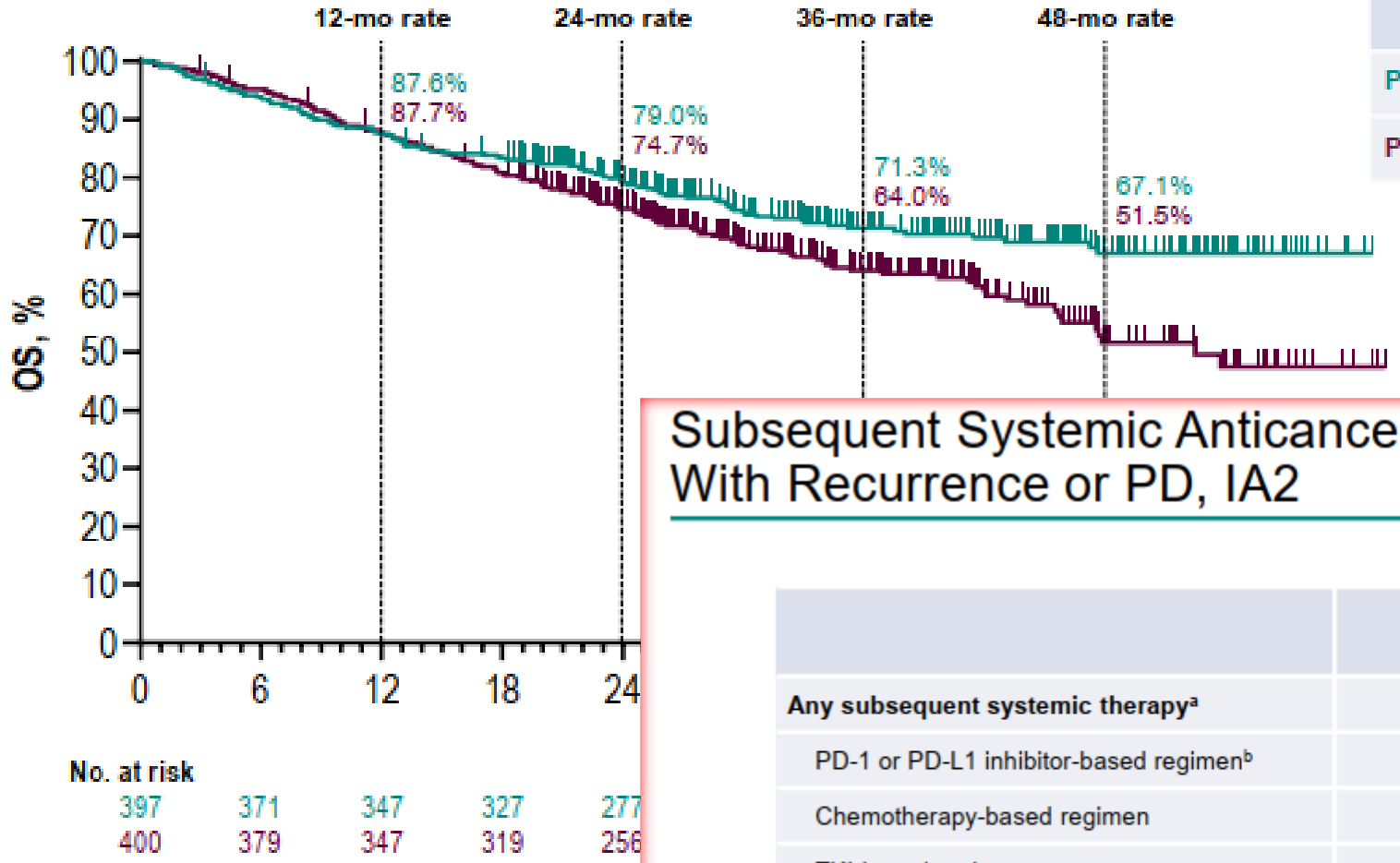


Subgroup	Events/participants Pembro Arm	Events/participants Placebo Arm	Hazard ratio (95% CI)
Overall	174/397	248/400	0.59 (0.48-0.72)
Clinical stage			
II	40/118	62/121	0.59 (0.40-0.88)
IIIA	100/217	145/224	0.57 (0.44-0.74)
IIIB	34/62	41/55	0.57 (0.36-0.90)
N status			
cN0	59/148	83/142	0.58 (0.41-0.81)
cN1	29/81	39/71	0.56 (0.35-0.91)
cN2	86/168	126/187	0.63 (0.48-0.82)
PD-L1 TPS			
≥50%	41/132	70/134	0.48 (0.33-0.71)
1-49%	55/127	76/115	0.52 (0.36-0.73)
<1%	78/138	102/151	0.75 (0.56-1.01)
***EGFR* mutation**			
No	42/111	72/124	0.55 (0.38-0.81)
Yes	5/14	13/19	0.32 (0.11-0.91)
Unknown	127/272	163/257	0.62 (0.49-0.79)
***ALK* translocation**			
No	42/104	85/132	0.50 (0.35-0.73)
Unknown	126/281	160/259	0.62 (0.49-0.78)



Overall Survival, IA2

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



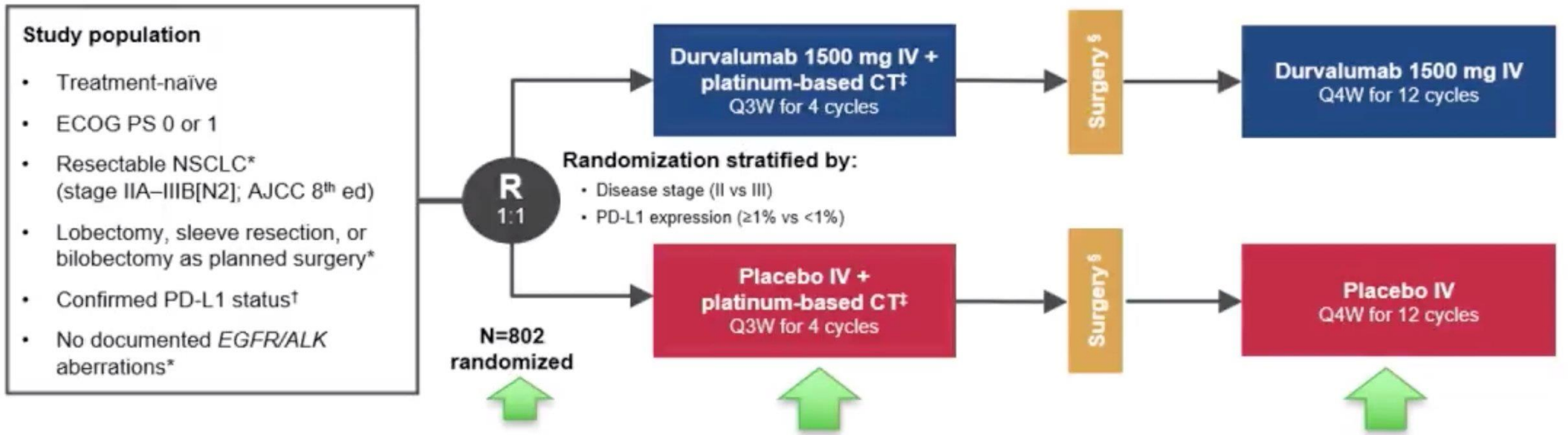
	Pts w/ Event	Median (95% CI), mo
Pembro arm	27.7%	NR (NR-NR)
Placebo arm	36.0%	52.4 (45.7-NR)

Subsequent Systemic Anticancer Therapy In Participants With Recurrence or PD, IA2

	Pembro Arm (n = 125)	Placebo Arm (n = 208)
Any subsequent systemic therapy[a]	88 (70.4%)	160 (76.9%)
PD-1 or PD-L1 inhibitor-based regimen[b]	27 (21.6%)	104 (50.0%)
Chemotherapy-based regimen	54 (43.2%)	72 (34.6%)
TKI-based regimen[c]	23 (18.4%)	25 (12.0%)
Other	9 (2.7%)	3 (1.4%)

Schema of the AEGEAN Trial

AACR American Association for Cancer Research ANNUAL MEETING 2023
APRIL 14-19 • #AACR23



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

Primary:

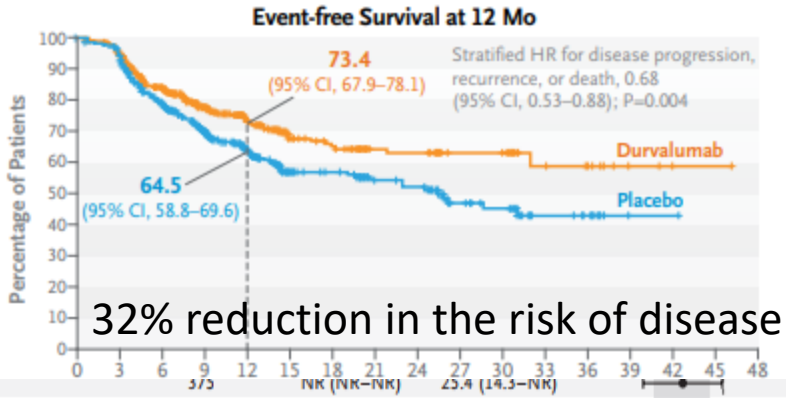
- pCR by central lab (per IASLC 2020[1])
- EFS using BICR (per RECIST v1.1)

Key secondary:

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

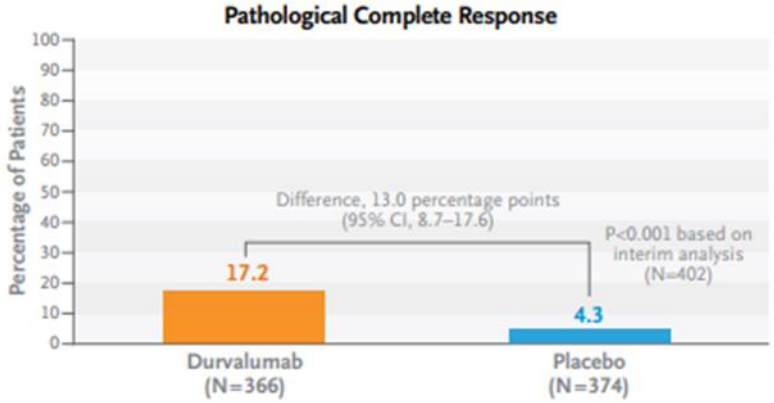
Table 1. Characteristics at Baseline and Planned Treatment, Modified Intention-to-Treat Population.*

Characteristic†	Durvalumab Group (N=366)	Placebo Group (N=374)
Age		
Median (range) — yr	65 (30–88)	65 (39–85)
≥75 yr — no. (%)	44 (12.0)	36 (9.6)
Disease stage — no. (%)¶		
II	104 (28.4)	110 (29.4)
IIIA	173 (47.3)	165 (44.1)
IIIB	88 (24.0)	98 (26.2)
TNM classification, primary tumor — no. (%)		
T1	44 (12.0)	43 (11.5)
T2	97 (26.5)	108 (28.9)
T3	128 (35.0)	129 (34.5)
T4	97 (26.5)	94 (25.1)
TNM stage, regional lymph nodes — no. (%)		
N0	110 (30.1)	102 (27.3)
N1	75 (20.5)	87 (23.3)
N2	181 (49.5)	185 (49.5)
Single-station	141 (38.5)	132 (35.3)
Multistation	34 (9.3)	40 (10.7)



32% reduction in the risk of disease progression

Nonsquamous	375	NR (NR–NR)	25.4 (14.5–NR)	0.69 (0.48–0.99)
Disease stage				
II	214	NR (NR–NR)	31.1 (25.4–NR)	0.76 (0.43–1.34)
IIIA	338	NR (NR–NR)	19.5 (11.7–NR)	0.57 (0.39–0.83)
IIIB	186	31.9 (11.7–NR)	18.9 (11.8–NR)	0.83 (0.52–1.32)
Lymph node station				
N2 single	273	NR (NR–NR)	22.8 (12.6–NR)	0.61 (0.39–0.94)
N2 multi	74	31.9 (9.3–NR)	12.2 (7.2–NR)	0.69 (0.33–1.38)
PD-L1 expression at baseline				
Tumor cell <1%	247	NR (14.9–NR)	20.6 (13.9–NR)	0.76 (0.49–1.17)
Tumor cell 1–49%	277	NR (31.9–NR)	25.4 (12.2–NR)	0.70 (0.46–1.05)
Tumor cell ≥50%	216	NR (NR–NR)	26.2 (14.3–NR)	0.60 (0.35–1.01)
Planned neoadjuvant platinum agent				



Disease stage				
II	214	21.2 (13.8 to 30.3)	4.5 (1.5 to 10.3)	16.6 (8.1 to 26.0)
IIIA	338	18.5 (13.0 to 25.1)	4.8 (2.1 to 9.3)	13.6 (7.1 to 20.7)
IIIB	186	10.2 (4.8 to 18.5)	3.1 (0.6 to 8.7)	7.2 (0.1 to 15.7)
Lymph node station				
N2 single	273	18.4 (12.4 to 25.8)	4.5 (1.7 to 9.6)	13.9 (6.6 to 21.7)
N2 multi	74	8.8 (1.9 to 23.7)	5.0 (0.6 to 16.9)	3.8 (−9.2 to 18.8)
PD-L1 expression at baseline				
Tumor cell <1%	247	9.0 (4.6 to 15.6)	3.2 (0.9 to 8.0)	5.8 (−0.2 to 12.7)
Tumor cell 1–49%	277	16.3 (10.5 to 23.6)	4.9 (2.0 to 9.9)	11.4 (4.3 to 19.1)
Tumor cell ≥50%	216	27.5 (19.4 to 36.9)	4.7 (1.5 to 10.6)	22.9 (13.7 to 32.5)
Planned neoadjuvant platinum agent				

Erken evre KHDAK'nde Perioperatif İmmunoterapi

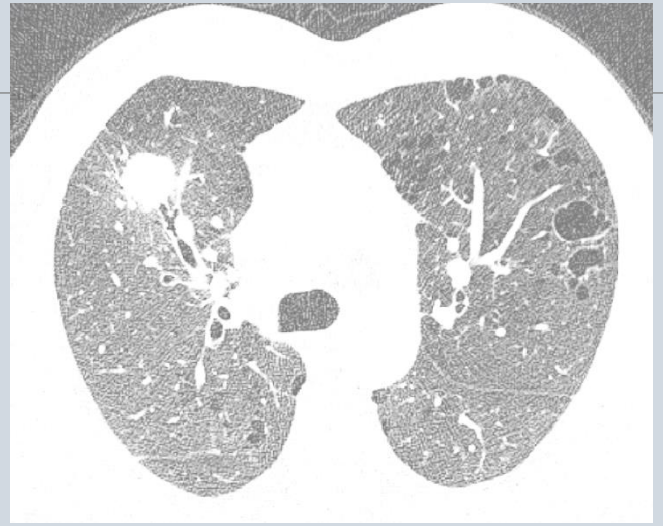
	NADIM II	CM-816	KN-671	AEGEAN	NEOTORCH	CM 77T
İlaç	Nivolumab	Nivolumab	Pembrolizumab	Durvalumab	Torpalimab	Nivolumab
Evre	IIIA-IIIB	IB-IIIA	IIA- IIIB	IIA- IIIB	II-III	IIA-IIIB
Adjuvan süre	6 ay	Opsiyonel	1 yıl	1 yıl	1 yıl	1 yıl
Definitif cerrahi	%93	%96	%98		%98	%89
ORR	%75					
pCR	%37	%24	%18	%17	%25	%25
MPR	%53		%30	%33	%48	%35
2-y EFS	%67	%64	%62	%63	%65	NR
OS	NR	NR	NR	NR	NR*	NR

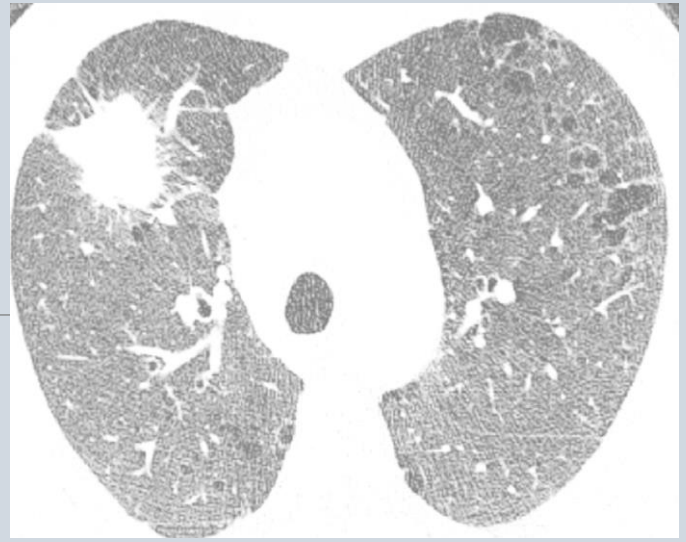
HR 0.72

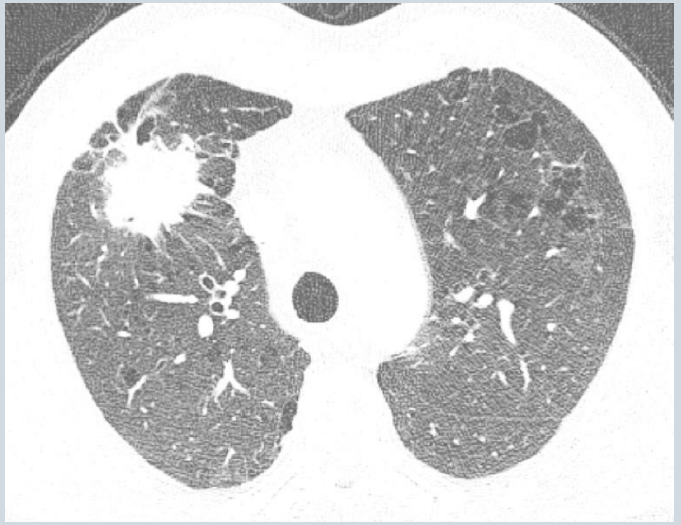
VAKA 3 : İK, yaş Erkek hasta

Temmuz 2023

- Kilo kaybı, halsizlik, öksürük
- Kronik hast yok, 30 p/y
- 04/22de Acil Appendektomi
- Aile öyküsü: Dayı Akc Ca
- **FM:** Spesifik bulgu yok
- **PAAC:** Sağ Akc üst zonda opasite



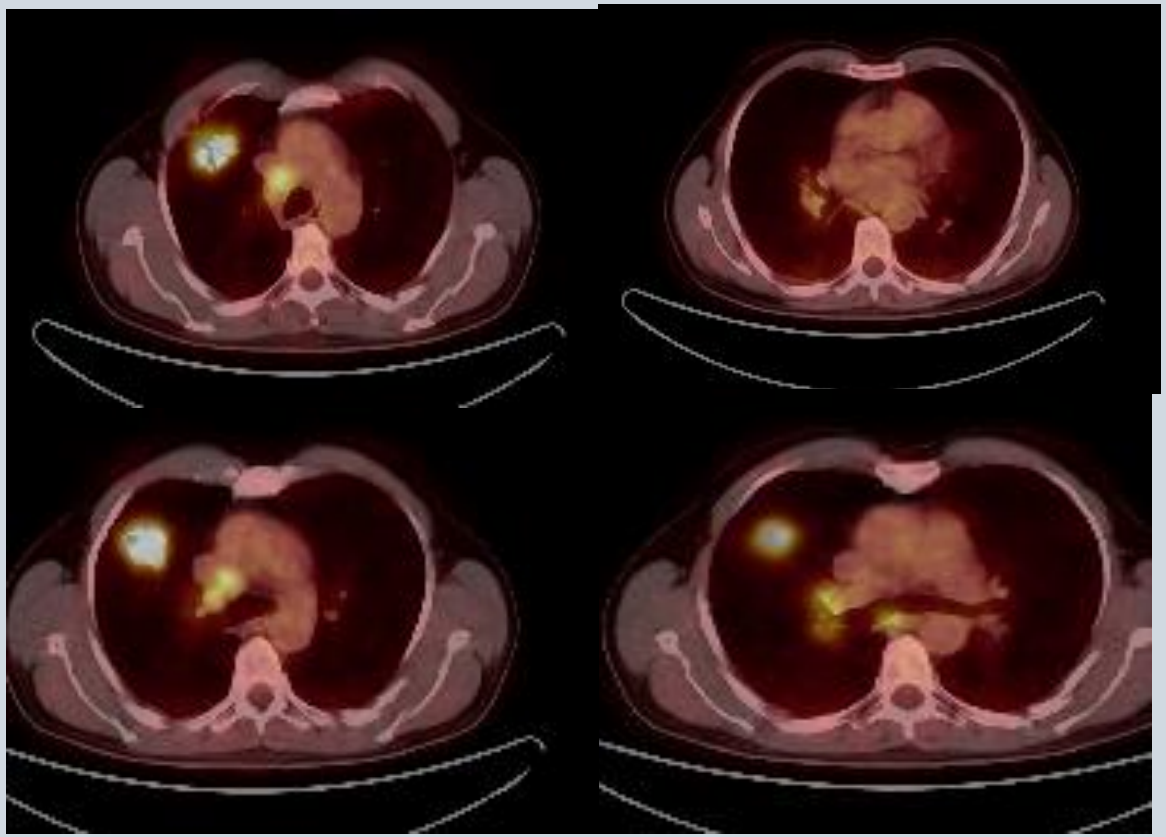


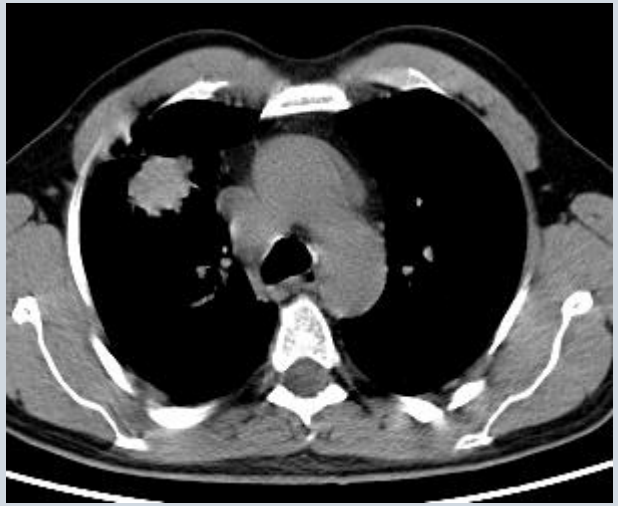


Subkarinal 15 mm LAP ile uyumlu oval nodüler dansite izlenmektedir.
Sağ akciğer üst lob anterior segmentte yaklaşık 41x43x37 mm boyutlara ulaşan konturu düzensiz - spiküler kitle (Primer malignite?, PET CT inceleme ile korelasyon ve sitolojik değerlendirmesi önerilir).

6 Ağustos 2023 PET-CT: Sağ akciğer üst lob anterior segment te 40x38 mm boyutların daki kitle lezyonun da (SUD max 11.0) , mediasten de sağ da paratrakeal alan da 37 mm boyutların da nodal lezyon da (SUD max 8.5) , sağ da hiler bölge de en büyüğü 25 mm boyutların da nodal lezyonlar da (SUD max 6.3) , subcarinal alan da 27 mm boyutların da nodal lezyon da (SUD max 9.3) artmış FDG tutulumları dikkati çekmiştir.

10.08.2023 Kontrastlı Kranial MRG: Normal limitlerde inceleme



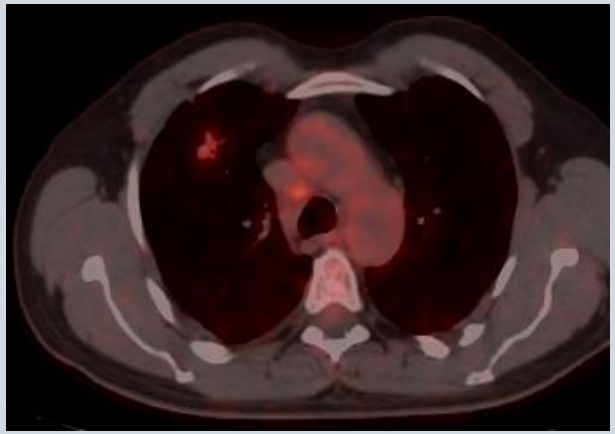


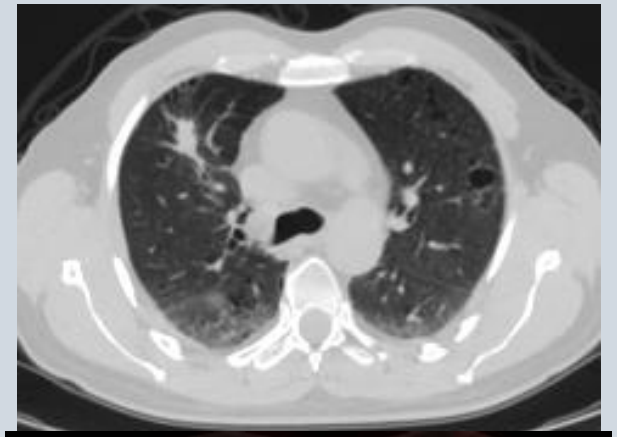
TİİAB Patoloji: SCC; PDL-1 %30

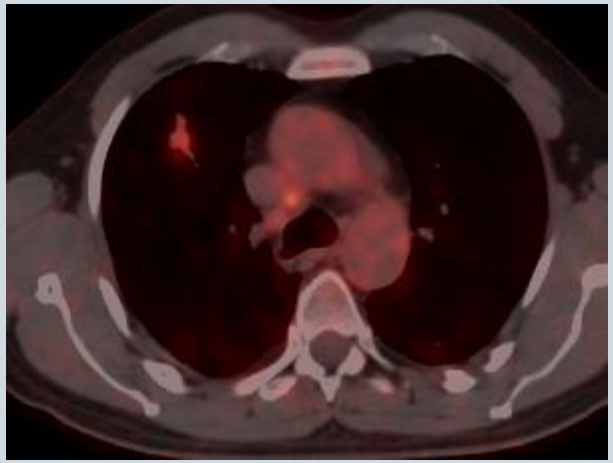
Paklitaksel 200 mg/m2; Karboplatin AUC 5; Nivolumab 360 mg X 3 kür

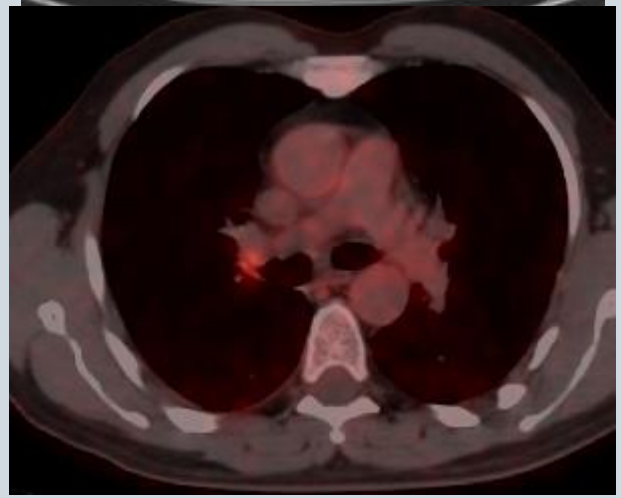
Preop PET-BT:

20.10.2023: Ağustos 2023 tarihli PET/BT incelemesi ile kaşılaştırmalı olarak yapılmıştır. Sağ akciğer üst lob anterior segmentte yer alan primer malign tümöral lezyonun boyut ve metabolik aktivitesi kısmen azalmıştır (eski çap 40x33mm, yeni çap 21x18mm, eski SUDmax 11, yeni SUDmax 4.7).
- Sağ alt paratrakeal, trakeabronşial ve sağ hiler nodal istasyonlarda izlenilen metastatik lenf nodlarının boyut ve metabolik aktivitesi kısmen azalırken, subkarinal lenf nodu bu çalışmada gözlenmemiştir.

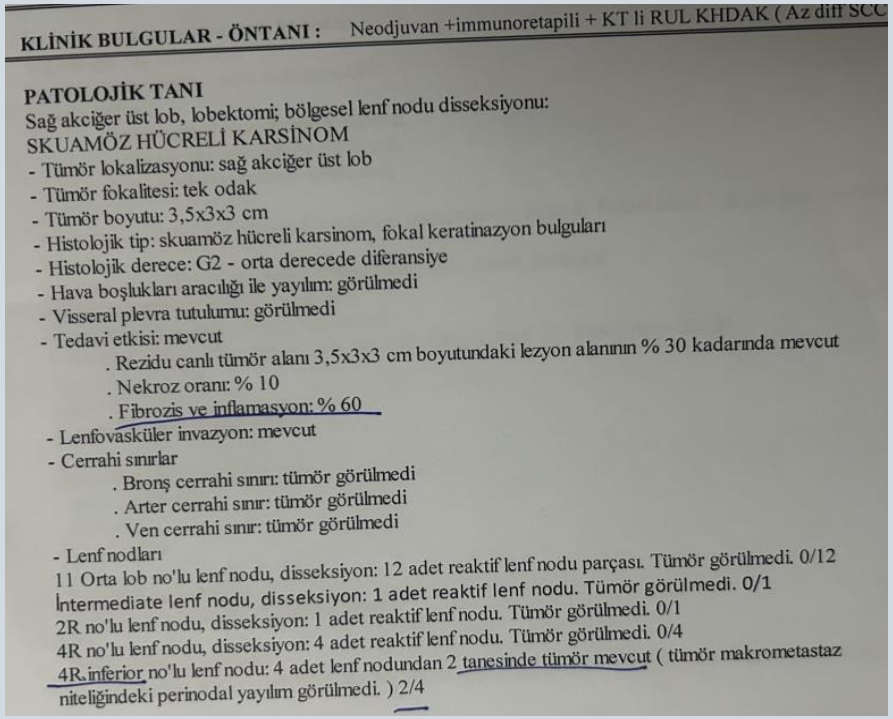








Operasyon Patolojisi ile MDT



KLİNİK BULGULAR - ÖNTANI : Neodjuvan +immunoretapili + KT li RUL KHDAK (Az diff SCC

PATOLOJİK TANI

Sağ akciğer üst lob, lobektomi; bölgesel lenf nodu disseksiyonu:
SKUAMÖZ HÜCRELİ KARSİNOM
- Tümör lokalizasyonu: sağ akciğer üst lob
- Tümör fokalitesi: tek odak
- Tümör boyutu: 3,5x3x3 cm
- Histolojik tip: skuamöz hücreli karsinom, fokal keratinazyon bulguları
- Histolojik derece: G2 - orta derecede diferansiye
- Hava boşlukları aracılığı ile yayılım: görülmedi
- Visseral plevra tutulumu: görülmedi
- Tedavi etkisi: mevcut
  - . Rezidu canlı tümör alanı 3,5x3x3 cm boyutundaki lezyon alanının % 30 kadarında mevcut
  - . Nekroz oranı: % 10
  - . Fibrozis ve inflamasyon: % 60
- Lenfovasküler invazyon: mevcut
- Cerrahi sınırlar
  - . Bronş cerrahi sınırı: tümör görülmedi
  - . Arter cerrahi sınır: tümör görülmedi
  - . Ven cerrahi sınır: tümör görülmedi
- Lenf nodları

11 Orta lob no'lu lenf nodu, disseksiyon: 12 adet reaktif lenf nodu parçası. Tümör görülmedi. 0/12
İntermediate lenf nodu, disseksiyon: 1 adet reaktif lenf nodu. Tümör görülmedi. 0/1
2R no'lu lenf nodu, disseksiyon: 1 adet reaktif lenf nodu. Tümör görülmedi. 0/1
4R no'lu lenf nodu, disseksiyon: 4 adet reaktif lenf nodu. Tümör görülmedi. 0/4
4R.inferior no'lu lenf nodu: 4 adet lenf nodundan 2 tanesinde tümör mevcut (tümör makrometastaz niteliğindeki perinodal yayılım görülmedi.) 2/4

Ek Adjuvan 3 kür Paklitaksel/Karboplatin
+ Nivolumab 360 mg/3w

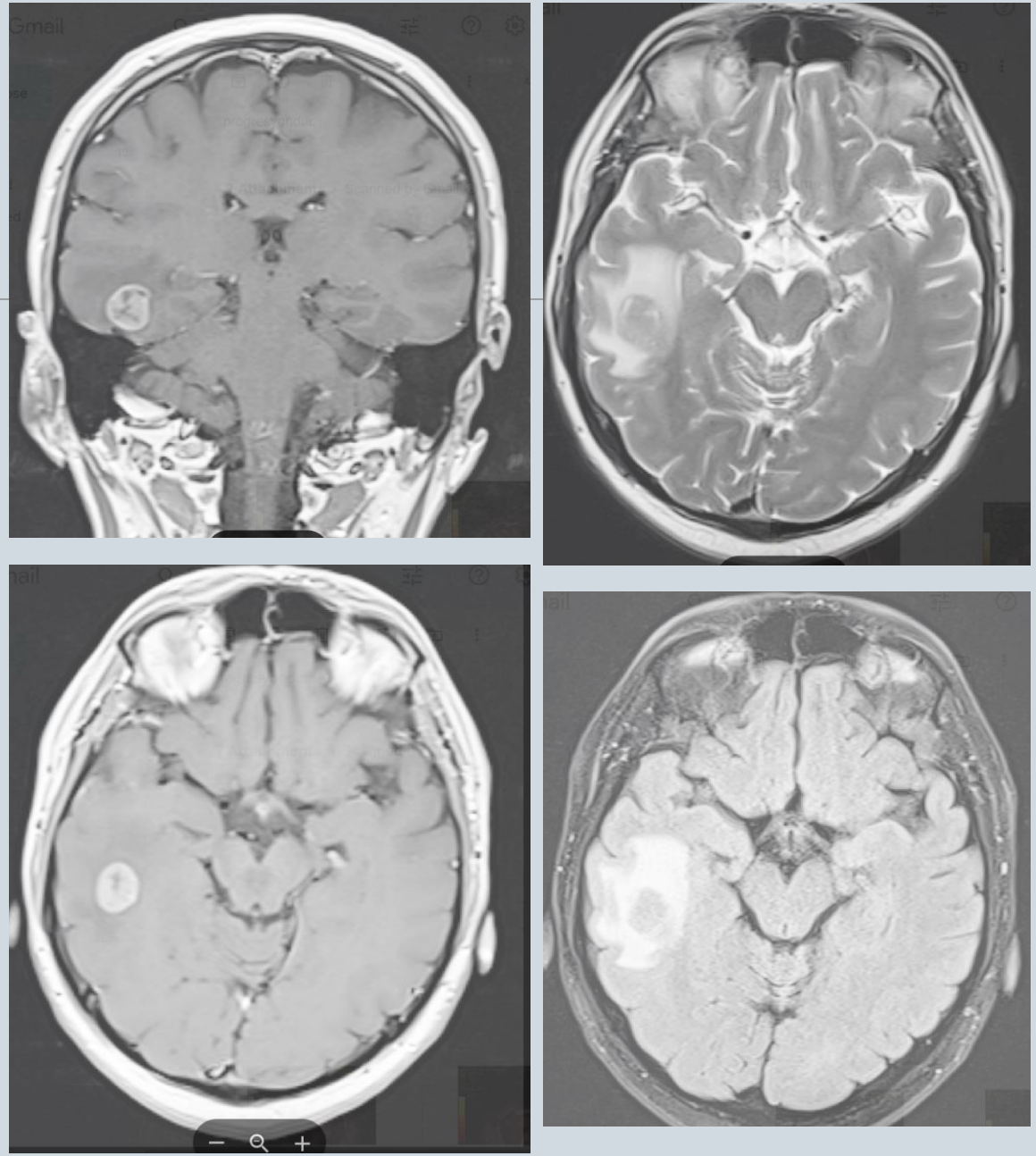
Bitiminde Nivolumab 480 mg / 4 haftada bir adjuvan devam edildi

Haziran 2024: Bayılma

Kontrastlı MRI: Sağ inferodorsal temporal kortikosubkortikal yerleşimli, 18 mm çapta nodüler nonhomojen sinyal özelliklerinde solid mass. Perilezyonel orta derecede vazojenik ödem.

PET-CT: Belirgin FDG afiniteli malignite bulgusunun saptanmadığı tüm vücut PET/CT çalışması

CTC/ctDNA → Epitelyal malignite bulgusu Negatif



SRS uygulandı, Nivolumab 480 mg devam edildi (Son doz 6 Ekim 2024)

Kasım 2024: Şikayeti yok, Kontrol MRIda lezyonda büyüme

MR Spektorokopi incelemesinde nekroz ile uyumlu yaygın laktat pikleri izlendi.
Bulgular nekroz/radyasyon nekrozu lehine yorumlanmıştır.

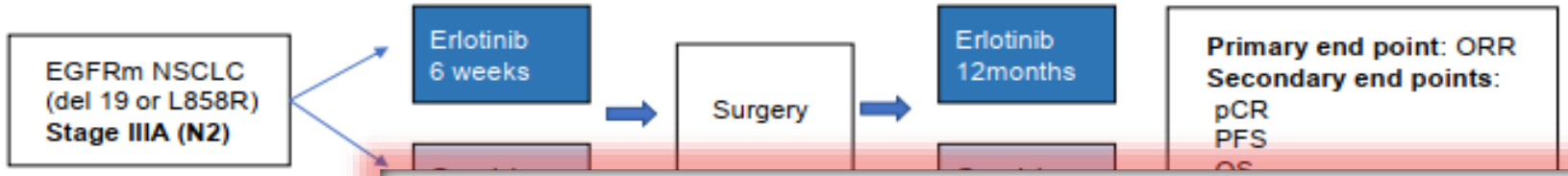
03.06.2024 tarihli PET-BT ile karşılaştırıldığında:
Belirgin FDG afiniteli malignite bulgusunun saptanmadığı tüm vücut PET/CT çalışması.

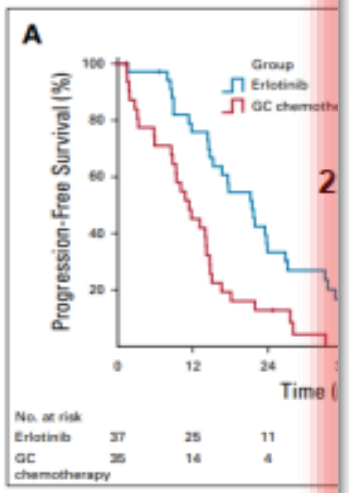
NRŞ konseyinde tartışıldı; Cerrahi bir seçenek; görüntülerin radyonekroz olasılığı sebebiyle öncelikle sistemik tedavi ile 2 ay sonra kontrol

Bevasizumab 7.5 mg/kg/2w başlandı

Perioperatif TKI??

CTONG 1103: Neoadjuvant Erlotinib in N2 *EGFR*m NSCLC (RPII)



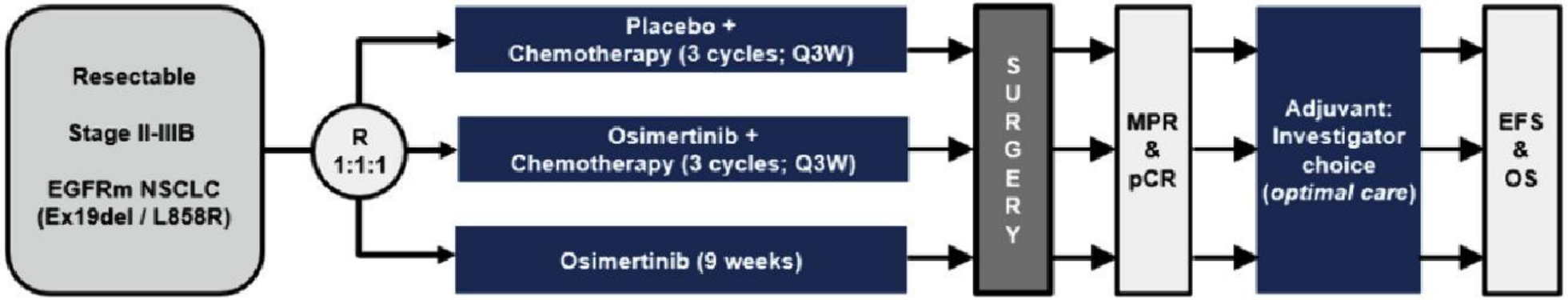


Neoadjuvant Osimertinib Trials in Operable *EGFRm* NSCLC

Author	Phase	Stage	EGFR	N	Regimen	ORR	pCR	MPR
Lyu et al	II	II-IIIB	Del 19 or L858R	40	Osimertinib 6 weeks	71.1%	3.6%	10.7%
Blackely et al	II	I-IIIA	Del 19 or L858R	13	Osimertinib 6 weeks	46%	0%	15%
Zhong et al	RPII	IIIA	Del 19 or L858R	7 8	Erlotinib 6 weeks	54.1%	0%	9.7%

2011-2017 China; 72 pts

NeoAdaura



Ex19del, Exon 19 deletion; NSCLC, non-small cell lung cancer; EGFRm, epidermal growth factor receptor mutation-positive; R, randomisation, Q3W, every three weeks; MPR, major pathological response; pCR, complete pathological response; EFS, event-free survival; OS, overall survival.

Table 2
Ongoing clinical trials investigating (neo)adjuvant TKIs in oncogenic NSCLCs.

Oncogene	(Neo) adjuvant	Study	Phase	Stage	Regimen	No.	Primary endpoint
EGFR mutation	Adjuvant	ICTAN (NCT01996098)	III	IIA–IIIA	CT vs CT + icotinib for 6 or 12 mo	318	DFS
		CORIN (NCT02264210)	II	IB	Clinical observation vs icotinib for 12 mo	128	OS
		ALCHEMIST (NCT02193282)	III	IB (T ≥ 4cm) – IIIA	CT vs CT + erlotinib for 2 y	450	OS
		APEX (NCT04762459)	III	II–IIIA	CT vs CT + Almonertinib for 3 y vs Almonertinib for 3 y	606	DFS
	Neoadjuvant	NeoADAURA (NCT04351555)	III	II–IIIB (N2)	Osimertinib vs osimertinib + CT vs placebo + CHT → surgery → investigator choice (osimertinib for 3 y)	328	MPR
		ANSWER (NCT04455594)	II	IIIA N2	Almonertinib vs Erlotinib/CT	168	ORR
		NeoIpower (NCT05104788)	II	II–IIIB	Icotinib + CT for 2 cycles → surgery	27	MPR
		NCT04201756	II	III	Afatinib 16 weeks → surgery → Afatinib for 1 y	47	ORR
		NCT03749213	II	IIIA N2	Icotinib for 8 w → surgery → icotinib for 2 y	36	ORR
ALK rearrangement	Adjuvant	ALCHEMIST (NCT02193282)	III	IB (T ≥ 4 cm) – IIIA	CT vs CT + crizotinib for 2 y	450	OS
		NCT05241028	II	IB (T ≥ 4 cm) – IIIA	Ensartinib for 3 y	80	3 y-DFSR
	Neoadjuvant	ALINA (NCT03456076)	III	IB (T ≥ 4 cm) – IIIA	CT vs alectinib for 2 y	255	DFS
		ALNeo (NCT05015010)	II	III	Alectinib 2cycles → surgery → alectinib for 2 y	33	MPR
RET	Adjuvant	LIBRETTO-432 (NCT04819100)	III	IB–IIIA	Surgery/radiation → selpercatinib for 3 y	170	EFS
MET	Neoadjuvant	Geometry-N (NCT04926831)	II	Stages IB–IIIA, N2 and selected IIIB (T3N2 or T4N2)	Capmatinib → surgery → adjuvant capmatinib	38	MPR
Other mutations *ALK/ ROS1/BRAF/ RET/ NTRK*	Neoadjuvant	NAUTIKA1 (NCT04302025)	II	II–III	TKI 2cycles → Surgery → CT + TKI for 2 y (alectinib, entrectinib, pralsetinib, vemurafenib + cobimetinib)	60	MPR

DFS, disease-free survival; DFSR, disease-free survival rate; OS, overall survival; MPR, major pathological response; ORR, objective response rate; RR, resection rate; CT, chemotherapy; TKI, tyrosine kinase inhibitor.

Sorular

❖%20'ye yakın hasta cerrahiye gidemiyor → Tedavi ilişkili yan etkiler <%5 ;
En sık sebep hastalık progresyonu →Kötü prognostik grup nasıl seçilmeli?

❖Optimal Adjuvan tedavi?
Ek olarak→ Upfront cerrahi sonrası Adjuvan ile karşılaştırılmıyorlar

❖Diğer Hedefler?

❖ctDNA based tedavi yönlendirmeleri

TEŞEKKÜRLER..

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