Küçük hücreli dışı Akciğer kanserinde Lokal ileri Hastalıkta Sistemik Tedavide Gelişmeler

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Tıbbi Onkoloji

Ders Planı

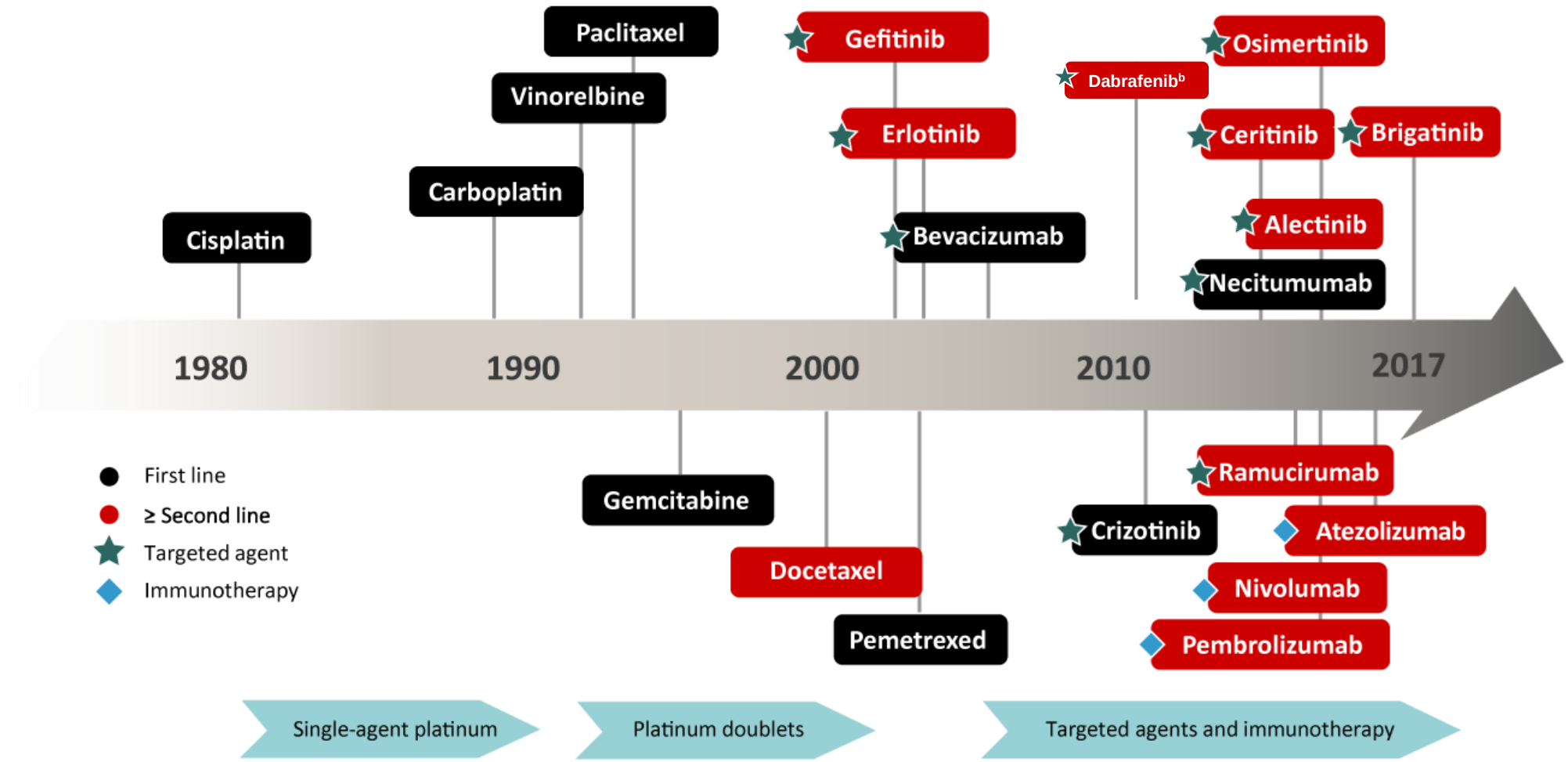
Giriş

Küçük hücreli dışı akciğer kanserinde

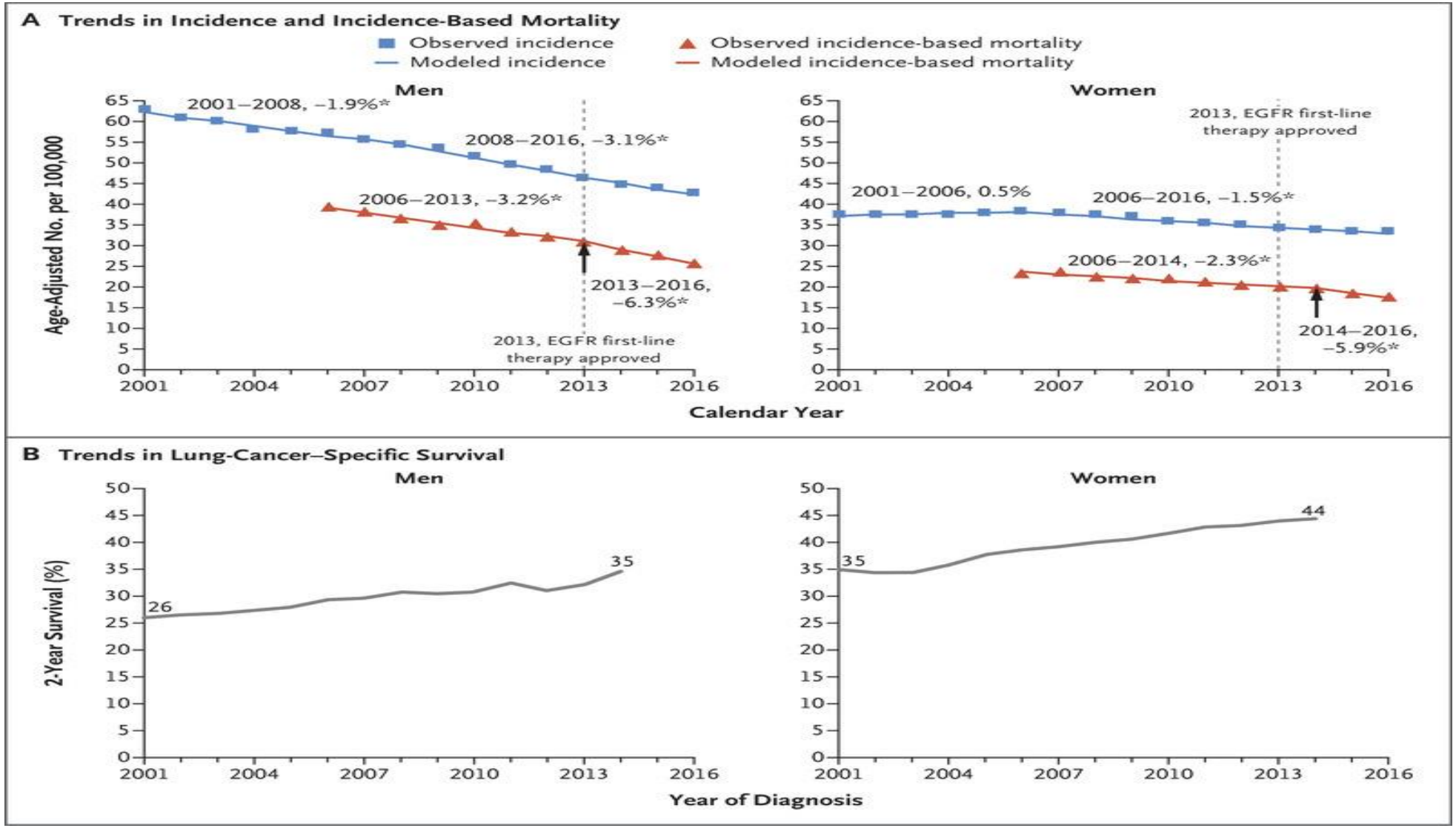
- Neoadjuvan sistemik tedavi
- Lokal ileri hastalıkta idame tedavi
- Lokal ileri hastalıkta eşzamanlı tedavi
- Gelecek perspektif ve devam eden çalışmalar

- Sonuç

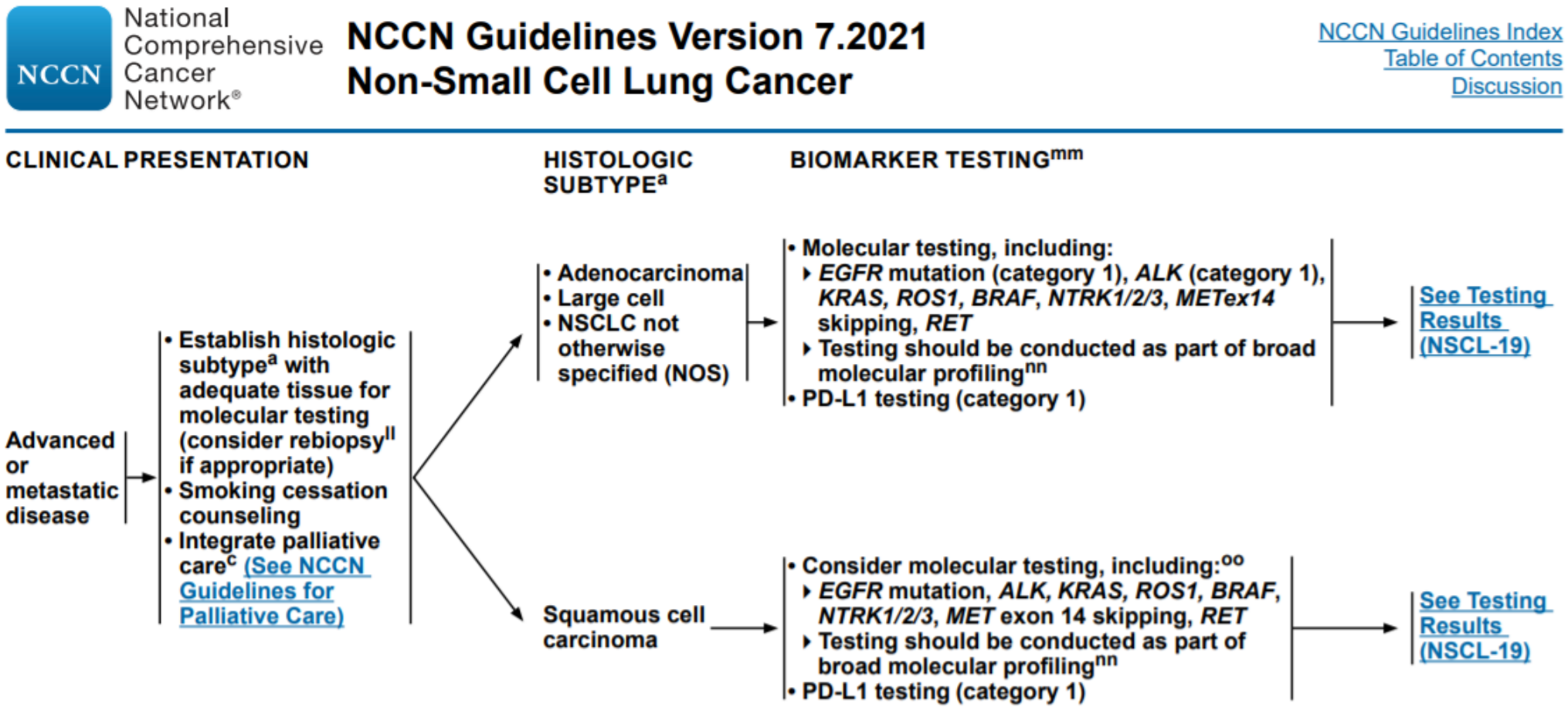
KHDAK'de Sistemik Tedavilerin Tarihsel Yolculuğu



Evre IV Akciğer Kanseri İnsidans ve Mortalite



Histoloji ve Genomik Özeliklere Göre Tedavi



Histoloji ve Genomik Özeliklere Göre Tedavi

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Non-Small Cell Lung Cancer

NCCN Guidelines Index
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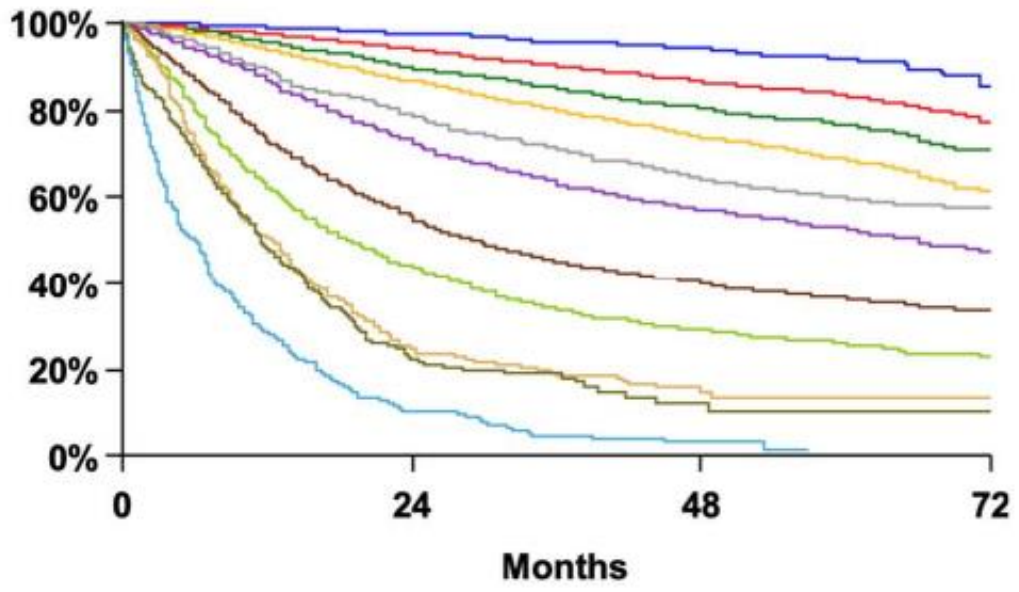
Discussion

TESTING RESULTS[ll,mm]

EGFR exon 19 **deletion or** ***L858R*** **mutation positive**	NSCL-20
EGFR S768I, L861Q, **and/or** ***G719X*** **mutation positive**	NSCL-23
EGFR exon 20 **insertion mutation positive**	NSCL-24
KRAS G12C **mutation positive**	NSCL-25
ALK **rearrangement positive**	NSCL-26
ROS1 **rearrangement positive**	NSCL-29
BRAF **V600E mutation positive**	NSCL-31
NTRK1/2/3 **gene fusion positive**	NSCL-32
METex14 **skipping mutation positive**	NSCL-33
RET **rearrangement positive**	NSCL-34
PD-L1 ≥50% and negative for actionable molecular biomarkers above	NSCL-35
PD-L1 ≥1%–49% and negative for actionable molecular biomarkers above	NSCL-36
PD-L1 <1% and negative for actionable molecular biomarkers above	NSCL-37

Metastatik Olmayan KHDAK Sistemik Tedaviye İhtiyaç Varmı



Stage (8th edition)	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

UCLA Health | David Geffen School of Medicine

The Journal of Thoracic Oncology. Vol. 11 No. 1: 39-51.

Devam eden çalışmalar

TABLE. Selected ongoing neoadjuvant and adjuvant clinical trials in earlier-stage NSCLC.

Trial Name	Study ID	Stage/timing	Treatment	Trial Dates*
Immunotherapy				
CheckMate 159	NCT02259621	I-IIIA, neoadjuvant	nivolumab ± ipilimumab	2014-2023
IMpower010	NCT02486718	IB-IIIA, adjuvant	Atezolizumab	2015-2022
KEYNOTE-091	NCT02504372	IB-IIIA	pembrolizumab	2015-2024
ANVIL	NCT02595944	IB-IIIA, adjuvant	nivolumab	2016-2024
LCMC3	NCT02927301	IB-IIIB, both neo/adjuvant	atezolizumab	2017-2025
PRINCEPS	NCT02994576	IB-IIIA, neoadjuvant	atezolizumab	2016-2022
NEOSTAR	NCT03158129	I-IIIA, neoadjuvant	nivolumab ± ipilimumab or chemotherapy	2017-2022
EMPOWER-CSCC-1	NCT03916627	I-IIIA, neoadjuvant	Cemiplimab	2019-2029
LUN0115	NCT04585477	I-III, adjuvant	Durvalumab	2021-2026
AAAT0800	NCT04625699	II-IIIB, adjuvant	durvalumab + tre	
NeoCOAST-2	NCT05061550	II-IIIA, both neo/adjuvant	durvalumab + ole	
Immunotherapy + chemotherapy				
CheckMate 816	NCT02998528	IB-IIIA, neoadjuvant	nivolumab + chemotherapy	2017-2028
KEYNOTE-671	NCT03425643	II-IIIB, both neo/adjuvant	pembrolizumab + chemotherapy	2018-2026
IMpower030	NCT03456063	IB-IIA, neoadjuvant	atezolizumab + platinum chemotherapy	2018-2026
AEGEAN	NCT03800134	II-III, both neo/adjuvant	durvalumab + chemotherapy	2018-2024
IMpower132	NCT04367311	IB-IIIA, adjuvant	atezolizumab + chemotherapy	2020-2024
MERMAID-1	NCT04385368	II-III, adjuvant	durvalumab + chemotherapy	2020-2026
GO42501	NCT04832854	II-IIIB, both neo/adjuvant	tiragolumab + atezolizumab ± chemotherapy	2021-2027
Targeted therapy				
ADAURA	NCT02511106	IB-IIIA, adjuvant	Osimertinib	2015-2023
BO40336	NCT03456076	IB-IIIA, adjuvant	Alectinib ± chemotherapy	2018-2026
NAUTIKA1	NCT04302025	IIA-IIIB, both neo/adjuvant	varied tyrosine kinase inhibitors	2020-2028
NeoADAURA	NCT04351555	II-IIIB, neoadjuvant	osimertinib ± chemotherapy	2020-2029
LIBRETTO-432	NCT04819100	IB-IIIA, adjuvant	Selpercatinib	2021-2032
Geometry-N	NCT04926831	IB-IIIA, both neo/adjuvant	capmatinib	2021-2028
	NCT05118854	IIA-IIIB, neoadjuvant	sotorasib + chemotherapy	2022-2023

*Study start date and estimated study completion date per clinicaltrials.gov accessed 2022/01/10.

www.onclive.com/view/happy-upheavals-are-unveiled-in-early-stage-lung-cancer
Cummings AL, January 26, 2022

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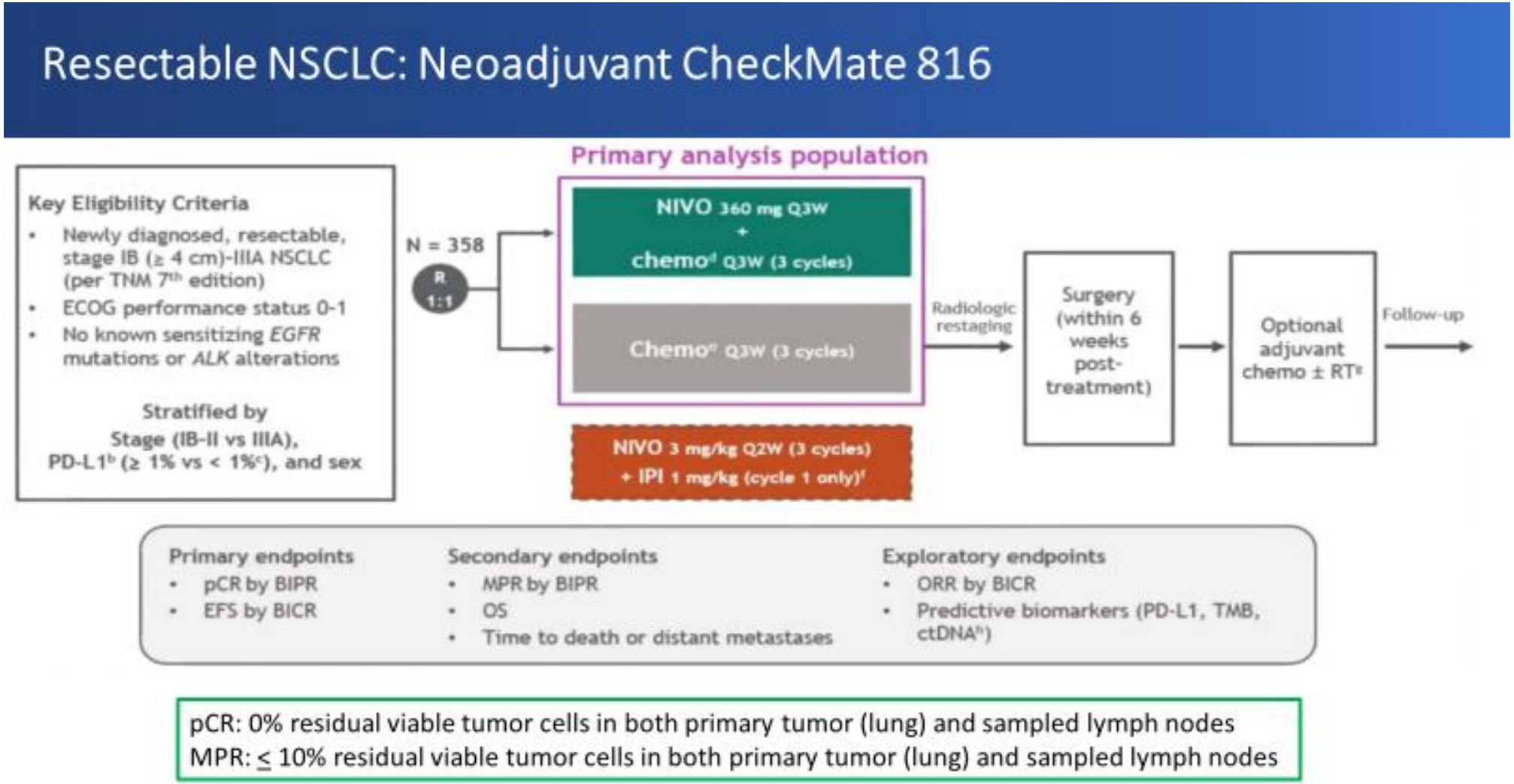
Küçük hücreli dışı akciğer kanserinde Neoadjuvan İmmünoterapi



pCR: 0% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes
MPR: ≤ 10% residual viable tumor cells in both primary tumor (lung) and sampled lymph nodes

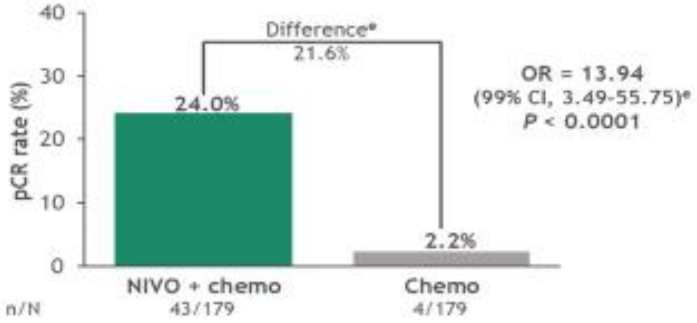
Forde et al. AACR 2021 Abstract CT003

Courtesy of Anne S Tsao, MD, MBA

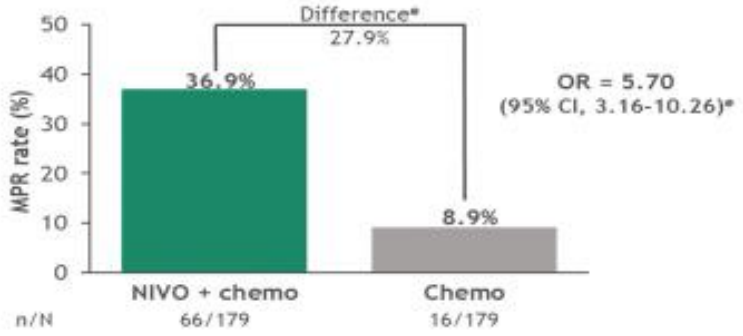
Küçük hücreli dışı akciğer kanserinde Neoadjuvan İmmünoterapi

CheckMate 816 Nivolumab + Chemo improves pCR, MPR, ORR

pCR[b,c] in ITT (ypT0N0)[d]



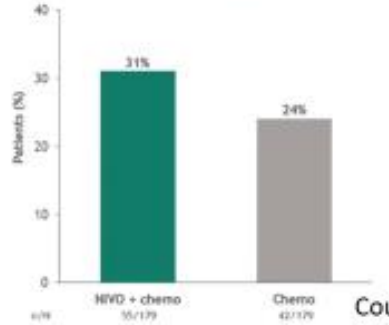
MPR[b,f] in ITT[d]



Objective response rate

Patients, n (%)	NIVO + chemo (n = 179)	Chemo (n = 179)
ORR[a]	96 (54)[b]	67 (37)[b]
Best overall response		
Complete response	1 (1)	3 (2)
Partial response	95 (53)	64 (36)
Stable disease	70 (39)	88 (49)
Progressive disease	8 (4)	11 (6)
Not evaluable	1 (1)	1 (1)
Not reported	4 (2)	12 (7)

Patients with radiographic down-staging[c]



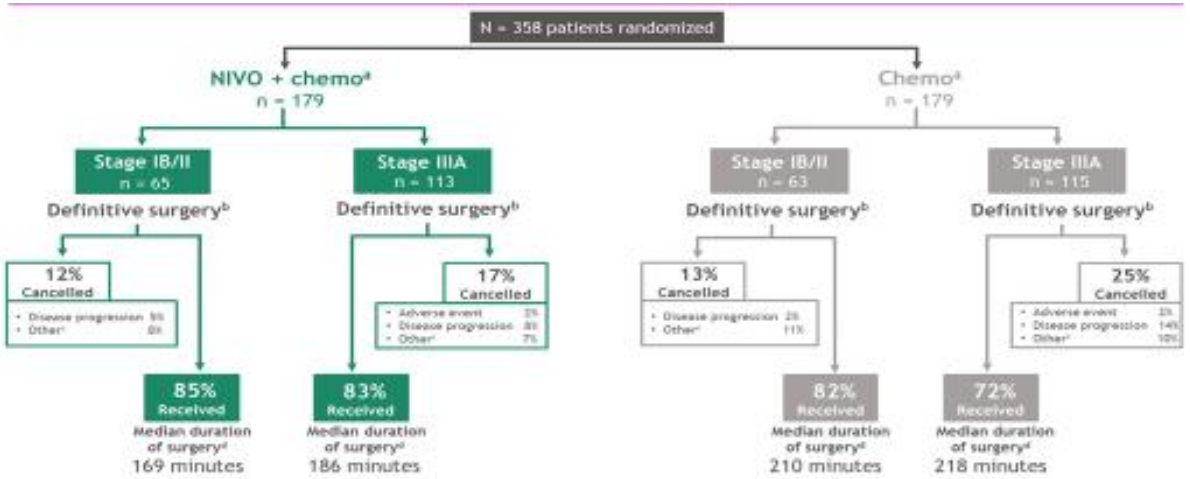
Forde et al. AACR 2021 Abstract CT003; Spicer et al. ASCO 2021 Abstract 8503

Courtesy of Anne S Tsao, MD, MBA

Küçük hücreli dışı akciğer kanserinde Neoadjuvan İmmünoterapi

İmmünoterapi+kemoterapi sonrası cerrahi olan /Kemoterapi sonrası Cerrahi olan

-Cerrahi op gecikme
-Komplikasyonlar
-Hastane yatış süreleri



Median time from last neoadjuvant dose to surgery nivo+chemo 5.3 weeks (4.6-6) vs chemo 5 weeks (4.6-5.9)

	NIVO + chemo (n = 135)	Chemo (n = 124)
Length of hospital stay, median (IQR), days	10.0 (7.0-14.0)	10.0 (7.0-14.5)
Length of hospital stay by surgery type,[a] median (IQR), days		
Lobectomy	10.0 (7.0-15.0)	9.0 (6.0-14.0)
Pneumonectomy	10.0 (8.0-13.0)	11.0 (9.0-16.0)
Other[b]	8.5 (4.0-13.0)	9.0 (7.0-14.0)
Length of hospital stay per region,[c,d] median (IQR), days		
North America	4.0 (4.0-7.0)	6.0 (4.0-8.0)
Europe	9.5 (8.0-14.0)	13.0 (7.0-18.0)
Asia	11.0 (9.0-16.0)	13.0 (10.0-16.0)

Courtesy of Anne S Tsao, MD, MBA

Küçük hücreli dışı akciğer kanserinde Neoadjuvan İmmünoterapi Çalışmaları

Ongoing Phase 3 NEO-Adj PD-(L)1 NSCLC IO

Drug	N	Stages	Description	Primary Endpoint
Nivo + platinum Chemo (ipi/nivo closed) CheckMate 816	350	Stage IB–IIIA, resectable NSCLC	Neo-adjuvant, no adjuvant	MPR / RFS
Atezo + platinum Chemo IMpower030	374	Stage II–IIIB (T3N2), resectable NSCLC	Neo-adjuvant chemo-ICI, then adjuvant IO	MPR / RFS
Pembro + platinum-doublet Chemo KEYNOTE-671	786	Stage IIB–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	RFS / OS
Durva + platinum-doublet Chemo	300	Stage II–IIIA, resectable NSCLC	Neo-adjuvant chemo-ICI then adjuvant IO	MPR

Courtesy of Heather Wakelee, MD

Lokal İleri KHDAK'de Sistemik Tedaviler

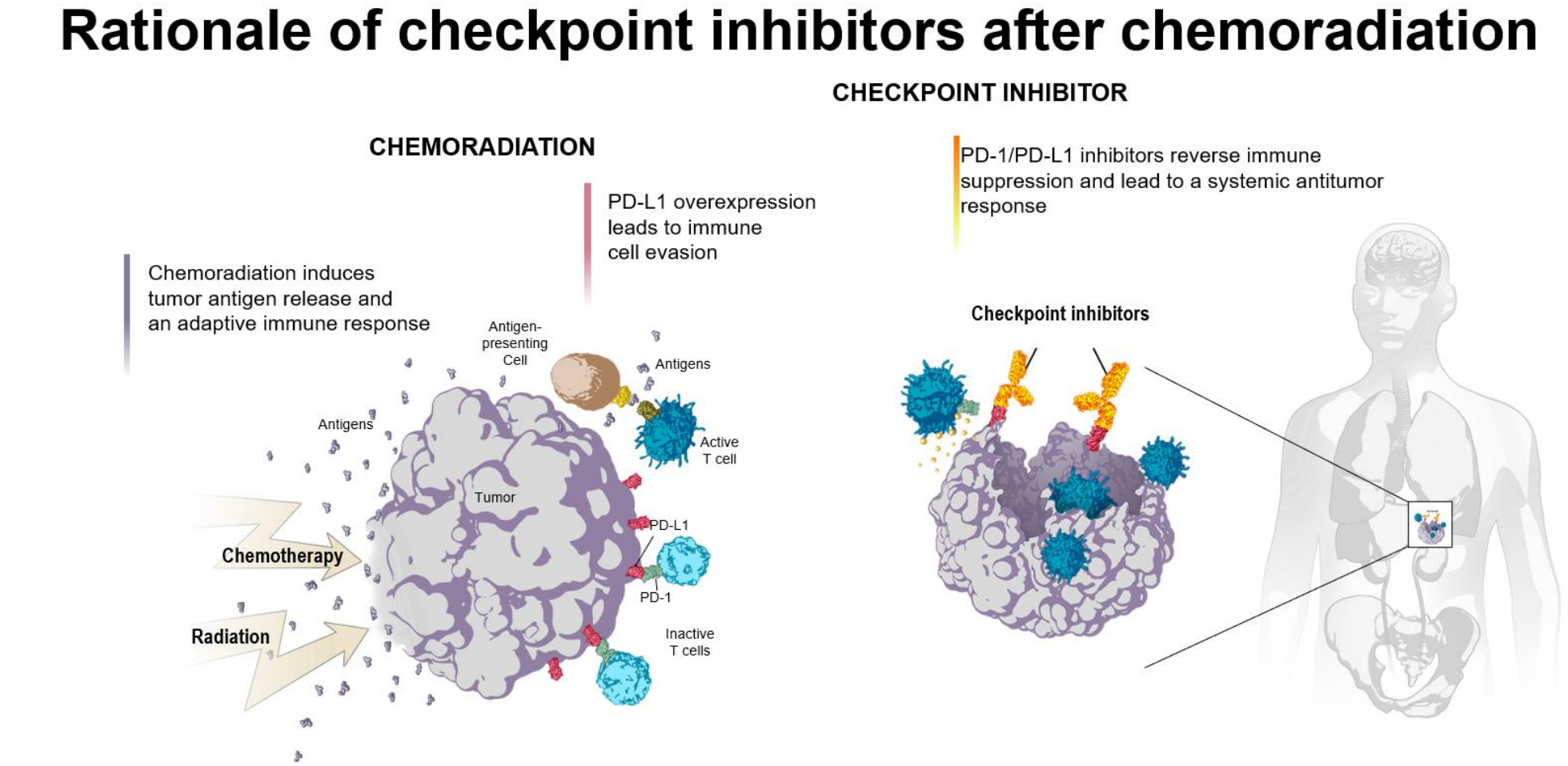
Selected Negative Trials after Concurrent Chemotherapy + Radiation

TRIAL	DESIGN	MEDIAN OS	HR	P VALUE
CALGB 39801[1]	Induction chemo → CRT vs cCRT	14 vs 12	N/R	0.3
LUN 01-24[2]	cCRT → docetaxel vs cCRT	23.2 vs 21.2	N/R	0.883
SWOG S0023[3]	cCRT → docetaxel → placebo vs cCRT → docetaxel → gefitinib	35 vs 23	0.63	.0013
RTOG 0617[4]	cCRT → chemo vs cCRT + cetuximab → chemo	24 vs 25	1.07	0.29
START[5]	Sequential or cCRT → placebo vs Sequential or cCRT → tecemotide	25.6 vs 22.3	0.88	.123

Courtesy of Benjamin Levy, MD

1. Vokes et al J Clin Oncol 2007
2. Hanna et al J Clin Oncol 2008
3. Kelly et al J Clin Oncol 2008
4. Bradley et al Lancet Oncol 2015
5. Butts et al Lancet Oncol 2014

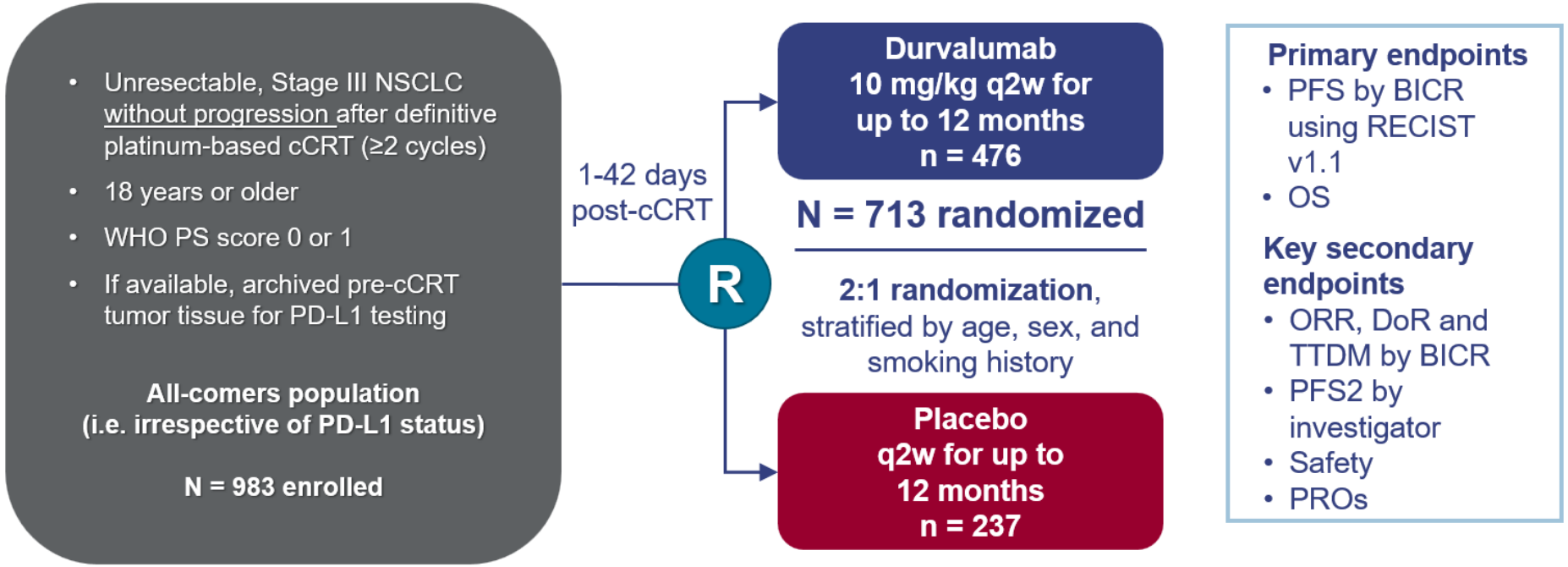
Lokal İleri KHDAK'de Sistemik Tedaviler



Courtesy of Benjamin Levy, MD

Lokal İleri KHDAK İdame İmmünoterapi

PACIFIC: Phase 3, Randomized, Double-blind, Placebo-controlled, Multicenter, International Study[1,2]



- Data cutoff (March 22, 2018) for the planned OS IA occurred after 299 events (61% of the target 491 events)
- OS sample size assumption: ≥85% power to detect an HR of 0.73 with 491 events, using a 2.5% 2-sided significance level

ClinicalTrials.gov number: NCT02125461

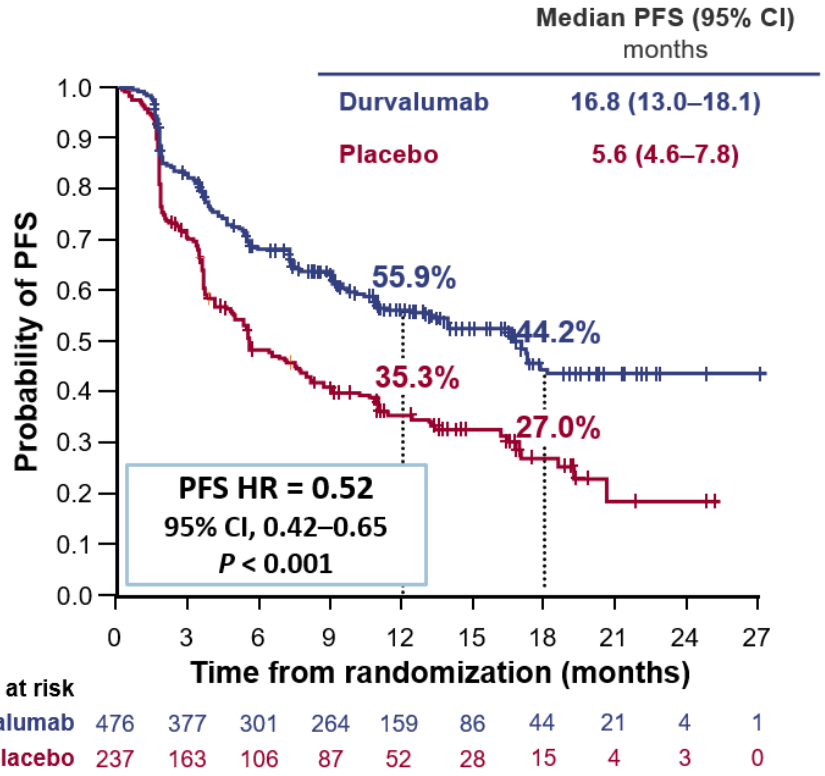
1. Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-1929.
2. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

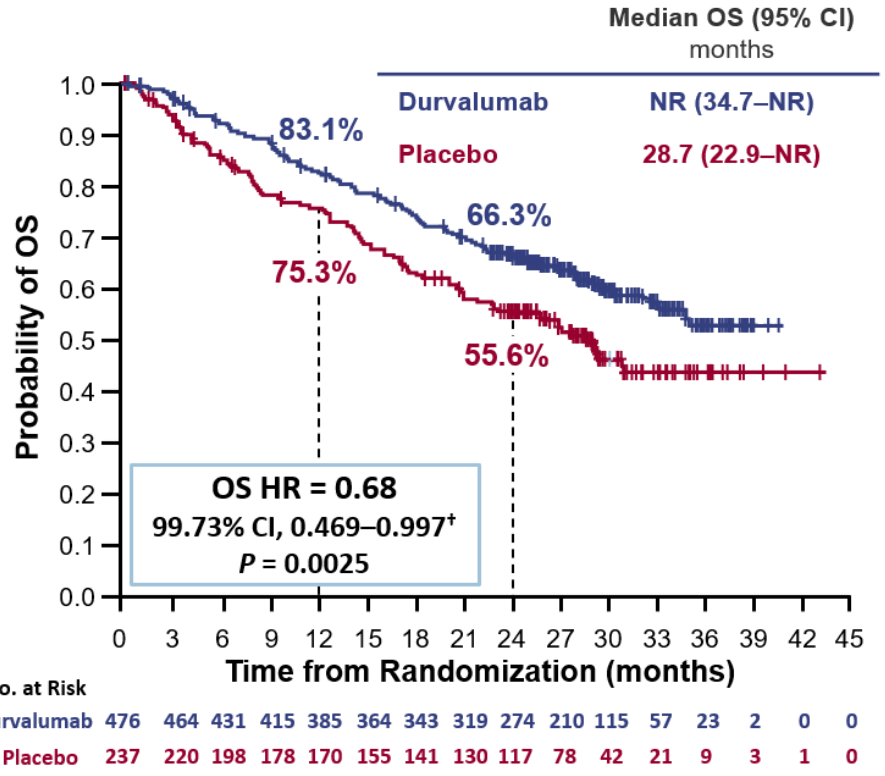
Lokal İleri KHDAK İdame İmmünoterapi

PACIFIC: Primary Endpoints (ITT)[1,2]

PFS (BICR)[1]



OS[2]*



*Median duration of follow-up was 25.2 months (range 0.2–43.1); †Adjusted for interim analysis; NR, not reached. Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of Mar 22, 2018.

1. Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-1929.
2. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
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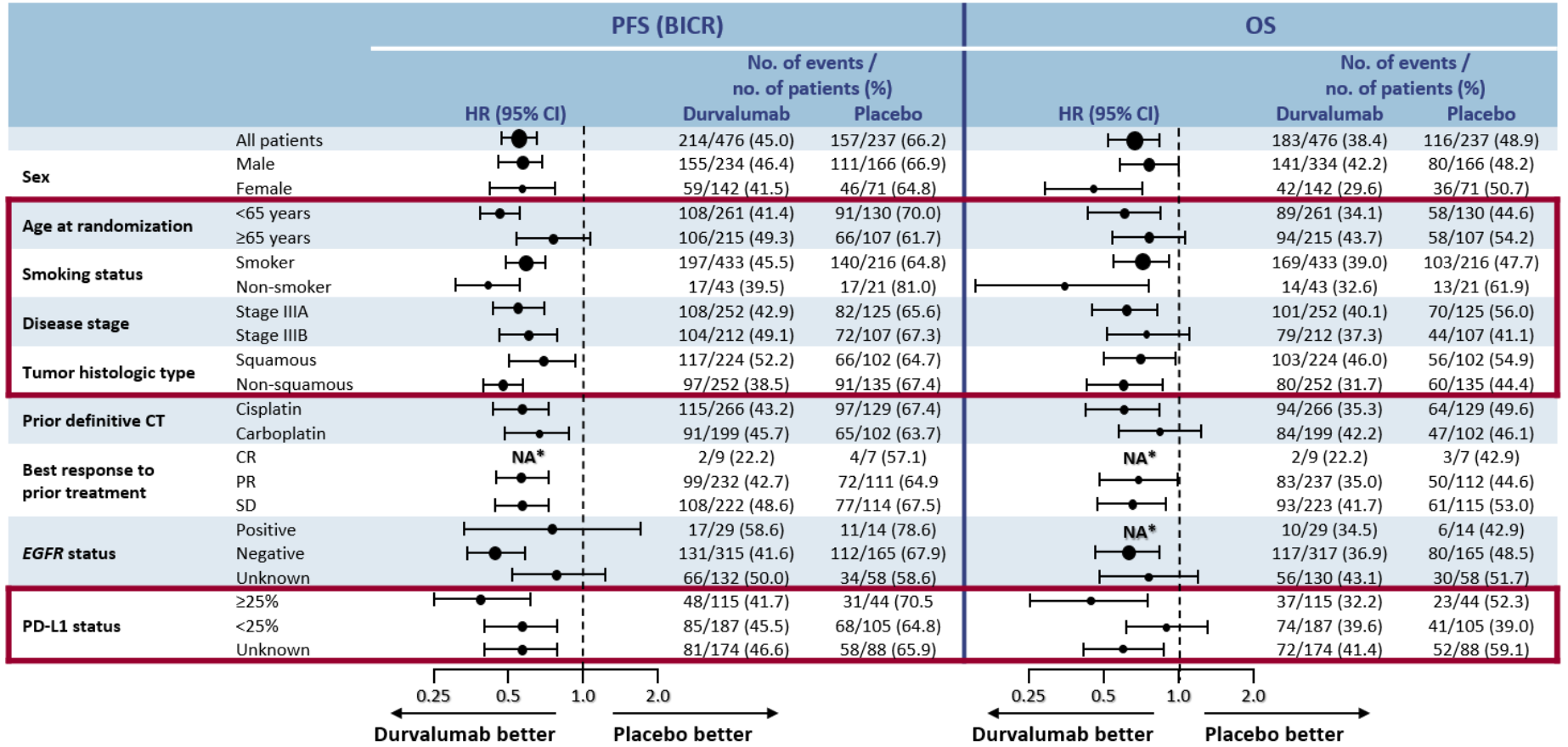
Lokal İleri KHDAK İdame İmmünoterapi

PFS and OS by Pre-specified Subgroup (ITT)[1,2]



		PFS (BICR)			OS		
		HR (95% CI)	No. of events / no. of patients (%) Durvalumab	Placebo	HR (95% CI)	No. of events / no. of patients (%) Durvalumab	Placebo
	All patients		214/476 (45.0)	157/237 (66.2)		183/476 (38.4)	116/237 (48.9)
Sex	Male		155/234 (46.4)	111/166 (66.9)		141/334 (42.2)	80/166 (48.2)
	Female		59/142 (41.5)	46/71 (64.8)		42/142 (29.6)	36/71 (50.7)
Age at randomization	<65 years		108/261 (41.4)	91/130 (70.0)		89/261 (34.1)	58/130 (44.6)
	≥65 years		106/215 (49.3)	66/107 (61.7)		94/215 (43.7)	58/107 (54.2)
Smoking status	Smoker		197/433 (45.5)	140/216 (64.8)		169/433 (39.0)	103/216 (47.7)
	Non-smoker		17/43 (39.5)	17/21 (81.0)		14/43 (32.6)	13/21 (61.9)
Disease stage	Stage IIIA		108/252 (42.9)	82/125 (65.6)		101/252 (40.1)	70/125 (56.0)
	Stage IIIB		104/212 (49.1)	72/107 (67.3)		79/212 (37.3)	44/107 (41.1)
Tumor histologic type	Squamous		117/224 (52.2)	66/102 (64.7)		103/224 (46.0)	56/102 (54.9)
	Non-squamous		97/252 (38.5)	91/135 (67.4)		80/252 (31.7)	60/135 (44.4)
Prior definitive CT	Cisplatin		115/266 (43.2)	97/129 (67.4)		94/266 (35.3)	64/129 (49.6)
	Carboplatin		91/199 (45.7)	65/102 (63.7)		84/199 (42.2)	47/102 (46.1)
Best response to prior treatment	CR	NA*	2/9 (22.2)	4/7 (57.1)	NA*	2/9 (22.2)	3/7 (42.9)
	PR		99/232 (42.7)	72/111 (64.9		83/237 (35.0)	50/112 (44.6)
	SD		108/222 (48.6)	77/114 (67.5)		93/223 (41.7)	61/115 (53.0)
***EGFR* status**	Positive		17/29 (58.6)	11/14 (78.6)	NA*	10/29 (34.5)	6/14 (42.9)
	Negative		131/315 (41.6)	112/165 (67.9)		117/317 (36.9)	80/165 (48.5)
	Unknown		66/132 (50.0)	34/58 (58.6)		56/130 (43.1)	30/58 (51.7)
PD-L1 status	≥25%		48/115 (41.7)	31/44 (70.5		37/115 (32.2)	23/44 (52.3)
	<25%		85/187 (45.5)	68/105 (64.8)		74/187 (39.6)	41/105 (39.0)
	Unknown		81/174 (46.6)	58/88 (65.9)		72/174 (41.4)	52/88 (59.1)

*Not calculated if subgroup has <20 events; NA, not available.
Note: PFS data based on data cutoff of Feb 13, 2017, and OS data based on data cutoff of Mar 22, 2018.

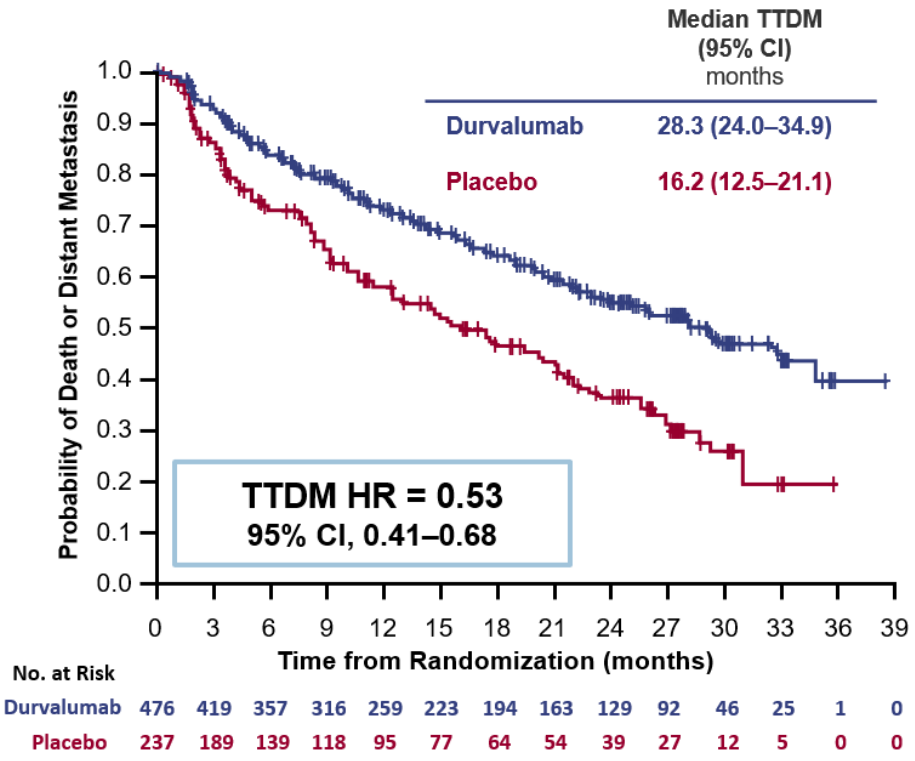
1. Antonia SJ, et al. *N Engl J Med.* 2017;377:1919-1929.
2. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Lokal İleri KHDAK İdame İmmünoterapi

Updates: ITT Population by BICR[1]

Time to Death or Distant Metastasis (TTDM)



Incidence of New Lesions

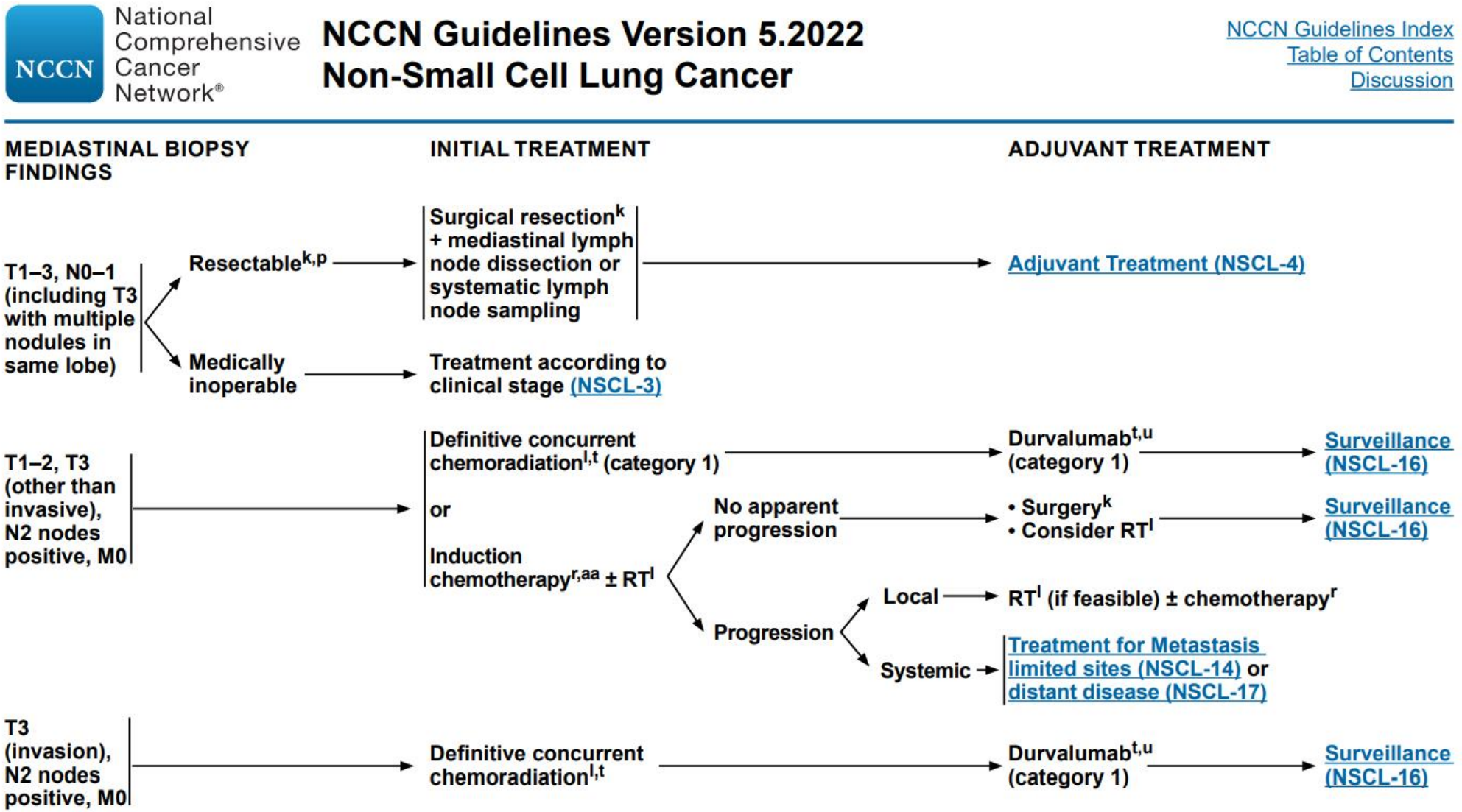
New Lesion Site*	Durvalumab N = 476	Placebo N = 237
Patients with any new lesion, n (%)	107 (22.5)	80 (33.8)
Lung	60 (12.6)	44 (18.6)
Lymph nodes	31 (6.5)	27 (11.4)
Brain†	30 (6.3)	28 (11.8)
Liver	9 (1.9)	8 (3.4)
Bone	8 (1.7)	7 (3.0)
Adrenal	3 (0.6)	5 (2.1)
Other	10 (2.1)	5 (2.1)

*A patient may have had more than one new lesion site;
†Monitoring for post-baseline CNS metastases was not specified in the protocol; brain scans were obtained at the investigator's discretion upon suspicion of new lesions.

1. Antonia SJ, et al. *N Engl J Med.* 2018;379:2342-2350.

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

Lokal İleri KHDAK İdame İmmünoterapi

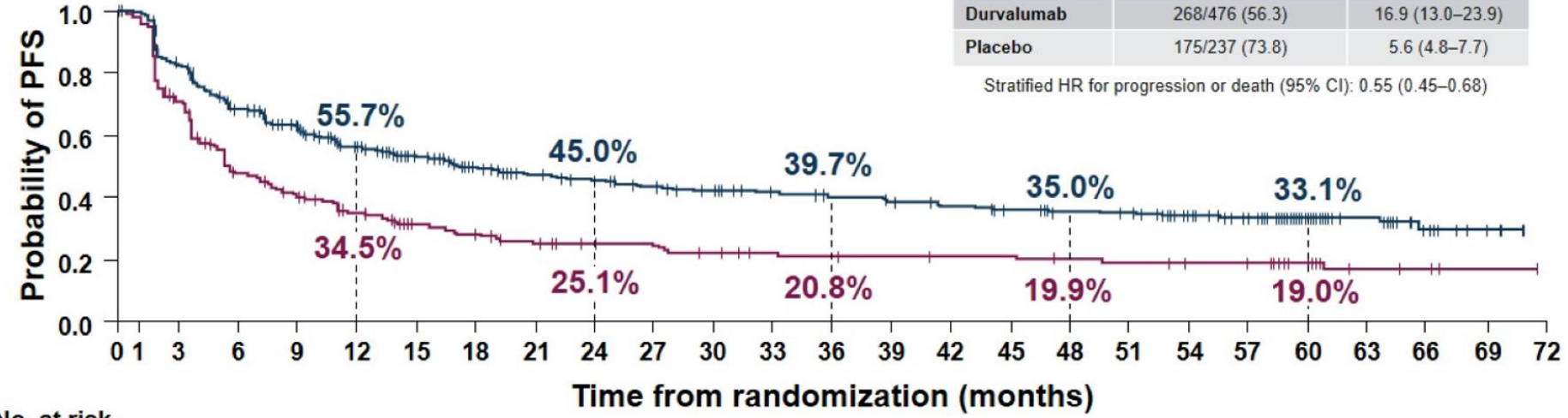


Lokal İleri KHDAK İdame İmmünoterapi

Post-hoc Efficacy Analysis: DCO5 Updated Progression-Free Survival (BICR;ITT)

	No. of events / No. of patients (%)	Median OS (95% CI) months
Durvalumab	268/476 (56.3)	16.9 (13.0–23.9)
Placebo	175/237 (73.8)	5.6 (4.8–7.7)

Stratified HR for progression or death (95% CI): 0.55 (0.45–0.68)



No. at risk

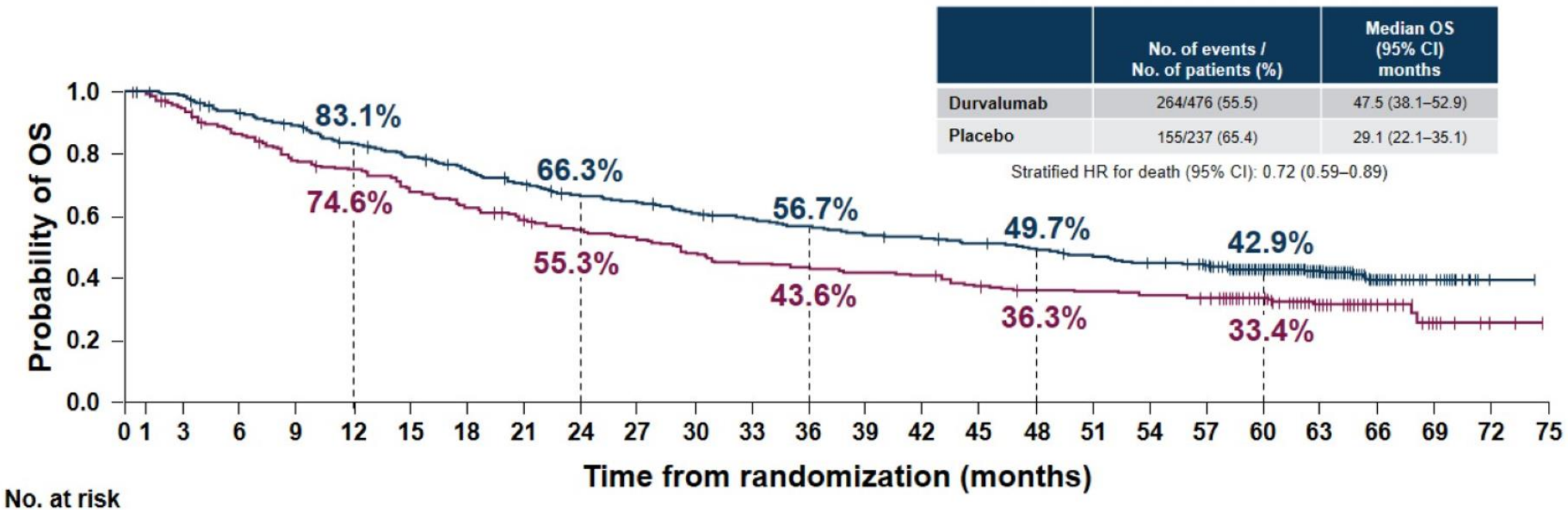
Durva.	476	377	301	267	215	190	165	147	137	128	119	110	103	97	92	85	81	78	67	57	34	22	11	5	0
Placebo	237	164	105	87	68	56	48	41	37	36	30	27	26	25	24	24	22	21	19	19	14	6	4	1	0

DCO5: January 11, 2021; median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7].
BICR = blinded independent central review; CI = confidence interval; DCO = data cutoff; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival
Spigel DR, et al. Poster presented at: ASCO Virtual Meeting; June 4-8, 2021.

Spigel DR et al. *J Clin Oncol* 2022;40(12):1301-1311.

Lokal İleri KHDAK İdame İmmünoterapi

Post-hoc Efficacy Analysis: DCO5 Updated Overall Survival (ITT)



No. at risk

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

DCO5: January 11, 2021; median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7].
CI = confidence interval; DCO = data cutoff; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival.
Spigel DR, et al. Poster presented at: ASCO Virtual Meeting; June 4-8, 2021.

Spigel DR et al. *J Clin Oncol* 2022;40(12):1301-1311.

Lokal İleri KHDAK İdame İmmünoterapi

Post-hoc Efficacy Analysis: Updated PFS in Pre-specified Subgroups

	PFS			
	No. of events / No. of patients (%)			
	Durvalumab	Placebo		Unstratified HR (95% CI)
All patients	268/476 (56.3)	175/237 (73.8)		0.58 (0.48–0.70)
Sex				
Male	192/334 (57.5)	122/166 (73.5)		0.61 (0.48–0.76)
Female	76/142 (53.5)	53/71 (74.6)		0.52 (0.36–0.74)
Age at randomization				
<65 years	140/261 (53.6)	100/130 (76.9)		0.46 (0.36–0.60)
≥65 years	128/215 (59.5)	75/107 (70.1)		0.76 (0.57–1.01)
Smoking status				
Smoker	246/433 (56.8)	158/216 (73.1)		0.61 (0.50–0.75)
Non-smoker	22/43 (51.2)	17/21 (81.0)		0.33 (0.17–0.63)
Disease stage				
IIIA	132/252 (52.4)	95/125 (76.0)		0.53 (0.40–0.69)
IIIB	130/212 (61.3)	77/107 (72.0)		0.64 (0.48–0.85)
Tumor histologic type				
Squamous	138/224 (61.6)	74/102 (72.5)		0.71 (0.54–0.94)
All other	130/252 (51.6)	101/135 (74.8)		0.48 (0.37–0.63)
Best response to prior treatment				
Complete response	5/9 (55.6)	4/7 (57.1)		Not calculated[a]
Partial response	126/237 (53.2)	85/112 (75.9)		0.56 (0.43–0.74)
Stable disease	133/223 (59.6)	84/115 (73.0)		0.57 (0.44–0.76)
Prior definitive CT				
Cisplatin	146/266 (54.9)	94/129 (72.9)		0.55 (0.42–0.71)
Carboplatin	114/199 (57.3)	76/102 (74.5)		0.62 (0.47–0.83)
EGFR mutation status				
Positive	21/29 (72.4)	11/14 (78.6)		0.82 (0.39–1.71)
Negative	169/317 (53.3)	124/165 (75.2)		0.52 (0.41–0.65)
Unknown	78/130 (60.0)	40/58 (69.0)		0.74 (0.51–1.09)
PD-L1 expression level				
≥25%	61/115 (53.0)	33/44 (75.0)		0.44 (0.29–0.67)
<25%	105/187 (56.1)	77/105 (73.3)		0.64 (0.48–0.86)
Unknown	102/174 (58.6)	65/88 (73.9)		0.60 (0.44–0.82)
1–24% (post-hoc analysis)	50/97 (51.5)	36/47 (76.6)		0.51 (0.33–0.78)
≥1% (post-hoc analysis)	111/212 (52.4)	69/91 (75.8)		0.47 (0.35–0.64)
<1% (post-hoc analysis)	55/90 (61.1)	41/58 (70.7)		0.80 (0.53–1.20)

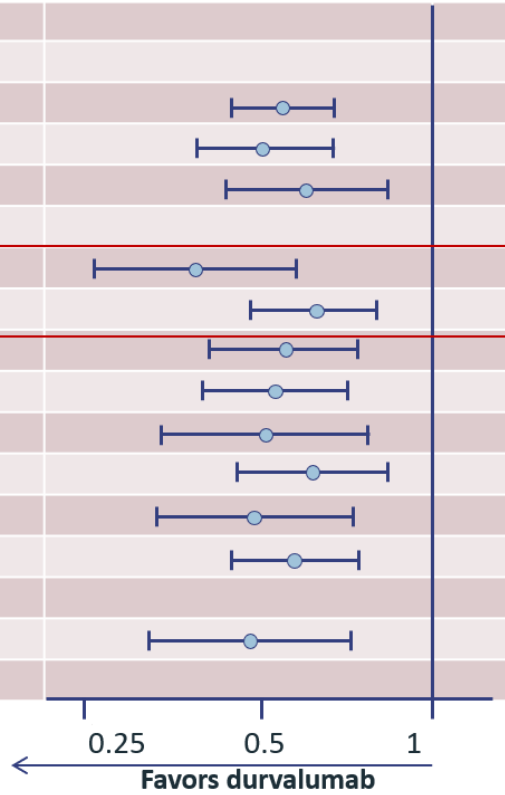
DCO5: January 11, 2021; [a]HRs and 95% CIs were not calculated if the subgroup had <20 events
CT = chemotherapy; DCO = data cutoff; EGFR = epidermal growth factor receptor; HR = hazard ratio; PD-L1 = programmed death ligand-1; PFS = progression-free survival.
Spigel DR, et al. Poster presented at: ASCO Virtual Meeting; June 4-8, 2021.

Spigel DR et al. *J Clin Oncol* 2022;40(12):1301-1311.

Lokal İleri KHDAK İdame İmmünoterapi

PACIFIC: Timing of start of durvalumab relative to CRT influences PFS

	Durvalumab	Placebo	Unstratified hazard ratio†
	No. of patients		(95% CI)
Type of chemotherapy gemcitabine-based	9	5	—
Type of chemotherapy non-gemcitabine-based	467	232	0.55 (0.45-0.68)
Cisplatin	266	129	0.51 (0.39-0.68)
Carboplatin	199	102	0.61 (0.44-0.83)
Cisplatin and carboplatin	8	5	—
Last radiation to randomization <14 days	120	62	0.39 (0.26-0.58)
Last radiation to randomization ≥ 14 days	356	175	0.63 (0.49-0.80)
Normal WHO performance status	234	114	0.56 (0.41-0.75)
Restricted WHO performance status	242	123	0.53 (0.40-0.71)
Asia	109	68	0.51 (0.34-0.77)
Europe	217	102	0.62 (0.46-0.84)
North America and South America	150	67	0.49 (0.33-0.73)
White	337	157	0.58 (0.45-0.75)
Black/African-American	12	2	—
Asian	120	72	0.48 (0.32-0.72)
Other	6	6	—

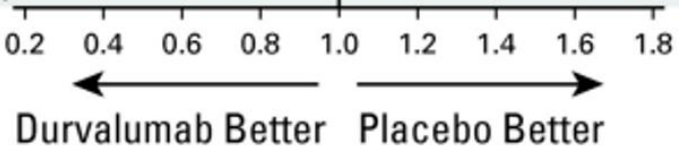


*Defined by RECIST v1.1. †Hazard ratio and 95% CI is not calculated if the subgroup level has less than 20 events.

Lokal İleri KHDAK İdame İmmünoterapi

PACIFIC *EGFR*, *ALK*, and PD-L1 Subsets

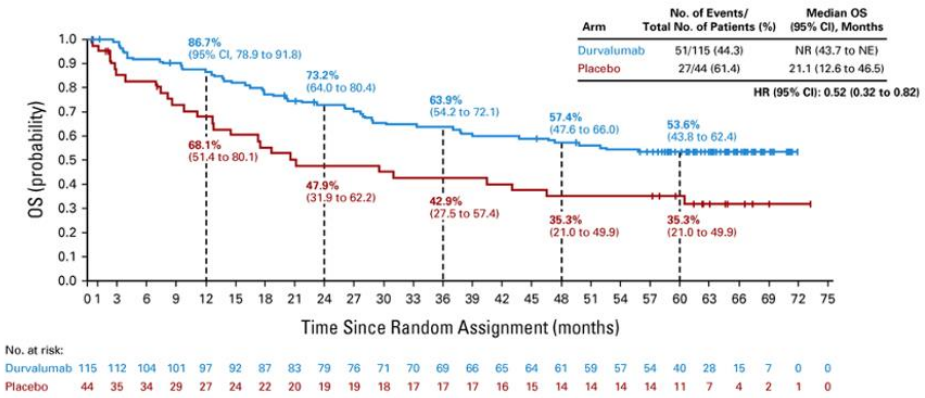
EGFR or *ALK* aberration status			
Positive[d]	17/29 (58.6)	8/14 (57.1)	0.85 (0.37 to 1.97)
Negative	166/317 (52.4)	109/165 (66.1)	0.66 (0.52 to 0.84)
Unknown	81/130 (62.3)	38/58 (65.5)	0.85 (0.57 to 1.24)
PD-L1 expression level			
≥ 25%	51/115 (44.3)	27/44 (61.4)	0.52 (0.32 to 0.82)
< 25%	111/187 (59.4)	64/105 (61.0)	0.90 (0.67 to 1.23)
Unknown	102/174 (58.6)	64/88 (72.7)	0.68 (0.50 to 0.93)
1%-24% (post hoc analysis)	52/97 (53.6)	29/47 (61.7)	0.73 (0.46 to 1.14)
≥ 1% (post hoc analysis)	103/212 (48.6)	56/91 (61.5)	0.61 (0.44 to 0.85)
< 1% (post hoc analysis)	59/90 (65.6)	35/58 (60.3)	1.15 (0.75 to 1.75)



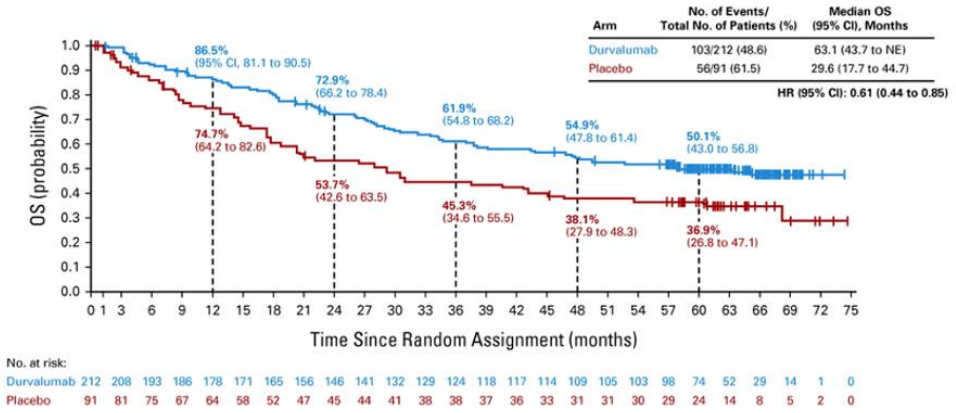
Spigel, JCO 2022

Lokal İleri KHDAK İdame İmmünoterapi

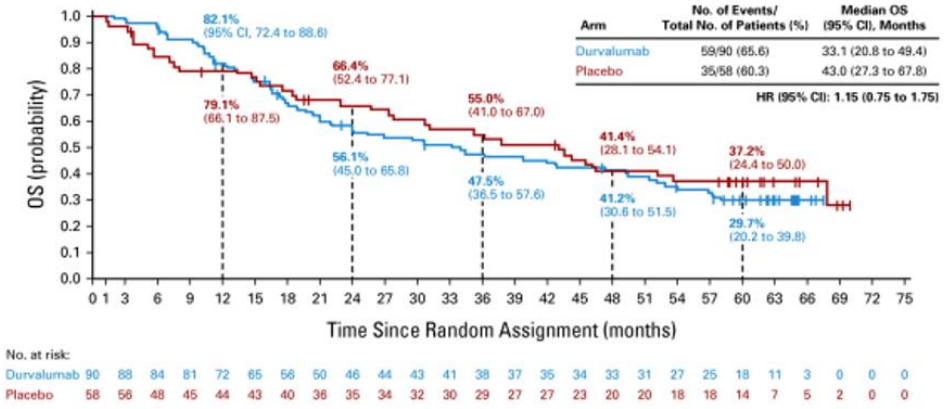
PACIFIC PD-L1 Subsets



PD-L1 >25%



PD-L1 >1%

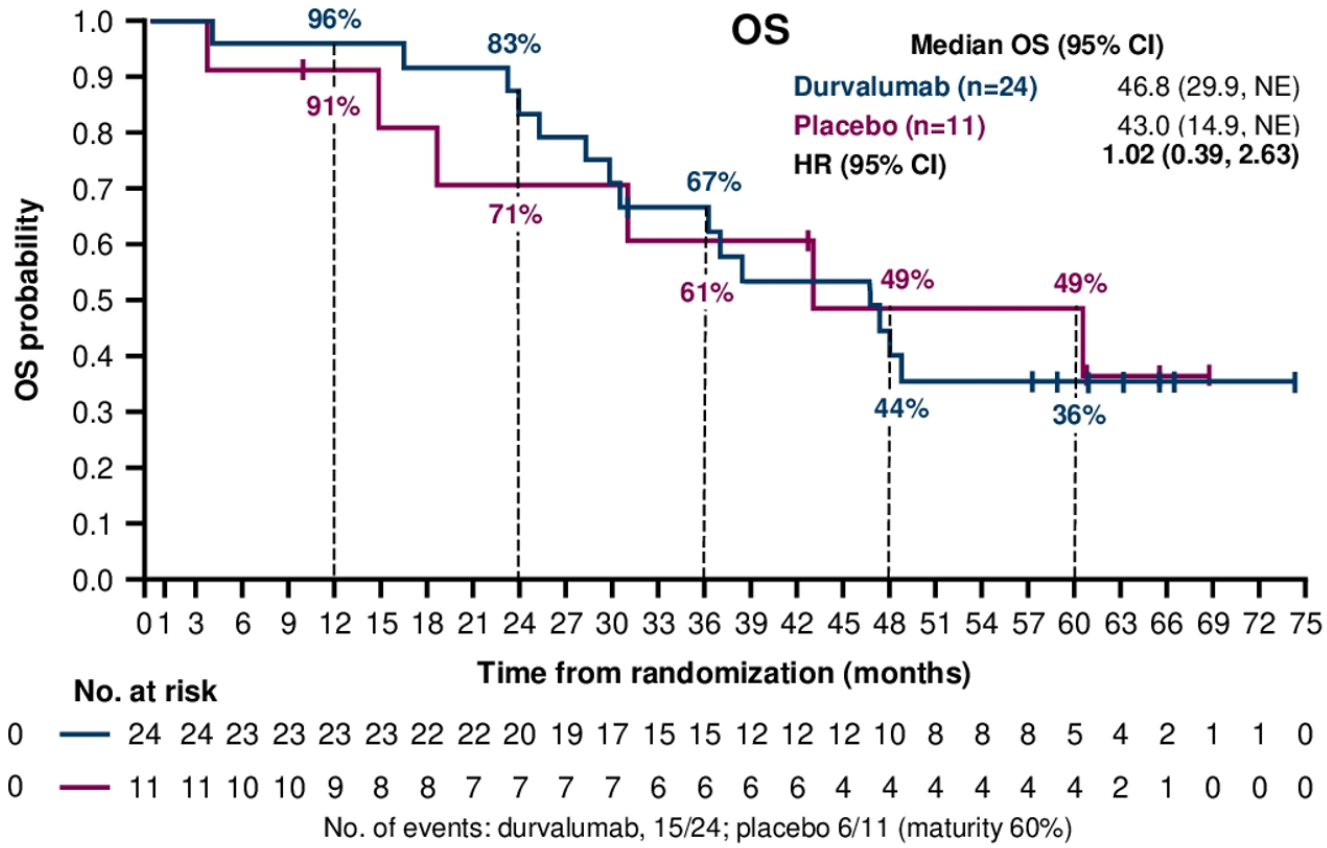


PD-L1 <1%

Spigel, JCO 2022

Lokal İleri KHDAK İdame İmmünoterapi

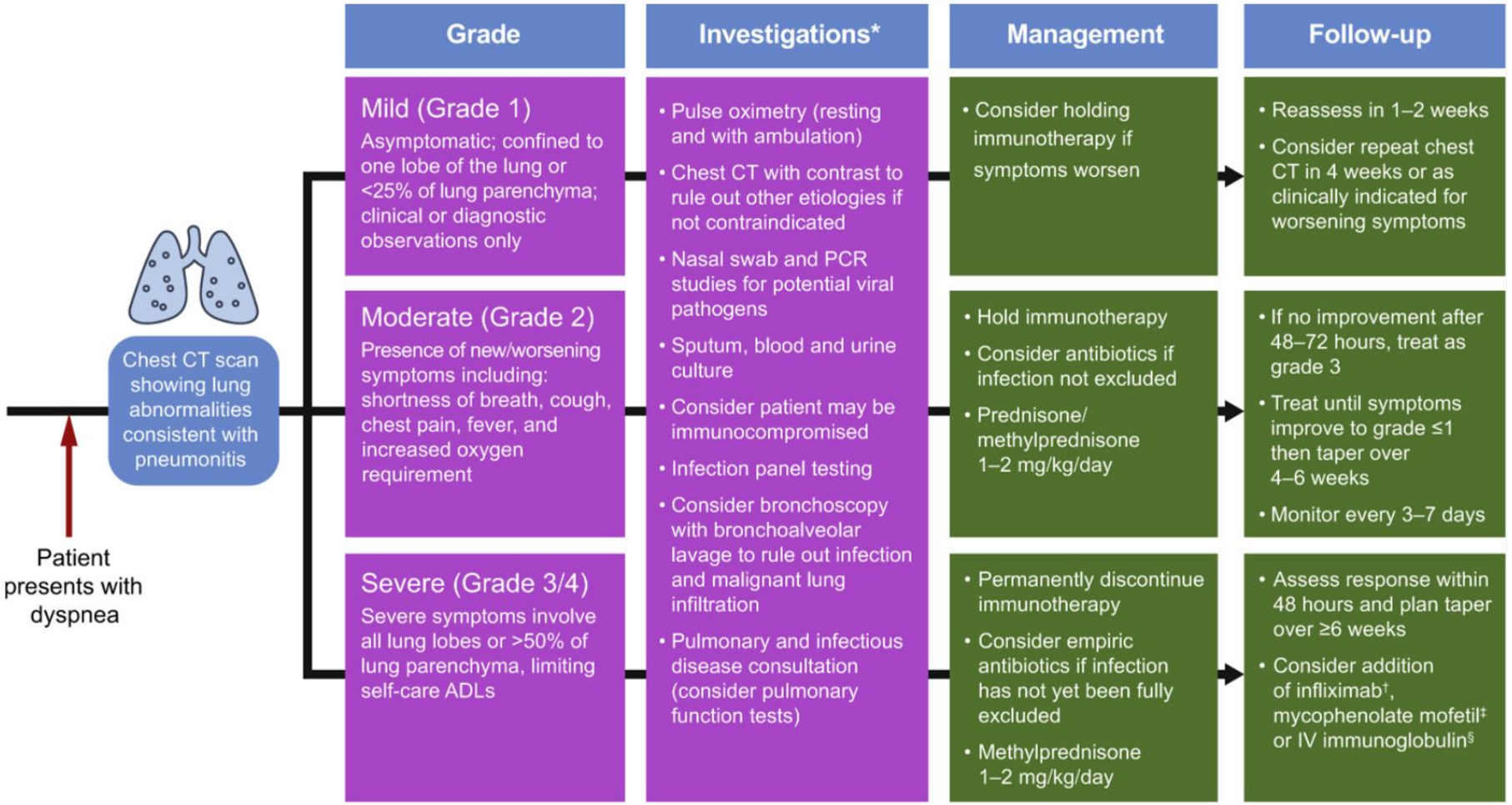
PACIFIC *EGFR* Subset (*post hoc*)



No. of events: durvalumab, 15/24; placebo 6/11 (maturity 60%)

Naidoo, ASCO 2022

Lokal İleri KHDAK İdame İmmünoterapi



Naidoo J. Clin Lung Cancer 2020:21(5):e435-e444

Lokal İleri KHDAK İdame İmmünoterapi

original reports

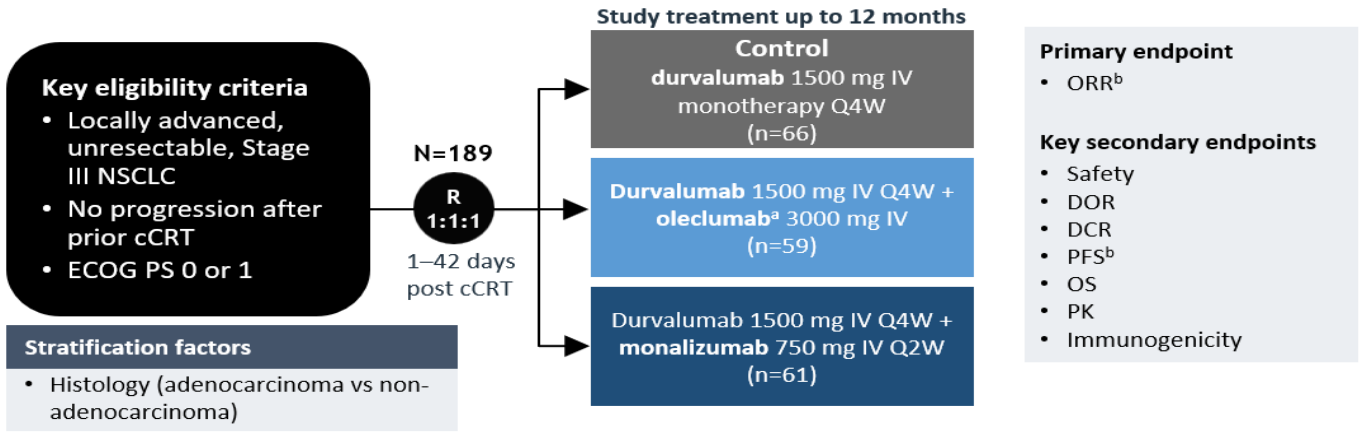
COAST: An Open-Label, Phase II, Multidrug Platform Study of Durvalumab Alone or in Combination With Oleclumab or Monalizumab in Patients With Unresectable, Stage III Non–Small-Cell Lung Cancer

Roy S. Herbst, MD, PhD[1]; Margarita Majem, MD, PhD[2]; Fabrice Barlesi, MD, PhD[3]; Enric Carcereny, MD[4]; Quincy Chu, MD[5]; Isabelle Monnet, MD, PhD[6]; Alfredo Sanchez-Hernandez, MD[7]; Shaker Dakhil, MD[8]; D. Ross Camidge, MD, PhD[9]; Leanne Winzer, MSc[10]; Yee Soo-Hoo, MPH[11]; Zachary A. Cooper, PhD[11]; Rakesh Kumar, MD, PhD[11]; John Bothos, PhD[11]; Charu Aggarwal, MD, MPH[12]; and Alex Martinez-Marti, MD[13]

Herbst RS et al. *J Clin Oncol* 2022;[Online ahead of print].

Lokal İleri KHDAK İdame İmmünoterapi

COAST (Phase 2, Open Label): Durvalumab ± Novel Agents in Patients with Locally Advanced, Unresectable, Stage III NSCLC



Monalizumab is a humanized IgG4 that inhibits NKG2A, an inhibitory cell surface receptor covalently bound to CD94, and expressed on tumor infiltrating NK cells and CD8 + T cells, which interacts with HLA-E

Oleclumab is a mAb that binds to CD73 and inhibits production of immunosuppressive adenosine

Data cutoff May 17, 2021; all patients had ≥10 months potential follow-up and median follow-up was 11.5 months (range 0.4–23.4; all patients).
[a]Oleclumab Q2W for cycles 1 and 2 then Q4W; [b]Investigator assessment by RECIST v1.1. cCRT, concurrent chemoradiotherapy; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; NK, natural killer; ORR, objective response rate; PK, pharmacokinetics.

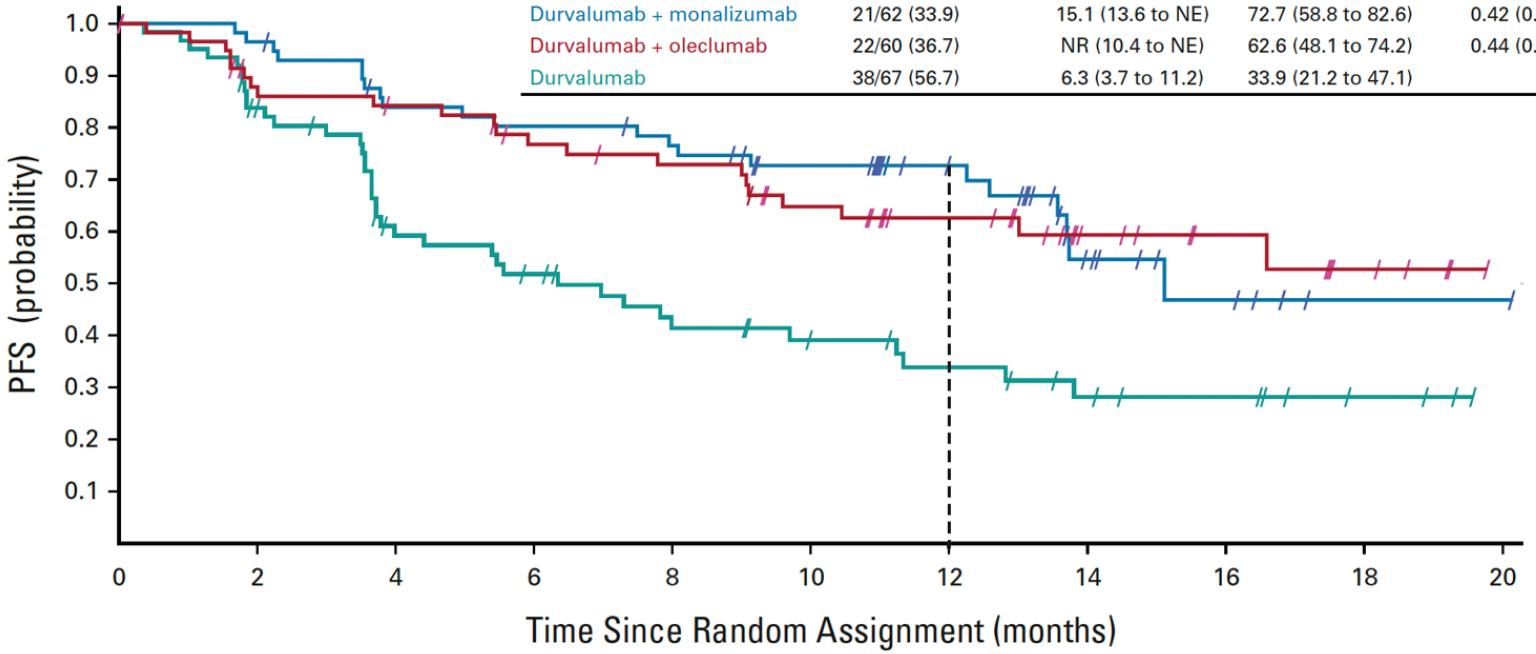
Martinez-Marti A et al. ESMO 2021;Abstract LBA42. Herbst RA et al. *JCO* 2022.

Courtesy of Heather Wakelee, MD, FASCO

Lokal İleri KHDAK İdame İmmünoterapi

COAST: Progression-Free Survival

Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)	0.44 (0.26 to 0.75)
Durvalumab	38/67 (56.7)	6.3 (3.7 to 11.2)	33.9 (21.2 to 47.1)	–

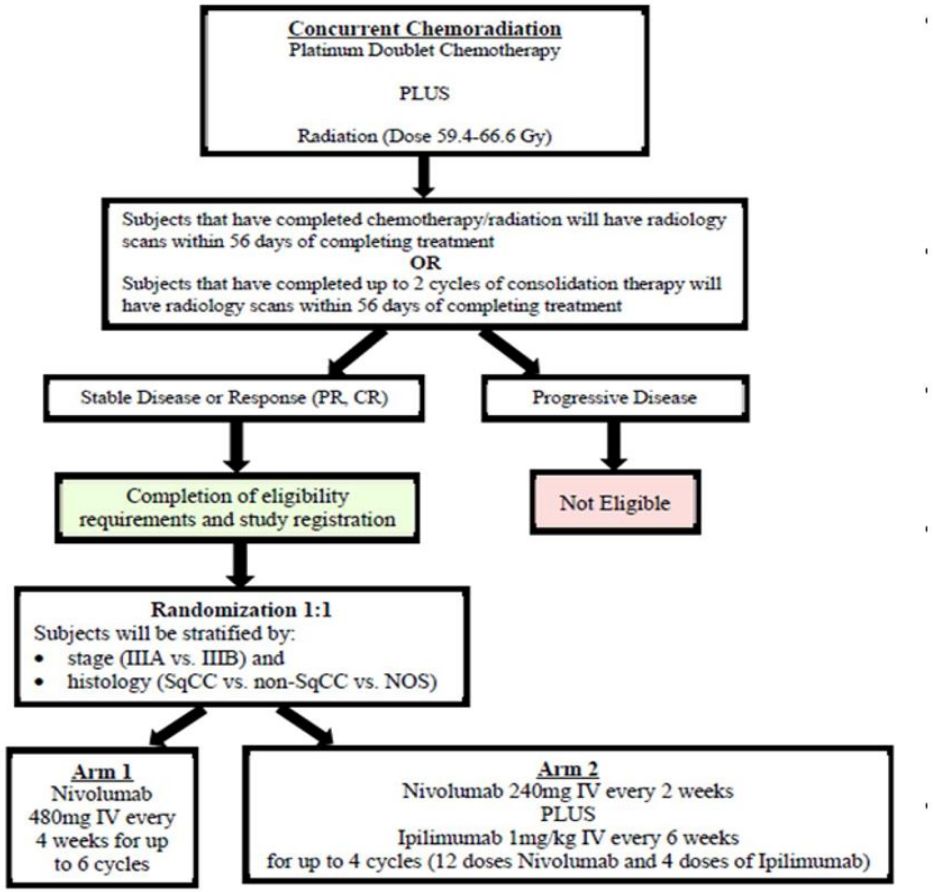


No. at risk:											
Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

Herbst RS et al. *J Clin Oncol* 2022;[Online ahead of print].

Lokal İleri KHDAK İdame İmmünoterapi

Nivolumab +/- Ipilimumab after ChemoRT



Durm, ASCO 2022

Lokal İleri KHDAK İdame İmmünoterapi

Nivolumab +/- Ipilimumab after ChemoRT

	Nivolumab Alone (N=54)	Nivolumab/Ipilimumab (N=51)
Any Treatment-Related AE (TRAE), n (%)	39 (72.2)	41 (80.4)
Any Grade ≥3 AE, n (%)*	21 (38.9)	27 (52.9)
Any Grade ≥3 TRAE, n (%)	10 (18.5)	14 (27.5)
TRAE Occurring in ≥ 10% Pts, n (%)		
Fatigue	17 (31.5)	16 (31.4)
Dyspnea	8 (14.8)	10 (19.6)
Rash	9 (16.7)	8 (15.7)
Hypothyroidism	7 (13)	8 (15.7)
Diarrhea	4 (7.4)	10 (19.6)
Pruritus	5 (9.3)	9 (17.7)
Arthralgia	2 (3.7)	6 (11.8)
Nausea	2 (3.7)	6 (11.8)
Pneumonitis		
Grade ≥2	12 (22.2)	16 (31.4)
Grade 3 (no Gr 4/5 pneumonitis)	5 (9.3)	9 (17.6)
Median time to Gr ≥2 Pneum, mo. (range)	11.9 (4.1-36.6)	7.3 (1.3-36.9)

Durm, ASCO 2022

Lokal İleri KHDAK İdame İmmünoterapi

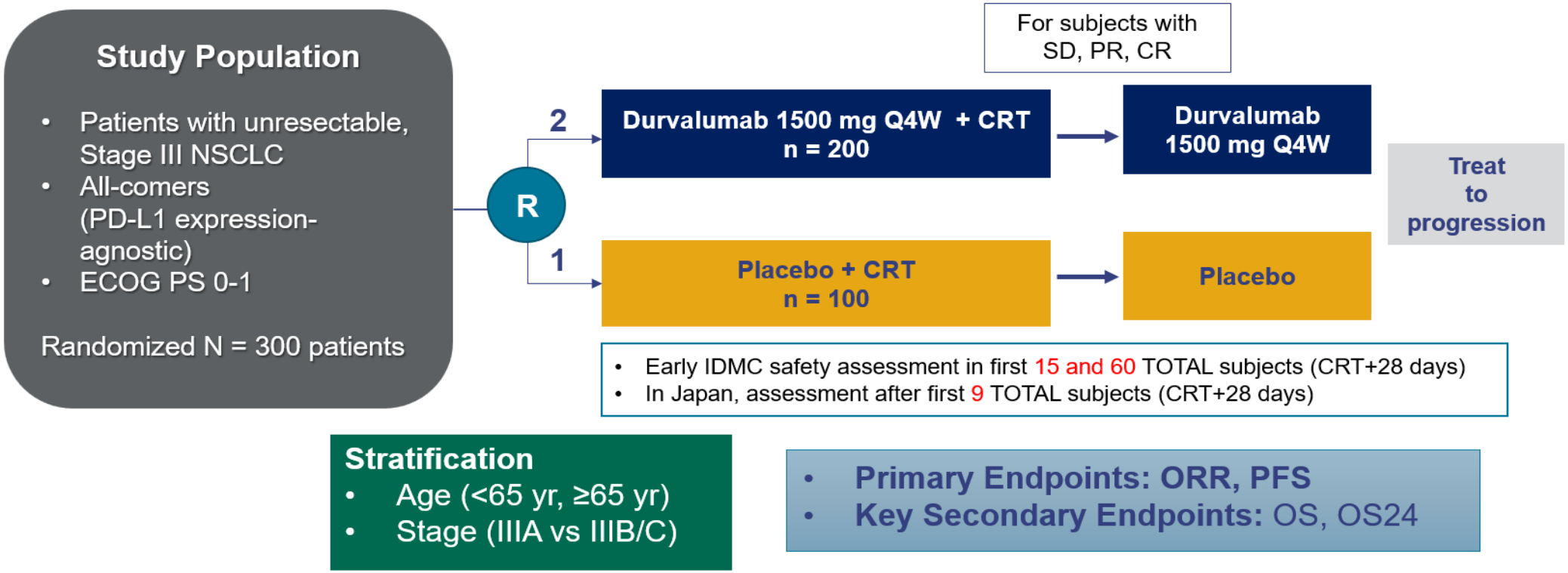
Nivolumab +/- Ipilimumab after ChemoRT

	Nivolumab Alone (N= 52)	Nivolumab/Ipilimumab (N= 47)
Median F/u, months (range)	27.7 (2-44.2)	29.2 (3.2-46.8)
Progression Free Survival*		
18- Month (95% CI)	63.7 (47.3-76.2)	67.6 (51.4-79.5)
P-value	<0.1	<0.1
Median, months (95% CI)	25.8 (16.5-NR)	25.4 (18.6-NR)
Overall Survival		
18- Month (95% CI)	82.7 (69.2-90.6)	85.7 (72.3-92.9)
24- Month (95% CI)	77.7 (63.1-87.1)	80.6 (65.8-89.5)
Median, months (95% CI)	NR (NR-NR)	NR (28.1-NR)

Durm, ASCO 2022

Lokal İleri KHDAK Eşzamanlı İmmünoterapi

PACIFIC 2: A Phase III Study of Durvalumab Given Concurrently With Platinum-based Chemo-RT for Patients With Stage III NSCLC



1. https://clinicaltrials.gov/ct2/show/NCT03519971

Courtesy of Walter J Curran Jr, MD
Winship Cancer Institute | Emory University

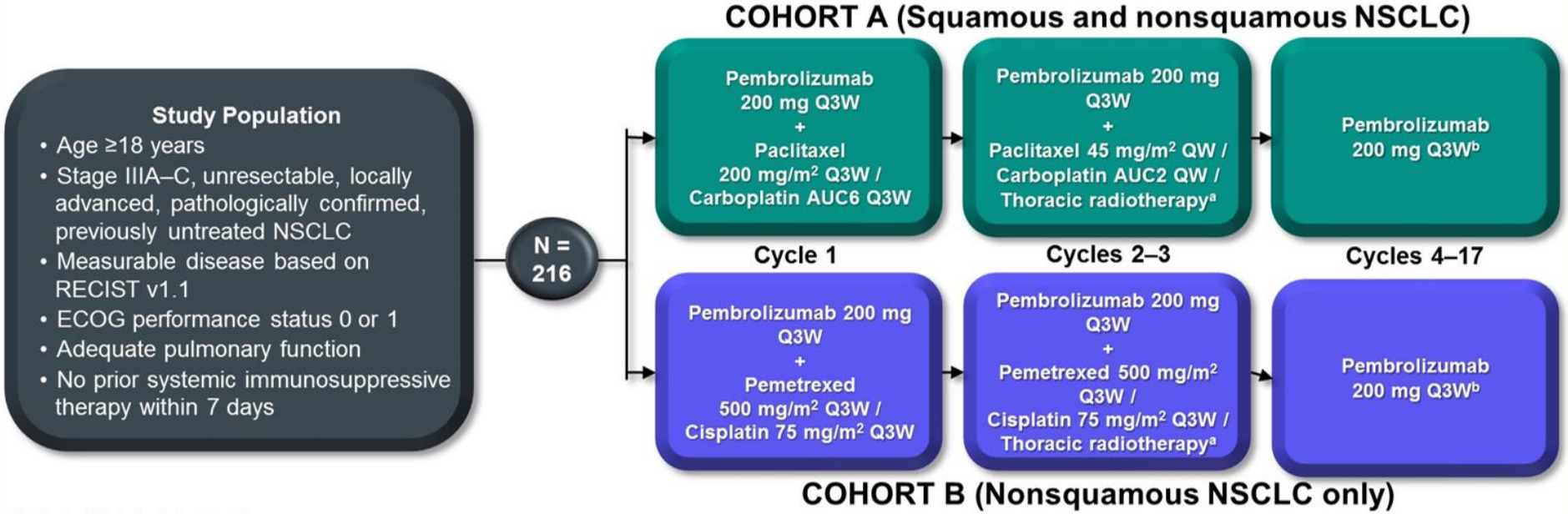
Lokal İleri KHDAK Eşzamanlı İmmünoterapi

Ongoing Phase II KEYNOTE-799 Trial Design

Study Design
- Nonrandomized, open-label study
- Choice of chemotherapy per investigator
- Nonsquamous NSCLC patients eligible for cohort A or B
- Squamous NSCLC patients eligible for cohort A only
- Cohort A fully accrued at data cutoff; cohort B is still accruing

Primary Objectives
- ORR per RECIST version 1.1 by BICR
- Percentage of patients who develop grade ≥3 pneumonitis

Secondary Objectives
- PFS, OS, safety



[a]60 Gy in 30 daily 2-Gy fractions.
[b]Treatment will continue until cycle 17 is completed or until documented disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, or study withdrawal. Pembrolizumab therapy will be discontinued permanently in patients who develop grade ≥3 or recurrent grade 2 pneumonitis.

Jabbour SK et al. ASCO 2020;Abstract 9008.

Lokal İleri KHDAK Eşzamanlı İmmünoterapi

KEYNOTE-799: Baseline Characteristics

All Treated Patients

	Cohort A (N = 112)	Cohort B (N = 73)
Age, median (range), y	66.0 (46–90)	64.0 (35–78)
Men, n (%)	76 (67.9)	40 (54.8)
ECOG PS 1, n (%)	61 (54.5)	34 (46.6)
Squamous, n (%)	73 (65.2)	0
Nonsquamous, n (%)	39 (34.8)	73 (100)
Former/current smoker, n (%)	106 (94.6)	70 (95.9)
PD-L1 TPS ≥1%	66 (58.9)	30 (41.1)

TPS, tumor proportion score.
Data cutoff date: January 3, 2020.

Jabbour SK et al. ASCO 2020;Abstract 9008.

Lokal İleri KHDAK Eşzamanlı İmmünoterapi

KEYNOTE-799: ORR and Duration of Response

Pts with ≥15 wks follow-up	Cohort A (N = 112)	Cohort B (N = 53)
ORR, n (%) [90% CI]	75 (67.0) [58.9–74.3]	30 (56.6) [44.4–68.2]
CR	3 (2.7)	2 (3.8)
PR	72 (64.3)	28 (52.8)
SD, n (%)	23 (20.5)	18 (34.0)
PD, n (%)	1 (0.9)	0
Not evaluable, n (%)	3 (2.7)	0
No assessment, n (%)	10 (8.9)	5 (9.4)
Duration of response, median (range),[a] mo	NR (1.6+ to 10.5+)	NR (1.7+ to 10.5+)
Response duration ≥6 mo,[a] n (%)	30 (91.1)	9 (100)
6-mo PFS rate,[a] %	81.4	85.2
6-mo OS rate,[a] %	87.2	94.8

[a]Kaplan-Meier estimate. "+" indicates there is no progressive disease by the time of last disease assessment.
Data cutoff date: January 3, 2020.

Jabbour SK et al. ASCO 2020;Abstract 9008.

Lokal İleri KHDAK Eşzamanlı İmmünoterapi

KEYNOTE-799: Incidence of Grade ≥3 Pneumonitis (Safety)

	Cohort A (N = 112)	Cohort B (N = 73)
Grade ≥3 pneumonitis (all cause),[a] n (%) [90% CI]	**9 (8.0) [4.3–13.6]**	**4 (5.5) [1.9–12.1]**
Treatment-related adverse events	105 (93.8)	64 (87.7)
Grades 3–5	72 (64.3)	30 (41.1)
Led to death	4[a] (3.6)	0
Led to discontinuation of any treatment component	32 (28.6)	9 (12.3)
Immune-mediated adverse events and infusion reactions	53 (47.3)	20 (27.4)
Grades 3–5	17 (15.2)	6 (8.2)
Led to death	4 (3.6)	0

[a]Four (3.6%) patients in cohort A and none in cohort B had treatment-related grade 5 pneumonitis.
Data cutoff date: January 3, 2020.

Jabbour SK et al. ASCO 2020;Abstract 9008.

Lokal İleri KHDAK Eşzamanlı İmmünoterapi

KEYNOTE-799: Conclusions

- Pembrolizumab plus CCRT shows promising antitumor activity in patients with unresectable, locally advanced stage III NSCLC
  - ORR in both cohorts exceeded 50%
  - Estimated response duration was ≥6 months for most patients with a response
- Incidence of adverse events among patients who received pembrolizumab plus CCRT was consistent with the established toxicity profiles of CCRT for stage III NSCLC[1] and pembrolizumab monotherapy[2]
  - Incidence of grade ≥3 pneumonitis was 8.0% in cohort A and 5.5% in cohort B
  - Observed rates of grade ≥3 pneumonitis were within the expected range for immunotherapy combined with CCRT[3]

1. Yoon SM, *World J Clin Oncol* 2017;8:1-20. 2. Mok T, et al. *Lancet* 2019;393:1819-1830. 3. Peters S, et al. *Lung Cancer* 2019;133:83-87.

Jabbour SK et al. ASCO 2020;Abstract 9008.

Gelecek perspektif

ctDNA and Disease Monitoring

Figure 4. Patient-specific changes in ctDNA levels in response to treatment

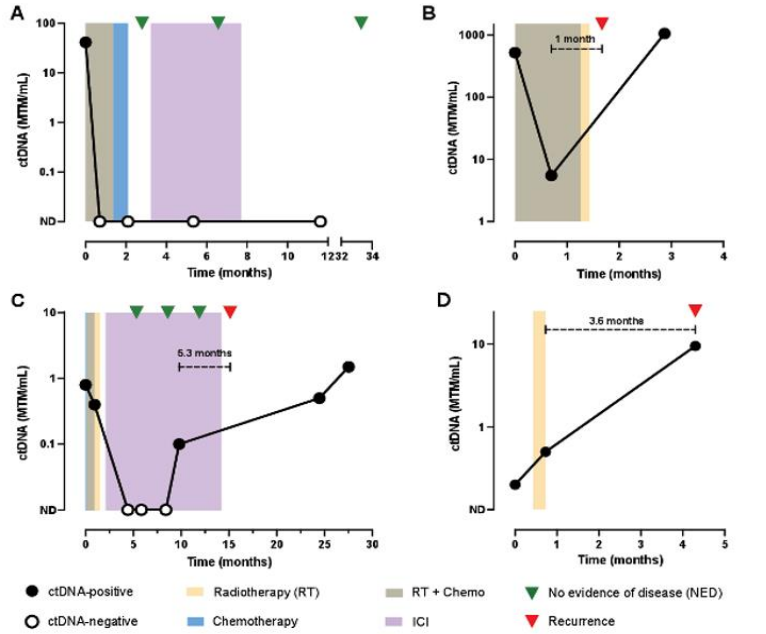


Figure 4. For stage I-III NSCLC patients undergoing RT+/- chemotherapy, ctDNA serves as a prognostic biomarker for disease progression. **A**. ctDNA clearance indicates response to RT+/- chemotherapy. **B-D**. ctDNA detection at the end of treatment or during follow-up period precedes radiographic disease recurrence. RT: radiotherapy; ICI: immune checkpoint inhibitors.

- ctDNA detection in patients with stage I-III NSCLC undergoing definitive RT +/- chemotherapy/immunotherapy is feasible and showed a baseline detection rate of 82%.
- Post-definitive RT ctDNA status is highly prognostic of DRFS at single time point (HR=19.9; p=0.007) and longitudinally (p=0.0002; sensitivity=100%, specificity=100%).
- ctDNA can detect disease progression with an average lead-time of 5.4 months over radiographic imaging. When monitored serially, ctDNA detection at any time point is a predictor of recurrence and can identify patients who may benefit from treatment intensification.
- In univariate and multivariate analyses, ctDNA detection at post-RT time point was a strong prognostic factor associated with DRFS.

Lebow, ASCO 2022

Lokal İleri KHDAK Devam Eden Çalışmalar

Ongoing Phase III Trials in Unresectable NSCLC

- NCT03521154 (LAURA)
  Osimertinib after ChemoRT in EGFRm
- NCT04513925 (SKYSCRAPER-03)
  Atezolizumab + Tiragolumab (Anti-TIGIT Ab) v. Durvalumab after ChemoRT
- NCT04951635
  Almonertinib (3rd-Gen EGFR Inhibitor) after ChemoRT in EGFRm
- NCT05221840 (PACIFIC-9)
  Oleclumab (Anti-CD73 Ab) + Durvalumab v. Monalizumab (NKG2A Ab) + Durvalumab after ChemoRT
- NCT03519971
  Concurrent Durvalumab and ChemoRT

Lokal İleri KHDAK Devam Eden Çalışmalar

Ongoing Phase III Trials in Unresectable NSCLC

- NCT05211895 (PACIFIC-8)

  Durvalumab + Domvanalimab (Anti-TIGIT Ab) after ChemoRT

- NCT04866017

  Tislelizumab (Anti-PD1) + Ociperlimab (Anti-TIGIT Ab) v. Tislelizumab v. Durvalumab after ChemoRT

- NCT04380636 (KEYLYNK-012)

  Pembrolizumab + Concurrent ChemoRT followed by Pembrolizumab +/- Olaparib

Sonuç

- Neoadjuvan KT+İmmünoterpi ile daha iyi MRR
- Lokal İler KHDAK eş zamanlı KRT sonrası Durvalumab idame tedavi standart
- EGFR mutant hastalarda idame tedavi için devam eden çalışma sonuçları gösterecek
- Eş zamanlı RT+İmmünoterapi çalışma sonuçları beklemek lazım
- Çok sayıda devam eden hedefe yönelik ve immünoterapi neoadjuvan/adjuvan/idame ve eş zamanlı çalışmalar devam ediyor