AstraZeneca

IMFINZI® (durvalumab) for the Treatment of Adult Patients With Resectable NSCLC and No Known EGFRm or ALK Rearrangements

United States Food and Drug Administration
Oncologic Drugs Advisory Committee

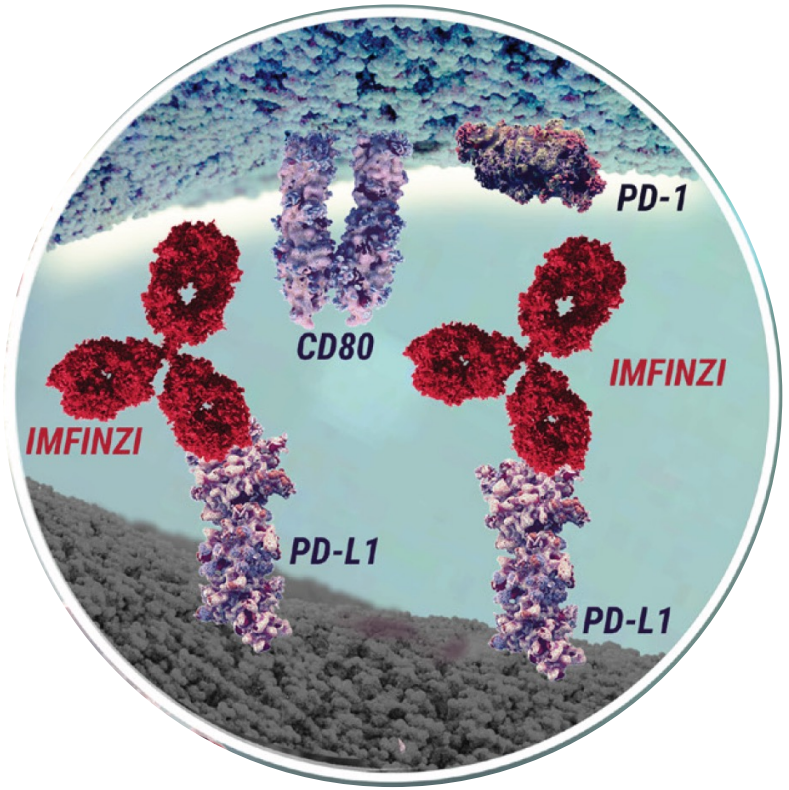
July 25, 2024

AstraZeneca

Introduction

Leora Horn, MD, MSC, MHPE, FRCPC
VP, Head of Clinical Development, Late Development Oncology
Global Clinical Strategy Head for Lung Cancer
AstraZeneca

IMFINZI® (durvalumab): An Anti-PD-L1 Monoclonal Antibody

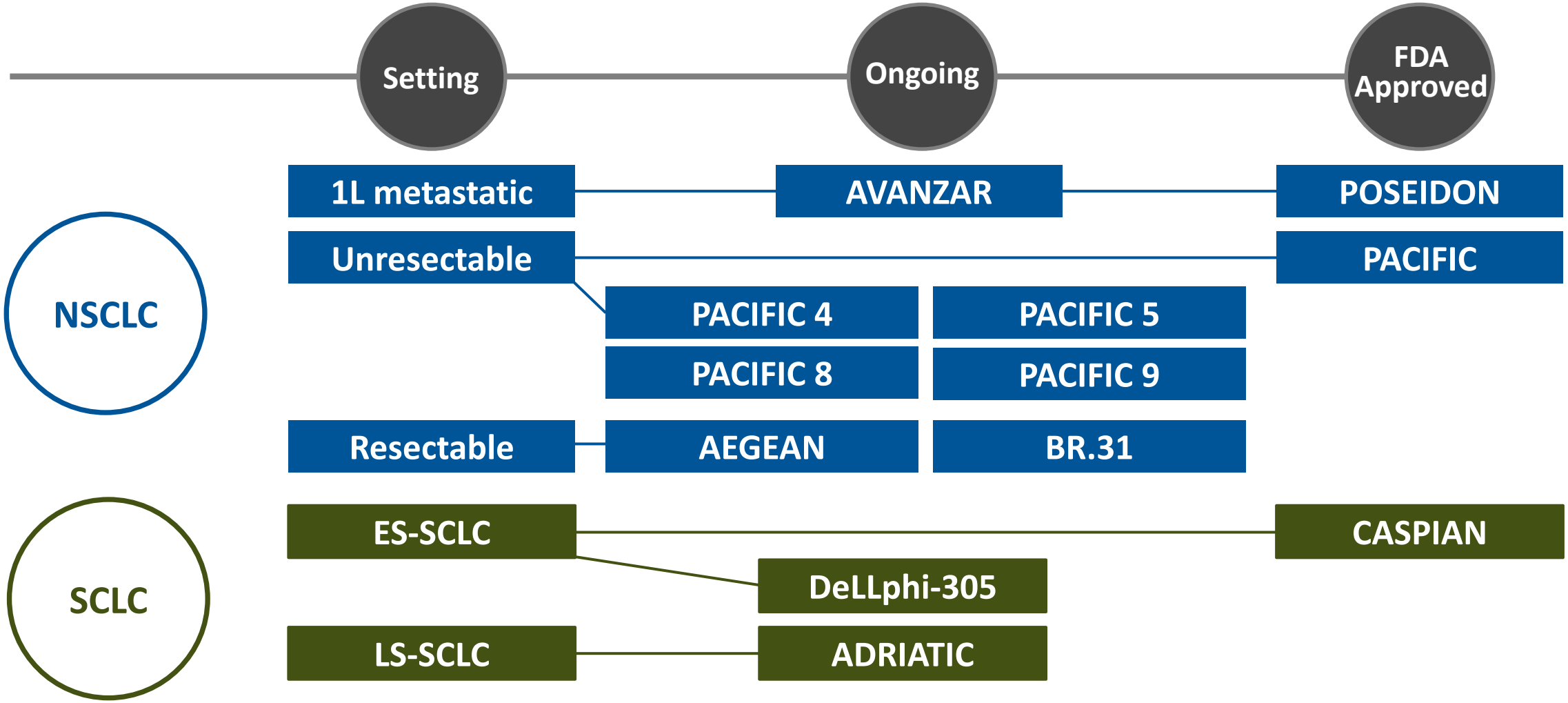


Proposed Indication

Durvalumab in combination with platinum-containing chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, for the treatment of adult patients with resectable (tumors ≥ 4 cm and/or node positive) NSCLC and no known EGFR mutations or ALK rearrangements.

ALK=anaplastic lymphoma kinase; CD=cluster of differentiation; EGFR=epidermal growth factor receptor; NSCLC=non-small cell lung cancer; PD-1=programmed cell death protein 1; PD-L1=programmed death-ligand 1.

Extensive Phase 3 Development With Durvalumab in Lung Cancer



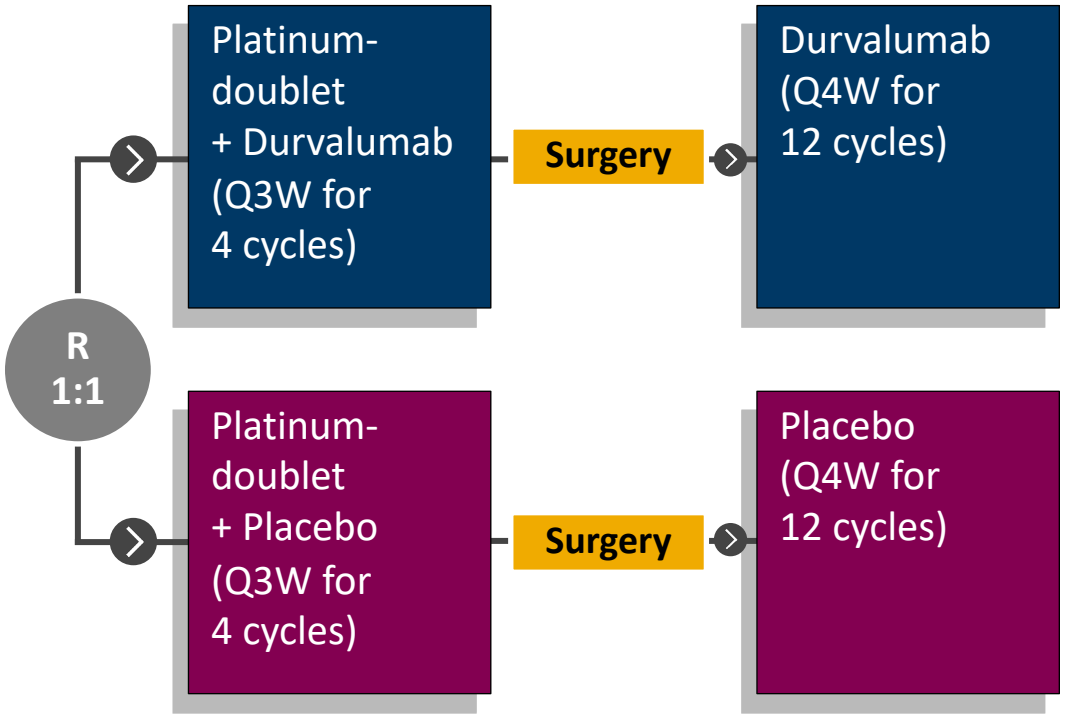
Durvalumab approved in more than 70 countries in NSCLC, SCLC, endometrial, biliary, and HCC indications

1L=first-line; ES=extensive stage; HCC=hepatocellular carcinoma; LS=limited stage; SCLC=small cell lung cancer.

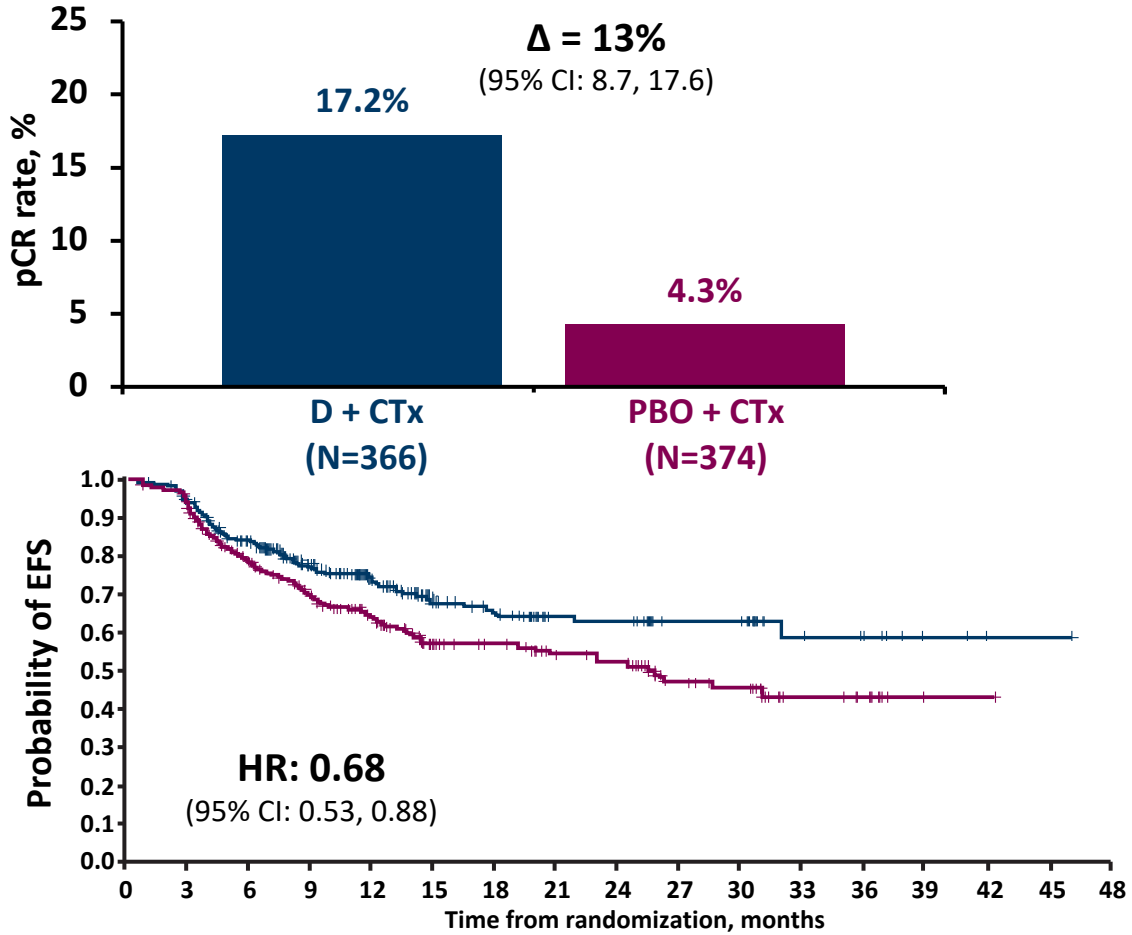
AEGEAN Met Its Primary Endpoints

Design

The single-study design allows the delineation of both short-term benefit through pCR and longer-term EFS to be evaluated in the same patient population



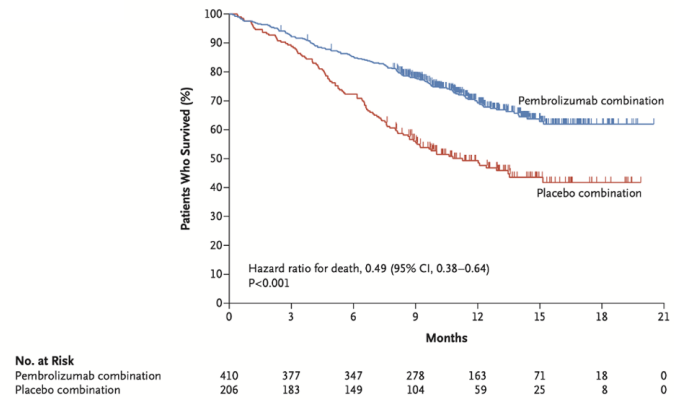
Primary Endpoints: pCR and EFS



CI=confidence interval; CTx=chemotherapy; D=durvalumab; EFS=event-free survival; HR=hazard ratio; PBO=placebo; pCR=pathologic complete response; Q3W=every 3 weeks; Q4W=every 4 weeks; R=randomization.

Key Factors Considered in AEGEAN Design

1



KN189: Transformative OS in mNSCLC After 4 Cycles of Induction Platinum-Doublet + IO Followed by Maintenance IO

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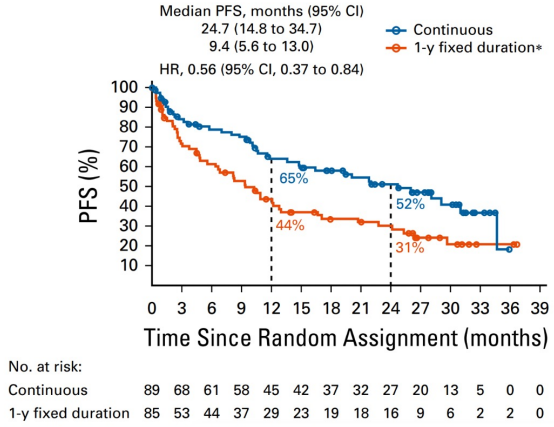
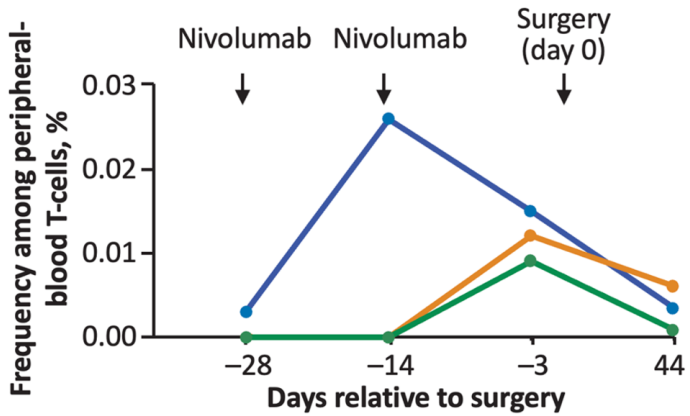


CM153: Better Outcomes With Longer Treatment

3



Forde: Neoadjuvant Alone (2 Doses Nivo) Is Not Adequate for Sustained T-cell Activation + Maximizing IO Response

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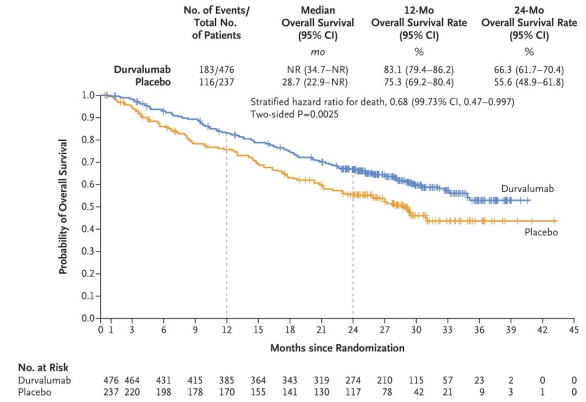

PACIFIC: 1 Year of Durvalumab After Chemo-RT Improved Survival and Is Global SOC

Chemo-RT=chemoradiotherapy; IO=immunotherapy; mNSCLC=metastatic non-small cell lung cancer; mo=month; NR=not reached; OS=overall survival; PFS=progression-free survival; SOC=standard of care; y=year.

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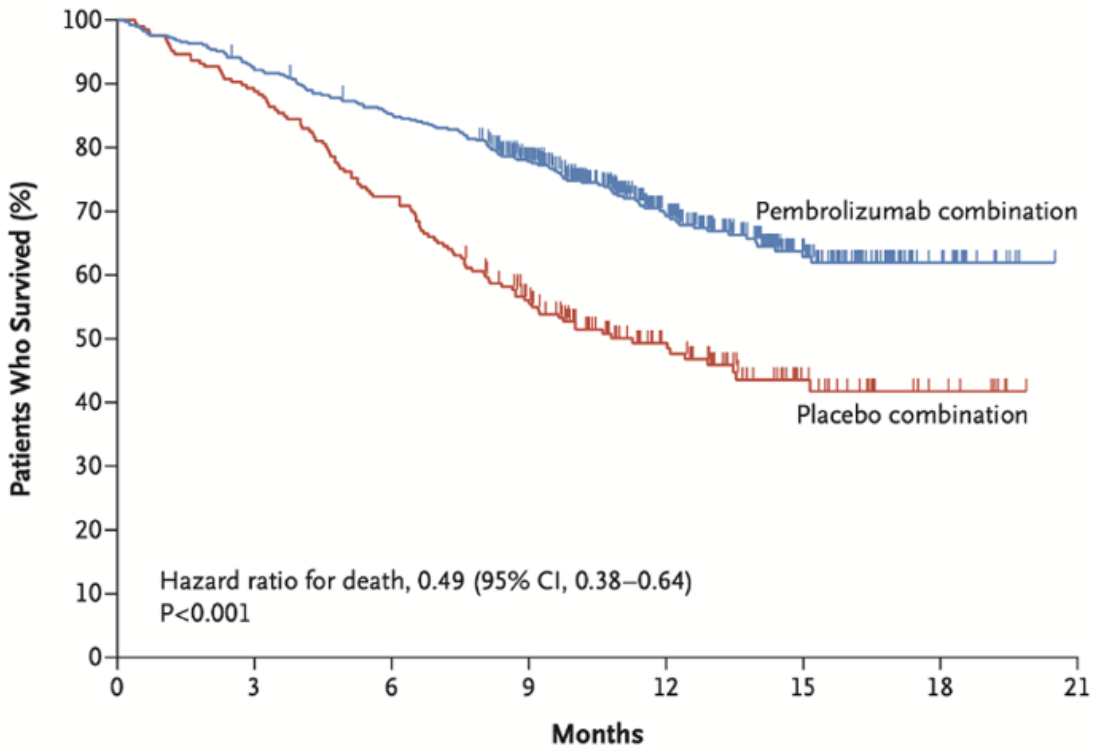

No. at Risk								
Pembrolizumab combination	410	377	347	278	163	71	18	0
Placebo combination	206	183	149	104	59	25	8	0

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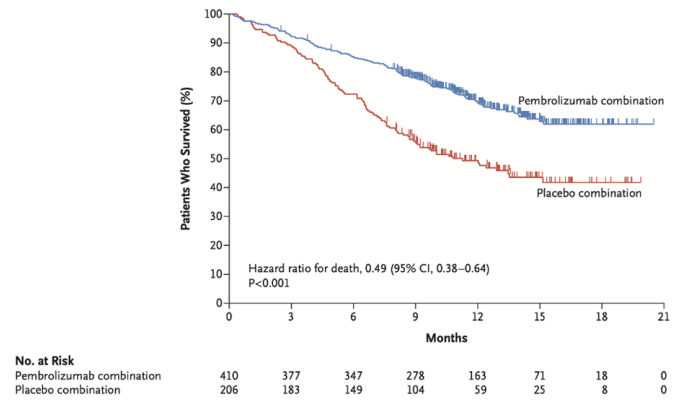

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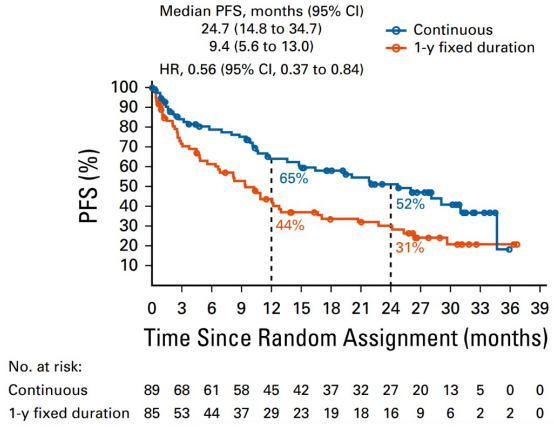

CM153: Better Outcomes With Longer Treatment

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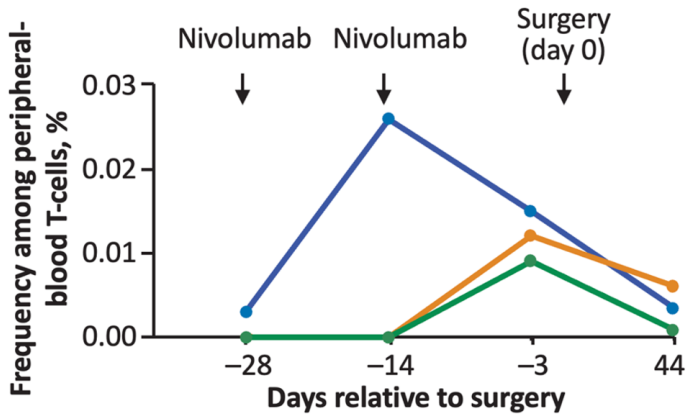

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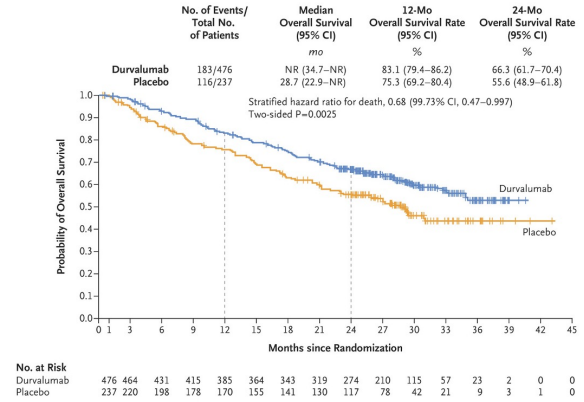

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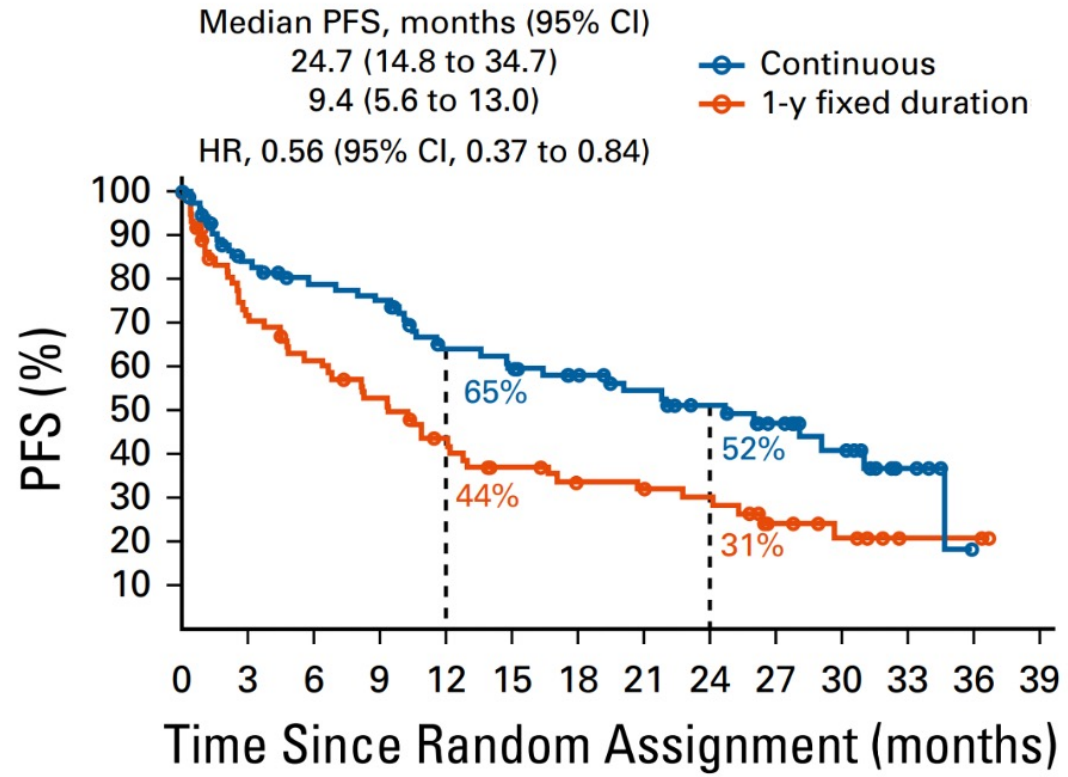

No. at risk:

Continuous	89	68	61	58	45	42	37	32	27	20	13	5	0	0
1-y fixed duration	85	53	44	37	29	23	19	18	16	9	6	2	2	0

CM153: Better Outcomes With Longer Treatment

Reprinted with permission from Waterhouse DM, et al. Continuous versus 1-year fixed-duration nivolumab in previously treated advanced non–small-cell lung cancer: CheckMate 153. *J Clin Oncol*. 2020;38(33): 3863-3873. https://ascopubs.org/doi/full/10.1200/JCO.20.00131.

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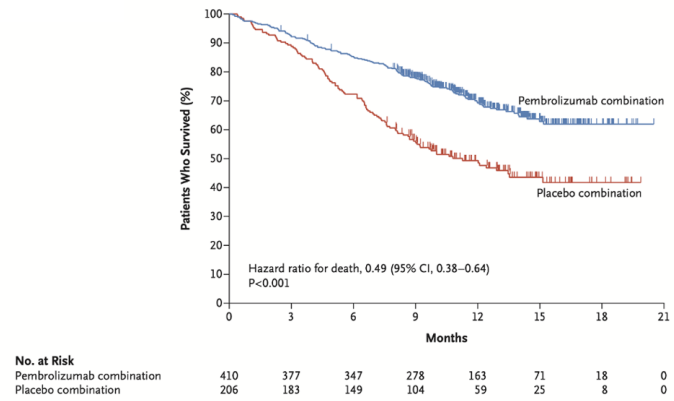

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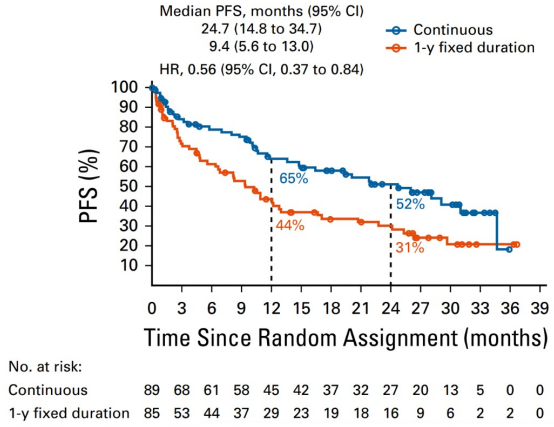

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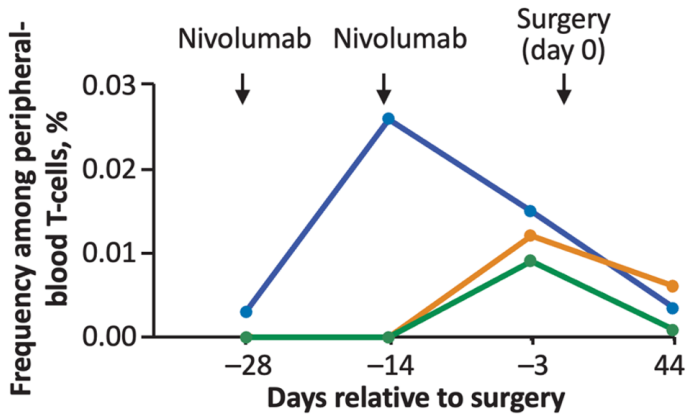

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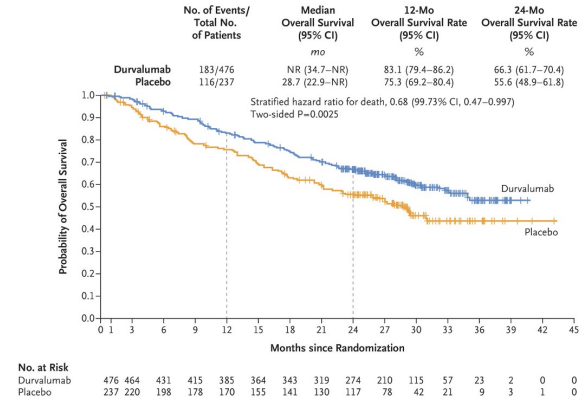

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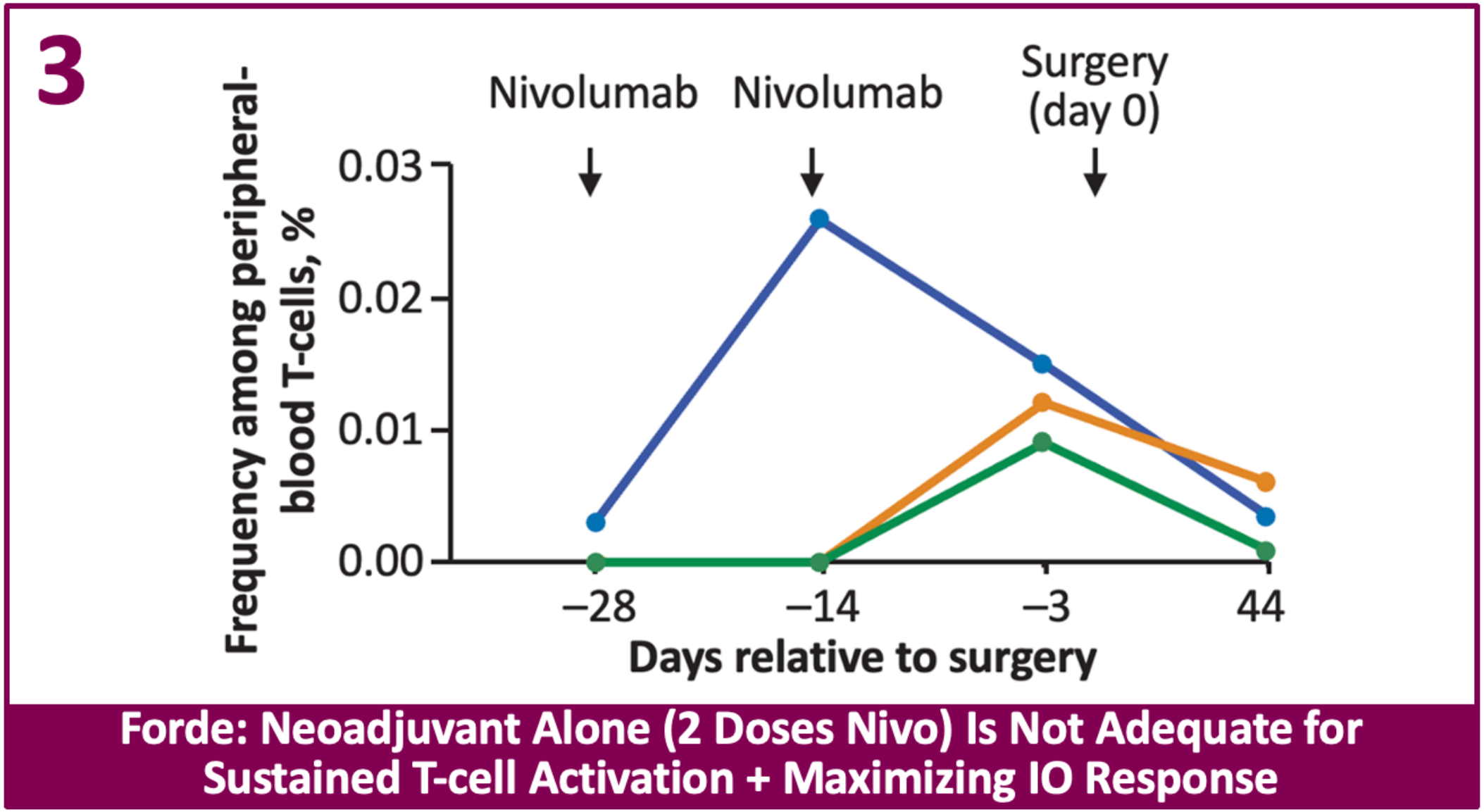
Panel 4: From *N Engl J Med*, Antonia SJ, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC, 379(24), 2342-2350. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Key Factors Considered in AEGEAN Design



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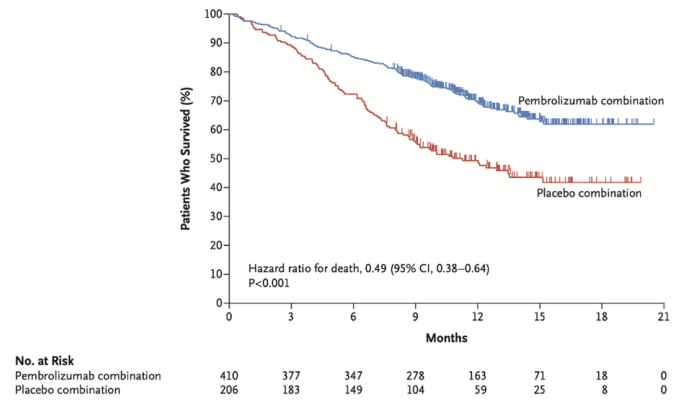

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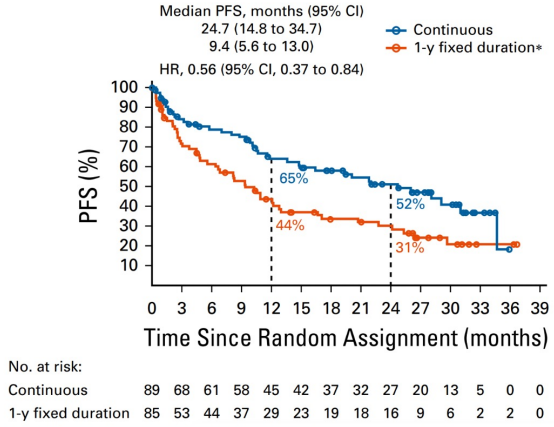

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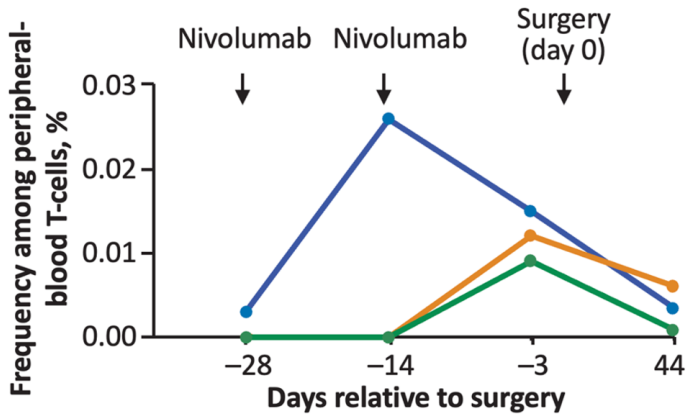

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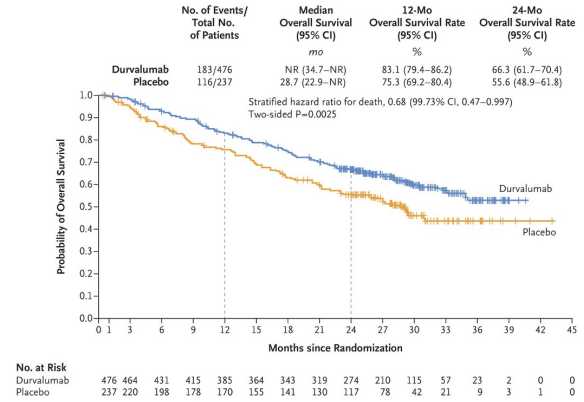

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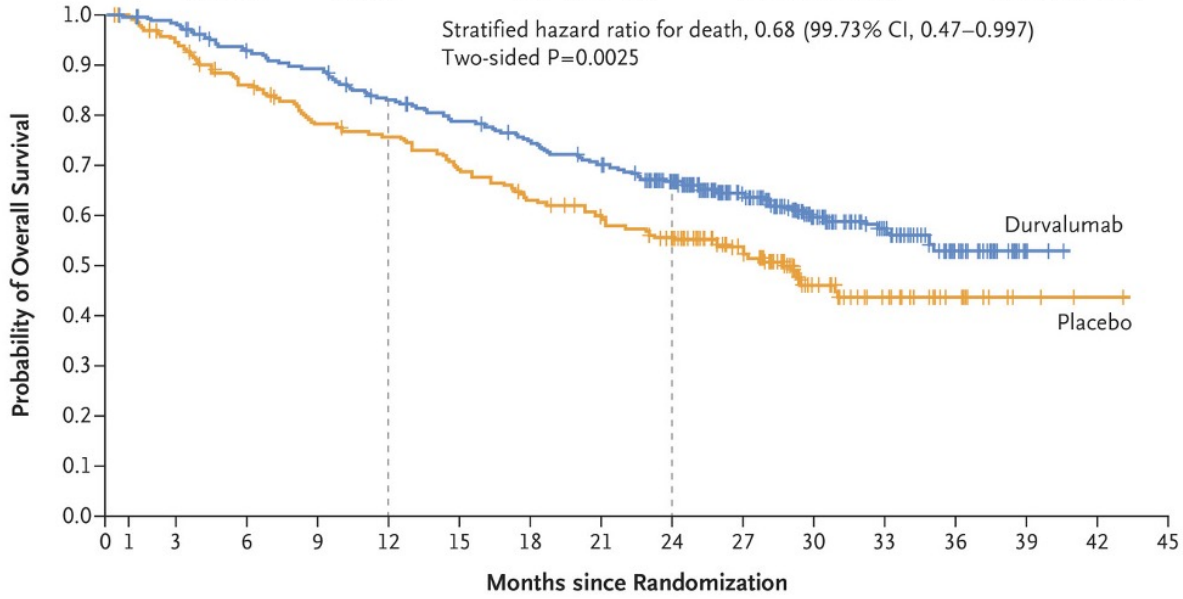
	No. of Events/ Total No. of Patients	Median Overall Survival (95% CI)	12-Mo Overall Survival Rate (95% CI)	24-Mo Overall Survival Rate (95% CI)
		mo	%	%
Durvalumab	183/476	NR (34.7–NR)	83.1 (79.4–86.2)	66.3 (61.7–70.4)
Placebo	116/237	28.7 (22.9–NR)	75.3 (69.2–80.4)	55.6 (48.9–61.8)



No. at Risk															
Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
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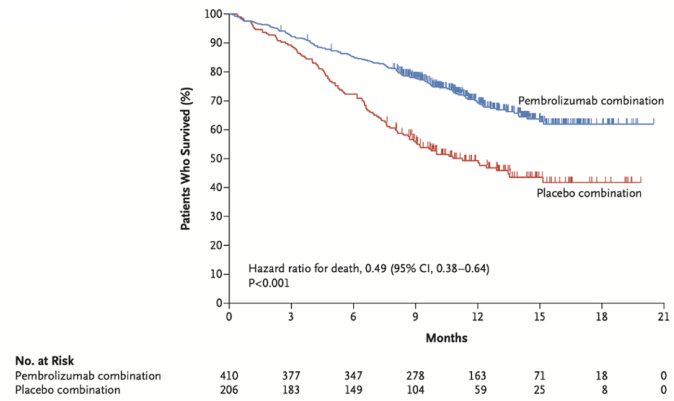

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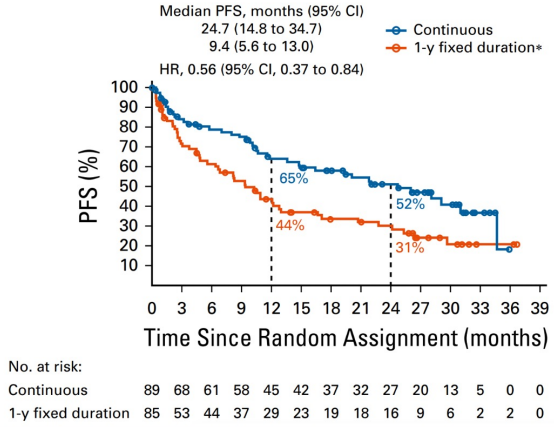

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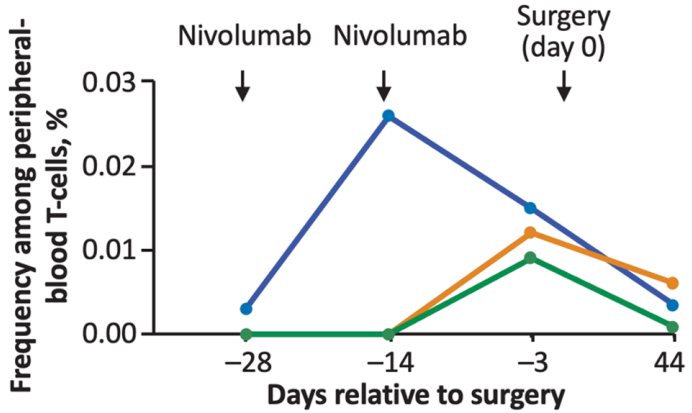

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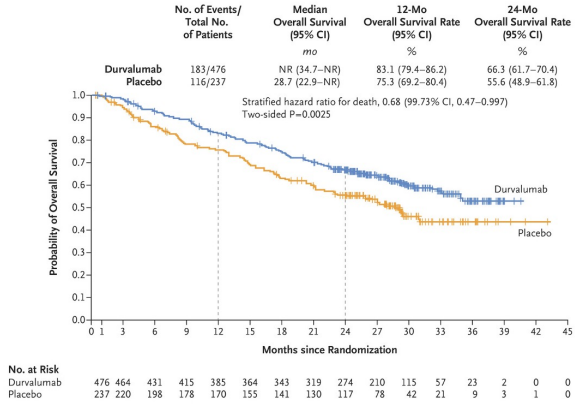

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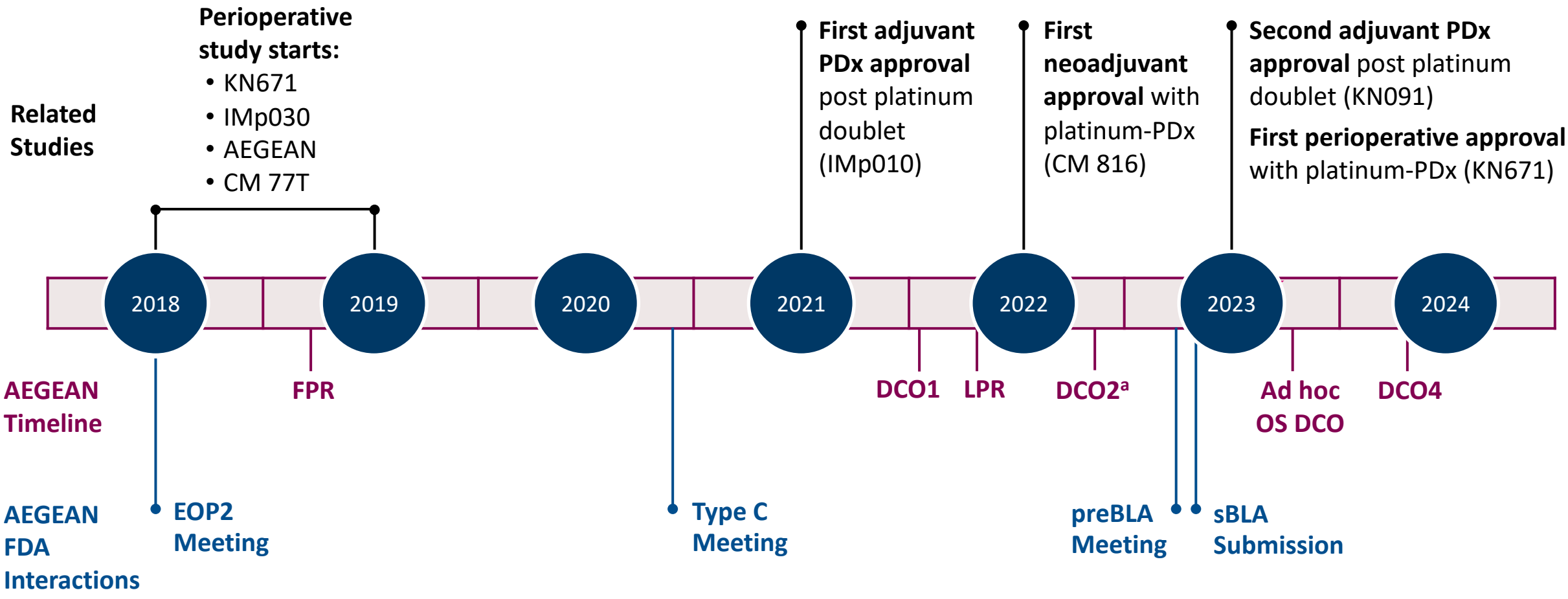
AEGEAN Milestones



BLA=Biologics License Application; CM=CheckMate; DCO=data cutoff; EOP2=end of phase 2; FDA=US Food and Drug Administration; FPR=first patient randomized; IMp=IMpower; KN=Keynote; LPR=last patient randomized; OS=overall survival; PDx=anti-PD-(L)1 immunotherapy; sBLA=supplemental Biologics License Application.

[a] Met primary endpoint of EFS.

What You Will Hear Today

Disease Background
Marina Garassino, MD
University of Chicago

Clinical Efficacy
Gary Doherty, MB, BChir, MA, PhD, FRCP
AstraZeneca

Clinical Safety
Mayur Patel, PharmD
AstraZeneca

Clinical Perspective
John Heymach, MD, PhD
MD Anderson

Closing Remarks & Future Perspectives
Leora Horn, MD, MSC, MHPE, FRCPC
AstraZeneca

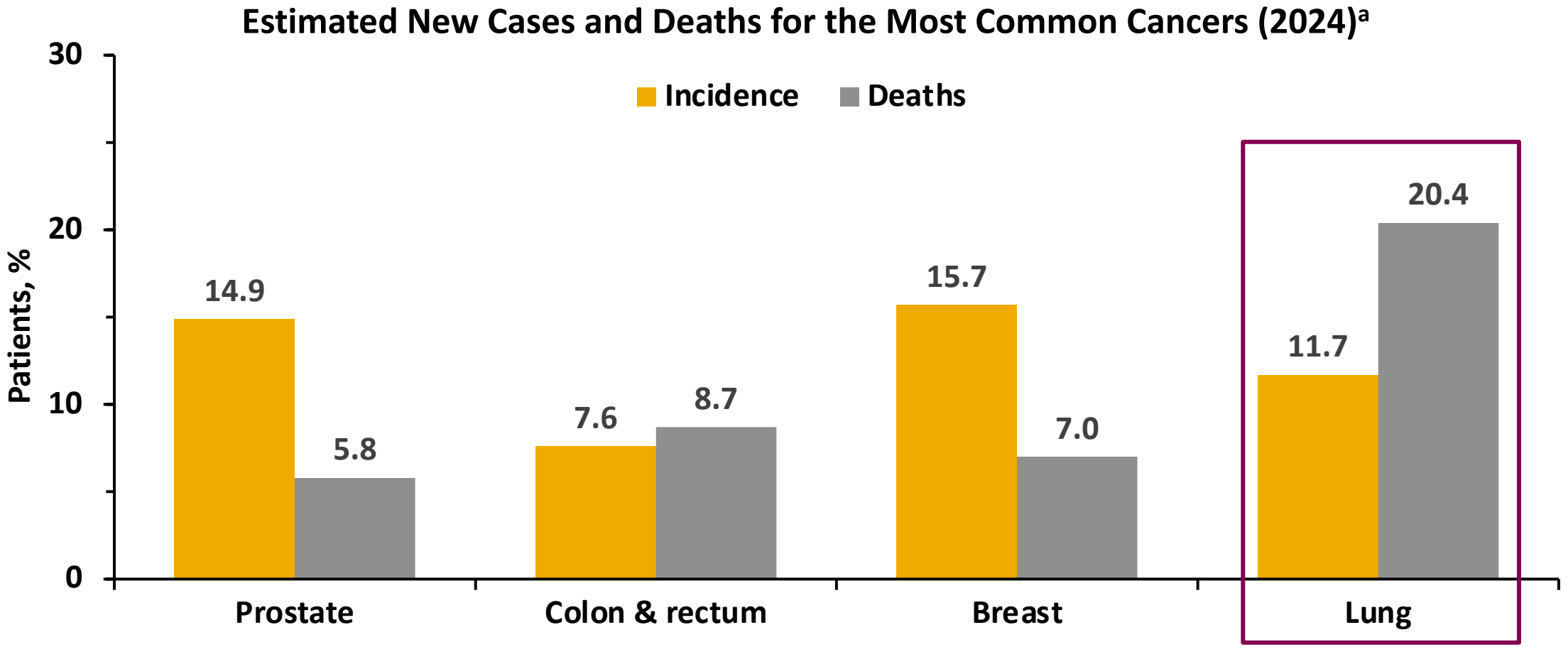
1. AEGEAN has a positive benefit-risk profile
2. AEGEAN helps address remaining unmet need for patients with resectable NSCLC
3. Considerations of designs for future perioperative studies to further improve patient outcomes

AstraZeneca

Disease Background

Marina Garassino, MD
University of Chicago

Lung Cancer Is the Leading Cause of Cancer Death in the US



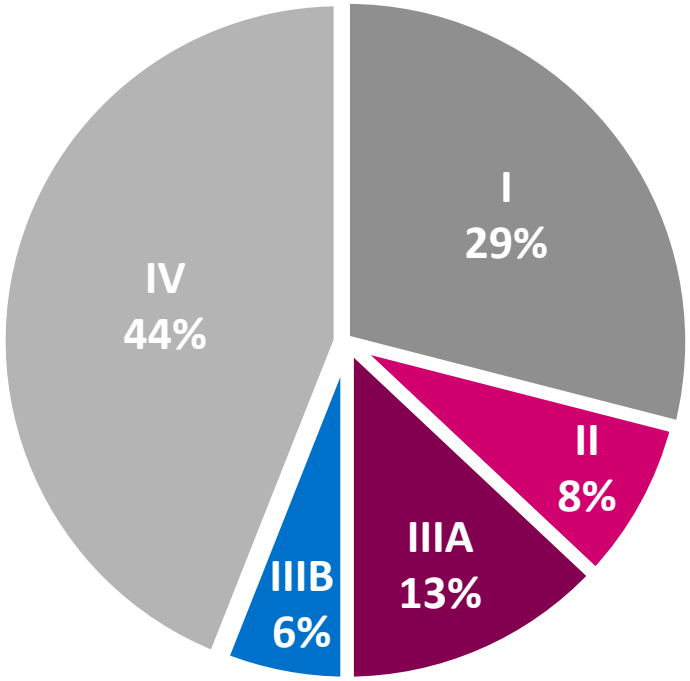
Lung cancer is the second most common cancer in both sexes.

[a] Both sexes, all ages.

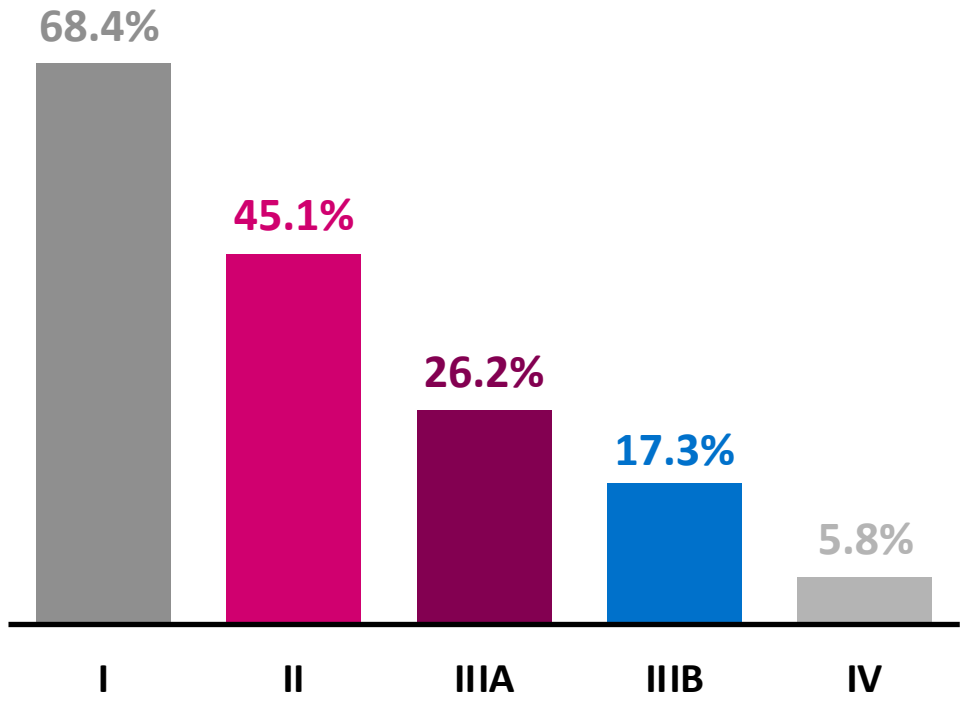
American Cancer Society. *Cancer Facts & Figures 2024*. Atlanta: American Cancer Society; 2024.

Epidemiology of NSCLC (US)

Proportion of New NSCLC Cases Diagnosed by Stage

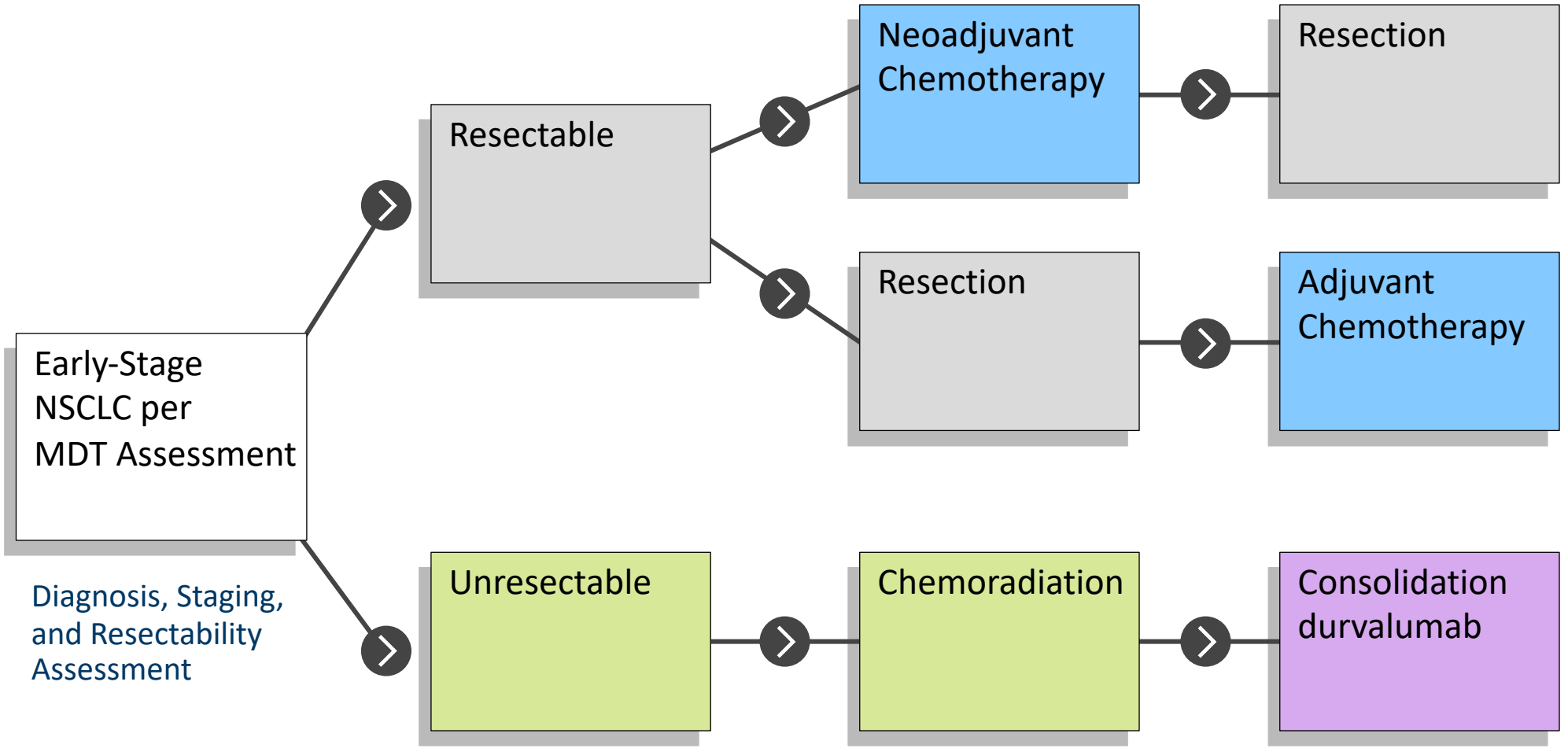


5-Year Survival Rates by Clinical Stage



Ganti AK, et al. *JAMA Oncol*. 2021;7(12):1824-1832.

2018 Treatment Landscape: Early-Stage NSCLC[1-3]



MDT=multidisciplinary team.

1. Antonia SJ, et al. *N Engl J Med*. 2017;377(20):1919-1929; 2. Pignon JP, et al. *J Clin Oncol*. 2008;26(21):3552-3559; 3. NSCLC Meta-analysis Collaborative Group. *Lancet*. 2014;383(9928):1561-1571.

Unresectable NSCLC in 2018: PACIFIC Established 1 Year of Durvalumab After Chemoradiation as the SOC

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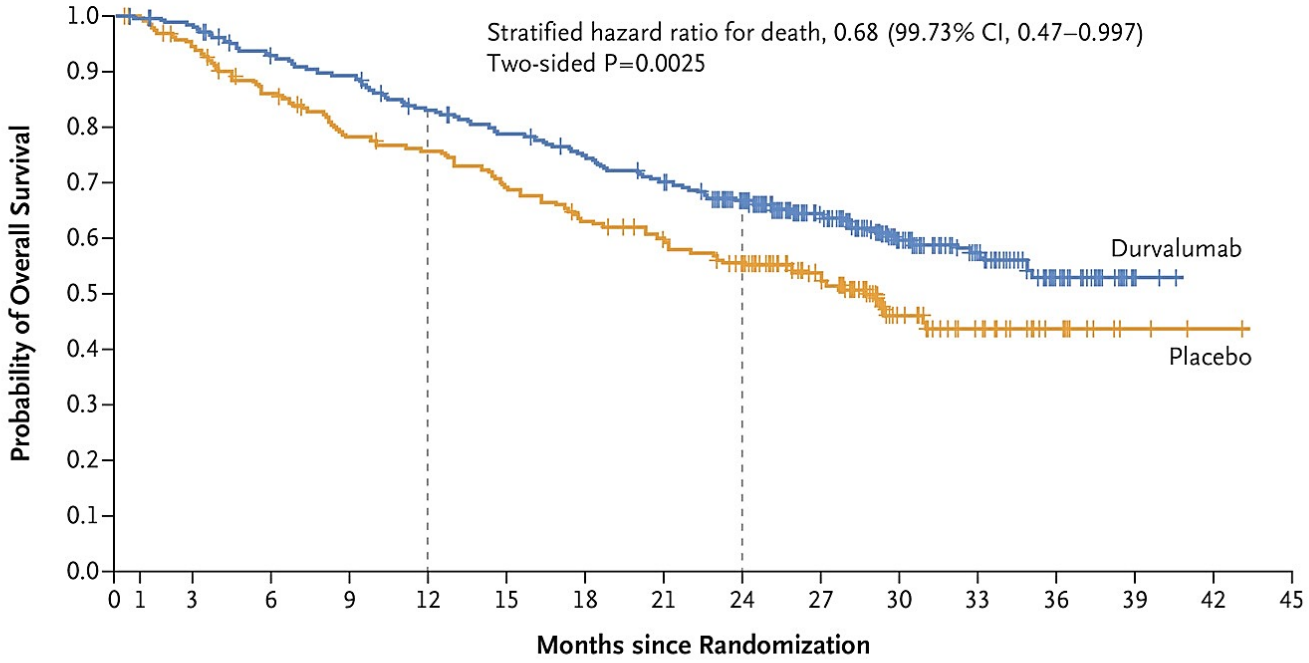

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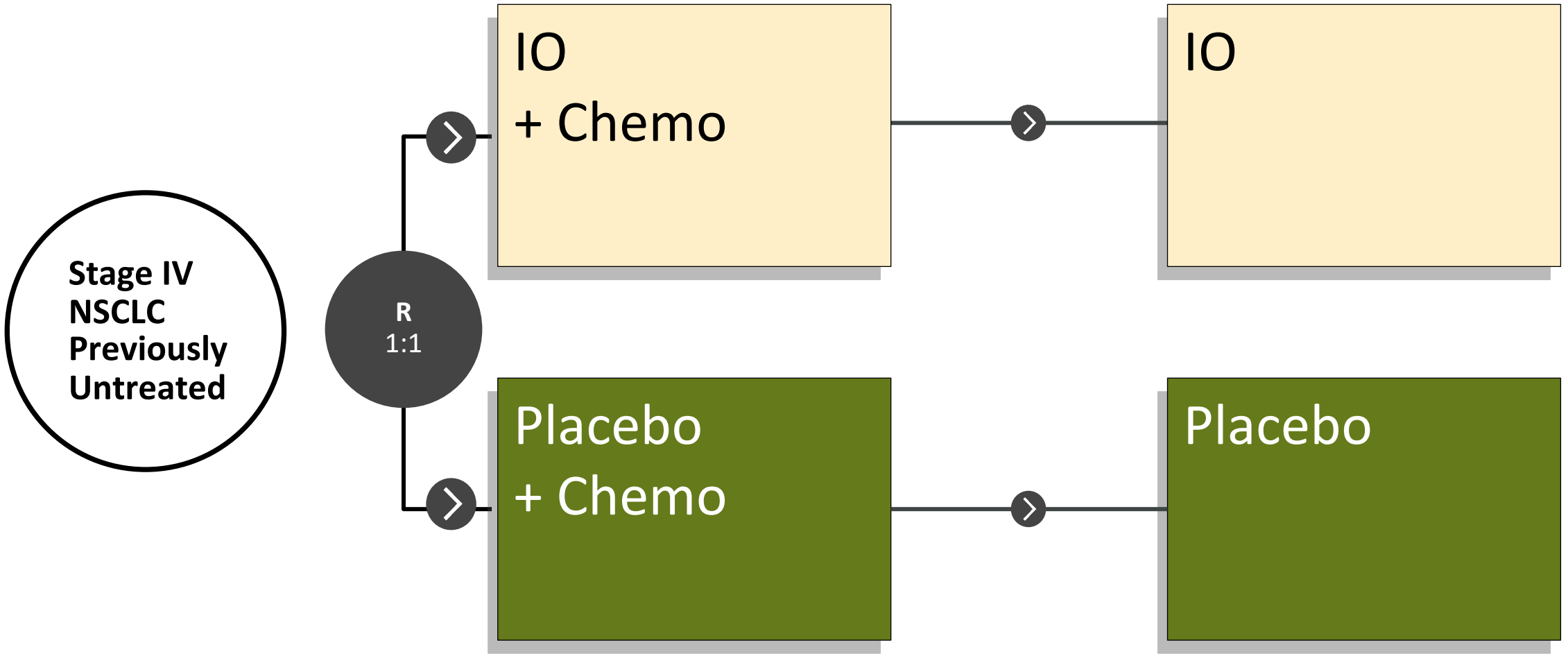
- **Grade 3-4 AEs:** 30.5% [durvalumab arm] vs 26.1% [placebo arm]
- **AEs leading to discontinuation:** 15.4% [durvalumab arm] vs 9.8% [placebo arm]

AE=adverse event.

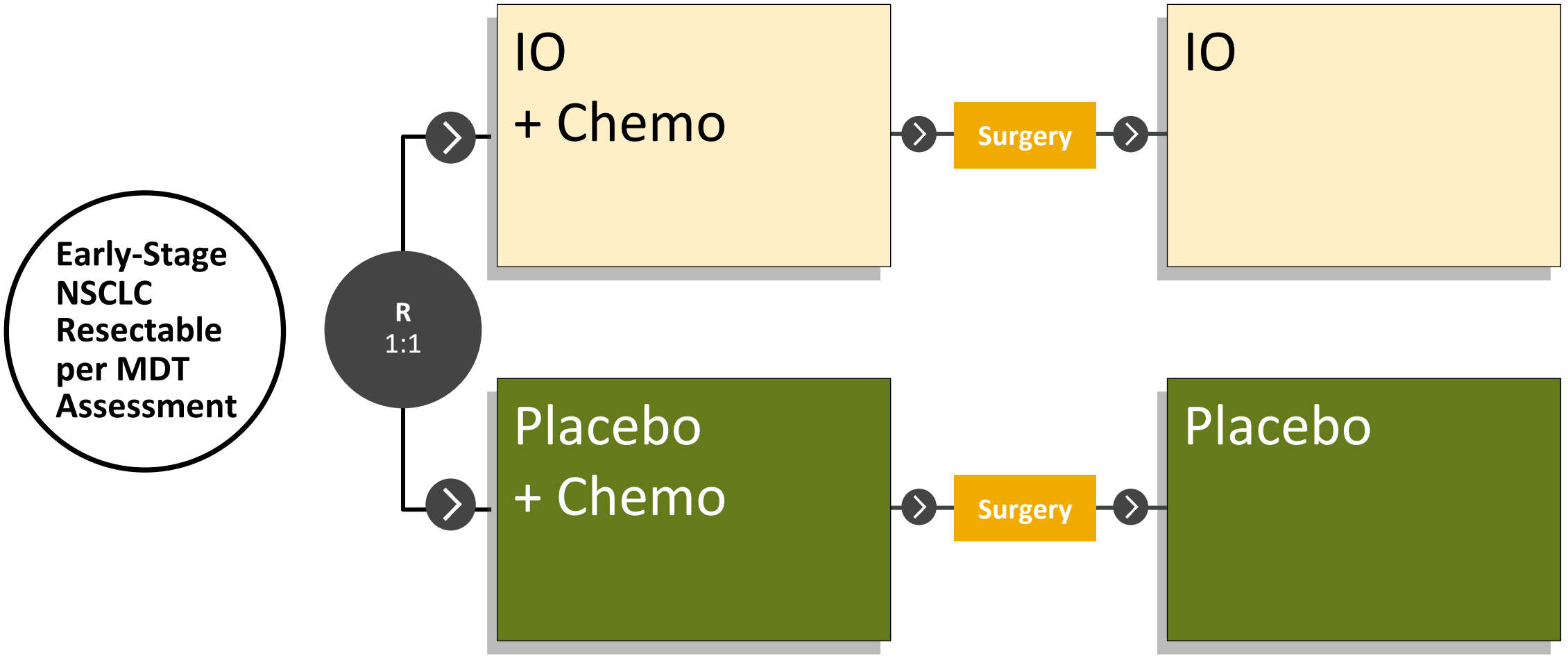
Perioperative IO Design Was Extrapolated From IO Trials in 1L Metastatic NSCLC



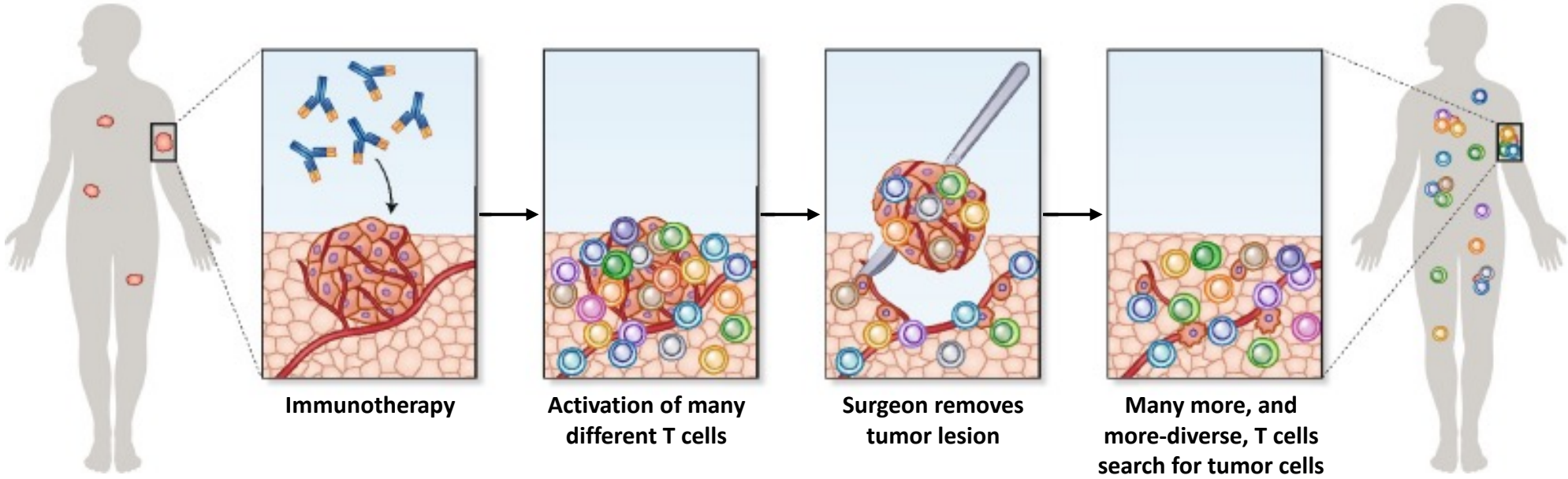
Chemo=chemotherapy.

Paz-Ares L, et al. *N Engl J Med*. 2018;379(21):2040-2051.

Perioperative IO Design Was Extrapolated From IO Trials in 1L Metastatic NSCLC (cont'd)



Rationale for Perioperative Immunotherapy Treatment



Neoadjuvant Immunotherapy

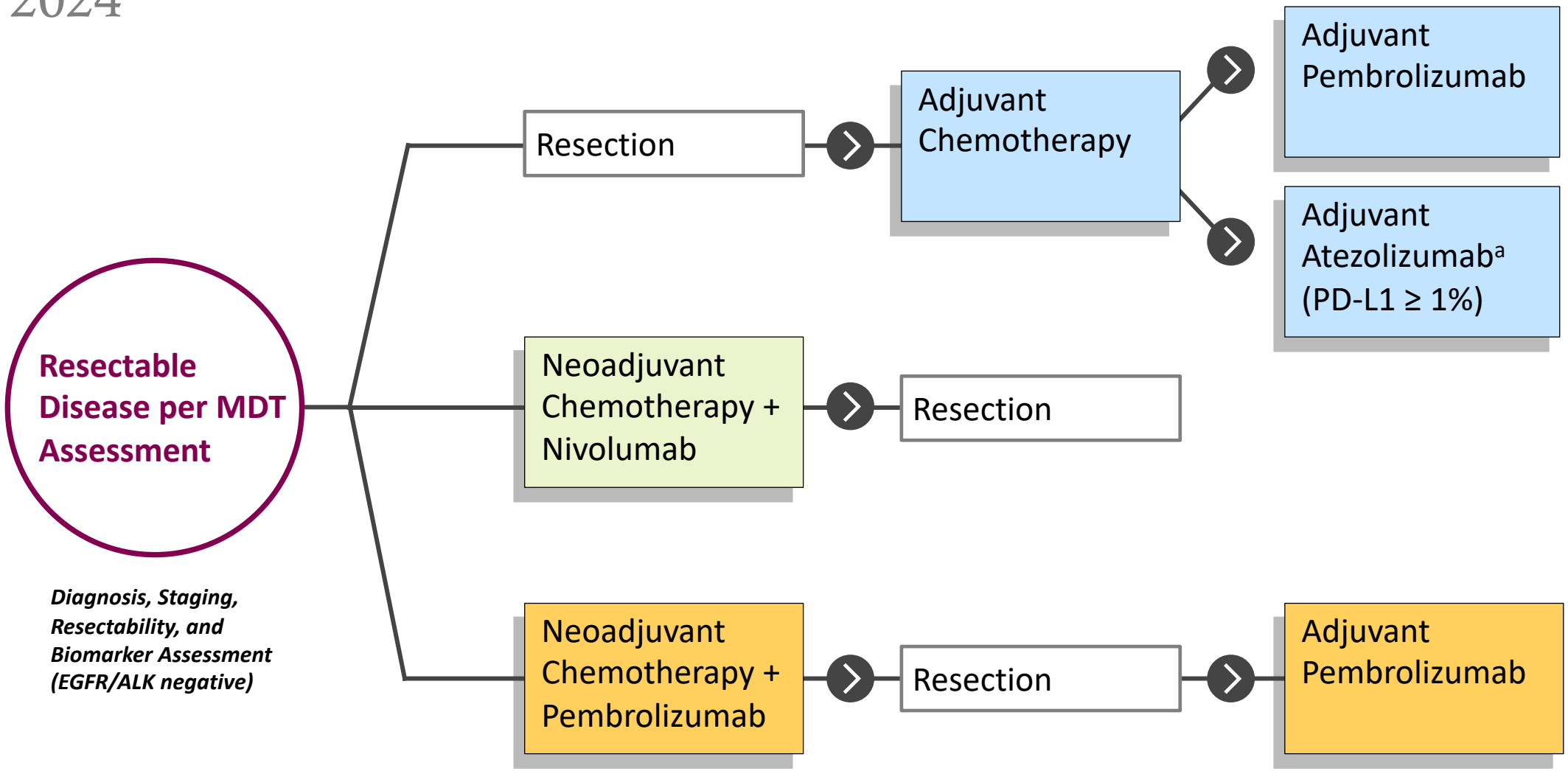
- Optimal initial immune response stimulation (with primary tumor and LNs in situ)
- Combination with chemotherapy to induce maximal response and enhance locoregional disease control
- Early suppression/elimination of micrometastatic disease

Adjuvant Immunotherapy

- Consolidation of antitumor immunity
- Ongoing suppression of tumor PD-L1–mediated resistance to antitumor immunity
- Suppression/elimination of micrometastatic disease

LN=lymph node.

Treatment Landscape for Resectable IO-Sensitive NSCLC
2024



[a] Stage II-IIIA only (American Joint Committee on Cancer [AJCC] 7th edition).

Garassino MC, et al. *N Engl J Med*. 2024;390(19):1816-1818.

Randomized Adjuvant Trials Demonstrate a Modest Benefit in the ITT Populations

Adjuvant (N=2182)

Study	KEYNOTE-091[1] N=1177		IMpower010[2] N=1005	
Regimen	**Pembro**	**Placebo**	**Atezo**	**BSC**
Median DFS (95% CI), mo	53.9 (46.2-67.0)	43.0 (35.0-51.6)	65.6 (NA, NA)	47.8 (NA, NA)
DFS HR (95% CI)	**0.81 (0.68, 0.96)**		**0.85 (0.71, 1.01)**	
Maturity	**48%**		**50%**	
Median follow-up	51.7 months		65.0 months	

- IO monotherapy after complete resection ± adjuvant chemotherapy
- DFS includes recurrence after surgery and death
- ~15% to 20% reduction in the risk of a DFS event

Note: Most recent data from all studies (regardless of PD-L1). Randomization is after surgery and adjuvant chemotherapy.
Atezo=atezolizumab; BSC=best supportive care; DFS=disease-free survival; ITT=intent to treat; NR=not reached/not estimable; NA=not available; Pembro=pembrolizumab.
1. Besse B, et al. ESMO-IO 2023. Abstract 120MO; 2. Wakelee HA, et al. ASCO 2024. Poster 297.

Neoadjuvant Treatment Benefit Is Characterized by a Single Randomized Phase 3 Trial

Neoadjuvant

Study	**CheckMate 816[1] N=358**	
Regimen	**Nivo + Chemo**	**Chemo**
Median EFS (95% CI), mo	43.8 (30.6, NR)	18.4 (14.0, 26.7)
EFS HR (95% CI)	**0.66 (0.49, 0.90)**	
Maturity	**52% (planned)[2]**	
Median follow-up	57.6 months	

- Combined IO plus chemotherapy before surgery
- EFS includes progression precluding surgery in addition to recurrence and death
- 34% reduction in the risk of an EFS event

Note: Most recent data from all studies (regardless of PD-L1).
Nivo=nivolumab.
1. Spicer JD, et al. ASCO 2024 [oral]. Abstract LBA8010; 2. Forde PM, et al. *N Engl J Med*. 2022;386(21):1973-1985.

Randomized Perioperative Trials Show a Consistent Treatment Benefit

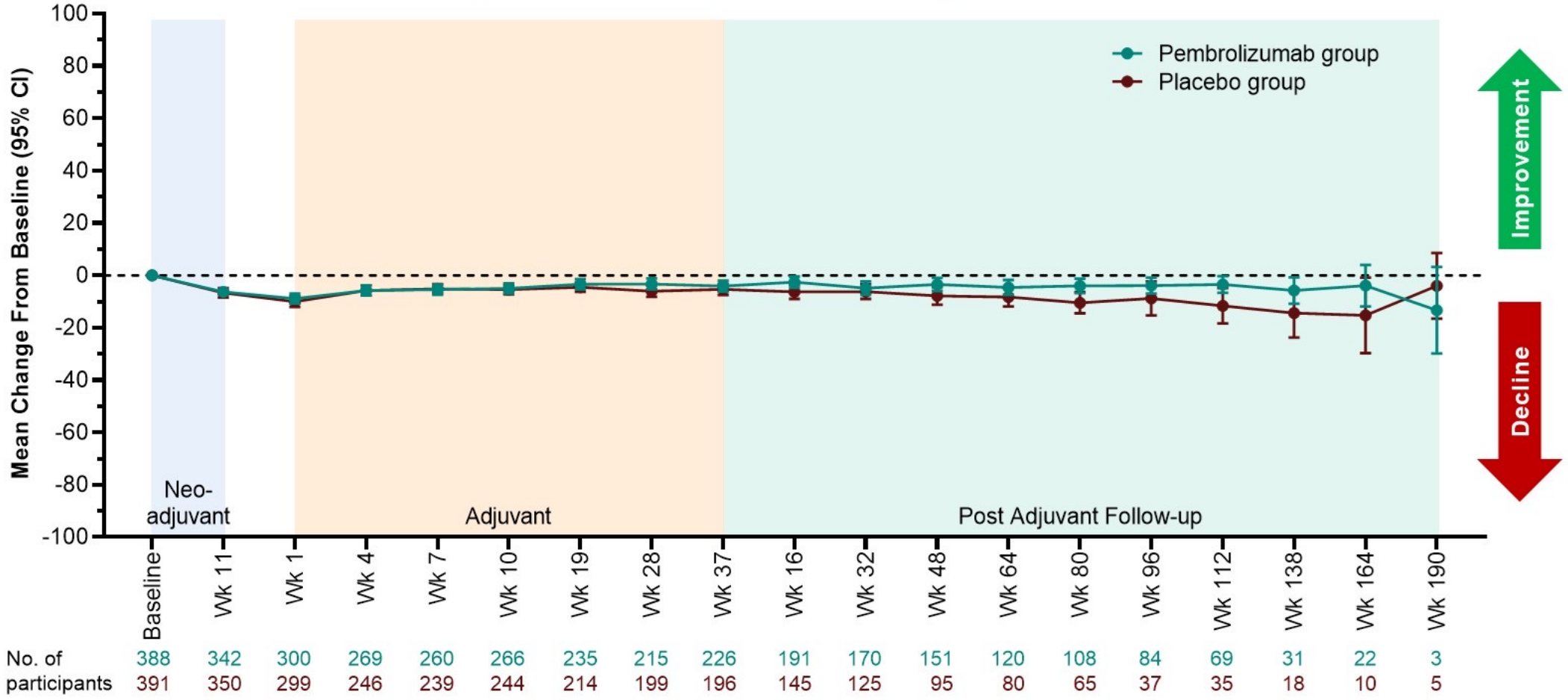
Perioperative (N=1998)

Study	KEYNOTE-671[1] N=797		AEGEAN N=740		CheckMate 77T[2] N=461	
Regimen	**Pembro + Chemo →Pembro**	**Placebo + Chemo →Placebo**	**Durva + Chemo →Durva**	**Placebo + Chemo →Placebo**	**Nivo + Chemo →Nivo**	**Placebo + Chemo →Placebo**
Median EFS (95% CI), mo	47.2 (32.9, NR)	18.3 (14.8, 22.1)	NR (42.3, NR)	30.0 (20.6, NR)	NR (28.9, NR)	18.4 (13.6, 28.1)
EFS HR (95% CI)	**0.59 (0.48, 0.72)**		**0.69 (0.55, 0.88)**		**0.58 (0.42, 0.81)**	
Maturity	**53%**		**39%**		**40%**	
Median follow-up	36.6 months		25.9 months		25.4 months	

- Combined IO plus chemotherapy before surgery and IO monotherapy after surgery
- EFS includes progression precluding surgery in addition to recurrence and death
- KN671 permitted only cisplatin
- AEGEAN and CM 77T allowed either cisplatin or carboplatin
- ~30% to 40% reduction in the risk of an EFS event

Note: Most recent data from all studies (regardless of PD-L1).
Durva=durvalumab.
1. Spicer JD, et al. ESMO 2023. Abstract LBA56; 2. Cascone T, et al. ESMO 2023. Abstract LBA1.

Empirical Mean Change From Baseline Over Time EORTC QLQ-C30 Physical Functioning (KEYNOTE 671)



Completion of the European Organisation for Research and Treatment of Cancer Core Quality of Life questionnaire (EORTC QLQ-C30) at baseline and adjuvant week 10 was ≥68.6% in the pembrolizumab group and ≥62.1% in the placebo group; compliance was ≥92.2% and ≥92.9%, respectively.

A ≥10-point difference in EORTC QLQ-C30 scales is generally considered clinically relevant. Data cutoff date for IA2: July 10, 2023.

Garassino MC, et al. ASCO 2024. Abstract 8012.

Conclusions

- Immunotherapy has transformed outcomes for NSCLC patients
- 14 FDA-approved immunotherapy regimens in addition to other targeted regimens for patients with metastatic NSCLC
- Early stage is where we can intervene to maximize chance of cure
  - 4 FDA-approved immunotherapy regimens (and 2 TKIs)
- Durvalumab is the established SOC with substantial experience as consolidation therapy in stage III unresectable NSCLC
- AEGEAN is an important study that adds to the treatment choices for patients with resectable NSCLC, with no detriment to patients' quality of life

TKI=tyrosine kinase inhibitor.

AstraZeneca

Clinical Efficacy

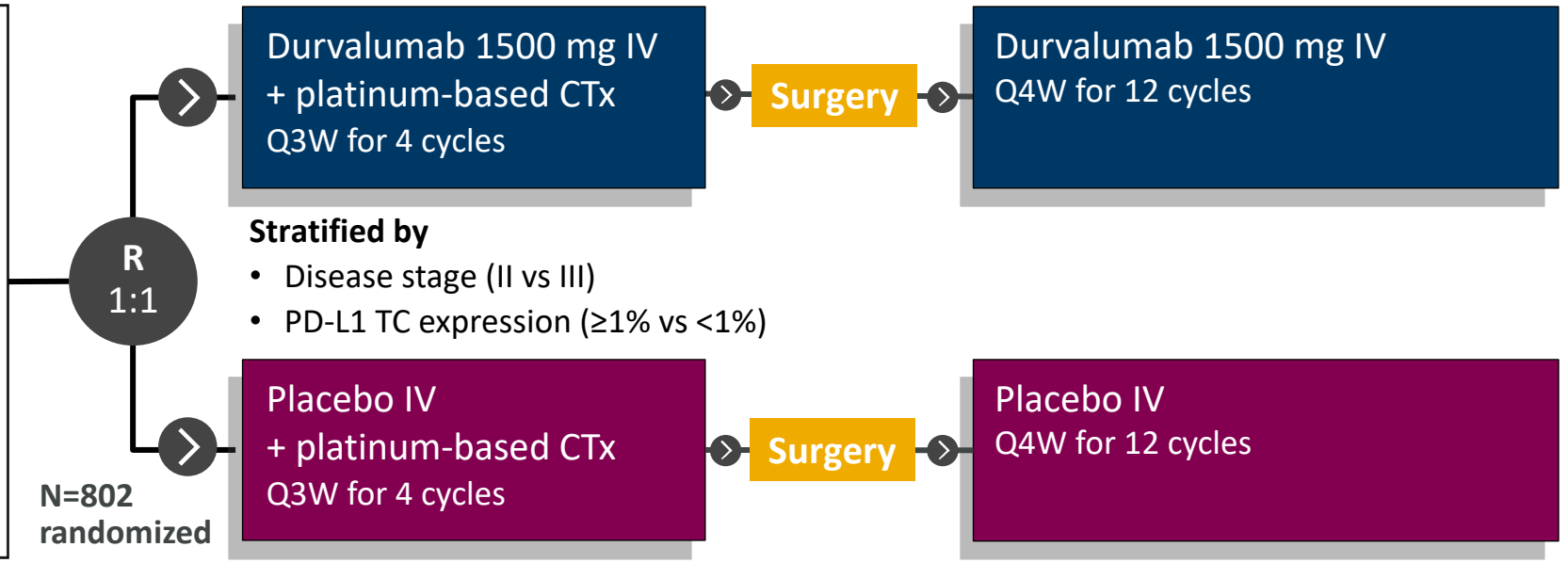
Gary Doherty, MB, BChir, MA, PhD, FRCP

Global Clinical Program Lead
AstraZeneca

AEGEAN: Study Design

Study population

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

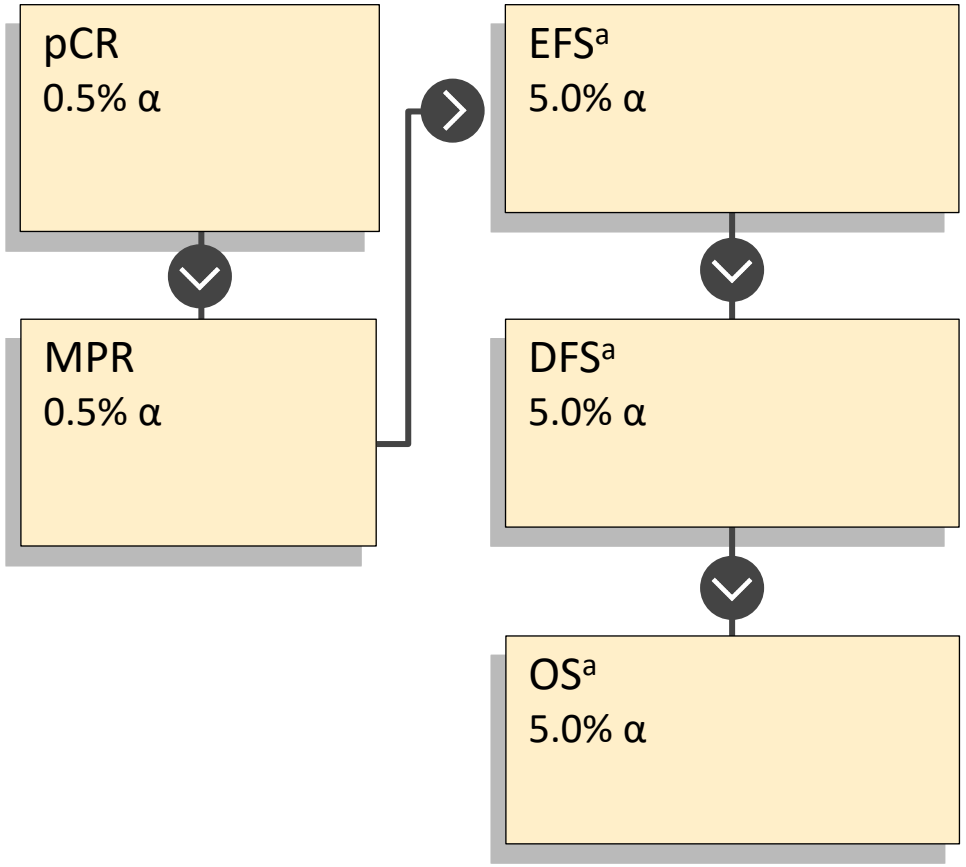


Endpoints	Primary	Key secondary	Other secondary includes
	• pCR (central lab) • EFS (BICR)	• MPR (central lab) • DFS (BICR) • OS	• Safety and tolerability • HRQoL/PRO • PD-L1 TC ≥1%: pCR, MPR, EFS, DFS, OS

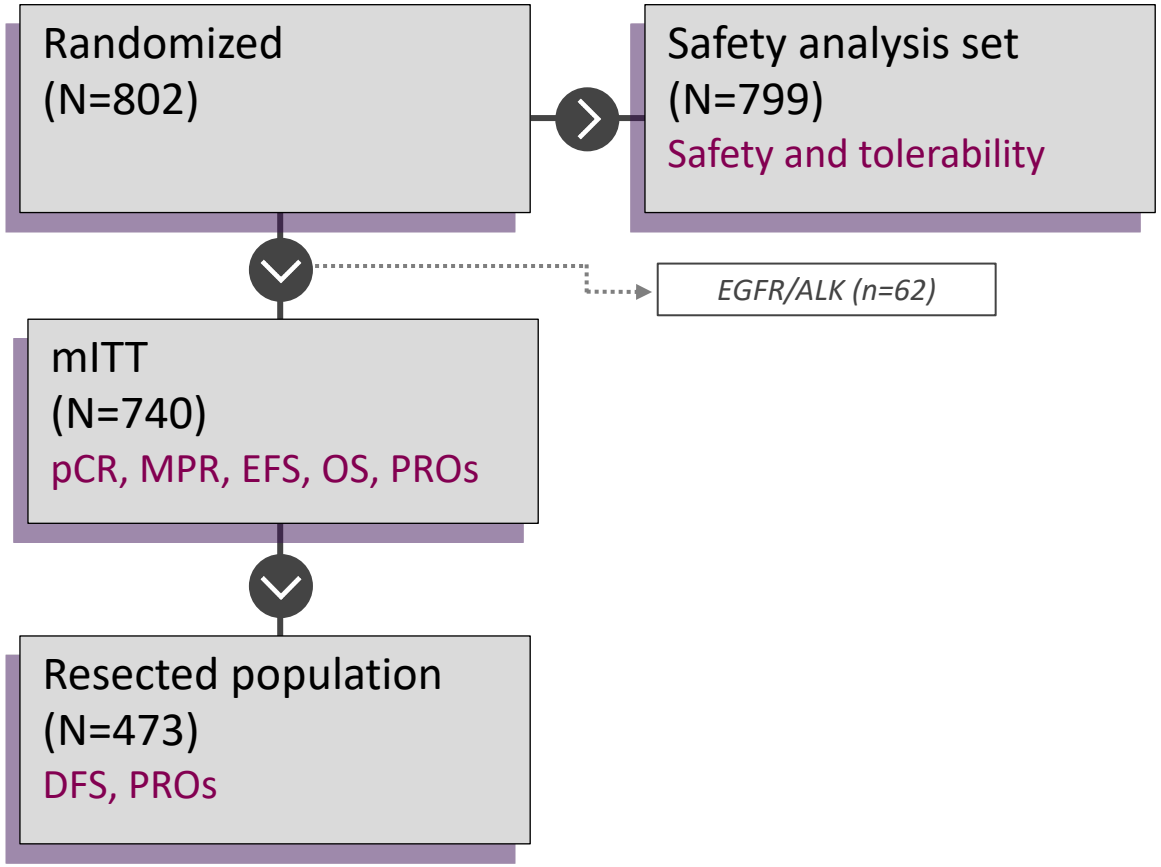
ALK=anaplastic lymphoma kinase; AJCC=American Joint Committee on Cancer; BICR=blinded independent central review; CTx=chemotherapy; DFS=disease-free survival; ECOG PS=Eastern Cooperative Oncology Group performance status; EFS=event-free survival; EGFR=epidermal growth factor receptor; HRQoL=health-related quality of life; IV=intravenous; MPR=major pathologic response; NSCLC=non-small cell lung cancer; OS=overall survival; pCR=pathologic complete response; PD-L1=programmed death-ligand 1; PRO=patient-reported outcome; Q3W=every 3 weeks; Q4W=every 4 weeks; R=randomization; TC=tumor cell.

AEGEAN: Statistical Considerations

Multiple Testing Procedure

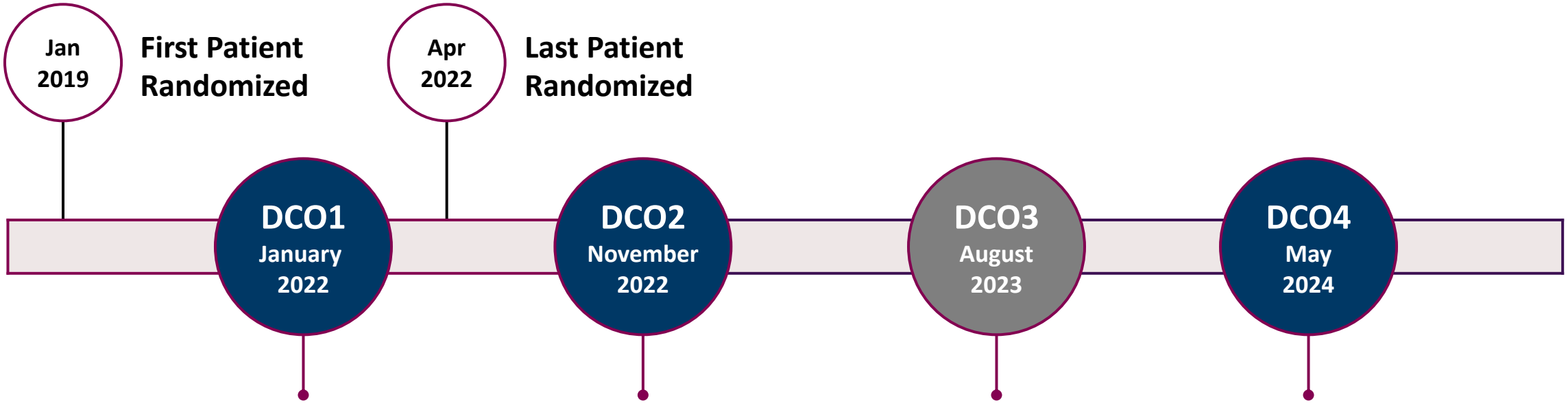


Analysis Sets



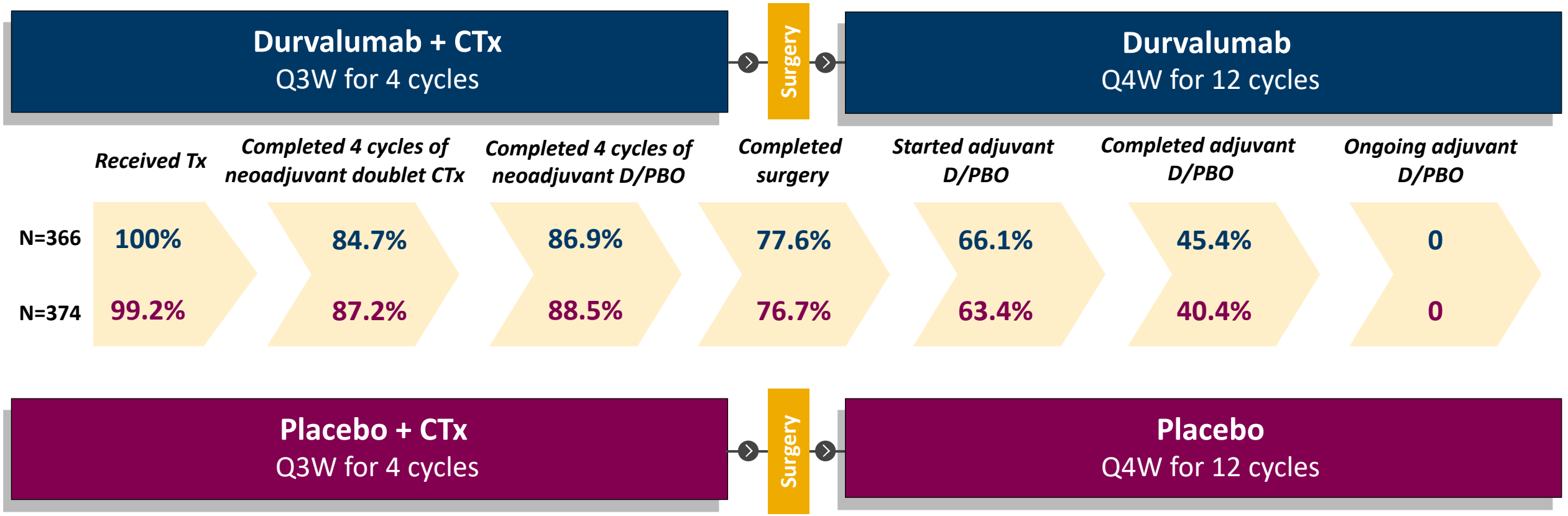
[a] Initial total α (alpha) of 4.5% (2 sided); tested with 5% α (2 sided) given recycling from MPR.
mITT=modified intent to treat (population).

AEGEAN: Analysis Plan



Bold: Primary analysis (where statistical significance was first achieved).
DCO1 analysis occurred after study enrollment was complete.
DCO=data cutoff.

Patient Disposition
mITT, DCO4



D/PBO=durvalumab/placebo; Tx=treatment.

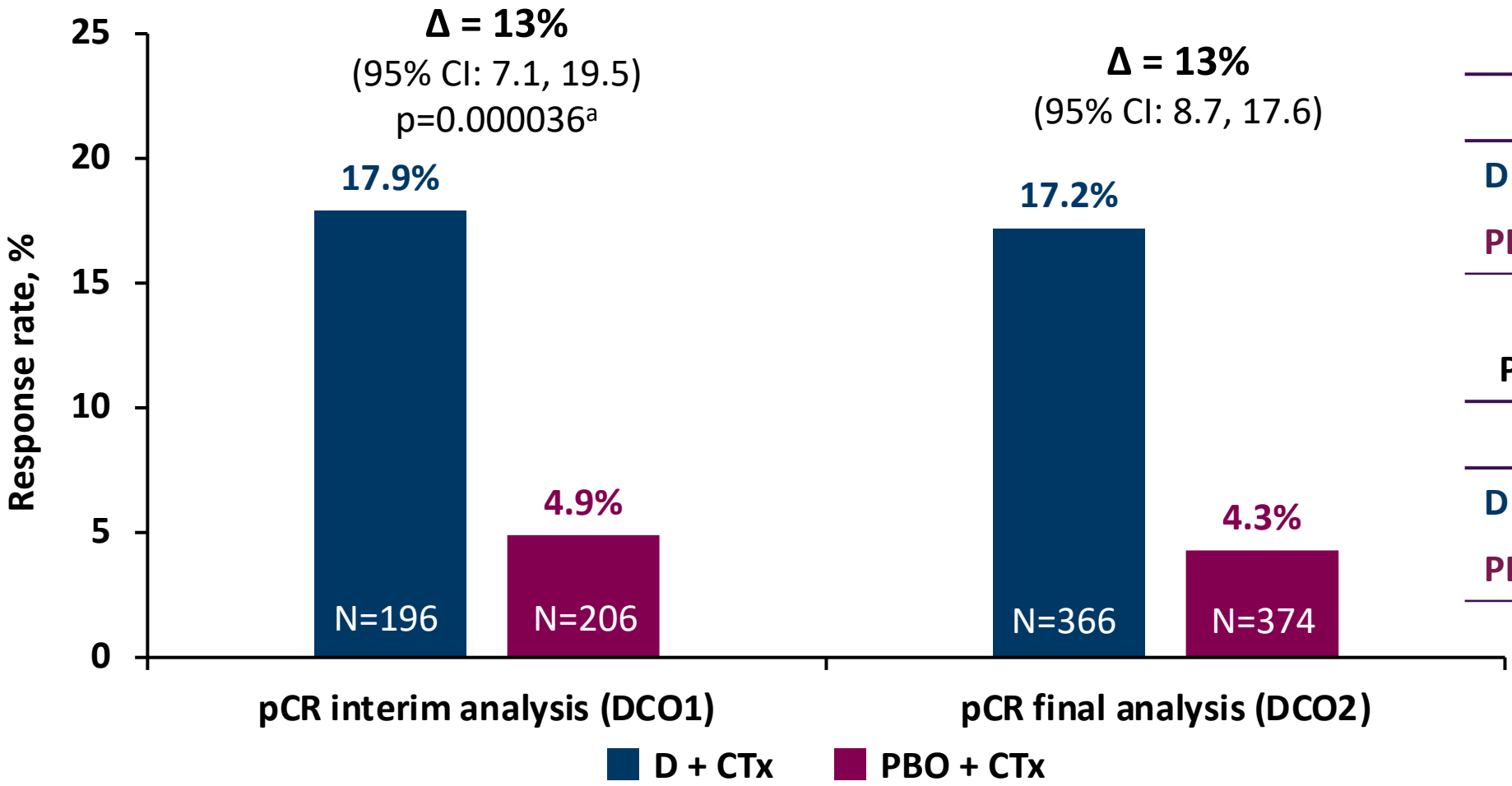
Baseline Patient Characteristics Are Generally Well Balanced

Patient Characteristics (mITT)		D + CTx (N=366)	PBO + CTx (N=374)
Age	Median (range), years	65.0 (30-88)	65.0 (39-85)
	≥75 years, %	12.0	9.6
Sex, %	Male	68.9	74.3
	Female	31.1	25.7
ECOG PS, %	0	68.6	68.2
	1	31.4	31.8
Race, %	Asian	39.1	43.9
	White	56.3	51.1
	Other	4.6	5.1
Region, %	Asia	38.8	43.6
	Europe	38.5	37.4
	North America	11.7	11.5
	South America	10.9	7.5
Smoking status, %	Current	26.0	25.4
	Former	60.1	59.6
	Never	13.9	15.0

Baseline Disease Characteristics and Planned Platinum Agent Are Generally Well Balanced

Disease Characteristics (mITT)		D + CTx (N=366)	PBO + CTx (N=374)
Disease stage (AJCC 8th ed.), %	II	28.4	29.4
	IIIA	47.3	44.1
	IIIB	24.0	26.2
Primary tumor, %	T1	12.0	11.5
	T2	26.5	28.9
	T3	35.0	34.5
	T4	26.5	25.1
Regional lymph nodes, %	N0	30.1	27.3
	N1	20.5	23.3
	N2	49.5	49.5
Histology, %	Squamous	46.2	51.1
	Non-squamous	53.6	47.9
PD-L1 expression, %	TC <1%	33.3	33.4
	TC 1%-49%	36.9	38.0
	TC ≥50%	29.8	28.6
Planned platinum agent, %	Cisplatin	27.3	25.7
	Carboplatin	72.7	74.3

Statistically Significant Improvement in pCR and MPR
DCO1, DCO2



MPR Final Analysis[b]

	MPR, %
D + CTx	33.3%
PBO + CTx	12.3%

Pre-surgical ORR by BICR[c]

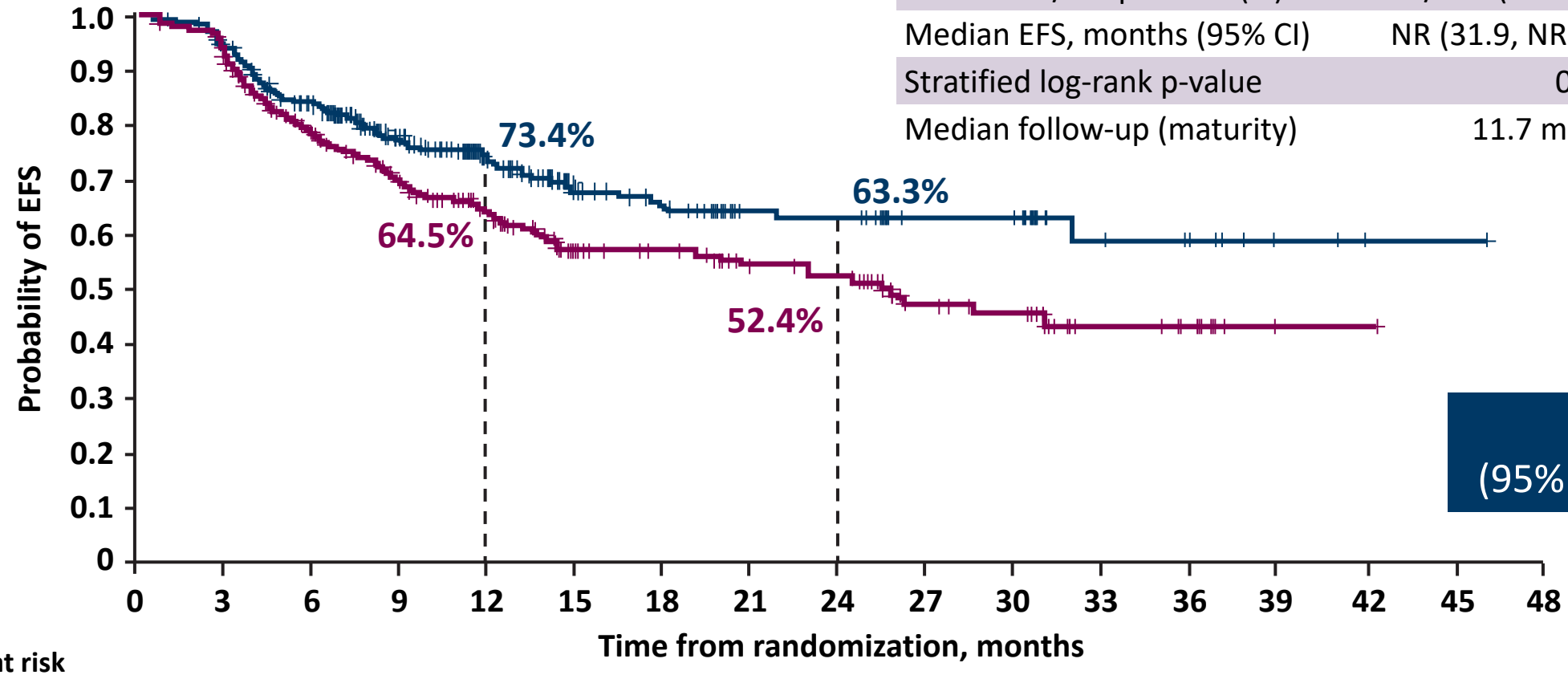
	ORR, %
D + CTx	56.3%
PBO + CTx	38.0%

As the interim analysis was statistically significant per the multiple testing procedure, pCR was not re-tested for statistical significance at the final analysis.
ORR=objective response rate.
[a] Based on interim analysis (N=402). [b] Based on final analysis (N=740; DCO2); p-value = 0.000002 based on interim analysis (N=402; DCO1). [c] Based on N=740; DCO2.
Figure from *N Engl J Med*, Heymach JV, et al. Perioperative durvalumab for resectable non-small cell lung cancer, 389(18), 1672-1684.

Statistically Significant and Clinically Meaningful Improvement in Event-Free Survival (BICR) at First Interim Analysis

DCO2

	D + CTx	PBO + CTx
No. events/no. patients (%)	98/366 (26.8)	138/374 (36.9)
Median EFS, months (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
Stratified log-rank p-value	0.0039	
Median follow-up (maturity)	11.7 months (32%)	



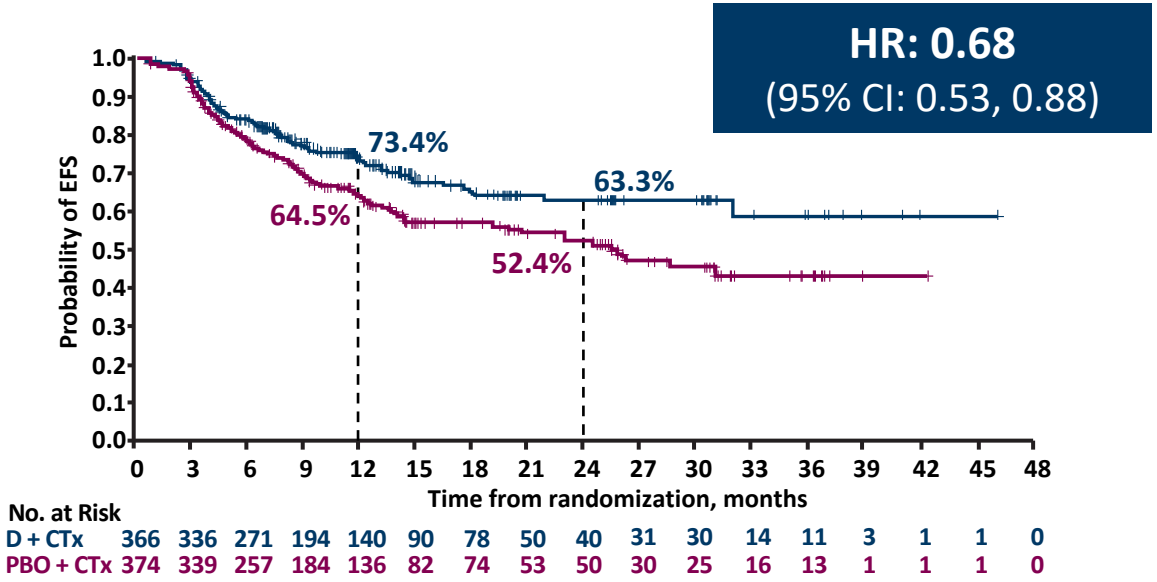
HR: 0.68
(95% CI: 0.53, 0.88)

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

EFS Results Maintained From DCO2 to DCO4

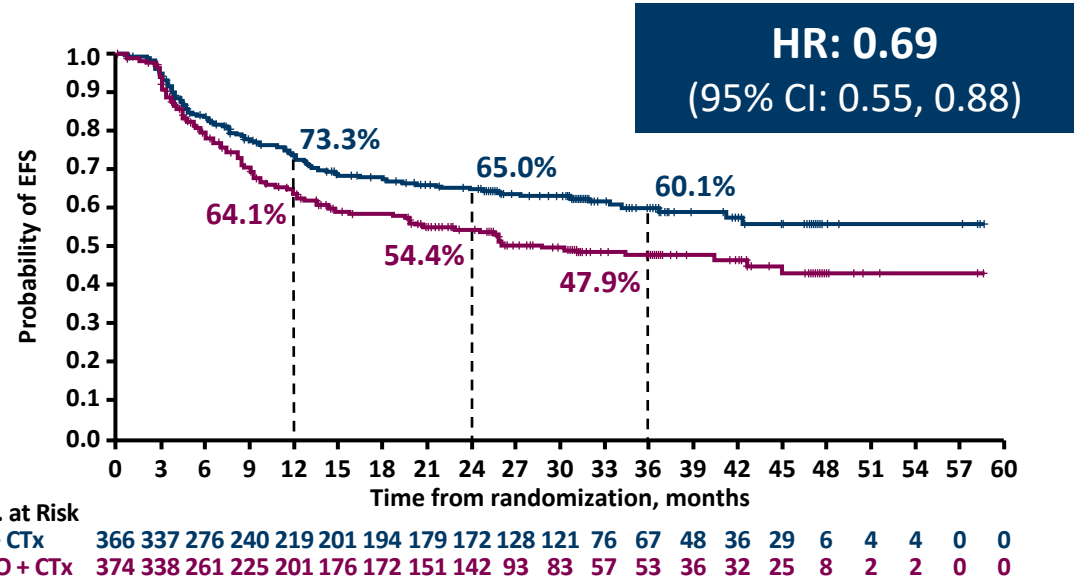
EFS at First Interim Analysis (DCO2)

	D + CTx	PBO + CTx
No. events/no. patients (%)	98/366 (26.8)	138/374 (36.9)
Median EFS, months (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
Median follow-up[a] (maturity)	11.7 months (32%)	



EFS at Second Interim Analysis (DCO4)

	D + CTx	PBO + CTx
No. events/no. patients (%)	124/366 (33.9)	165/374 (44.1)
Median EFS, months (95% CI)	NR (42.3, NR)	30.0 (20.6, NR)
Median follow-up[a] (maturity)	25.9 months (39%)	

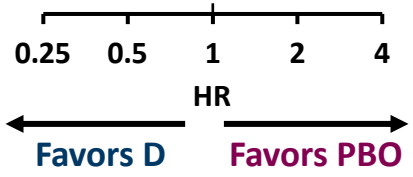


[a] Median follow-up in censored patients (range at DCO2: 0-46.1 months; range at DCO4: 0-58.6 months).

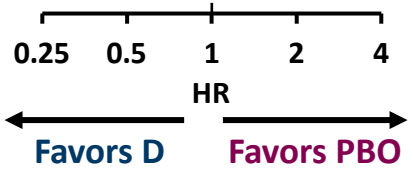
EFS Improvement Observed Across All Prespecified Subgroups

DCO4

Subgroup	n	HR (95% CI)
All patients	740	0.69 (0.55, 0.88)
Age at randomization		
<65 years	358	0.69 (0.48, 0.97)
≥65 years	382	0.71 (0.52, 0.97)
Sex		
Male	530	0.66 (0.50, 0.88)
Female	210	0.80 (0.52, 1.23)
ECOG PS		
0	506	0.66 (0.50, 0.88)
1	234	0.79 (0.52, 1.20)
Race		
Asian	307	0.66 (0.45, 0.95)
Non-Asian	433	0.73 (0.54, 0.99)
Smoking		
Current	190	0.52 (0.32, 0.82)
Former	443	0.75 (0.56, 1.02)
Never	107	0.88 (0.47, 1.61)

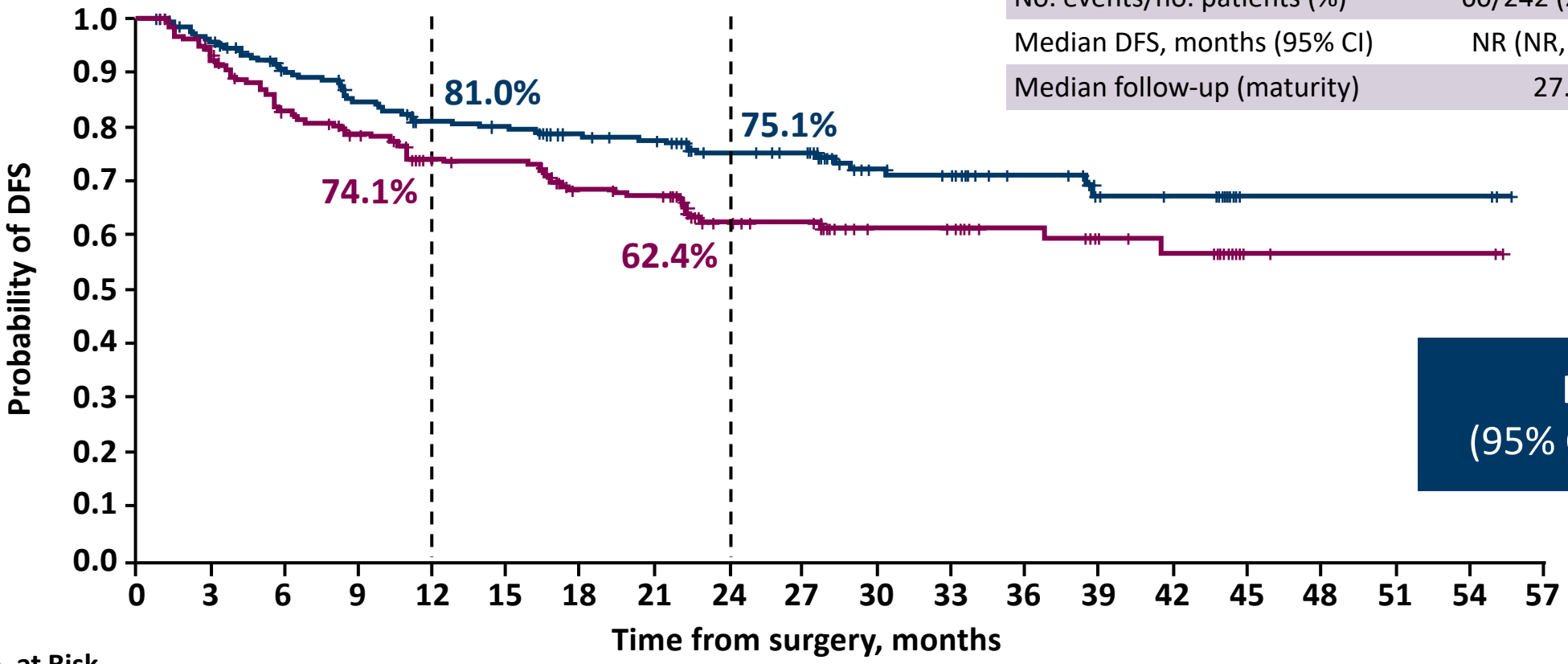


Subgroup	n	HR (95% CI)
All patients	740	0.69 (0.55, 0.88)
Histology		
Squamous	360	0.70 (0.49, 0.98)
Non-squamous	375	0.73 (0.53, 1.00)
Disease stage (AJCC 8th ed.)		
Stage II	214	0.82 (0.49, 1.34)
Stage IIIA	338	0.60 (0.42, 0.84)
Stage IIIB	186	0.81 (0.53, 1.23)
PD-L1 expression at baseline		
TC <1%	247	0.69 (0.46, 1.02)
TC 1%-49%	277	0.73 (0.50, 1.05)
TC ≥50%	216	0.71 (0.44, 1.12)
Planned neoadjuvant platinum agent		
Cisplatin	196	0.58 (0.35, 0.93)
Carboplatin	544	0.75 (0.57, 0.97)



Disease-Free Survival
Resected Population, DCO4

	D + CTx	PBO + CTx
No. events/no. patients (%)	60/242 (24.8)	81/231 (35.1)
Median DFS, months (95% CI)	NR (NR, NR)	NR (41.5, NR)
Median follow-up (maturity)	27.3 months (30%)	



HR: 0.66
(95% CI: 0.47, 0.92)

No. at Risk

D + CTx	242	226	201	186	171	168	155	151	113	110	65	61	45	27	26	4	4	4	4	0
PBO + CTx	231	212	185	172	152	150	125	122	74	71	46	45	31	23	21	3	2	2	2	0

Overall Survival
DCO2, DCO4

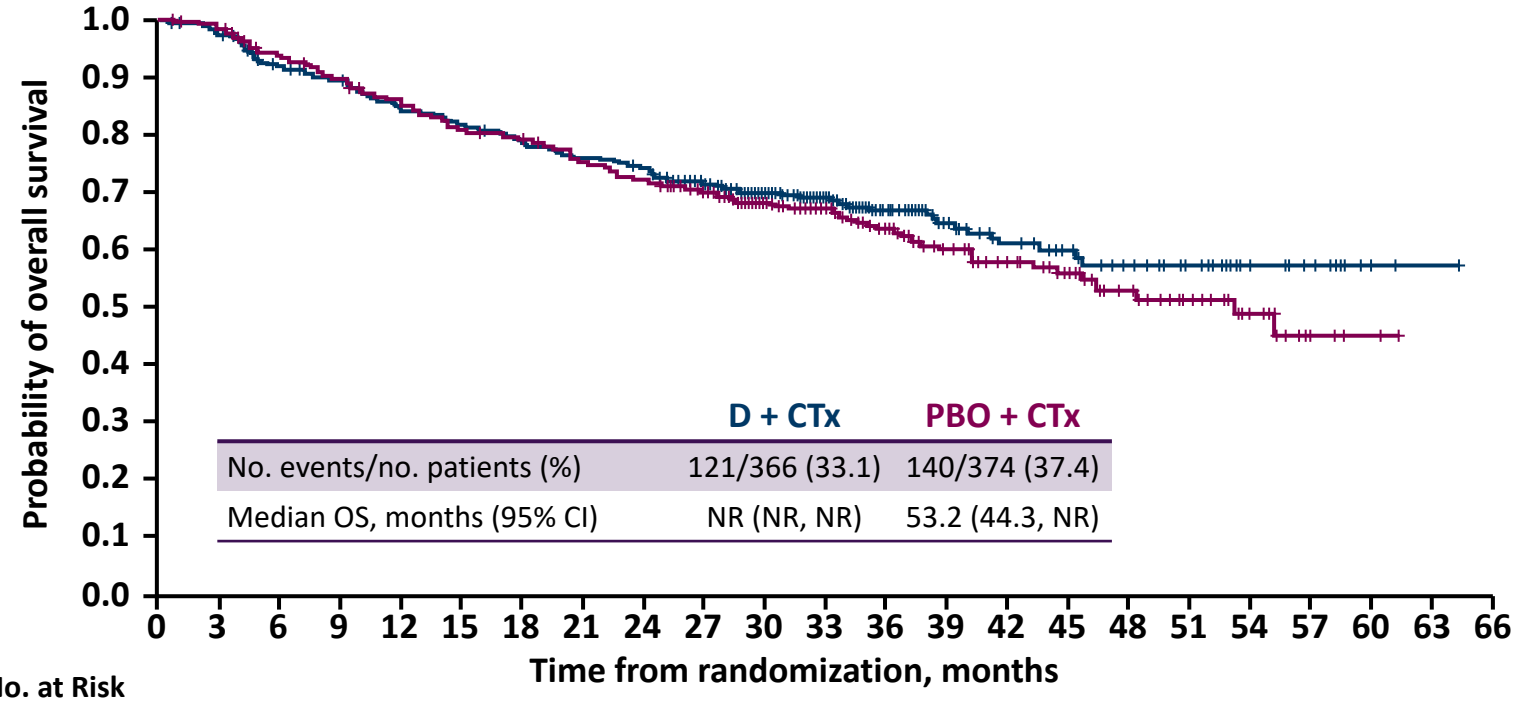
Prespecified OS Analyses

DCO2	
OS HR (95% CI)	1.02 (0.75, 1.39)
Maturity	22%

No new fatal AEs

DCO4	
OS HR (95% CI)	0.89 (0.70, 1.14)
Maturity	35%

Overall Survival (DCO4)



	D + CTx	PBO + CTx
No. events/no. patients (%)	121/366 (33.1)	140/374 (37.4)
Median OS, months (95% CI)	NR (NR, NR)	53.2 (44.3, NR)

No. at Risk

D + CTx	366	356	327	316	297	288	277	267	260	227	182	141	104	80	62	50	39	29	16	12	3	1	0
PBO + CTx	374	367	342	327	309	292	287	270	259	230	183	149	116	87	68	58	41	28	16	7	2	0	0

Preplanned COVID-19 sensitivity analysis for OS (DCO4): HR=0.84 (95% CI: 0.66, 1.08)

COVID-19=coronavirus disease 2019.

AEGEAN Efficacy Summary

- Statistically significant improvements in primary endpoints:
  - pCR: 17.9% vs 4.9% (p=0.00004)
    - Improvement maintained at final analysis
  - EFS: HR=0.68; 95% CI: 0.53, 0.88 (p=0.0039)
    - Clinically meaningful improvement maintained at second interim analysis
- A trend for DFS improvement: HR=0.66; 95% CI: 0.47, 0.92
- A trend for OS improvement: HR=0.89; 95% CI: 0.70, 1.14

Follow up on the AEGEAN trial continues.

AstraZeneca

Clinical Safety

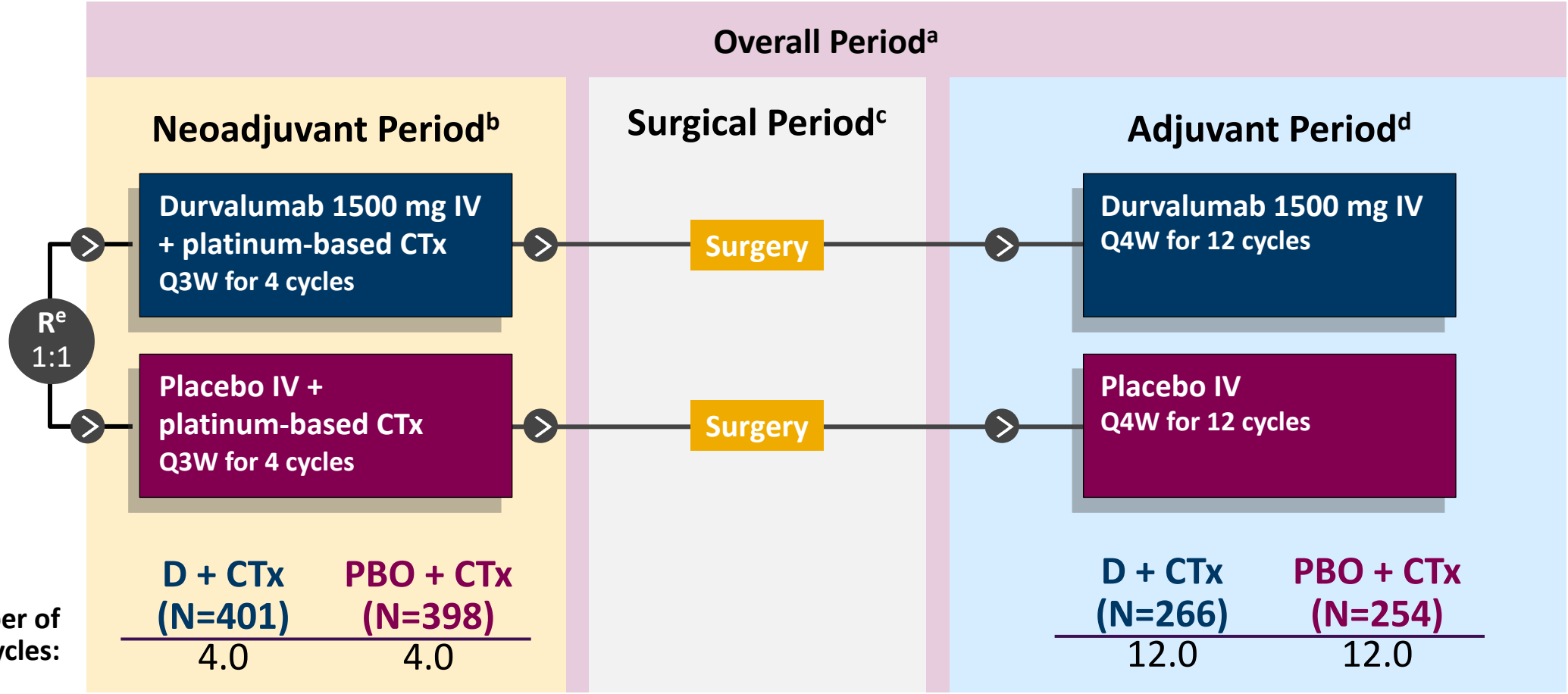
Mayur Patel, PharmD
VP Patient Safety Oncology
AstraZeneca

Durvalumab Has a Well-Established Safety Profile

Extensive Exposure Across Multiple Tumor Types	Adverse Drug Reactions (ADRs)	Immune-Mediated Events (imAEs)
• >5825 patients in the clinical development program • >144,273 patient-years in post-marketing settings	Rash, pruritus, pyrexia, diarrhea, cough, and abdominal pain	Hypothyroid events, pneumonitis, diarrhea/colitis, hepatic events, and rash/dermatitis

ADR=adverse drug reaction; imAE=immune-mediated adverse event.

AEGEAN: Exposure and Safety Periods



[a] AEs occurring between the first dose of study treatment and the earliest or maximum of (last dose of study treatment or surgery) + 90 days, the date of the DCO, or start of subsequent anticancer therapy.
[b] AEs occurring between the date of first dose of study treatment and the day before surgery, or for patients without surgery up to the 90 days post last dose of neoadjuvant treatment or start of subsequent anticancer therapy.
[C] AEs occurring between the date of surgery (including day of surgery) and the earliest of date of surgery + 90 days, or first dose of subsequent anticancer therapy.
[d] AEs occurring after the first dose of study treatment post surgery and the earliest of 90 days following the last dose adjuvant or first dose of subsequent anticancer therapy.
[e] N=802 randomized.

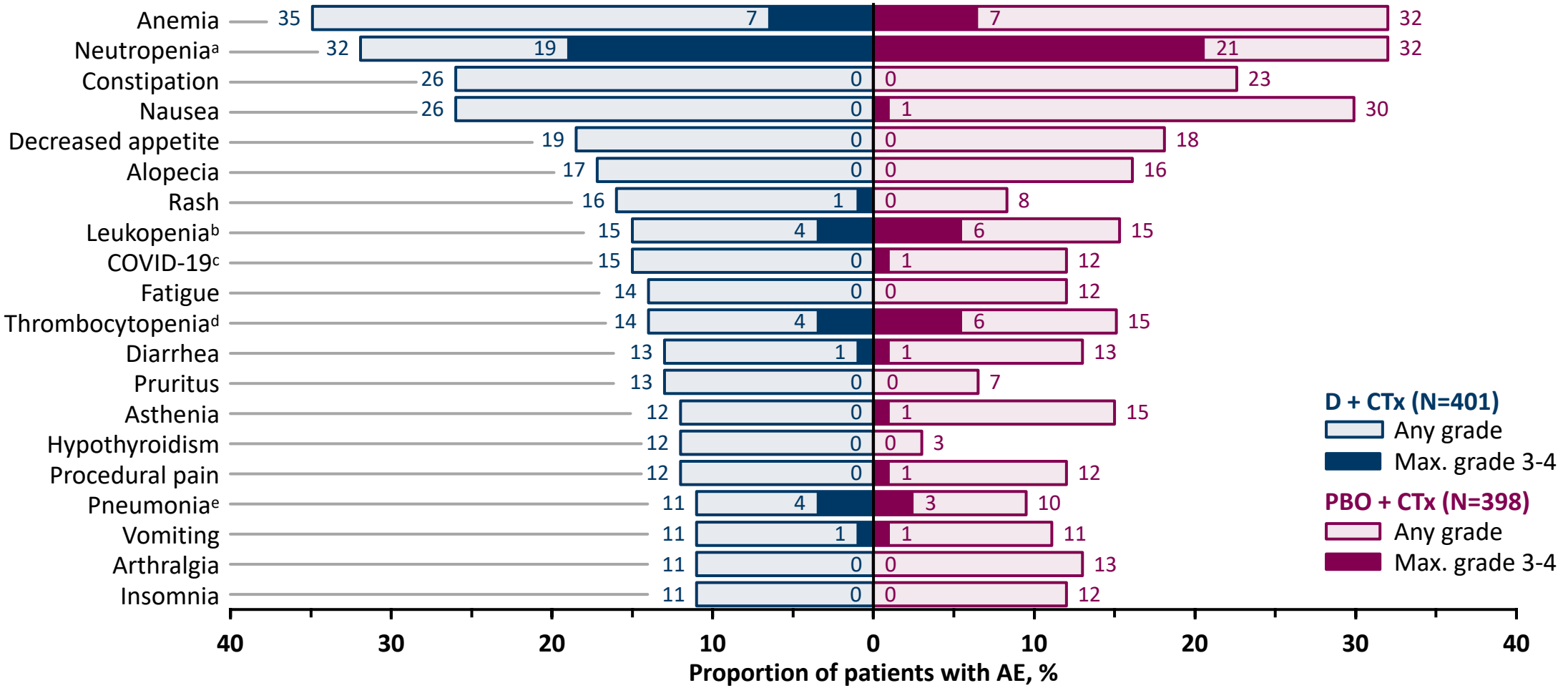
Summary of AEs by Category and Treatment Period
DCO4

Event	Overall		Neoadjuvant Period		Surgical Period		Adjuvant Period	
	D + CTx (N=401)	PBO + CTx (N=398)	D + CTx (N=401)	PBO + CTx (N=398)	D + CTx (N=325)	PBO + CTx (N=326)	D + CTx (N=266)	PBO + CTx (N=254)
Any-grade AEs, n (%)	**387 (96.5)**	**379 (95.2)**	**365 (91.0)**	**357 (89.7)**	**239 (73.5)**	**227 (69.6)**	**224 (84.2)**	**195 (76.8)**
Max. grade 3-4	175 (43.6)	172 (43.2)	131 (32.7)	145 (36.4)	56 (17.2)	43 (13.2)	41 (15.4)	27 (10.6)
Serious adverse events (SAEs)	157 (39.2)	126 (31.7)	83 (20.7)	66 (16.6)	61 (18.8)	51 (15.6)	41 (15.4)	26 (10.2)
Leading to discontinuation of any study treatment	78 (19.5)	39 (9.8)	54 (13.5)	30 (7.5)	2 (0.6)	2 (0.6)	26 (9.8)	10 (3.9)
Outcome of death[a]	23 (5.7)	15 (3.8)	8 (2.0)	4 (1.0)	13 (4.0)	9 (2.8)	4 (1.5)	2 (0.8)
Any-grade imAEs	102 (25.4)	41 (10.3)	33 (8.2)	19 (4.8)	19 (5.8)	2 (0.6)	61 (22.9)	21 (8.3)
Grade 3-4	18 (4.5)	10 (2.5)	6 (1.5)	5 (1.3)	6 (1.8)	1 (0.3)	6 (2.3)	4 (1.6)

[a] Two events; ILD and aortic aneurysm rupture (1 patient each) were captured in both the surgical and adjuvant periods.
ILD=interstitial lung disease; max=maximum.

Most Frequent AEs (≥10% of Patients in D + CTx Arm)

Overall Period, DCO4



[a] Includes Neutropenia and Neutrophil count decreased.
[b] Includes Leukopenia and White blood cell count decreased.
[c] Includes COVID-19 and COVID-19 pneumonia.
[d] Includes Thrombocytopenia and Platelet count decreased.
[e] Includes Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia chlamydial, Pneumonia cryptococcal, Pneumonia fungal, Pneumonia pseudomonal, Pneumonia streptococcal, and Pneumonia viral.

SAEs by Preferred Term (>1% Patients in Either Arm)
Overall Period, DCO4

Preferred Term	D + CTx (N=401)	PBO + CTx (N=398)
Patients with any SAE[a]	**157 (39.2)**	**126 (31.7)**
Pneumonia[b]	29 (7.2)	18 (4.5)
Pneumonitis[c]	12 (3.0)	4 (1.0)
COVID-19[d]	11 (2.7)	8 (2.0)
Anemia	7 (1.7)	5 (1.3)
Neutropenia[e]	7 (1.7)	4 (1.0)
Myelosuppression	6 (1.5)	2 (0.5)
Thrombocytopenia[f]	6 (1.5)	1 (0.3)
Vomiting	5 (1.2)	2 (0.5)
Drug-induced liver injury	5 (1.2)	1 (0.3)
Pneumothorax	4 (1.0)	9 (2.3)

[a] Subjects with multiple SAEs are counted once for each preferred term.
[b] Includes Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia fungal, Pneumonia streptococcal and Pneumonia viral.
[c] Includes Pneumonitis, Interstitial lung disease, and Immune-mediated lung disease.
[d] Includes COVID-19 and COVID-19 Pneumonia.
[e] Includes Neutropenia and Neutrophil count decreased.
[f] Includes Thrombocytopenia and Platelet count decreased.

Fatal TEAEs
Overall Period, DCO4

Event	D + CTx (N=401)	PBO + CTx (N=398)
Patients with AE with outcome of death, n (%)	**23 (5.7)**	**15 (3.8)**
COVID-19[a]	5	1
Pneumonia[b]	4	4
Infection/sepsis/septic shock[c]	4	2
Pneumonitis[d]	4	0
Myocarditis	1	0
Hemoptysis	1	0
Decreased appetite	1	0
Postprocedural pulmonary embolism	1	0
Aortic aneurysm rupture	1	0
Death	1	0
Cardiac failure	0	1
Cardiac failure acute	0	1
Myocardial ischemia	0	1
Pulmonary hemorrhage	0	1
Acute respiratory failure	0	1
Subarachnoid hemorrhage	0	1
Multiple organ dysfunction syndrome	0	1
Duodenal ulcer perforation	0	1

Patients with multiple causes of death are represented once based on primary cause of death.

[a] Includes COVID-19 and COVID-19 Pneumonia. [b] Includes Pneumonia, Pneumonia aspiration, and Pneumonia streptococcal.

[c] Includes Infection, Sepsis, Septic shock, and Infectious pleural effusion. [d] Includes Pneumonitis, interstitial lung disease, and immune-mediated lung disease.

Immune-Mediated AEs by Category
Overall Period, DCO4

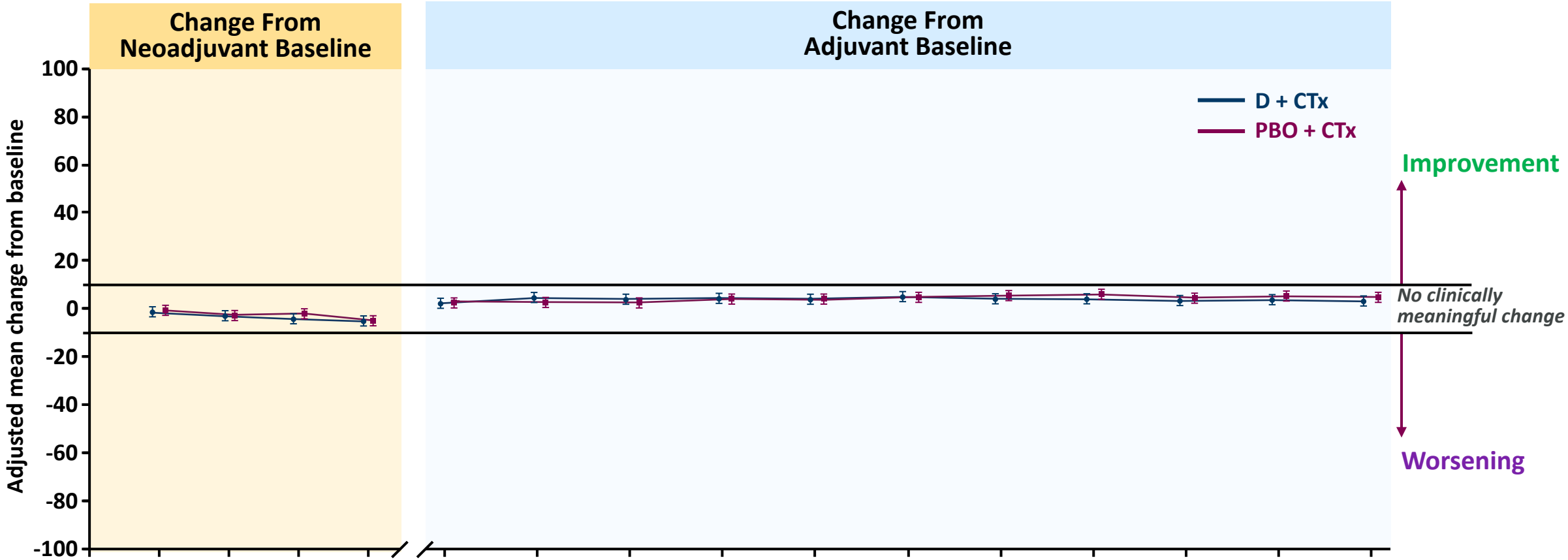
	D + CTx (N=401)	PBO + CTx (N=398)
Patients with any imAE, n (%)	102 (25.4)	41 (10.3)
Grade 3-4	18 (4.5)	10 (2.5)
SAEs	21 (5.2)	10 (2.5)
Leading to discontinuation of any study treatment	19 (4.7)	4 (1.0)
Resolved[a]	59 (14.7)	21 (5.3)
Unresolved[b]	38 (9.5)	20 (5.0)
Resolving	20 (5.0)	3 (0.8)
Not resolved	20 (5.0)	17 (4.3)
Fatal	5 (1.2)	0

Majority of unresolved events were endocrine events requiring hormone replacement therapy: 32 (of 38) in D + CTx arm and 10 (of 20) in PBO + CTx arm

[a] Includes the outcomes of Resolved and Resolved with sequelae.
[b] Includes the outcomes of Resolving and Not resolved. Resolving and Not resolved categories are not mutually exclusive given that patients may have experienced multiple imAEs.

Minimal Impact on Patient-Reported **Physical Function**

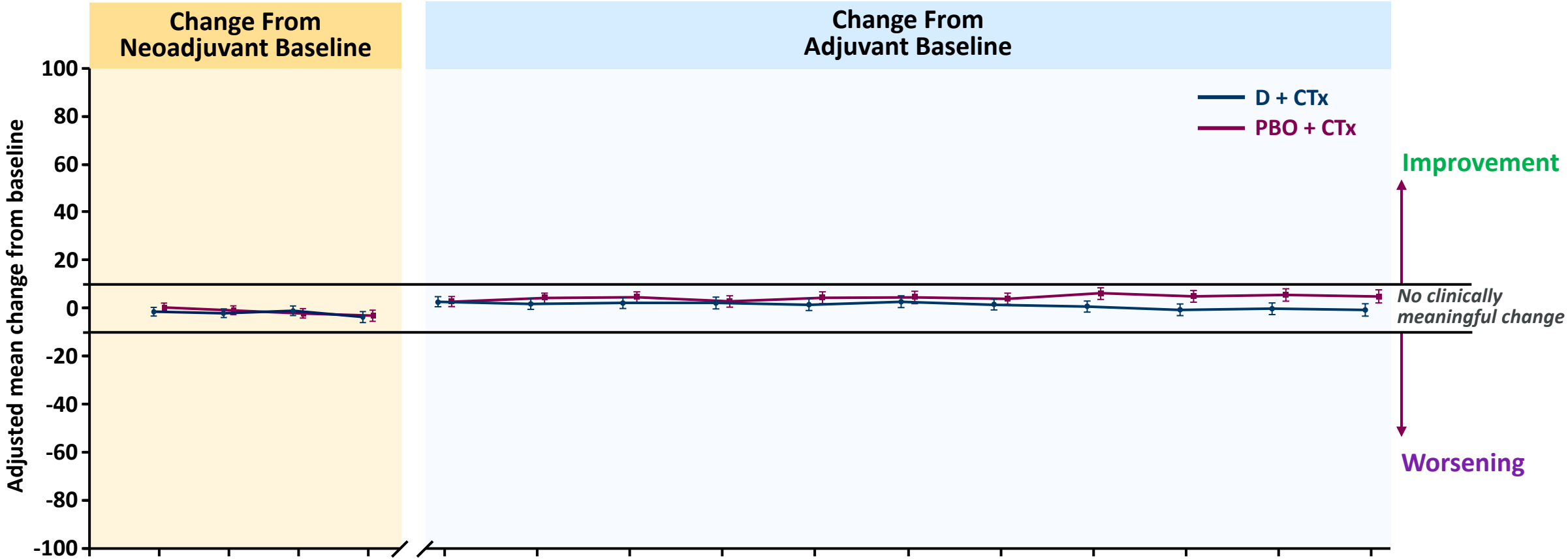
EORTC QLQ-C30, MMRM, DCO4



Patients, n	3	6	9	12	4	8	12	16	20	24	28	32	36	40	44
D + CTx	304	273	252	184	174	167	163	155	152	148	139	139	137	135	128
PBO + CTx	293	276	256	199	160	161	153	152	143	139	128	131	128	117	117

Minimal Impact on Patient-Reported **Global Health Status/QoL**

EORTC QLQ-C30, MMRM, DCO4



Patients, n															
D + CTx	304	273	252	184	174	167	163	155	152	148	139	139	137	135	128
PBO + CTx	293	276	256	199	160	161	153	152	143	139	128	131	128	117	117

Summary of Safety

- AEGEAN demonstrated a manageable safety profile consistent with the individual agents
- Majority of imAEs were nonserious, low grade (CTCAE grade 1-2), and manageable
- Minimal impact on patient-reported physical function and global health status/QoL from adjuvant treatment
- No new safety findings were observed

CTCAE=Common Terminology Criteria for Adverse Events.

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Clinical Perspective

John Heymach, MD, PhD
MD Anderson

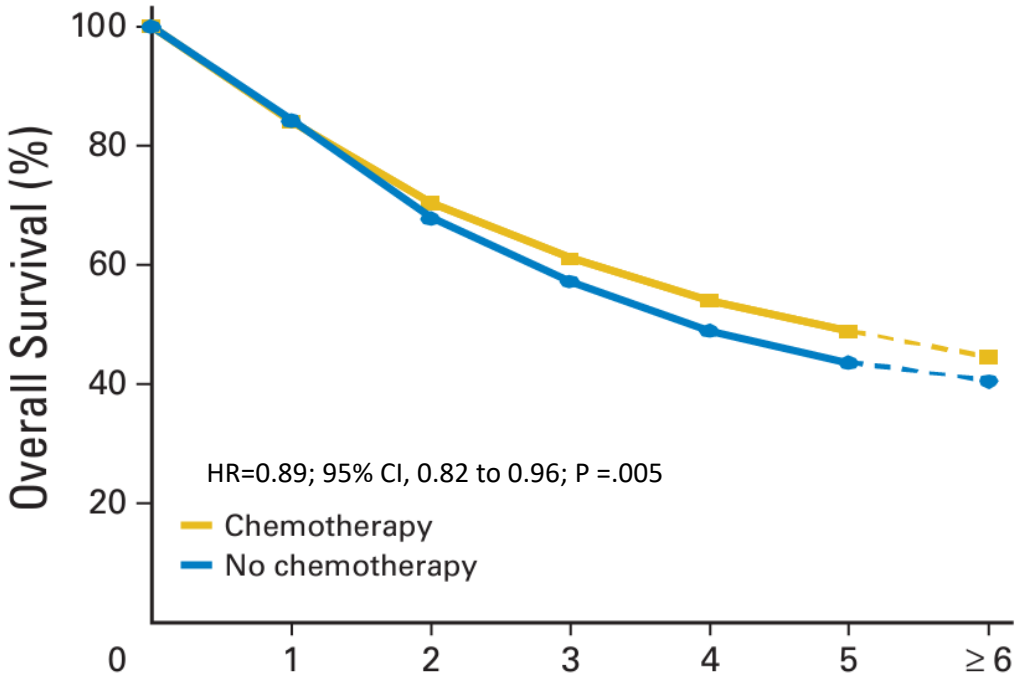
Clinical Perspective on Resectable NSCLC and AEGEAN

1. The goal of treatment is to remain disease-free, or be cured, and most patients are destined to recur with standard therapy
   - Most patients would choose more- vs less-intensive therapy
2. Physicians and patients prefer a choice among multiple effective options, enabling them to tailor treatment
3. Data from multiple large RCTs strongly suggest neoadjuvant + adjuvant IO is more effective than neoadjuvant or adjuvant IO for rNSCLC
4. AEGEAN is a highly effective and safe regimen

RCT=randomized controlled trial; rNSCLC=resectable non-small cell lung cancer.

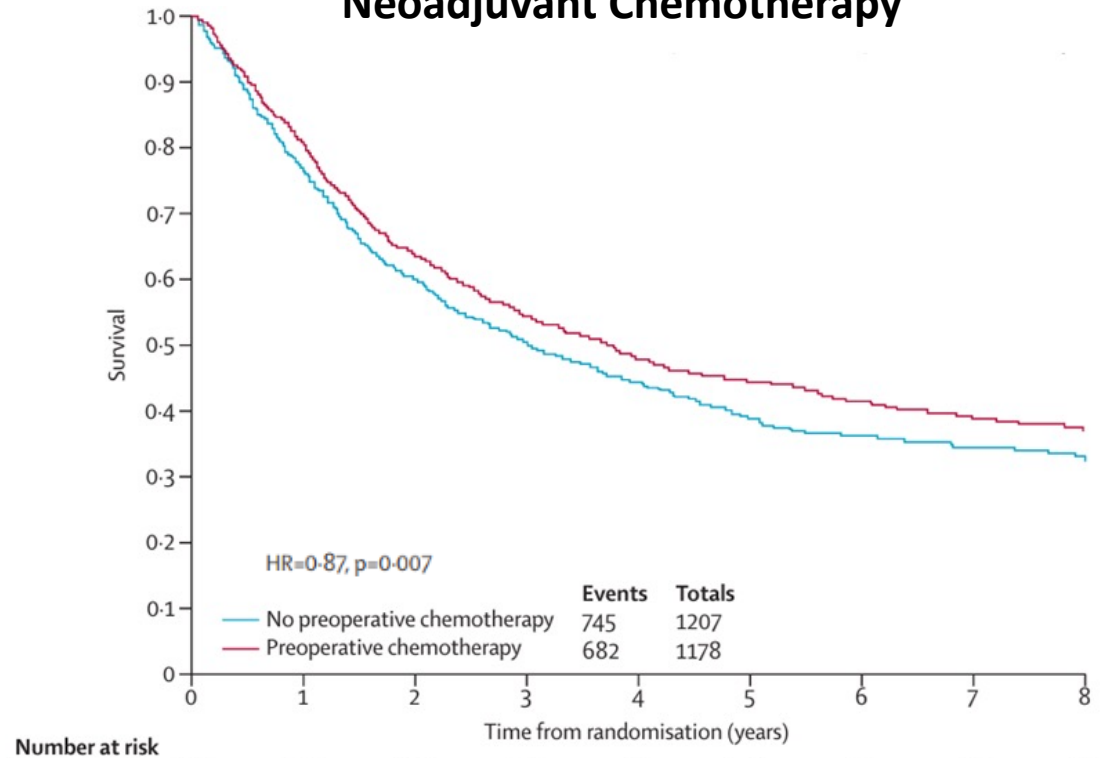
Meta-analyses Show a Similar, Modest Survival Benefit With Adjuvant or Neoadjuvant CTx

Adjuvant Chemotherapy



Deaths / person years by period	Years 0-3	Years 4-5	Years ≥ 6
Control	966 / 5,155	239 / 1,668	49 / 720
Chemotherapy	857 / 5,181	203 / 1,817	76 / 790

Neoadjuvant Chemotherapy



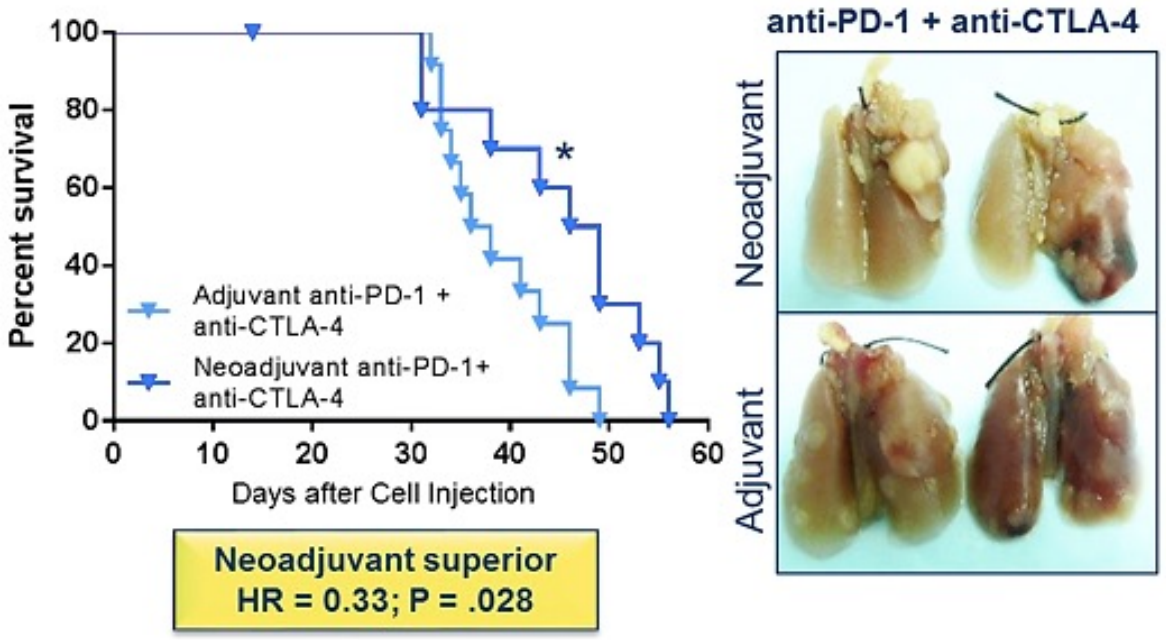
Number at risk									
No preoperative chemotherapy	1207	893	674	527	409	300	209	147	102
Preoperative chemotherapy	1178	928	712	570	442	346	253	172	123

Left figure adapted with permission from Pignon JP, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552-3559. https://ascopubs.org/doi/10.1200/JCO.2007.13.9030.

Right figure reprinted with permission from NSCLC Meta-analysis Collaborative Group. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet*. 2014;383(9928):1561-1571. © 2014. https://creativecommons.org/licenses/by/3.0/

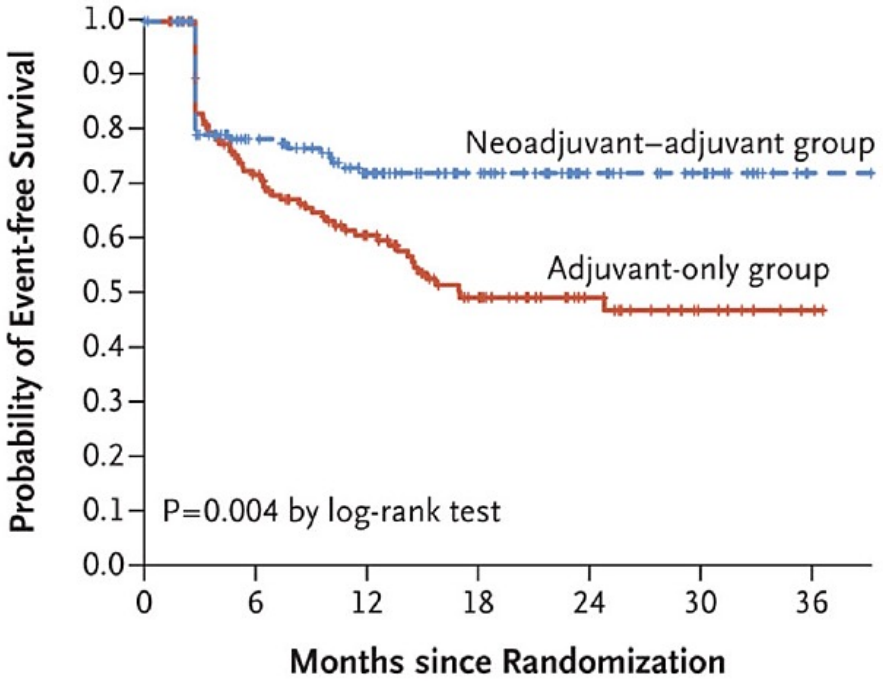
Preclinical and Clinical Studies Support the Superiority of Neoadjuvant or Perioperative IO vs Adjuvant IO

Murine NSCLC Model[1]



Similar observations using murine breast cancer model[3]

SWOG S1801 (Melanoma)[2]



No. at Risk							
Neoadjuvant–adjuvant group	154	96	69	46	25	17	1
Adjuvant-only group	159	98	67	40	22	10	2

Left figure reprinted with permission from Cascone T, et al. Superior efficacy of neoadjuvant compared to adjuvant immune checkpoint blockade in non-small cell lung cancer. AACR 2018. Poster 1719/14.

Right figure from *N Engl J Med*, Patel SP, et al. Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma, 388(9), 813-823. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

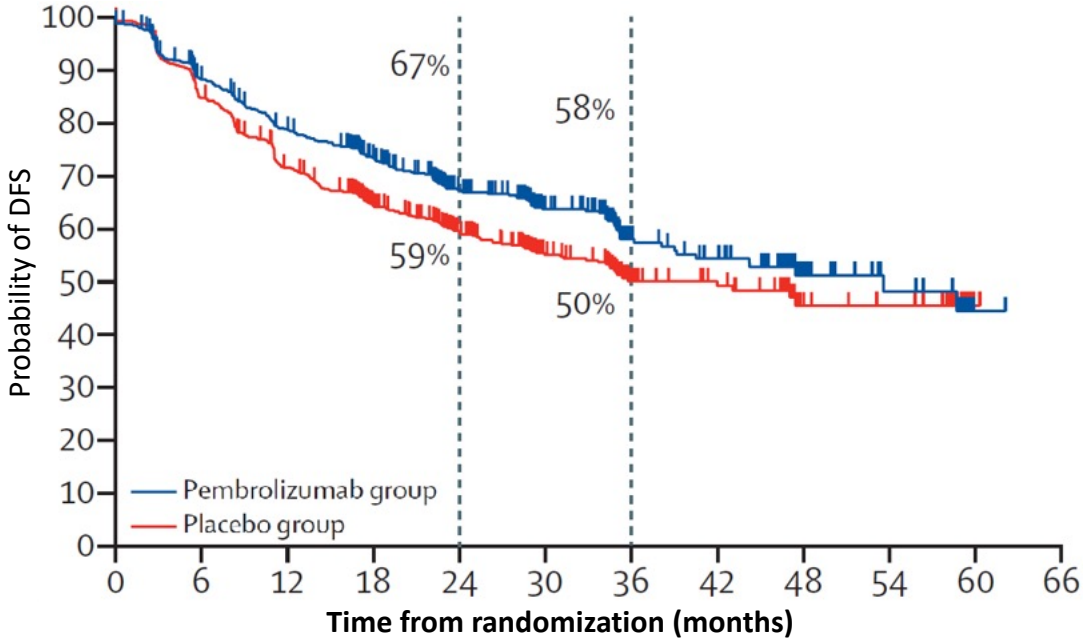
CTLA-4=cytotoxic T-lymphocyte-associated antigen 4; SWOG=Southwest Oncology Group.

1. Cascone T, et al. AACR 2018 Poster 1719/14; 2. Patel SP, et al. *N Engl J Med*. 2023;388(9):813-823; 3. Liu et al. *Cancer Discov*. 2016;6(12):1382-1399.

Perioperative IO Appears More Effective Than Adjuvant IO

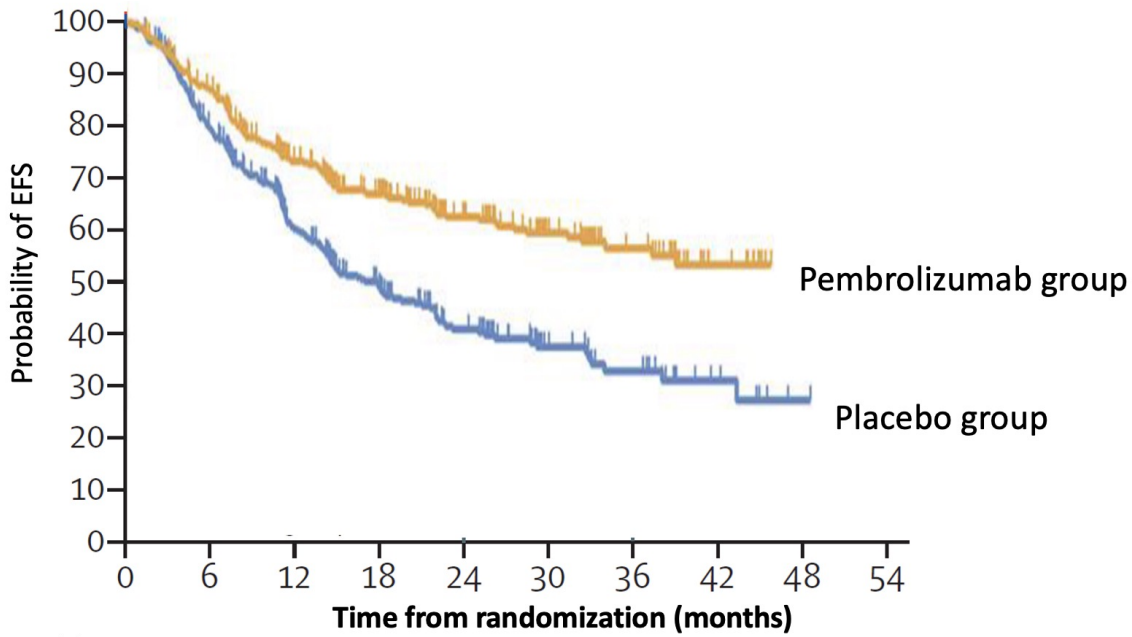
KEYNOTE-091 (Adjuvant Treatment)

HR: 0.76 (95% CI: 0.63, 0.91)



KEYNOTE-671 (Perioperative Treatment)

HR: 0.58 (95% CI: 0.46, 0.72)



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

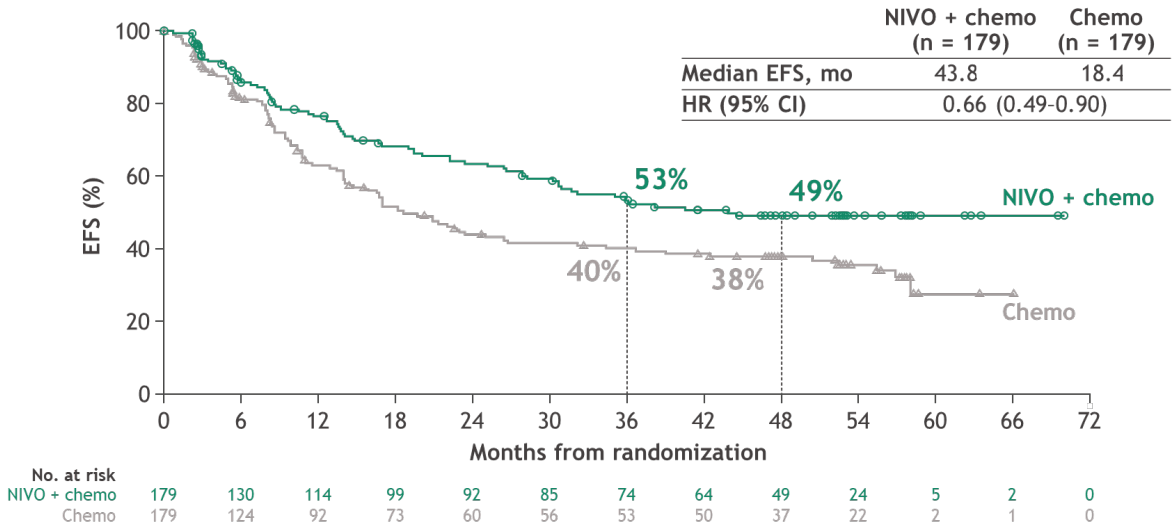
Left figure reprinted from *The Lancet Oncology*, 23(10), O'Brien M, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial, 1274-1286, Copyright 2022, with permission from Elsevier.

Right figure from *N Engl J Med*, Wakelee H, et al. Perioperative pembrolizumab for early-stage non-small-cell lung cancer, 389(6), 491-503. Copyright © 2023 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Perioperative IO Compared With Neoadjuvant IO

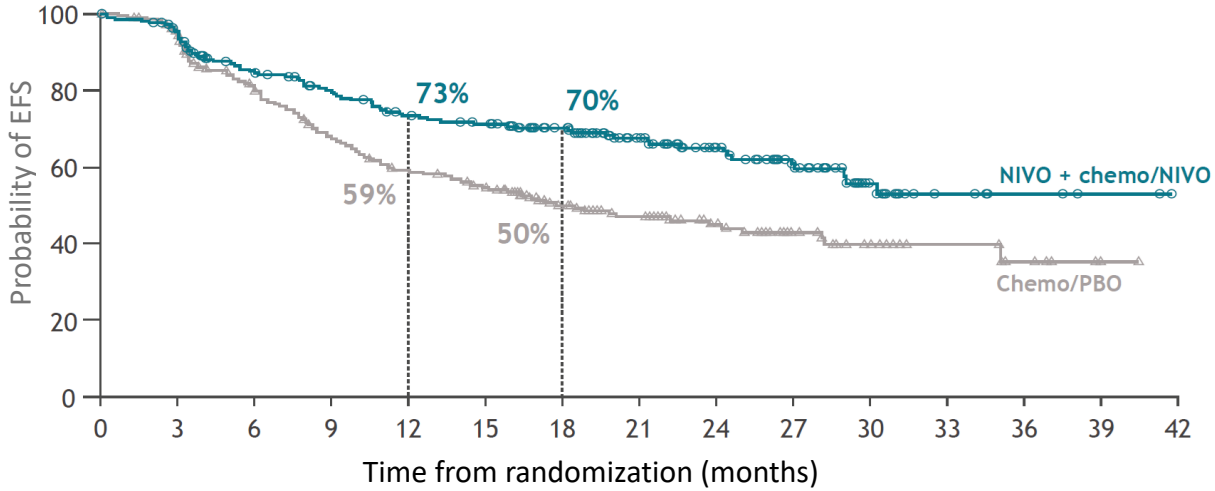
CheckMate 816 (Neoadjuvant Treatment)

HR: 0.66 (95% CI: 0.49, 0.90)



CheckMate 77T (Perioperative Treatment)

HR: 0.58 (97.36% CI: 0.42, 0.81)



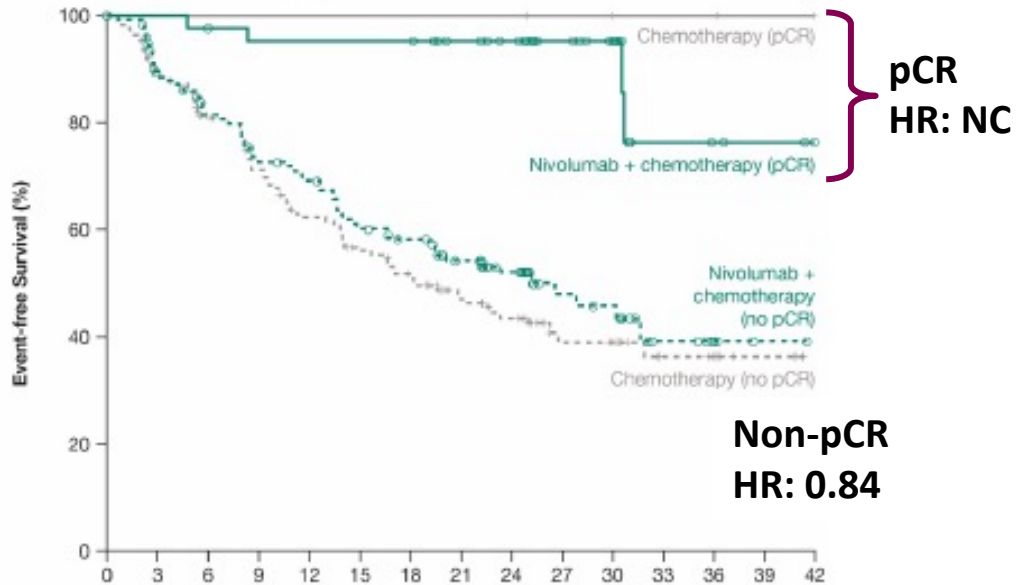
Left figure reprinted with permission from Spicer JD, et al. Neoadjuvant nivolumab plus chemotherapy vs chemotherapy in patients with resectable NSCLC: 4-year update from CheckMate 816 [oral]. Presented at 2024 ASCO Annual Meeting. ASCO 2024. Abstract LBA8010.

Right figure from *N Engl J Med*, Cascone T, et al. Perioperative nivolumab in resectable lung cancer, 390(19), 1756-1769. Copyright © 2024 Massachusetts Medical Society. Adapted with permission from Massachusetts Medical Society.

CM 816 and CM 77T: EFS Analysis (pCR vs non-pCR)

CheckMate 816 (Neoadjuvant Treatment)

	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†	

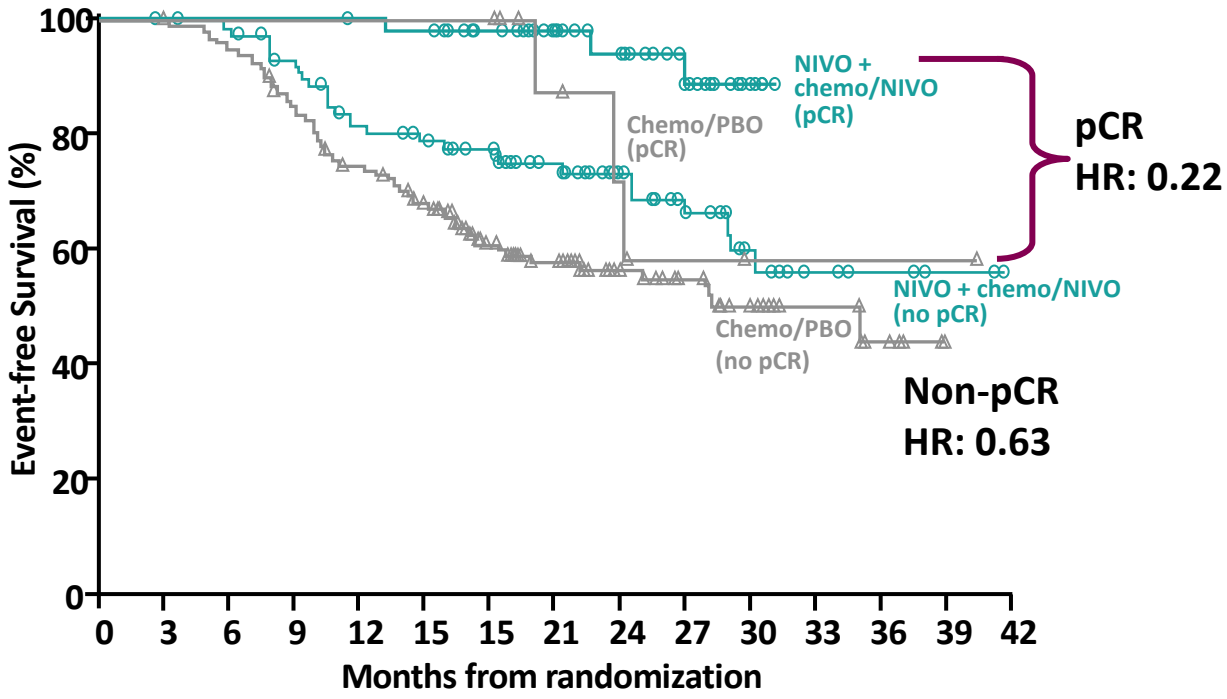


pCR
HR: NC

Non-pCR
HR: 0.84

No. at Risk															
Nivolumab + chemotherapy (pCR)	43	43	41	40	40	40	40	35	32	19	14	6	3	2	0
Chemotherapy (pCR)	4	4	4	4	4	4	4	4	4	3	2	2	2	1	0
Nivolumab + chemotherapy (no pCR)	136	108	95	84	78	67	62	52	42	22	20	7	3	1	0
Chemotherapy (no pCR)	175	140	122	105	90	79	71	57	48	23	22	11	9	3	0

CheckMate 77T (Perioperative Treatment)



pCR
HR: 0.22

Non-pCR
HR: 0.63

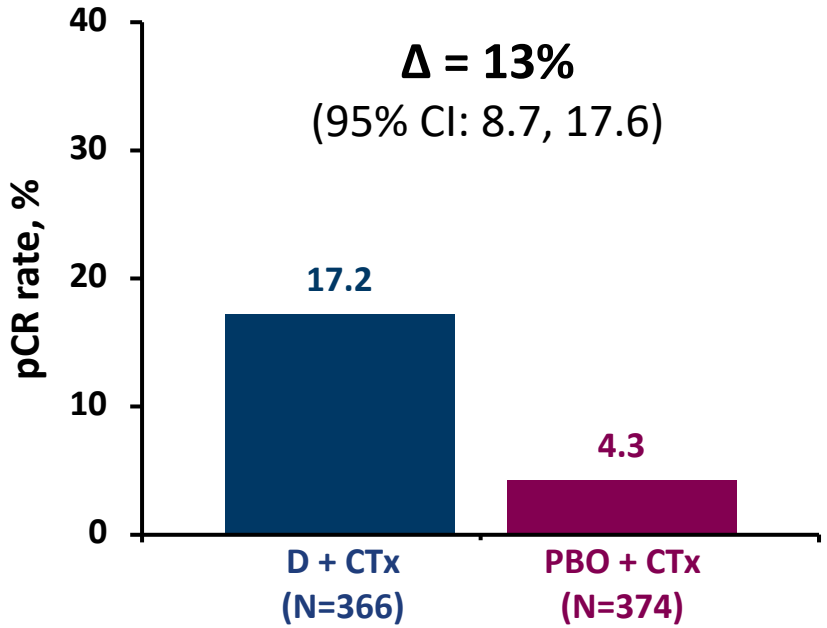
NC=not computed.

Left figure reprinted with permission from Girard N, et al. Nivolumab + platinum-doublet chemotherapy vs chemotherapy as neoadjuvant treatment for resectable (IB–IIIA) non-small cell lung cancer: event-free survival results from the phase 3 CheckMate 816 trial [oral]. Presented at AACR 2022; CT012.

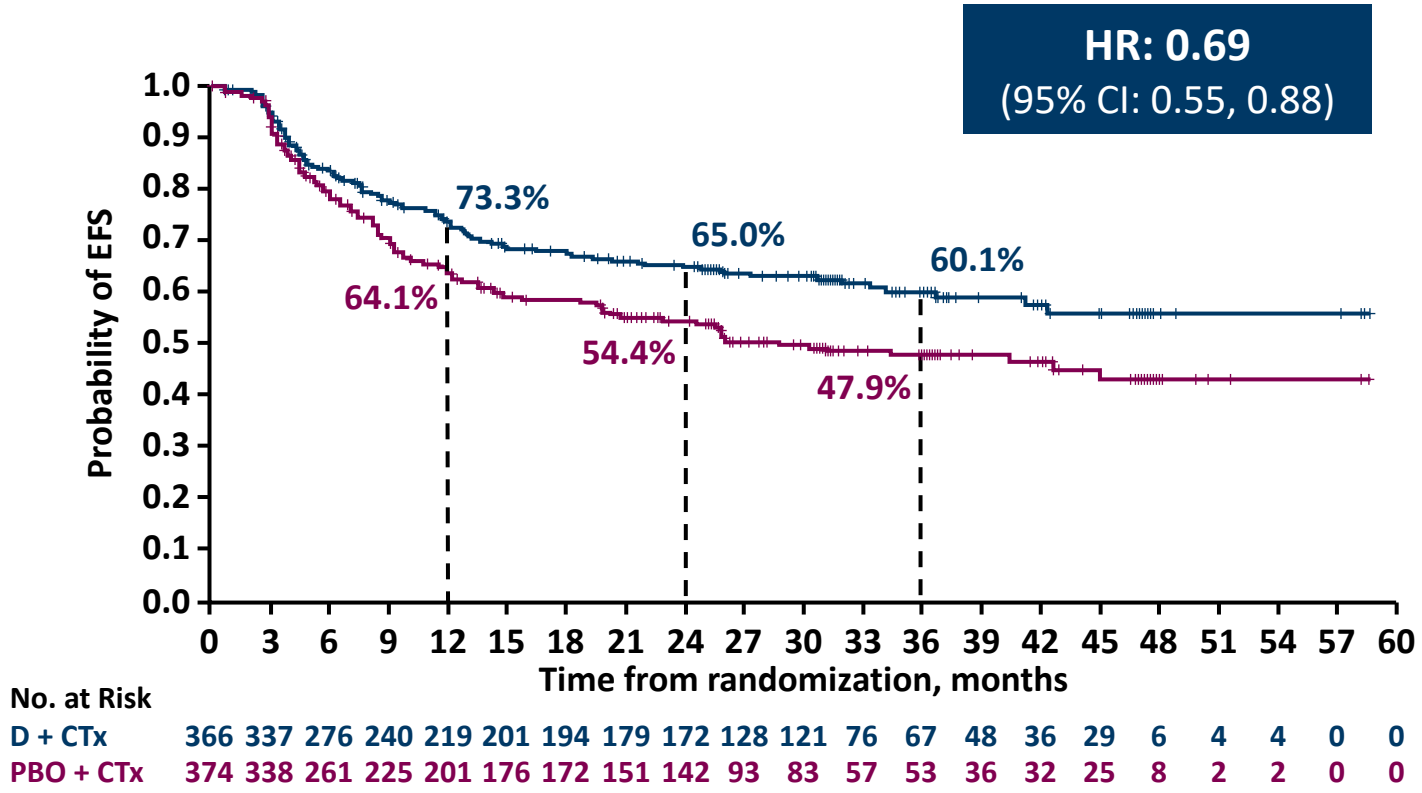
Right figure reprinted with permission from Cascone T, et al. CheckMate 77T: Phase 3 study comparing neoadjuvant nivolumab plus chemotherapy with neoadjuvant placebo plus chemotherapy followed by surgery and adjuvant nivolumab or placebo for previously untreated, resectable stage II–IIIB NSCLC. Presented at ESMO 2023; LBA1.

AEGEAN Achieved Both Primary Endpoints of pCR and EFS

pCR at Final Analysis[1]



EFS at Second Interim Analysis (DCO4)



EFS at DCO2: HR=0.68; 95% CI: 0.53, 0.88; p=0.0039[1]

1. Left figure from *N Engl J Med*, Heymach JV, et al. Perioperative durvalumab for resectable non-small cell lung cancer, 389(18), 1672-1684.

Multiple Large Randomized Trials Support Substantial Clinical Benefit of Immune Checkpoint Inhibitors in Resectable NSCLC

	Adjuvant[a] (N=2182)				Perioperative (N=1998)				Neoadjuvant (N=358)	
Study	**KEYNOTE-091[1] N=1177**		**IMpower010[2] N=1005**		**KEYNOTE-671[3] N=797**		**AEGEAN N=740**		**CheckMate 77T[4] N=461**		**CheckMate 816[5] N=358**	
Regimen	**Pembro**	**Placebo**	**Atezo**	**BSC**	**Pembro + Chemo →Pembro**	**Placebo + Chemo →Placebo**	**Durva + Chemo →Durva**	**Placebo + Chemo →Placebo**	**Nivo + Chemo →Nivo**	**Placebo + Chemo →Placebo**	**Nivo + Chemo**	**Chemo**
Median EFS/DFS (95% CI), mo	53.9 (46.2-67.0)	43.0 (35.0-51.6)	65.6 (NA, NA)	47.8 (NA, NA)	47.2 (32.9, NR)	18.3 (14.8, 22.1)	NR (42.3, NR)	30.0 (20.6, NR)	NR (28.9, NR)	18.4 (13.6, 28.1)	43.8 (30.6, NR)	18.4 (14.0, 26.7)
EFS/DFS HR (95% CI)	**0.81 (0.68, 0.96)**		**0.85 (0.71, 1.01)**		**0.59 (0.48, 0.72)**		**0.69 (0.55, 0.88)**		**0.58 (0.42, 0.81)**		**0.66 (0.49, 0.90)**	
Maturity	**48%**		**50%**		**53%**		**39%**		**40%**		**52% (planned)[6]**	
Median follow-up	51.7 months		65.0 months		36.6 months		25.9 months		25.4 months		57.6 months	

Note: Most recent data from all studies (regardless of PD-L1).

[a] For Adjuvant studies, randomization is after surgery and +/- adjuvant chemotherapy.

Atezo=atezolizumab; BSC=best supportive care; DFS=disease-free survival; Durva=durvalumab; EFS=event free survival; Nivo=nivolumab; NR=not reached/not estimable; NA=not available; Pembro=pembrolizumab.

1. Besse B, et al. ESMO-IO 2023. Abstract 120MO; 2. Wakelee HA, et al. ASCO 2024. Poster 297; 3. Spicer JD, et al. ESMO 2023. Abstract LBA56; 4. Cascone T, et al. ESMO 2023. Abstract LBA1; 5. Spicer JD, et al. ASCO 2024 [oral]. Abstract LBA8010; 6. Forde PM, et al. *N Engl J Med*. 2022;386(21):1973-1985.

Comparable Outcomes for Cisplatin-Treated Patients in AEGEAN and KEYNOTE-671

Study	KEYNOTE-671[1] (Only Cisplatin Allowed) N=797		AEGEAN (Cisplatin Subgroup) N=196		AEGEAN (mITT) N=740	
Regimen	**Pembro/Cis**	**Placebo/Cis**	**Durva/Cis**	**Placebo/Cis**	**Durva/Chemo**	**Placebo/Chemo**
Median EFS (95% CI), mo	47.2 (32.9, NR)	18.3 (14.8, 22.1)	**NR (NR, NR)**	**45.0 (13.9, NR)**	**NR (42.3, NR)**	**30.0 (20.6, NR)**
EFS HR (95% CI)	**0.59 (0.48, 0.72)**		**0.58 (0.35, 0.93)**		**0.69 (0.55, 0.88)**	
Maturity	**53%**		**39%**			
Median follow-up	36.6 months		**25.9 months**			

Note: Most recent data from all studies (regardless of PD-L1).
Cis=cisplatin-based chemotherapy.

1. Spicer JD, et al. ESMO 2023. Abstract LBA56.

Which Patients With Resectable NSCLC Would Be Suitable for AEGEAN?

- AEGEAN demonstrates a favorable benefit-risk profile
  - Benefit seen with cisplatin and carboplatin doublet therapy
  - Benefit across all prespecified subgroups
  - Long-standing experience with adjuvant durvalumab in locally advanced disease
- Undertreatment is a greater risk than overtreatment when the goal is to prevent recurrence and prolong survival
- AEGEAN is a new potential treatment option for all patients with rNSCLC
- Perioperative immunotherapy can form the foundation for building on future combinations for patients with rNSCLC

rNSCLC=resectable non-small cell lung cancer.

Future Trial Considerations With Current SOC

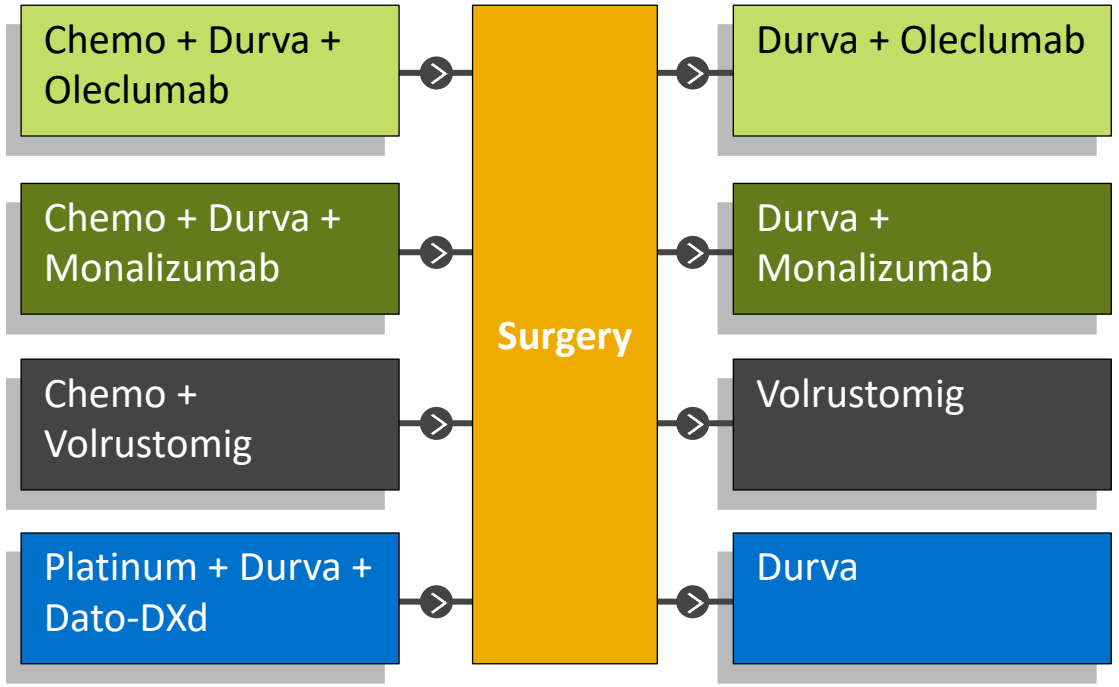
Current Treatment Landscape

- Perioperative therapy is preferred for majority of patients with rNSCLC
  - KN671 data for perioperative pembrolizumab are limited to combination with cisplatin[1]
  - AEGEAN provides data with cisplatin and carboplatin
- Issue of equipoise makes new RCT for CoP challenging in US
- Despite advances, poor outcomes necessitate new therapies and forward-looking trials

Novel Trials to Improve Outcomes

- Example: Phase 2 NeoCOAST-2 study[2]

Randomization to 4 arms (Resectable Stage II to IIIA NSCLC; *EGFR/ALK* wild type)



CoP=contribution of phase; Durva=durvalumab; Dato-DXd=datopotamab deruxtecan.

1. Wakelee H, et al. *N Engl J Med*. 2023;389(6):491-503.
2. ClinicalTrials.gov. NCT05061550. Updated July 9, 2024. Accessed July 16, 2024. https://clinicaltrials.gov/study/NCT05061550.

Concluding Remarks & Future Perspectives

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VP, Head of Clinical Development, Late Development Oncology
Global Clinical Strategy Head for Lung Cancer
AstraZeneca

AEGEAN: Perioperative Durvalumab Has a Positive Benefit-Risk for Patients With Resectable Stage II-IIIB NSCLC

- Significant improvement in pCR and EFS
  - Relevant endpoints for patients and clinicians
- Benefit across all preplanned subgroups
  - Broad applicability of the AEGEAN regimen in this heterogenous population
- A continued trend towards improved OS
  - Ongoing collection of OS, EFS, and DFS data
- No detriment in quality-of-life outcomes
- A manageable and tolerable safety profile across all treatment phases
  - Consistent with the known safety profile of the individual agents
- No evidence of increased chemotherapy-related toxicities
- No impact on patients' ability to undergo surgery
- Immune-mediated AEs were mostly non-serious, low grade, manageable, and resolved

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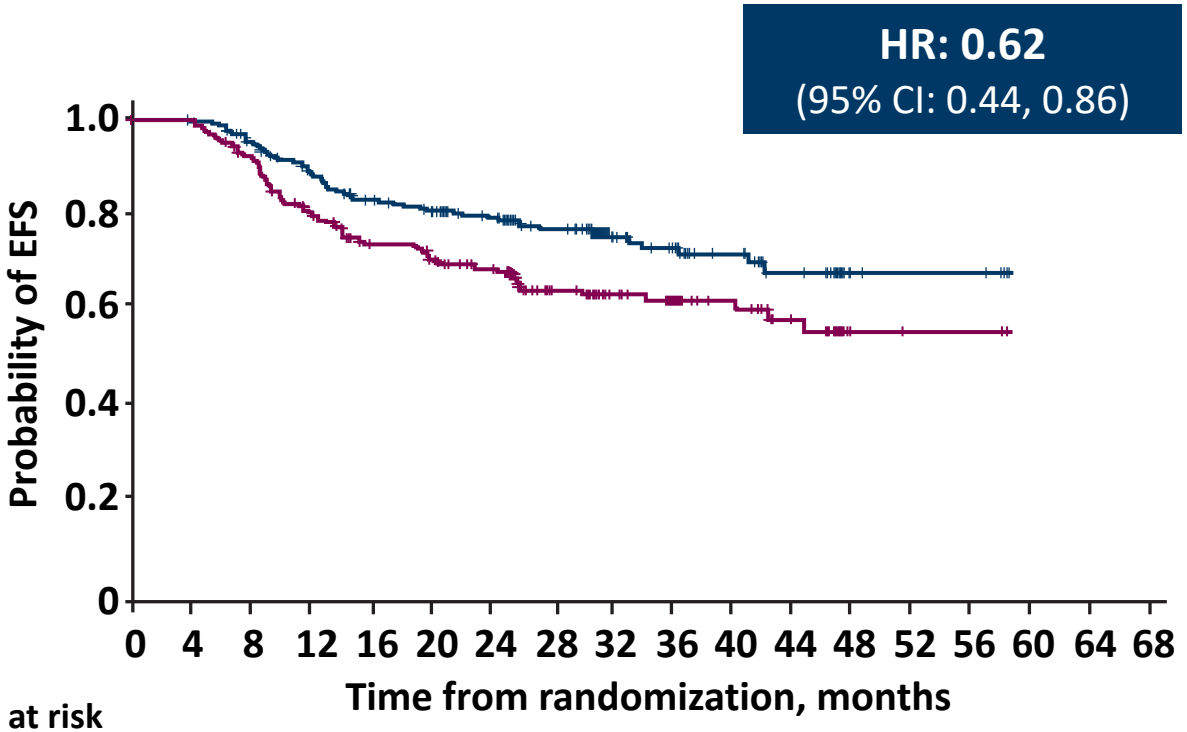
Future Perspectives

AEGEAN: EFS by Adjuvant Treatment Status

DCO4

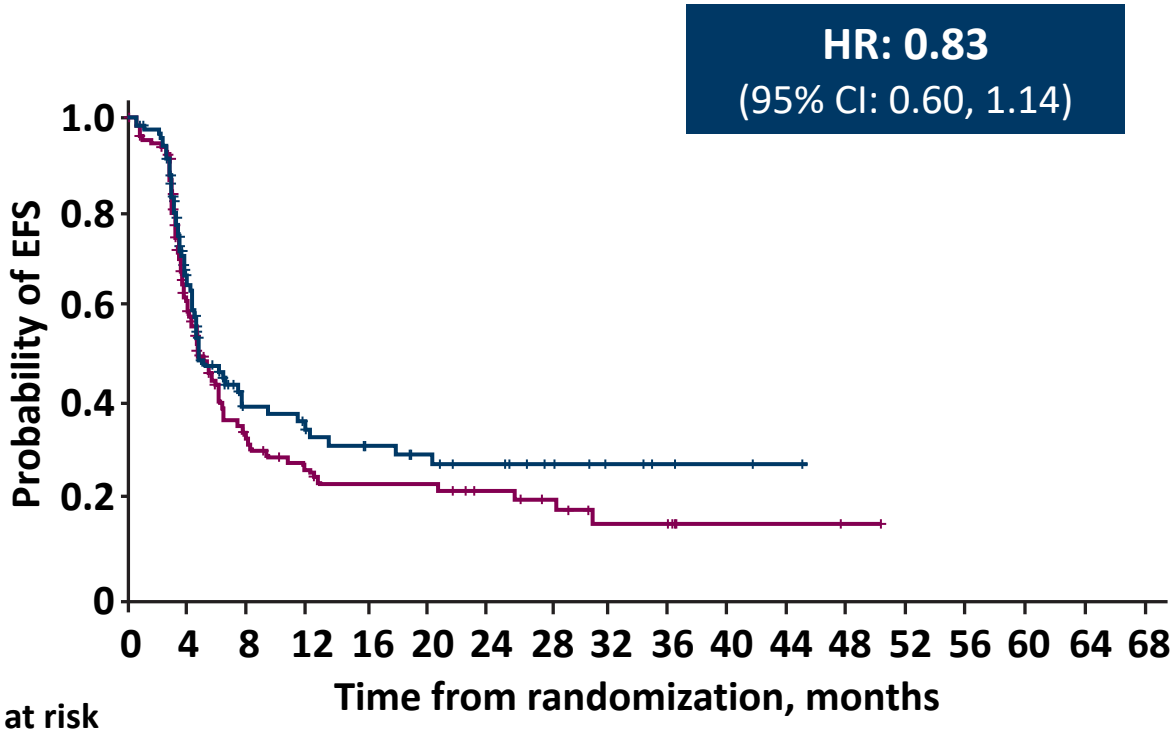
Received Adjuvant Treatment



No. at risk

D + CTx	242	239	222	198	181	173	159	118	73	64	46	29	6	4	4	0
PBO + CTx	237	234	212	181	155	145	129	77	53	47	33	24	7	2	2	0

Did Not Receive Adjuvant Treatment



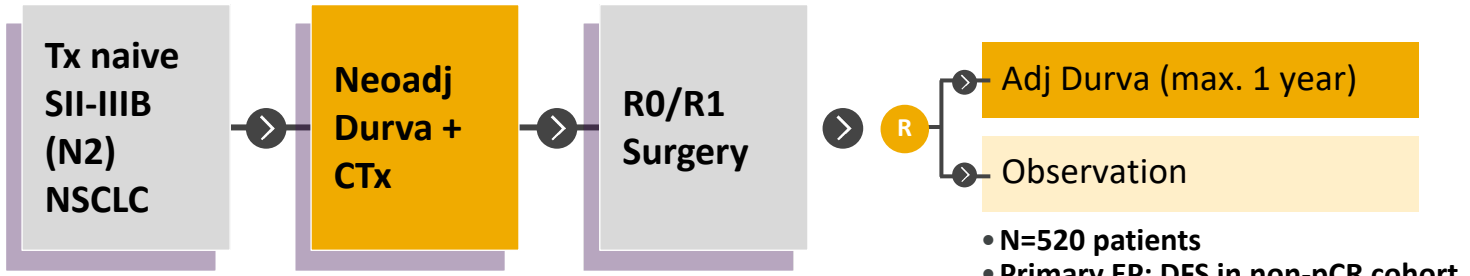
No. at risk

D + CTx	124	62	26	21	18	16	13	8	5	3	2	1	0
PBO + CTx	137	26	20	17	17	17	13	10	6	6	3	3	1	0

Key Practice-Informing Studies to Address Scientific Questions

ADOPT-Lung: ETOP

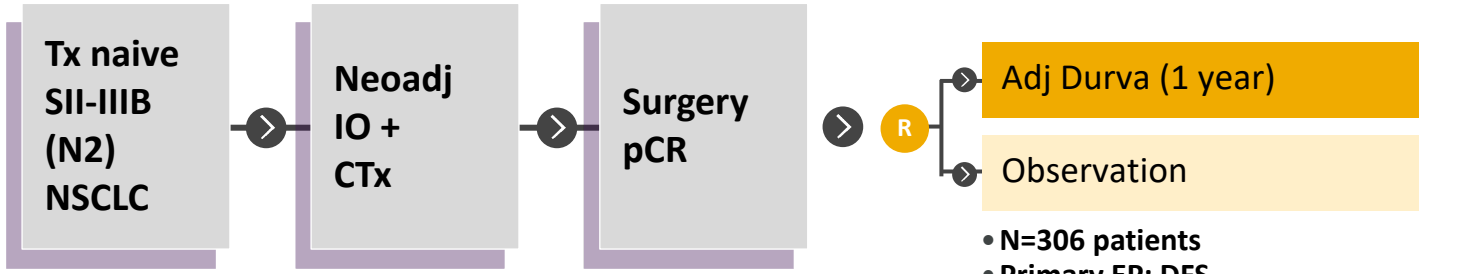
1 **What is the benefit of perioperative IO vs neoadjuvant IO?**



- **N=520 patients**
- **Primary EP: DFS in non-pCR cohort**

INSIGHT: SWOG Cancer Research Network

2 **Do patients who achieve pCR following neoadjuvant IO benefit from adjuvant durvalumab?**



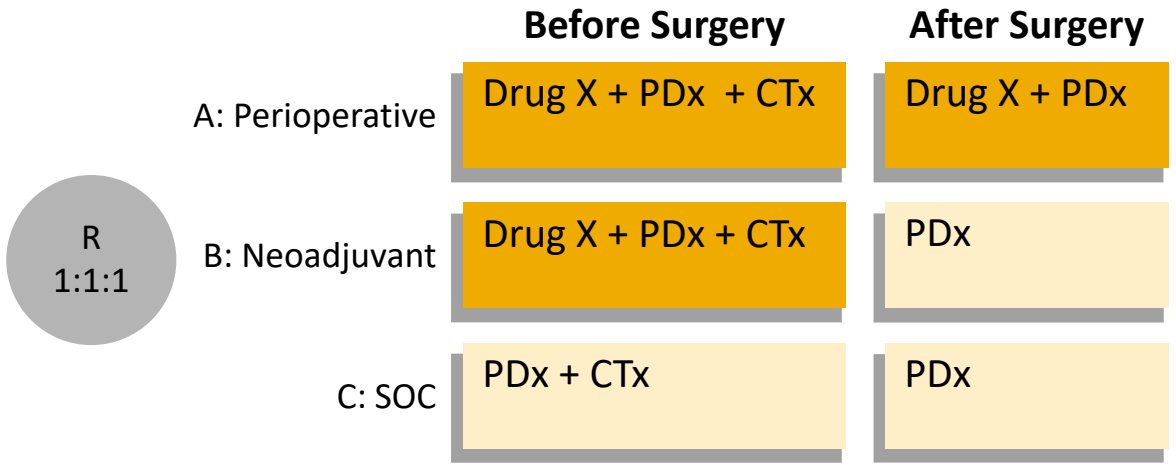
- **N=306 patients**
- **Primary EP: DFS**

ADOPT-Lung: NCT06284317; INSIGHT: NCT06498635.
Adj=adjuvant; EP=endpoint; ETOP=European Thoracic Oncology Platform; Neoadj=neoadjuvant.

Considerations for Future 3-Arm Design to Address CoP for Novel Treatments in rNSCLC

Trial Considerations

- Improved outcomes for SOC
- Events accrue slowly in the curative setting
- Risk that CoP (perioperative [A] versus neoadjuvant [B]) is not clearly defined
- Opportunities to explore novel endpoints



Scenario	Assumed EFS Hazard Ratios		Total Number of Events	Total Number of Patients	EFS Readout,[a] years	Power to Demonstrate A vs B Trend[b]
	A vs C	B vs C				
1	0.60	0.70	352	657	~10-12	44%
2	0.65	0.75	547	990		51%
3	0.70	0.80	908	1740		62%

[a] Assuming 24 patients/month recruitment (non-linear) and 47-month median for control. At least 80% power for A vs. C and B vs. C.
[b] Trend defined as probability of the upper 80% CI < 1.0.
PDx = Anti-PD-(L)1 immunotherapy.

Conclusions

Perioperative durvalumab demonstrated a favorable benefit-risk profile for patients with rNSCLC.

- AEGEAN met its prespecified primary endpoints
- AstraZeneca is leading the field with ongoing treatment-informing studies to explore the topic of contribution of phase
- Future add-on designs will require careful consideration and discussion with the Agency

Additional Slides

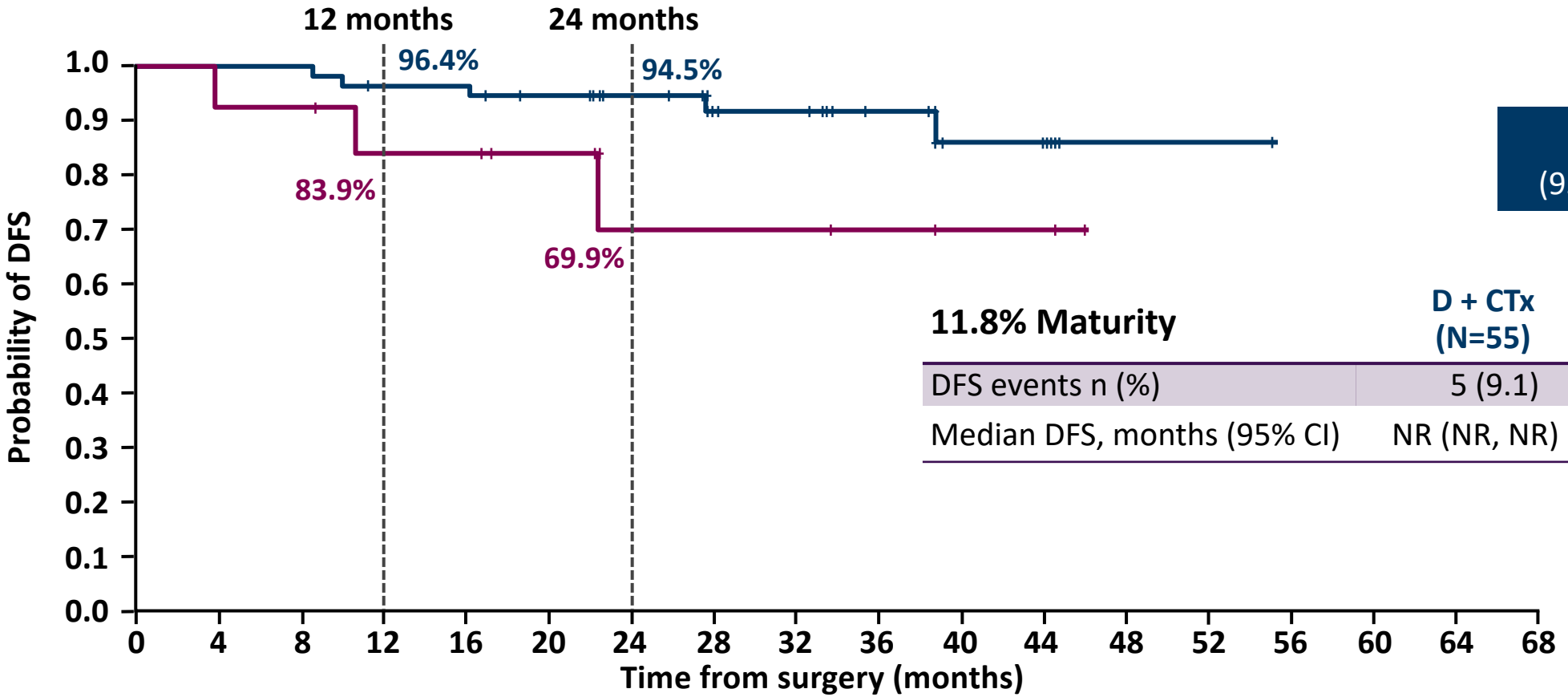
AEGEAN First Patient Randomised January 2019

Study			DCO2	DCO4	DCO5	Overall Size
AEGEAN Actual	EFS Maturity	Planned Actual	30% 32%	40% 39%	50%	740
	Timelines	Planned Actual	August 2022 November 2022	May 2023 May 2024	April 2024 TBD	
'3 arm'				40% Q1 2026	50% Q3 2026	1,893
'4 arm'				40% Q3 2027	50% Q2 2028	2,524
‘3 arm Re-randomised’				40% Q2 2027	50% Q2 2028	2,272

- Accrual: Non-linear accrual assumed (k=2, 24 patients/month). Time to event: Exponential data distribution
- Contribution of Phase arm, assume 80% power for Target EFS/DFS HR=0.80, 5% alpha (2-sided)
- Re-randomised option assumes 80% of patients proceed to adjuvant treatment

DFS (BICR) in Patients with pCR Response

mRS, DCO4



HR: 0.31
(95% CI: 0.07, 1.51)

11.8% Maturity	D + CTx (N=55)	PBO + CTx (N=13)
DFS events n (%)	5 (9.1)	3 (23.1)
Median DFS, months (95% CI)	NR (NR, NR)	NR (10.5, NR)

No. at Risk

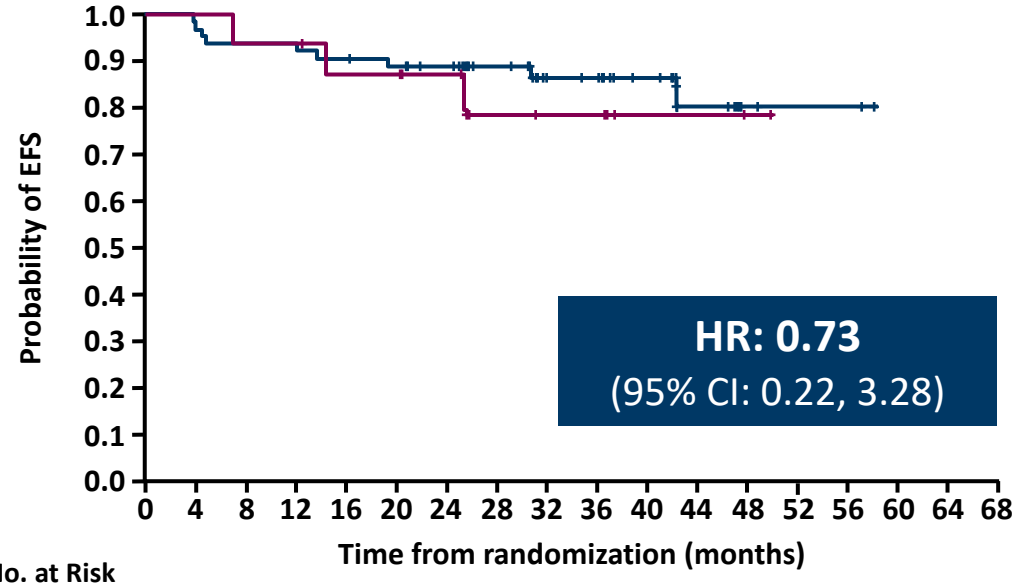
D + CTx	55	55	55	52	52	48	36	27	26	19	12	8	2	2	0
PBO + CTx	13	12	12	10	10	8	5	5	5	3	2	2	0		

Note: The small number of patients and events in the pCR subgroup results in greater uncertainty in the point estimate and confidence intervals

EFS (BICR) by pCR Response Status

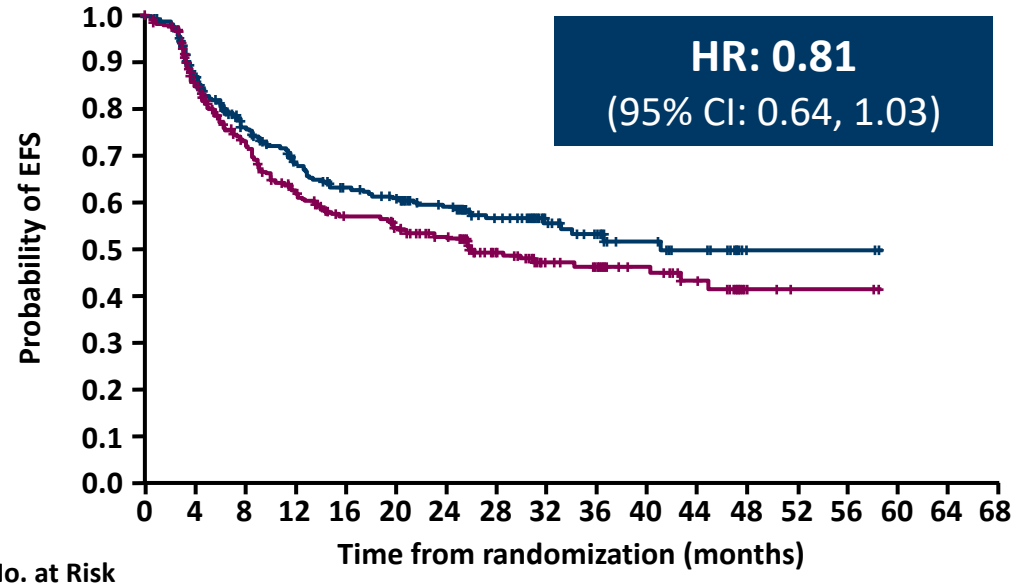
mITT, DCO4

Patients with pCR



No. at Risk

D + CTx	63	61	59	59	57	55	52	39	27	26	19	12	3	2	2	0
PBO + CTx	16	16	15	15	13	13	11	7	6	6	3	2	1	0		



No. at Risk

D + CTx	303	240	189	160	142	134	120	87	51	41	29	18	3	2	2	0
PBO + CTx	358	280	223	186	159	149	131	80	53	47	33	25	7	2	2	0

	D + CTx	PBO + CTx
Events/Randomized	9/63	3/16
Median EFS, months (95% CI)	NR (NR, NR)	NR (25.4, NR)

	D + CTx	PBO + CTx
Events/Randomized	115/303	162/358
Median EFS, months (95% CI)	41.2 (31.9, NR)	25.9 (19.8, 45.0)

Note: The small number of patients and events in the pCR subgroup results in greater uncertainty in the point estimate and confidence intervals

imAEs with Outcome Not Resolved

Adjuvant Period, DCO4

Category	D + CTx (N=266)	PBO + CTx (N=254)
Patients with at least 1 imAE, n (%)	**61 (22.9)**	**21 (8.3)**
Patients with imAEs Unresolved[a]	29 (10.9)	12 (4.7)
Resolving	15 (5.6)	2 (0.8)
Not resolved	15 (5.6)	10 (3.9)
Hypothyroidism	11 (4.1)	1 (0.4)
Pneumonitis	2 (0.8)	3 (1.2)
Diarrhea/colitis	1 (0.4)	1 (0.4)
Adrenal insufficiency	1 (0.4)	0
AST increased	1 (0.4)	0
Thyroiditis	0	2 (0.8)
Hyperthyroidism	0	2 (0.8)
Arthralgia	0	1 (0.4)
Arthritis	0	1 (0.4)

[a] Includes the outcomes of Resolving and Not resolved. Resolving and Not Resolved are not mutually exclusive given that patients may have experienced multiple imAEs

- All unresolved events in durvalumab arm **are low grade.**

Immune-Mediated AEs by Category
Adjuvant Period, DCO4

	D + CTx (N = 266)	PBO + CTx (N = 254)
Patients with any imAE, n (%)	61 (22.9)	21 (8.3)
Grade 3-4	6 (2.3)	4 (1.6)
SAEs	7 (2.6)	3 (1.2)
Leading to discontinuation of any study treatment	12 (4.5)	3 (1.2)
Resolved[a]	31 (11.7)	9 (3.5)
Unresolved[b]	29 (10.9)	12 (4.7)
Resolving	15 (5.6)	2 (0.8)
Not resolved	15 (5.6)	10 (4.0)
Fatal	1 (0.4)	0

[a] Includes the outcomes of Resolved and Resolved with Sequelae.
[b] Includes the outcomes of Resolving and Not resolved. Resolving and Not Resolved are not mutually exclusive given that patients may have experienced multiple imAEs

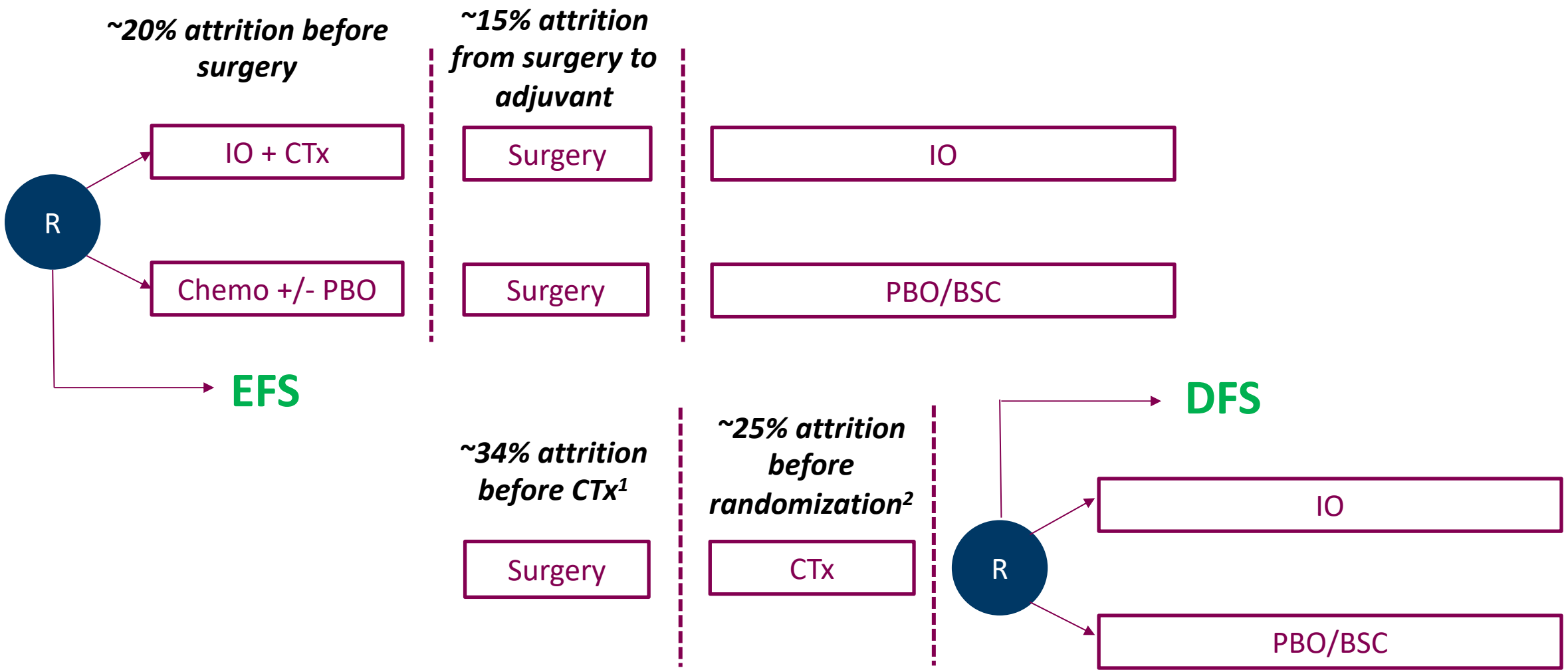
Majority of unresolved events were endocrine events requiring hormone replacement therapy: 25 (of 29 in D + CTx) and 7 (of 12 in PBO + CTx)

AEs by Category AEGEAN and PACIFIC

DCO4

Event	AEGEAN Overall Period D + CTx (N=401)	AEGEAN Adjuvant Period D + CTx (N=266)	PACIFIC D arm (N=475)
Median duration of exposure (weeks)	40.14	48.0	38.7
Any-grade AEs, n (%)	387 (96.5)	224 (84.2)	460 (96.8)
Max. grade 3 or 4	175 (43.6)	41 (15.4)	152 (32.0)
SAEs	157 (39.2)	41 (15.4)	136 (28.6)
Fatal	23 (5.7)	4 (1.5)	21 (4.4)
Leading to discontinuation of D/PBO/CT	78 (19.5)	26 (9.8)	73 (15.4)
Any-grade imAEs	102 (25.4)	61 (22.9)	115 (24.2)
Grade 3-4	18 (4.5)	6 (2.3)	16 (3.4)

Perioperative and Adjuvant IO Studies: Design and Attrition



[1]Felip E, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. *J Clin Oncol*. 2010;28(19):3138-3145.
[2]Felip E, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398(10308):1344-1357.