A Phase III Study of Neoadjuvant/Adjuvant Durvalumab for the Treatment of Patients with Resectable Stage II/III Non-Small Cell Lung Cancer (AEGEAN)

Contribution of Treatment Phase in Perioperative Trials

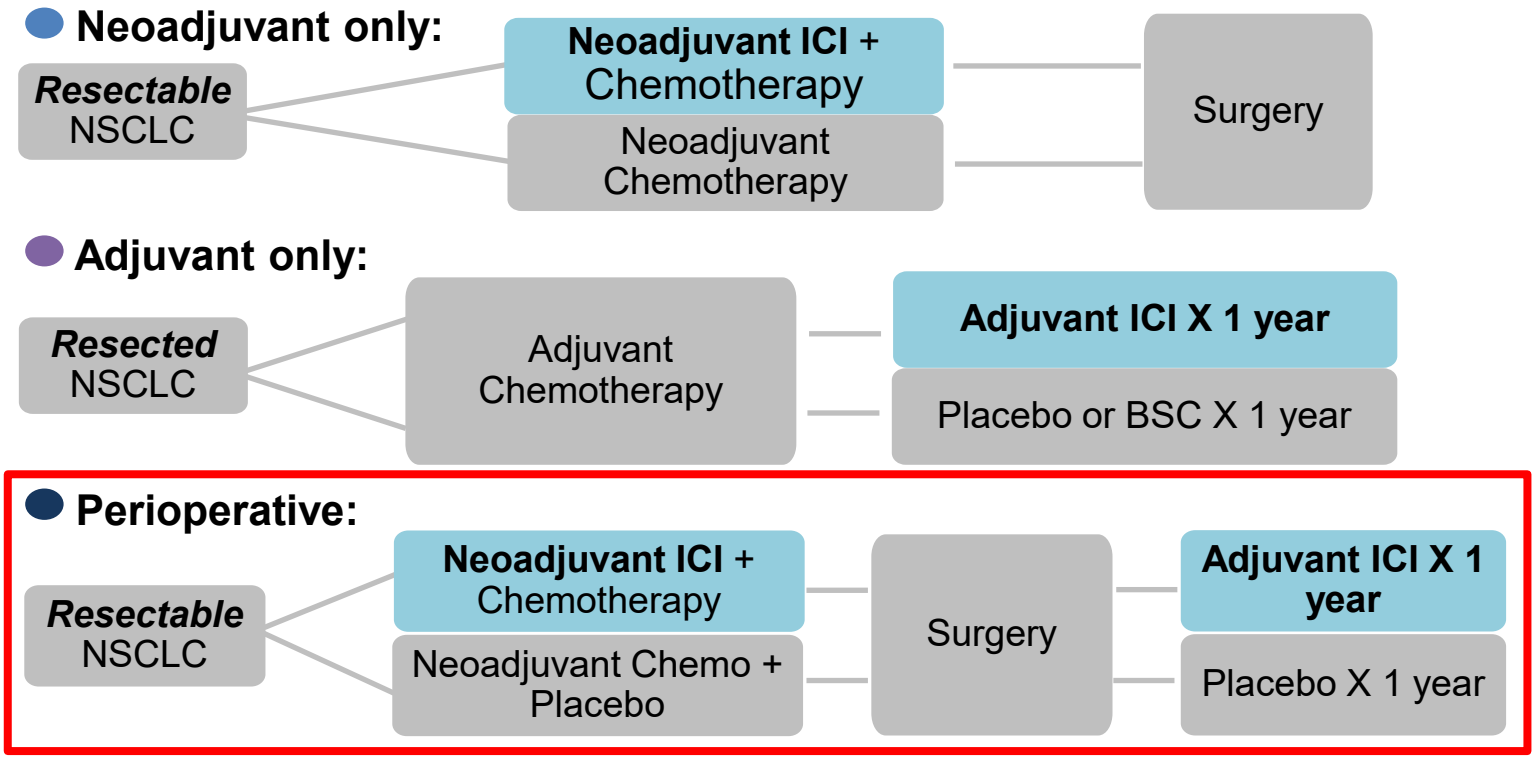
FDA Opening Remarks
Oncologic Drugs Advisory Committee (ODAC) Meeting
July 25, 2024

Erin Larkins, MD
Director (Acting), Division of Oncology 2
Office of Oncologic Diseases

Outline

- **Overview**
- AEGEAN Study Design and Results
- Key Review Issue: AEGEAN - Contribution of Phase
- Future Trial Designs for Add-on Therapies
- Discussion and Voting Questions for ODAC

Early-Stage Non-Small Cell Lung Cancer (NSCLC) Trial Designs



ICI = Immune checkpoint inhibitor, BSC = Best supportive care

Overview

- AEGEAN trial, considerations for future trial designs
- Trials containing multi-phase regimens
  - Relative contribution of each phase not established
  - Unclear if all patients need each phase of therapy
- In past, FDA has granted approval to entire regimen
  - Emerging data suggests further consideration is warranted
- Patients potentially overtreated and may experience avoidable toxicity and patient burden

Treatment Landscape for Resectable NSCLC

	Adjuvant Only		Neoadjuvant Only	Neoadjuvant followed by Adjuvant	
ICI	**Atezolizumab**	**Pembrolizumab**	**Nivolumab**	**Pembrolizumab**	**Durvalumab**
Time of approval	October 2021	January 2023	March 2022	October 2023	N/A
Stage	II-IIIA	IB[a]-IIIA	IB[a]-IIIA	II-IIIB	II-IIIB
Indication	PD-L1 ≥1%, following adjuvant chemotherapy	Following adjuvant chemotherapy	Concurrently with platinum-based chemotherapy X 3 cycles	Concurrently with neoadj platinum-based chemotherapy X 4 cycles → adj pembrolizumab X 13 cycles	Concurrently with neoadj platinum-based chemotherapy X 4 cycles → adj durvalumab X 12 cycles
Pivotal Trial	IMpower-010	KEYNOTE-091	CHECKMATE-816	KEYNOTE-671	AEGEAN
Primary Endpoint(s)	DFS	DFS	EFS/pCR	EFS/OS	EFS/pCR
HR (95% CI)	**0.66 (0.50, 0.88)**	**0.73 (0.60, 0.89)**	**0.63 (0.45, 0.87)**	**EFS: 0.58 (0.46, 0.72)** **OS: 0.72 (0.56, 0.93)**	**0.68 (0.53, 0.88)**

[a]Tumors ≥4cm, ICI: immune checkpoint inhibitor; N/A: not applicable; DFS: disease-free survival; EFS: event-free survival; pCR: pathologic complete response ;OS: overall survival; HR: hazard ratio; CI: confidence interval.

Anti-PD-(L)1-Based Regimens for Resectable NSCLC

	Adjuvant Only		Neoadjuvant Only	Neoadjuvant followed by Adjuvant		
ICI	**Atezolizumab**	**Pembrolizumab**	**Nivolumab**	**Pembrolizumab**	**Durvalumab**	**Nivolumab**
Stage	II-IIIA	IB[a]-IIIA	IB[a]-IIIA	II-IIIB	II-IIIB	II-IIIB
Pivotal Trial	IMpower-010	KEYNOTE-091	CHECKMATE -816	KEYNOTE-671	AEGEAN	CHECK MATE-77T
Primary Endpoint(s)	DFS	DFS	EFS/pCR	EFS/OS	EFS/pCR	EFS
DFS/EFS HR (95% CI)	**0.66 (0.50, 0.88)**	**0.73 (0.60, 0.89)**	**0.63 (0.45, 0.87)**	**0.58 (0.46, 0.72)**	**0.68 (0.53, 0.88)**	**0.58 (0.42, 0.81)**

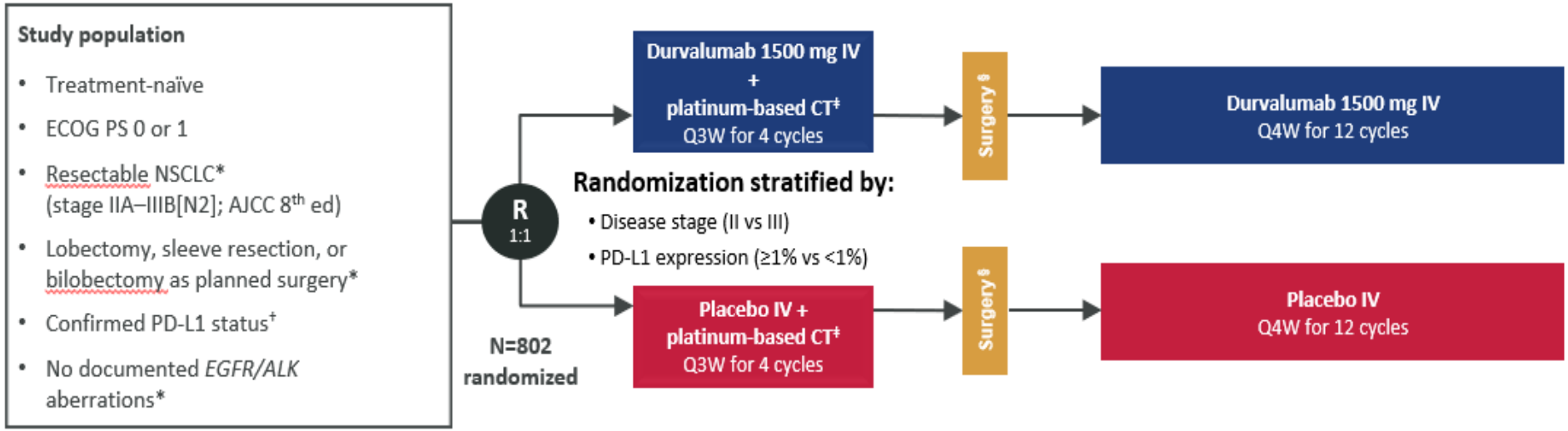
EFS/DFS treatment effect sizes comparable across trials

Cross-trial comparisons can provide an overall assessment of class effect, but are not appropriate to compare efficacy or establish contribution of treatment phase

Outline

- Overview
- **AEGEAN Study Design and Results**
- **Key Review Issue: AEGEAN - Contribution of Phase**
- Future Trial Designs for Add-on Therapies
- Discussion and Voting Questions for ODAC

AEGEAN – Durvalumab Neoadjuvant and Adjuvant



- **mITT population**: Excluded patients with *EGFR*/*ALK* gene aberrations (N=740)
- **Dual primary endpoints:** PCR and EFS
  - Key Secondary Endpoints: MPR, DFS, OS

AJCC: American Joint Committee on Cancer, ALK: anaplastic lymphoma kinase, EGFR: epidermal growth factor receptor, CT: chemotherapy, Q3W: every 3 weeks, Q4W: every 4 weeks, MPR: major pathologic response, mITT: modified intent to treat

Key Regulatory Information

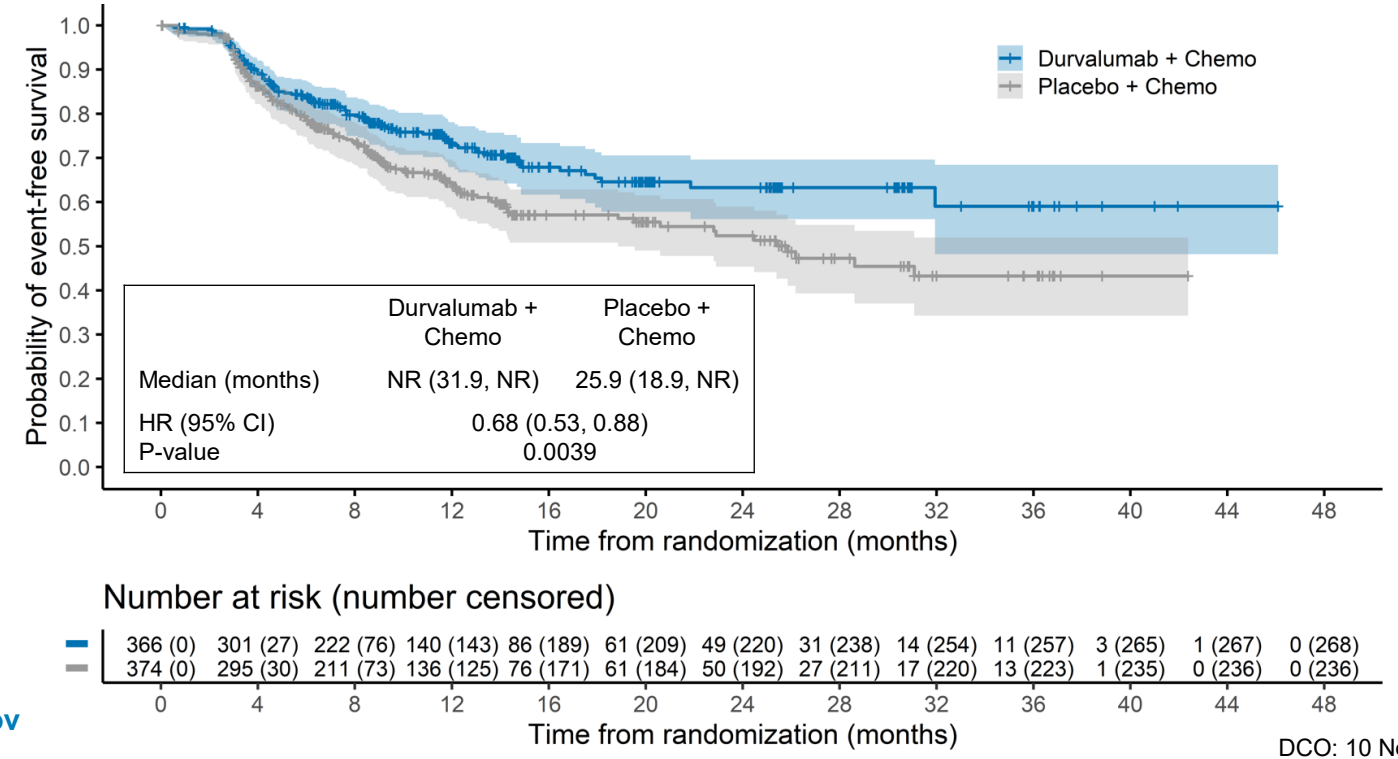
Date	Event
Nov 2018 End of Phase 2 (EOP2) Mtg	• FDA stated that the **proposed study design will not isolate the effect of neoadjuvant therapy** and recommended that MedImmune **consider an adaptive or factorial study design.**
May 2023 Pre-BLA Mtg	• FDA communicated that the **trial design does not isolate the effect of neoadjuvant durvalumab with chemotherapy from the effect of adjuvant durvalumab monotherapy.** Please provide **a method to assess the contribution of durvalumab** in the pre-surgery and post-surgery treatment phases to the treatment effect.

Dual Primary Endpoint – EFS:
First Interim Analysis (Statistically Significant)

EFS by BICR (mITT)	Durva + Chemo N=366	Placebo + Chemo N=374
Events, n (%)[1]	98 (27)	138 (37)
Censored, n (%)	268 (73)	236 (63)
Median, months (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
HR (95% CI) **P-value[2]**	**0.68 (0.53, 0.88)** **0.0039**	

Chemo = platinum-doublet chemotherapy, Durva = Durvalumab, BICR = blinded independent central review, NR = not reached. Data cutoff (DCO): 10 November 2022; [1]Information fraction = 64%, [2]P-value boundary= 0.009899

Dual Primary Endpoint – EFS:
First Interim Analysis (Statistically Significant)



Key Secondary Endpoints: DFS and OS

		Durva + Chemo	Placebo + Chemo
DFS[1]	N (resected mITT)	242	231
	Events, n (%)	60 (25)	81 (35)
	Median, months (95% CI)	NR	NR (41.5, NR)
	HR (95% CI)	0.66 (0.47, 0.92)	
	p-value[2]	0.0137	
OS[1,3]	N (mITT)	366	374
	Events, n (%)	121 (33)	140 (37)
	Median, months (95% CI)	NR	53.2 (44.3, NE)
	HR (95% CI)	0.89 (0.70, 1.14)	

Chemo = platinum-doublet chemotherapy, Durva = Durvalumab; NR = Not Reached; NE = Not Estimable

[1]DCO: 10 May 2024;[2] Compared to an alpha boundary of 0.0123; [3]Not formally tested since DFS was not statistically significant

AEGEAN - Results

- Statistically significant and clinically meaningful improvement in EFS
- No apparent detrimental effect on OS
- EFS is an accepted endpoint to support approvals for the treatment of early-stage resectable NSCLC

AEGEAN - Major Review Issue

- Inability to assess the contribution of each phase of therapy (neoadjuvant and adjuvant) to the treatment effect of the regimen
- Potentially exposing patients to unnecessary therapy with increased treatment burden and potential for long-term immune-related toxicities in a curative setting
- Even benefit in OS would not address this issue

Anti-PD-(L)1-Based Regimens for Resectable NSCLC

	Adjuvant Only		Neoadjuvant Only	Neoadjuvant followed by Adjuvant		
ICI	**Atezolizumab**	**Pembrolizumab**	**Nivolumab**	**Pembrolizumab**	**Durvalumab**	**Nivolumab**
Stage	II-IIIA	IB[a]-IIIA	IB[a]-IIIA	II-IIIB	II-IIIB	II-IIIB
Pivotal Trial	IMpower-010	KEYNOTE-091	CHECKMATE -816	KEYNOTE-671	AEGEAN	CHECK MATE-77T
Primary Endpoint(s)	DFS	DFS	EFS/pCR	EFS/OS	EFS/pCR	EFS
DFS/EFS HR (95% CI)	**0.66 (0.50, 0.88)**	**0.73 (0.60, 0.89)**	**0.63 (0.45, 0.87)**	**0.58 (0.46, 0.72)**	**0.68 (0.53, 0.88)**	**0.58 (0.42, 0.81)**

EFS/DFS treatment effect sizes comparable across trials

Cross-trial comparisons can provide an overall assessment of class effect, but are not appropriate to compare efficacy or establish contribution of treatment phase

Added Uncertainty

"High-level results from the ADJUVANT BR.31 Phase III trial, sponsored by the Canadian Cancer Trials Group (CCTG), showed Imfinzi (durvalumab) did not achieve statistical significance for the primary endpoint of disease-free survival (DFS) versus placebo in early-stage (IB-IIIA) non-small cell lung cancer (NSCLC) after complete tumour resection in patients whose tumours express PD-L1 on 25% or more tumour cells."

Press Release, June 25, 2024, Update on ADJUVANT BR.31 Phase III trial of Imfinzi in non-small cell lung cancer (astrazeneca.com)

Assessment in Post-Market Setting

- Ongoing efforts in the lung cancer research community highlight the need to address the contribution of each phase of therapy
- PROSPECT-LUNG and CLEAR-INSIGHT designed to address specific questions related to contribution of phase but not the full issue
- Will take years to complete and it is possible the field may have moved on

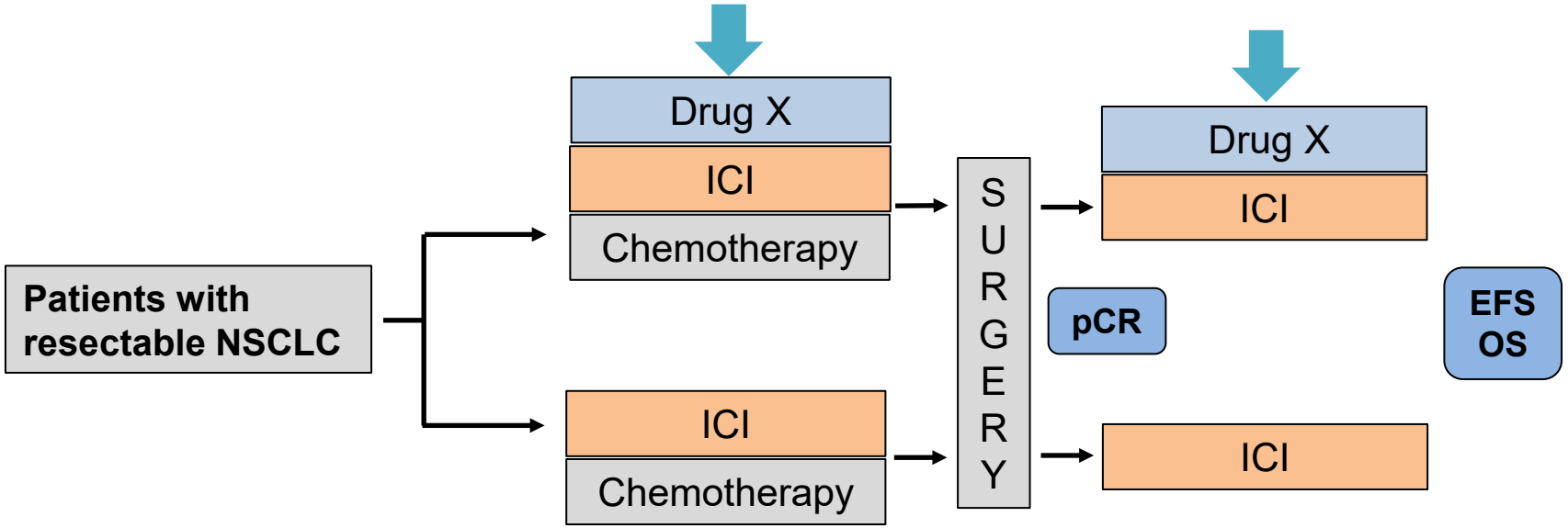
Outline

- Overview
- AEGEAN Study Design and Results
- Key Review Issue: AEGEAN - Contribution of Phase
- **Future Trial Designs for Add-on Therapies**
- Discussion and Voting Questions for ODAC

Future Two-Arm Trial Designs

✓	Standard of care (SOC) treatment with addition of new agent to only the **ADJUVANT** phase
✓	SOC treatment with addition of new agent to only the **NEOADJUVANT** phase
X	SOC treatment with addition of new agent to both the **NEOADJUVANT AND ADJUVANT** phases

Currently Proposed Add-on Trial Designs

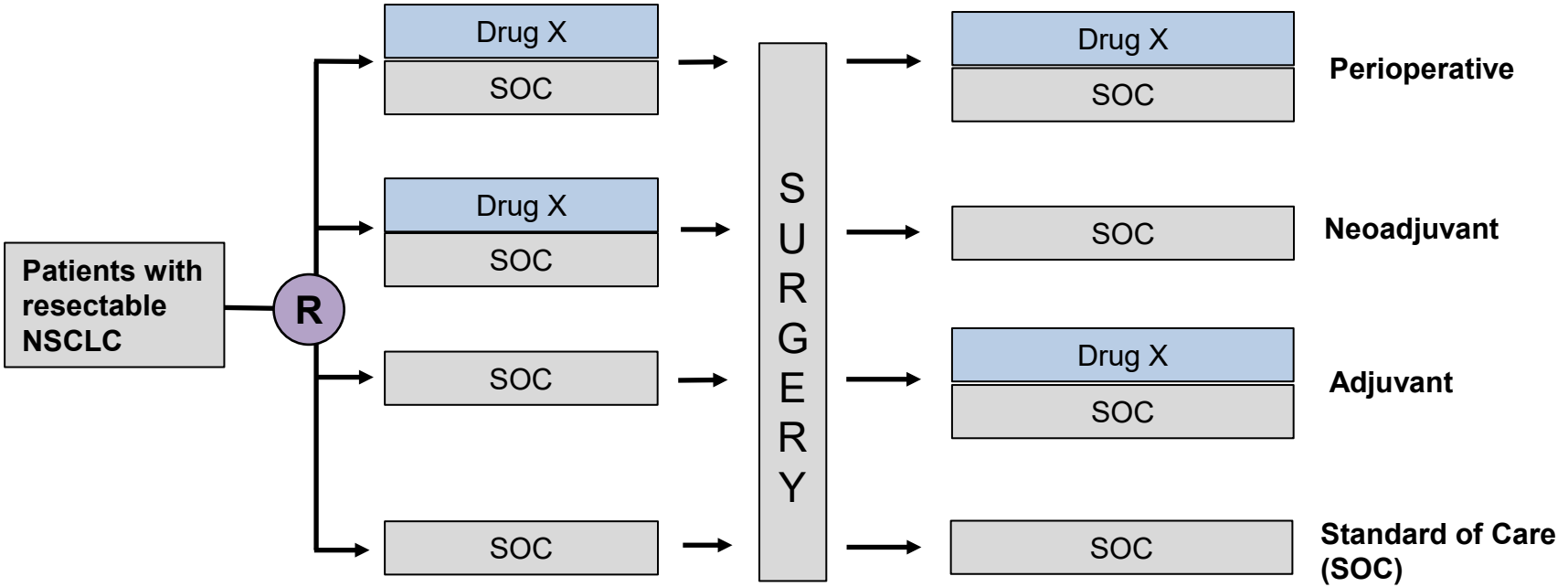


- Inability to isolate contribution of treatment phase for Drug X
- Exacerbation of risks due to intensification of therapy

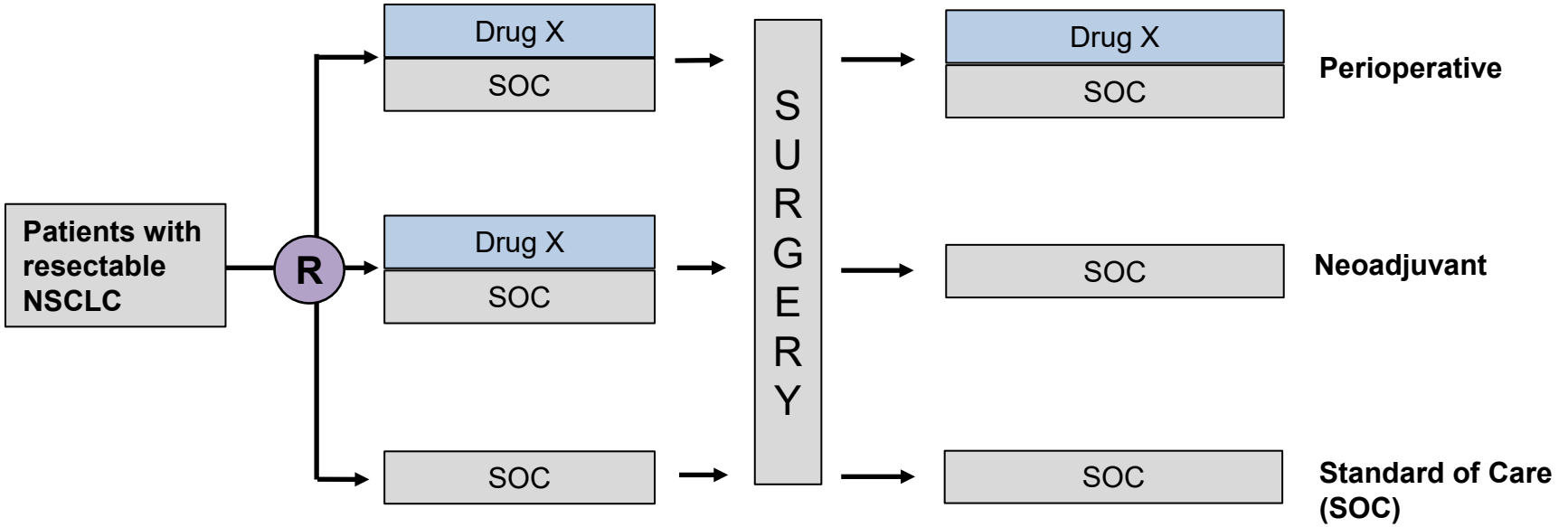
Design of Future Trials

- Use of two-arm trial designs even more problematic given expectation of increased toxicity with add on therapies/MOAs
- Multi-arm trials are necessary to allow for assessment of contribution of each phase
- This will require larger trials

Add-On Trial: 4-Arm Design



Add-On Trial: 3-Arm Design



Future Trials

- With intensification of treatment, increased toxicity is likely
- Continued use of two-arm trials designs assessing therapy added to both phases of therapy (perioperative) will further exacerbate the risk of overtreatment
- To best serve patients and the oncology community, multi-arm trials are needed to provide evidence of contribution of phase

Discussion Topics and Question

- In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.

- Should FDA require that new trial design proposals for perioperative regimens for resectable NSCLC include adequate within trial assessment of contribution of treatment phase?


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Durvalumab Before and After Surgery for the Treatment of Resectable Non-Small Cell Lung Cancer (AEGEAN)

Contribution of Treatment Phase in Perioperative Trials

Oncologic Drugs Advisory Committee Meeting
July 25, 2024

Bernardo Haddock Lobo Goulart, MD
Clinical Reviewer
Division of Oncology II
Office of Oncologic Diseases

Shabnam Ford, PhD
Senior Mathematical Statistician
Division of Biometrics V
Office of Biostatistics

FDA Review Team

Erin Larkins – Director (Acting), Division of Oncology 2 (DO2)
Idara Ojofeitimi – Regulatory Health Project Manager, Division of Regulatory Operations for Oncologic Diseases (DROOD)
Gautam Mehta – Associate Director of Oncology Clinical Policy, Oncology Center of Excellence (OCE)
Joseph Gibbons – Clinical Reviewer, DO2
Luckson Mathieu – Clinical Reviewer, DO2
Pallavi Mishra-Kalyani – Deputy Director, Division of Biometrics V (DBV)
Anup Amatya – Supervisory Mathematical Statistician, DBV
Flora Mulkey – Biostatistics Team Leader (Acting), DBV
Shabnam Ford – Senior Mathematical Statistician, DBV
Hong Zhao – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCPII)
Yue Xiang – Clinical Pharmacology Reviewer, DCPII
Claudia Miller – Nonclinical Reviewer Team Leader, Division of Oncology Therapeutics
Melissa Pegues – Nonclinical Reviewer, Division of Hematology Oncology Toxicology (DHOT)
Ram Sihag – CMC Reviewer Team Leader, Office of Pharmaceutical Quality (OPQ)
Xu (Michael) Di – CMC Reviewer, OPQ
Barbara Scepura – Senior Clinical Analyst, Office of Oncologic Diseases (OOD)

Overview

- Current Treatment Landscape for Resectable NSCLC

- AEGEAN:
- Trial Design
  - Efficacy
  - Safety

- Contribution of Treatment Phase in Perioperative Trials

- Discussion and Voting Questions

Non-Small Cell Lung Cancer

Lung Cancer in the US:

- Leading cause of cancer deaths
- 84% non-small cell lung cancer (NSCLC)

NSCLC Stages:

- IA-IIIB: approx. 55%
- IV: approx. 45%

Stage	5-year Overall Survival
I	68%
II	45%
IIIA	26%
IIIB	17%
IV	6%

Ganti AK, et al. JAMA Oncol. 2021 Dec 1;7(12):1824-1832.

Proposed Indication, Dosage, and Duration

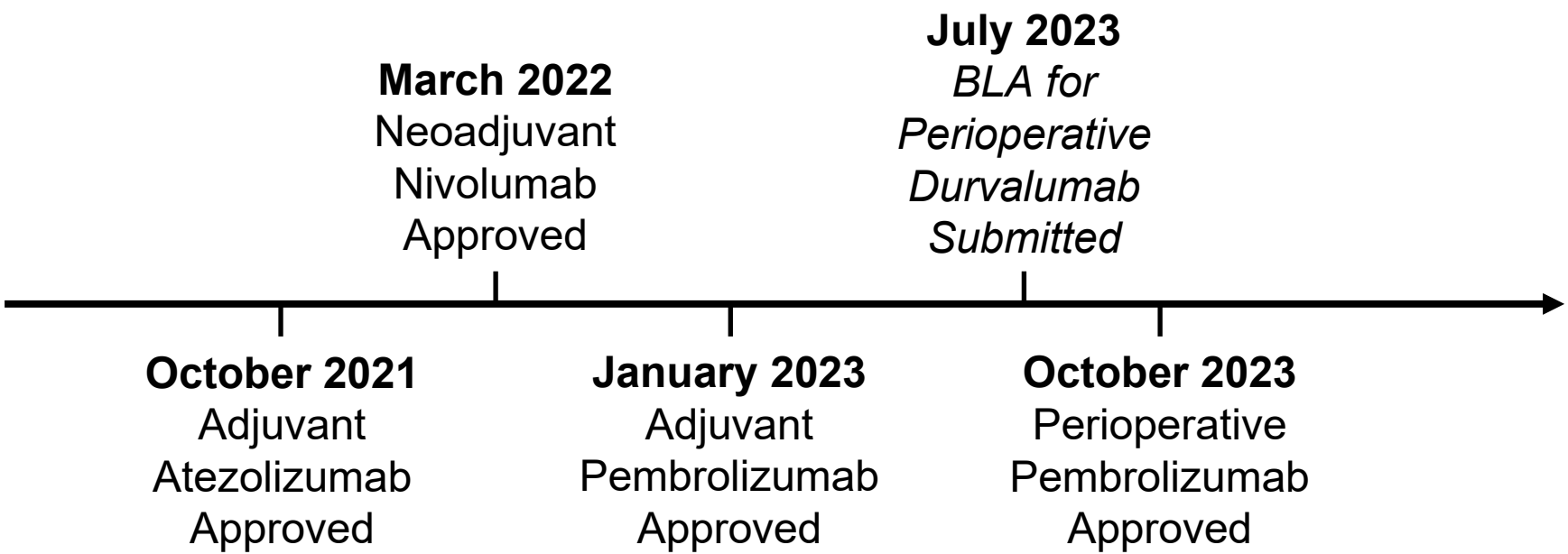
Durvalumab in combination with chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy after surgery, is indicated for the treatment of adult patients with resectable (tumors ≥ 4 cm and/or node positive) NSCLC and no known epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements.

Dose: Durvalumab 1500 mg in combination with chemotherapy* every 3 weeks for up to 4 cycles prior to surgery, followed by 1500 mg as a single agent every 4 weeks for up to 12 cycles after surgery.

Duration: until disease is deemed unresectable, recurrence, unacceptable toxicity, or a maximum of 12 cycles after surgery

**Administer durvalumab prior to chemotherapy on the same day.*

Treatment Landscape for Resectable NSCLC



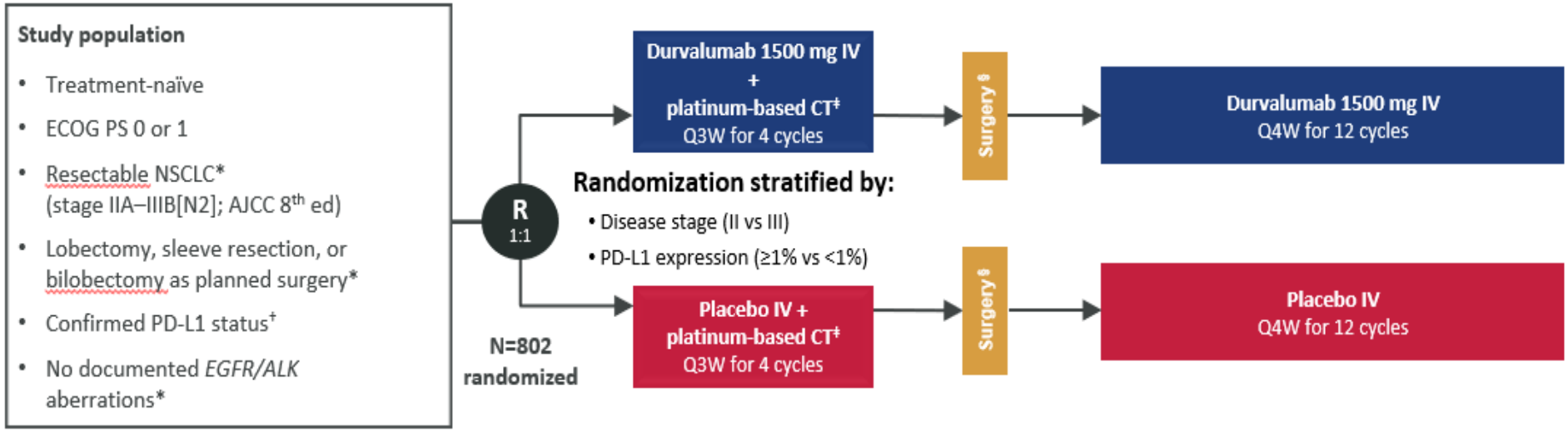
Key Regulatory Interactions

Date	Event
11/2018 EOP2 Mtg	• FDA stated that the **proposed study design will not isolate the effect of neoadjuvant therapy** and recommended that MedImmune **consider an adaptive or factorial study design.**
5/2023 Pre-BLA Mtg	• FDA communicated that the **trial design does not isolate the effect of neoadjuvant durvalumab with chemotherapy from the effect of adjuvant durvalumab monotherapy.** Please provide **a method to assess the contribution of durvalumab** in the pre-surgery and post-surgery treatment phases to the treatment effect.

Control arm for AEGEAN: neoadjuvant chemotherapy → surgery

- **Considered a standard of care (SOC) approach at the onset of trial**

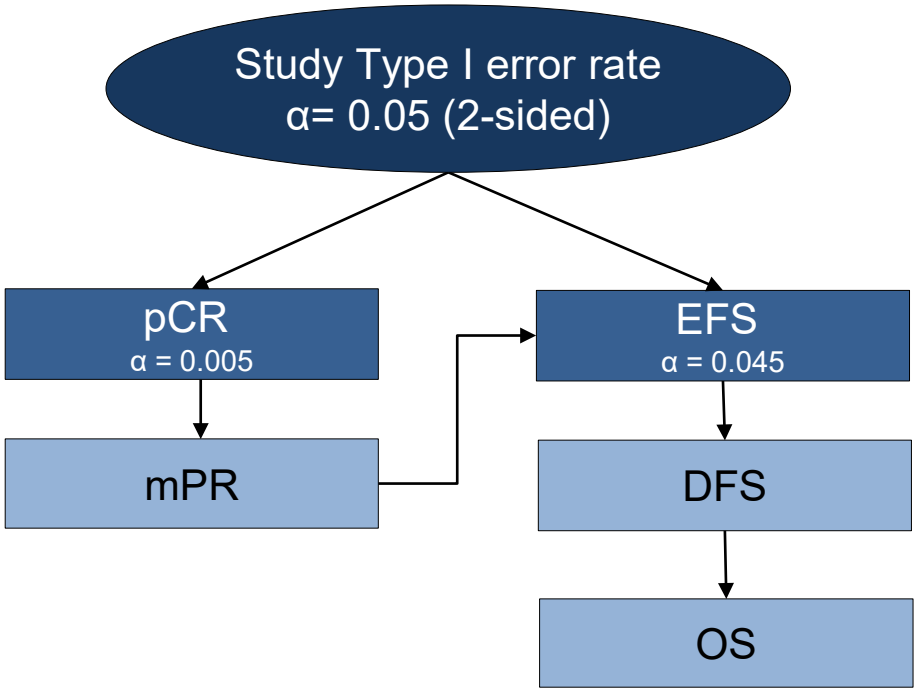
AEGEAN Trial Design



- **mITT population**: Excluded patients with *EGFR*/*ALK* gene aberrations (N=740)
- **Dual primary endpoints:** pathologic complete response (pCR) and event-free survival (EFS)
  - Key Secondary Endpoints: major pathologic response (mPR); disease-free survival (DFS); overall survival (OS)

Source: BLA 761069 Supplement 43 Application Orientation Materials
www.fda.gov

Endpoints and Statistical Analysis Plan



Dual Primary Endpoint – pCR:
Interim Analysis (Statistically Significant)

pCR by central lab (mITT)	Durva + Chemo N=196	Placebo + Chemo N=206
pCR, n	35	10
pCR, % (95% CI)	18 (13, 24)	5 (2.4, 9)
Difference in pCR, % (95% CI)	13 (7, 20)	
P-value[1]	0.000036	

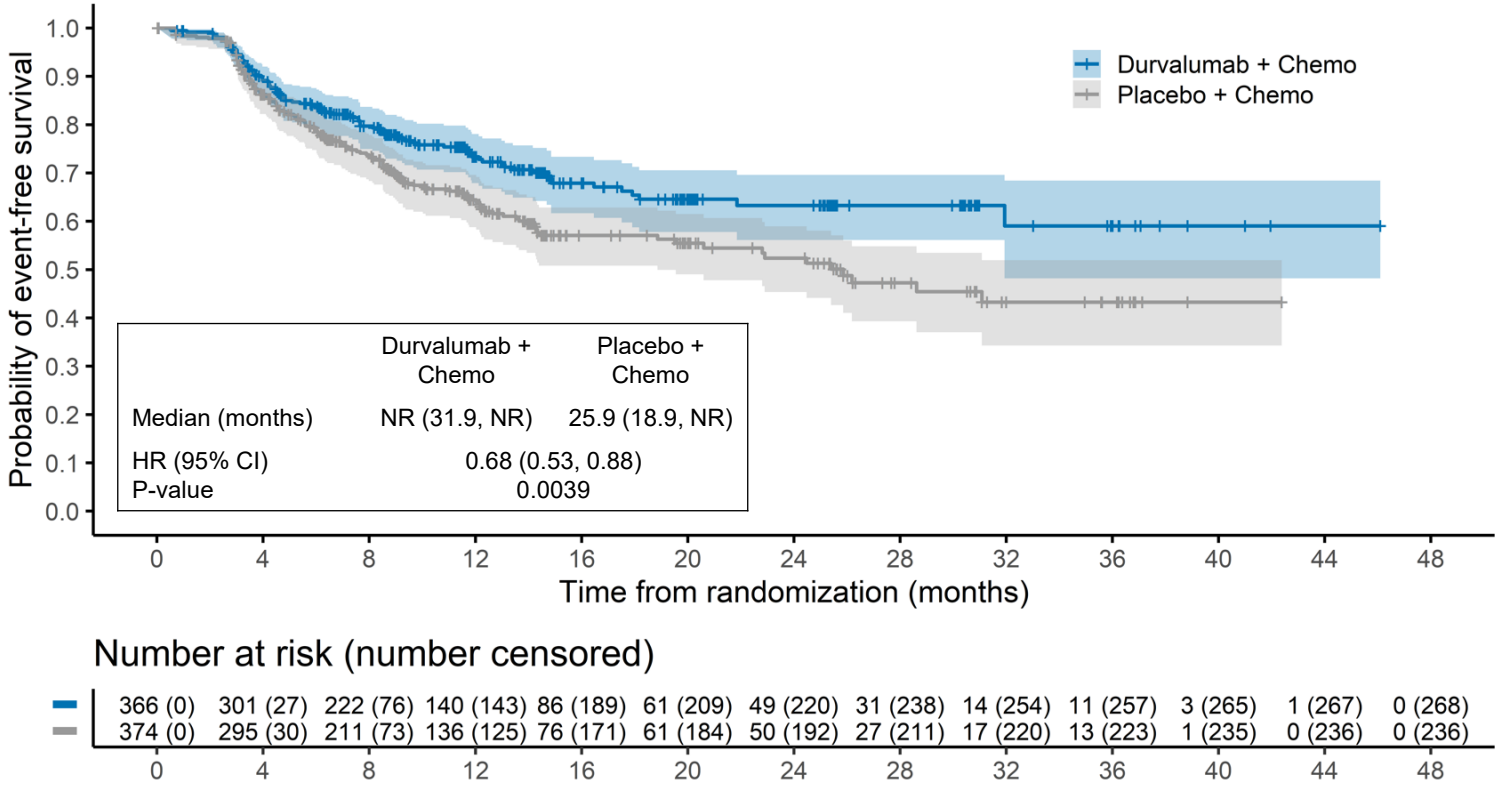
Chemo = platinum-doublet chemotherapy, Durva = Durvalumab
DCO: 14 January 2022; [1]P-value boundary= 0.000082

Dual Primary Endpoint – EFS:
First interim analysis (Statistically Significant)

EFS by BICR (mITT)	Durva + Chemo N=366	Placebo + Chemo N=374
Events*, n (%)[1]	98 (27)	138 (37)
Censored, n (%)	268 (73)	236 (63)
Median, months (95% CI)	NR (31.9, NR)	25.9 (18.9, NR)
HR (95% CI) P-value[2]	0.68 (0.53, 0.88) 0.0039	

Chemo = platinum-doublet chemotherapy, Durva = Durvalumab
DCO: 10 November 2022; [1]Information fraction = 64%, [2]P-value boundary= 0.009899
*Clinical progression was considered an EFS events if (a) unresectable (EFS event = PD that precludes surgery) or (b) unable to complete surgery (EFS event = PD discovered by the Investigator upon attempting surgery resulted in the surgery not being completed)

Dual Primary Endpoint – EFS:
First interim analysis (Statistically significant)



DCO: 10 November 2022

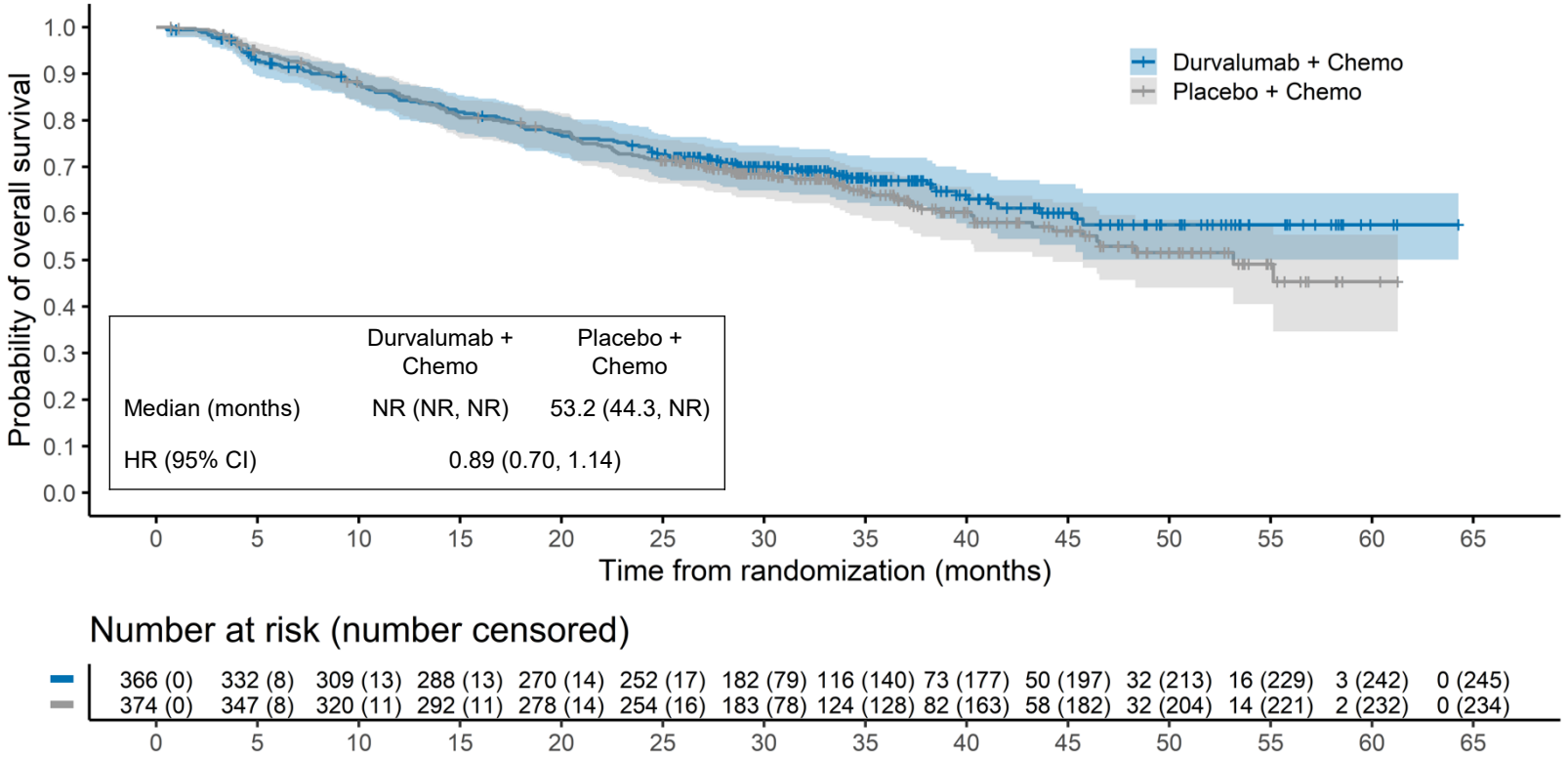
Key Secondary Endpoints: DFS and OS
Second Interim Analysis

		Durva + Chemo	Placebo + Chemo
DFS[1]	N (resected mITT)	242	231
	Events, n (%)	60 (25)	81 (35)
	Median, months (95% CI)	NR	NR (41.5, NR)
	HR (95% CI)	0.66 (0.47, 0.92)	
	p-value[2]	0.0137	
OS[1,3]	N (mITT)	366	374
	Events, n (%)	121 (33)	140 (37)
	Median, months (95% CI)	NR	53.2 (44.3, NE)
	HR (95% CI)	0.89 (0.70, 1.14)	

Chemo = platinum-doublet chemotherapy, Durva = Durvalumab; NR = Not Reached; NE = Not Estimable

[1]DCO: 10 May 2024;[2] Compared to an alpha boundary of 0.0123; [3]Not formally tested since DFS was not statistically significant

Key Secondary Endpoint: OS
Second Interim Analysis



Immune-related adverse events (IRAEs) during the Adjuvant Phase

	Durva + Chemo N=265 n (%)	Placebo + Chemo N=254 n (%)
All-Grade IRAEs	83 (31)	27 (11)
Grade 3-4 IRAEs	10 (3.8)	5 (2)
Grade 5 (Deaths due to IRAEs)	1 (0.4)	0 (0)
Study drug withdrawn due to IRAEs	14 (5)	3 (1.2)
Study drug interrupted due to IRAEs	14 (5)	3 (1.2)

Immune-related adverse events (irAEs) with durvalumab in the adjuvant phase

irAE Status	Durva + Chemo N=265 n (%)
Resolved	48 (18)
Resolved with sequalae	1 (0.4)
Resolving	18 (7)
Unresolved	23 (9)
Death	1 (0.4)

- Most common unresolved adjuvant irAEs: hypothyroidism (3.8%), rash (1.5%)
- Other unresolved irAEs: adrenal insufficiency, diarrhea, pneumonitis, musculoskeletal pain (0.4%)

AEGEAN: Summary of Results

Efficacy:

- Statistically significant improvement in EFS
- No formal testing of OS

Safety:

- Consistent with described toxicity profiles of platinum-based chemotherapy and ICIs
- 9% of patients who initiated adjuvant durvalumab had unresolved irAEs at end of study treatment
- No detrimental effects on OS

AEGEAN: Major Review Issue

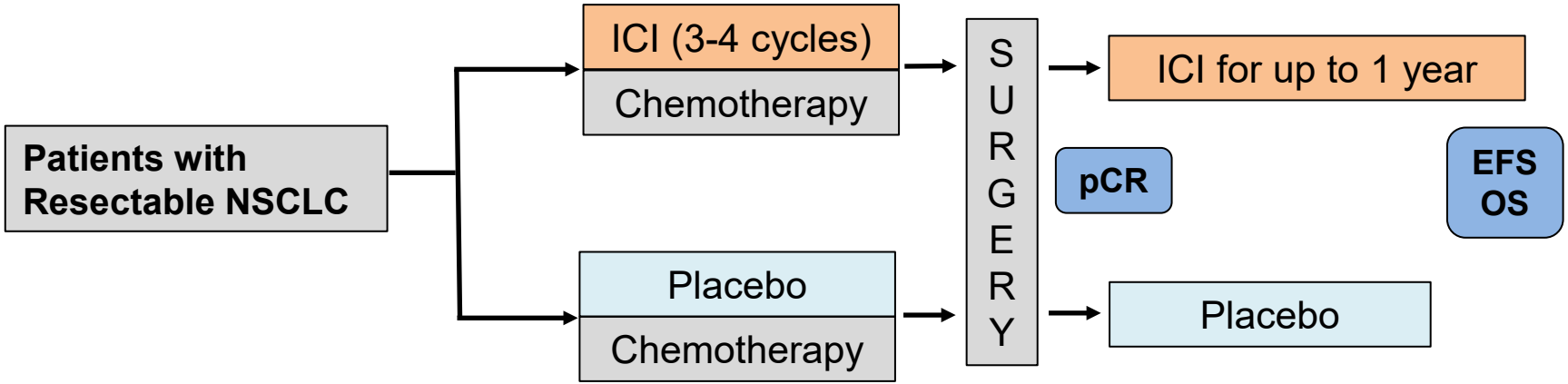
Inability to determine the contribution of effect of each treatment phase (neoadjuvant and adjuvant) to the overall effect of the perioperative regimen

- Potential for overtreatment:
  - Possible lasting immune-related toxicities in a curative setting
  - Increased treatment burden

Two-Arm Perioperative Trials

What is the relative contribution of neoadjuvant and adjuvant ICI on the EFS and OS endpoints?

- **Unanswerable in a 2-arm trial design**



ICI: Immune checkpoint inhibitor

Contribution of Treatment Phase for ICI-Based Regimens

FDA notified sponsors of concerns in perioperative ICI-based trials

- Two-arm design does not address contribution of phase
- Recommended factorial designs to assess contribution of treatment phase to perioperative regimen

Sponsors opted to proceed with two-arm trials

- Contribution of treatment phase remained unaddressed

EFS/DFS Treatment Effect Sizes Comparable Across Trials

	Neoadjuvant Only	Adjuvant Only		Neoadjuvant followed by Adjuvant		
ICI	**Nivolumab**	**Atezolizumab**	**Pembrolizumab**	**Pembrolizumab**	**Durvalumab**	**Nivolumab**
Stage	IB[a]-IIIA	II-IIIA	IB[a]-IIIA	II-IIIB	II-IIIB	II-IIIB
Trial	CHECKMATE-816	IMpower-010	KEYNOTE-091	KEYNOTE-671	AEGEAN	CHECK MATE-77T
Primary Endpoint(s)	EFS/pCR	DFS	DFS	EFS/OS	EFS/pCR	EFS
DFS/EFS HR (95% CI)	**0.63 (0.45, 0.87)**	**0.66 (0.50, 0.88)**	**0.73 (0.60, 0.89)**	**0.58 (0.46, 0.72)**	**0.68 (0.53, 0.88)**	**0.58 (0.42, 0.81)**

Lack of Benefit in an Adjuvant-Only Trial of Durvalumab

Update on ADJUVANT BR.31 Phase III trial of Imfinzi in non-small cell lung cancer

High-level results from the ADJUVANT BR.31 Phase III trial, sponsored by the Canadian Cancer Trials Group (CCTG), showed *Imfinzi* (durvalumab) did not achieve statistical significance for the primary endpoint of disease-free survival (DFS) versus placebo in early-stage (IB-IIIA) non-small cell lung cancer (NSCLC) after complete tumour resection in patients whose tumours express PD-L1 on 25% or more tumour cells.

https://www.astrazeneca.com/media-centre/press-releases/2024/update-on-imfinzi-adjuvant-br31-trial.html (Issued: June 25, 2024)

Risk of Not Demonstrating Contribution of Treatment Phase: Toxicities

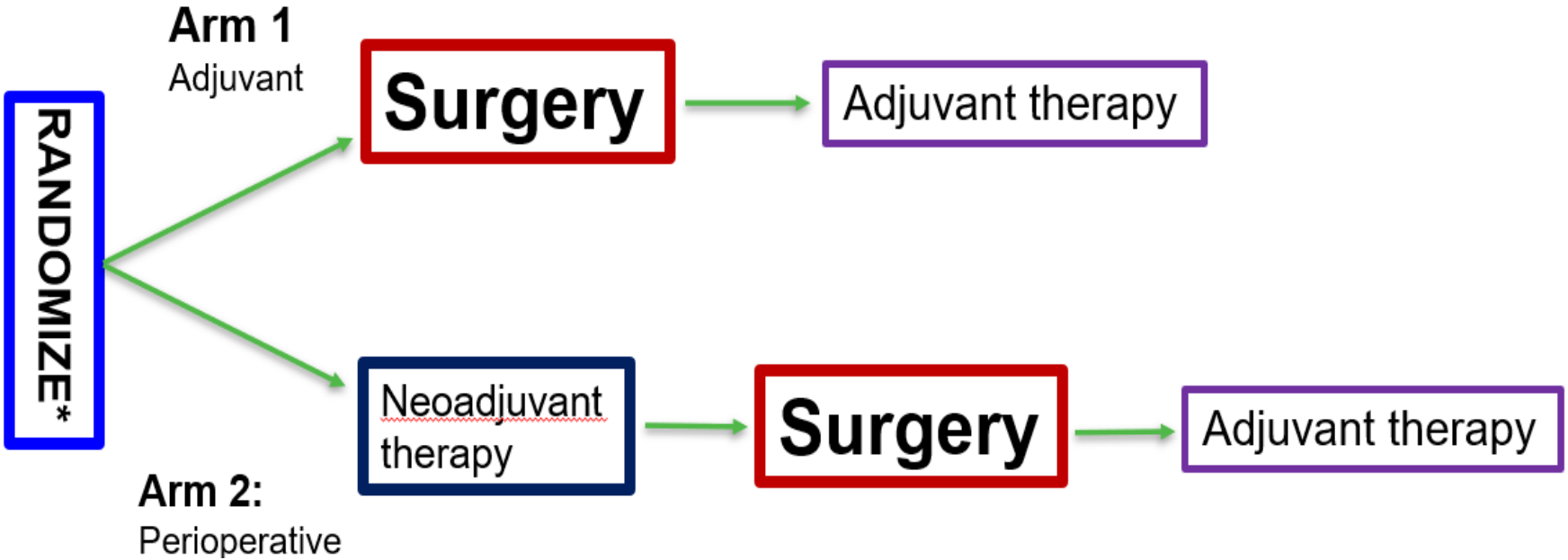
A Meta-Analysis of 28 randomized trials in solid tumors indicated that adjuvant ICIs were associated with a greater incidence of severe toxicities[1,3]

Adverse Event	Adjuvant ICI vs Control (N=13) Odds Ratio (95% CI)	Neoadjuvant ICI vs Control (N=11) Odds Ratio (95% CI)
Grade 3-4	5.58 (3.75, 8.29)	1.17 (0.90, 1.51)
Grade 5[2]	4.85 (1.66, 14.13)	1.11 (0.38, 3.29)

[1] Four trials of neoadjuvant followed by adjuvant therapy were not included in the below table
[2] Five adjuvant and six neoadjuvant trials had zero deaths due to AEs and did not contribute to the estimation of odds ratios
[3]Analysis not conducted or reviewed by the FDA

Fujiwara et al. Lancet Oncol 2024; 25:62-75.

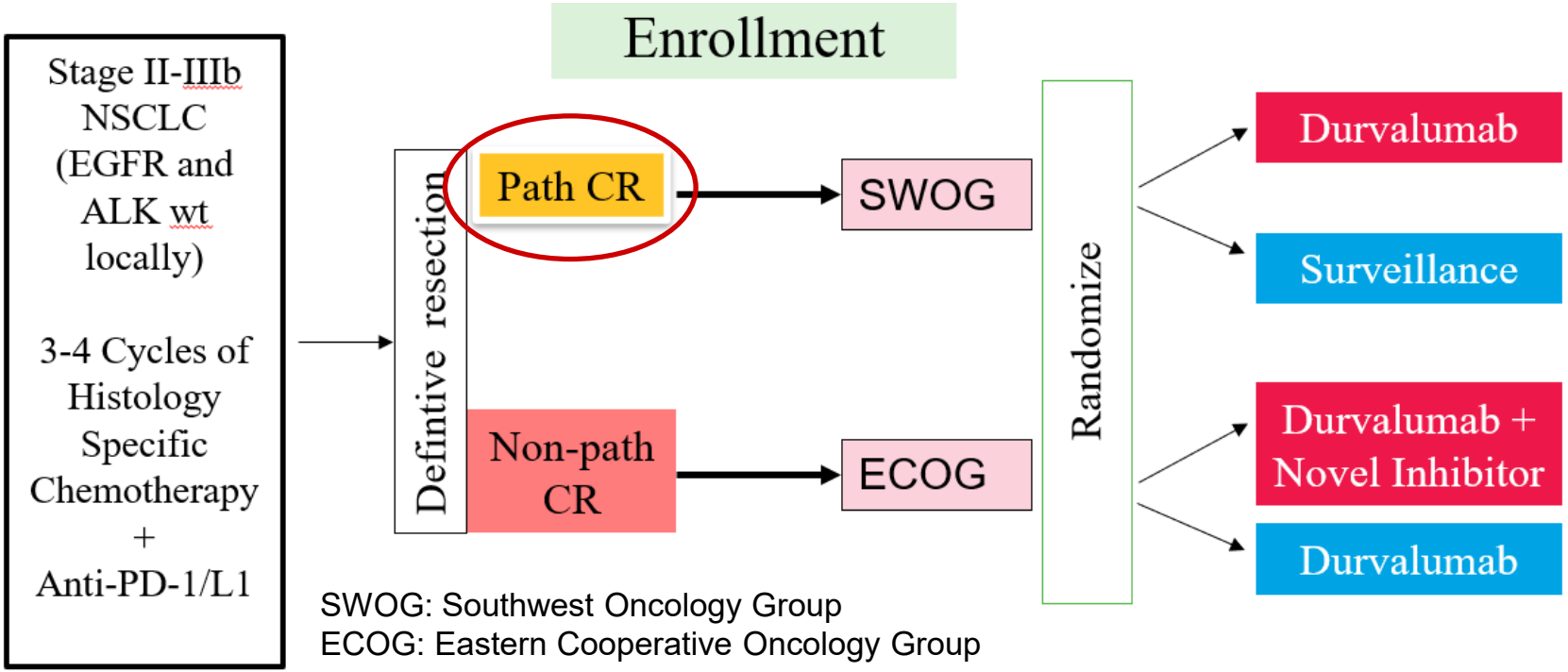
Cooperative Group Trials in the Post Market Setting: PROSPECT-LUNG



***Stage II-IIIB NSCLC**
ECOG PS 0-2

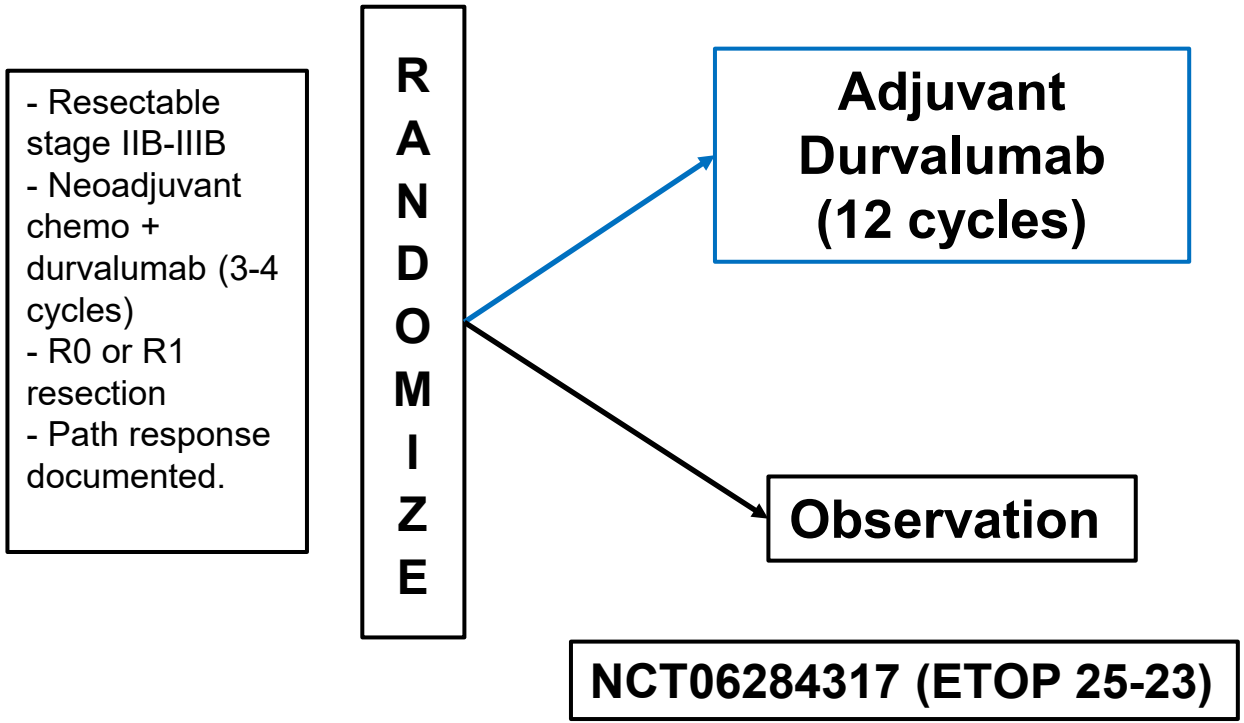
- Trial does not address contribution of adjuvant phase
- Treatment landscape may evolve by the time trial is complete

Cooperative Group Trials in the Post Market Setting: CLEAR-INSIGHT



SWOG: Southwest Oncology Group
ECOG: Eastern Cooperative Oncology Group

Cooperative Group Trials in the Post Market Setting: ADOPT-Lung



Primary Endpoint:
- DFS in non-PCR group

Sample Size:
- 290

Study Start:
- Oct 2024

Study Completion:
- Mar 2030

AEGEAN: Discussion Topic for Advisory Committee

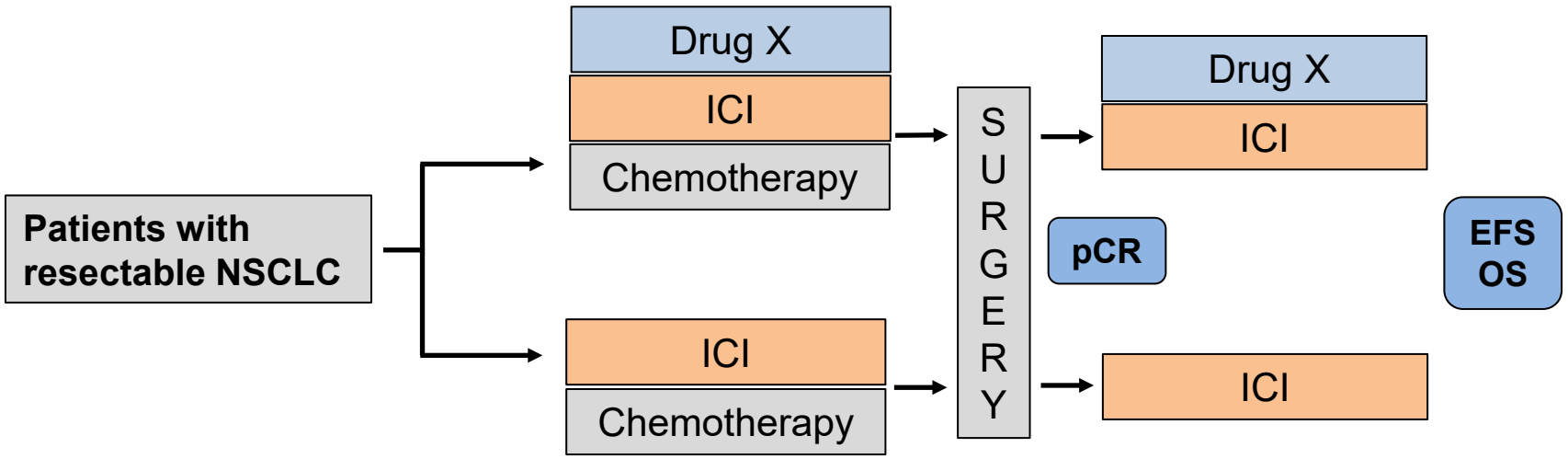
In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.

Contribution of Treatment Phase to Perioperative Regimens

Overview

- Contribution of treatment phase moving forward
  - Add-on Drug trials

Two-Arm Add-on Trials Exacerbate the Risks of Overtreatment



- Inability to isolate contribution of treatment phase for Drug X
- Exacerbation of risks due to intensification of therapy

Potential Two-Arm Trial Designs

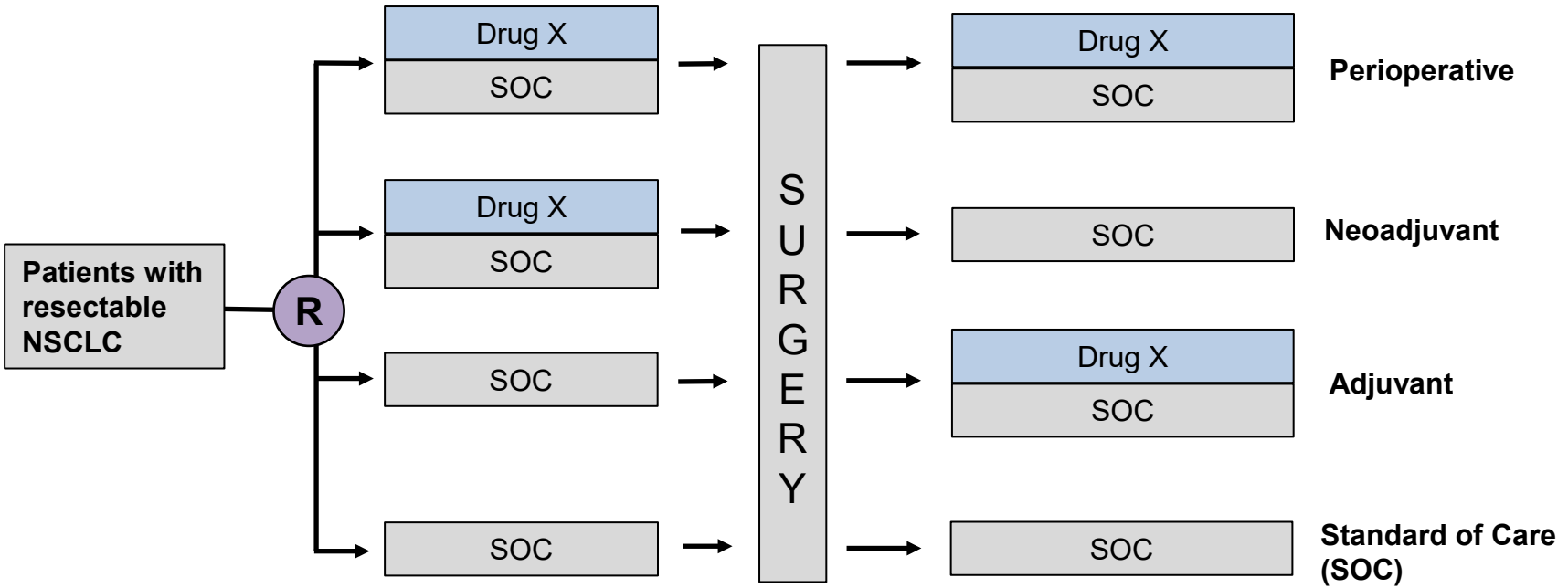
☑	Adjuvant-only add-on to SOC
☑	Neoadjuvant-only add-on to SOC
☒	Peri-operative add-on to SOC

Trial Designs that Assess Contribution of Drug Effects in Different Treatment Phases

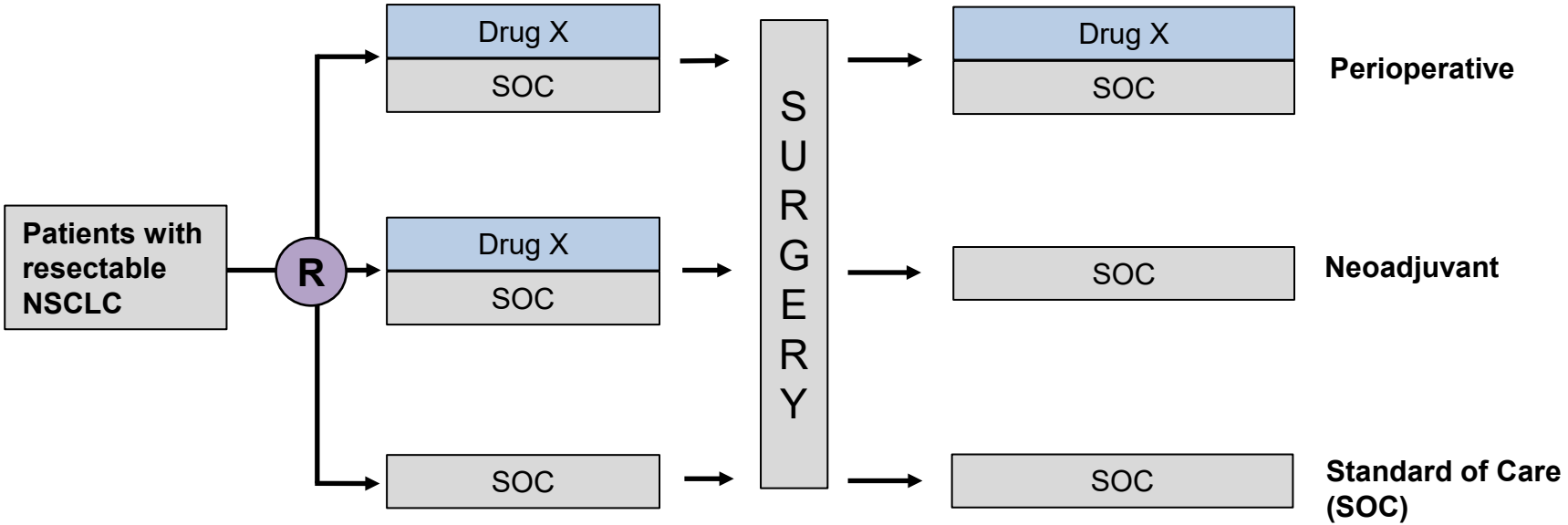
- Moving forward, trial designs for perioperative regimens should incorporate arms that isolate the contribution of neoadjuvant and/or adjuvant treatment:
  - **4 arm designs**: A factorial design is ideal for establishing contribution of components or phase to a combination therapy regimen
  - **3 arm designs**: For example, adding a neoadjuvant only arm given the higher potential for overtreatment in the adjuvant phase
- FDA is open to alternative trial designs as well (e.g., adaptive designs, re-randomization post-surgery)

In all cases, design should be adequately justified for the therapeutic context

Add-on Trial: 4-Arm Design



Add-on Trial: 3-Arm Design



Considerations for Study Design and Analysis

- FDA recommends a design and analysis plan that ensures formal comparisons of the peri-operative regimen arm and the individual phase arm(s) to SOC
- Statistical analysis plan can use various strategies to formally test these comparisons
- A pre-specified comparison for the peri-operative vs each individual phase arm(s) can support contribution of phase

If observed efficacy difference between experimental arms is modest, approval of peri-operative regimen is unlikely

Required Sample Sizes for Multi-Arm Trials

- Depending on the anticipated effect sizes for a trial that adds therapy to standard of care, FDA calculations indicate:
  - 3-arm trials may require 650-1700 patients
  - 4-arm trials may require 960-2400 patients

- These sample sizes include formal comparisons of each experimental arm to SOC control

- These sample sizes are comparable to completed perioperative and adjuvant trials of ICIs in NSCLC
  - Peri-operative NSCLC: KN-671 (N=797)
  - Adjuvant NSCLC: BR.31 (N=1415), ImPower010 (N=1005)

Summary: Contributions of Treatment Phase

For Completed ICI Trials

- Current perioperative trials of ICIs do not assess contribution of treatment phase
  - Concern for patient overtreatment
  - Proposed cooperative group trials do not address the issue fully

For Future Perioperative Trial Designs

- Proposed trials follow similar designs, exacerbating concerns for overtreatment
- Two-arm trials may be acceptable:
  - If given in the neoadjuvant phase only
  - If given in the adjuvant phase only
- Problematic if given in both neoadjuvant and adjuvant phases

Questions for the Committee

Discussion

In light of the uncertainty around the need for both phases of treatment, discuss whether an additional trial should be conducted to clarify the contribution of treatment phase for the durvalumab perioperative regimen prior to approval.

Discussion & Voting Question

Should FDA require that new trial design proposals for perioperative regimens for resectable NSCLC include adequate within trial assessment of contribution of treatment phase?


FDA
U.S. FOOD & DRUG
ADMINISTRATION