City of Hope®

Southeastern Multidisciplinary Approaches to Cancer Symposium

Management of Unresectable, Locally Advanced NSCLC

Kristin Higgins, MD

Professor, Dept of Radiation Oncology
Chief Clinical Officer
City of Hope Atlanta

Disclosures

- Consultant for AstraZeneca, Daiichi Sankyo & Picture Health.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

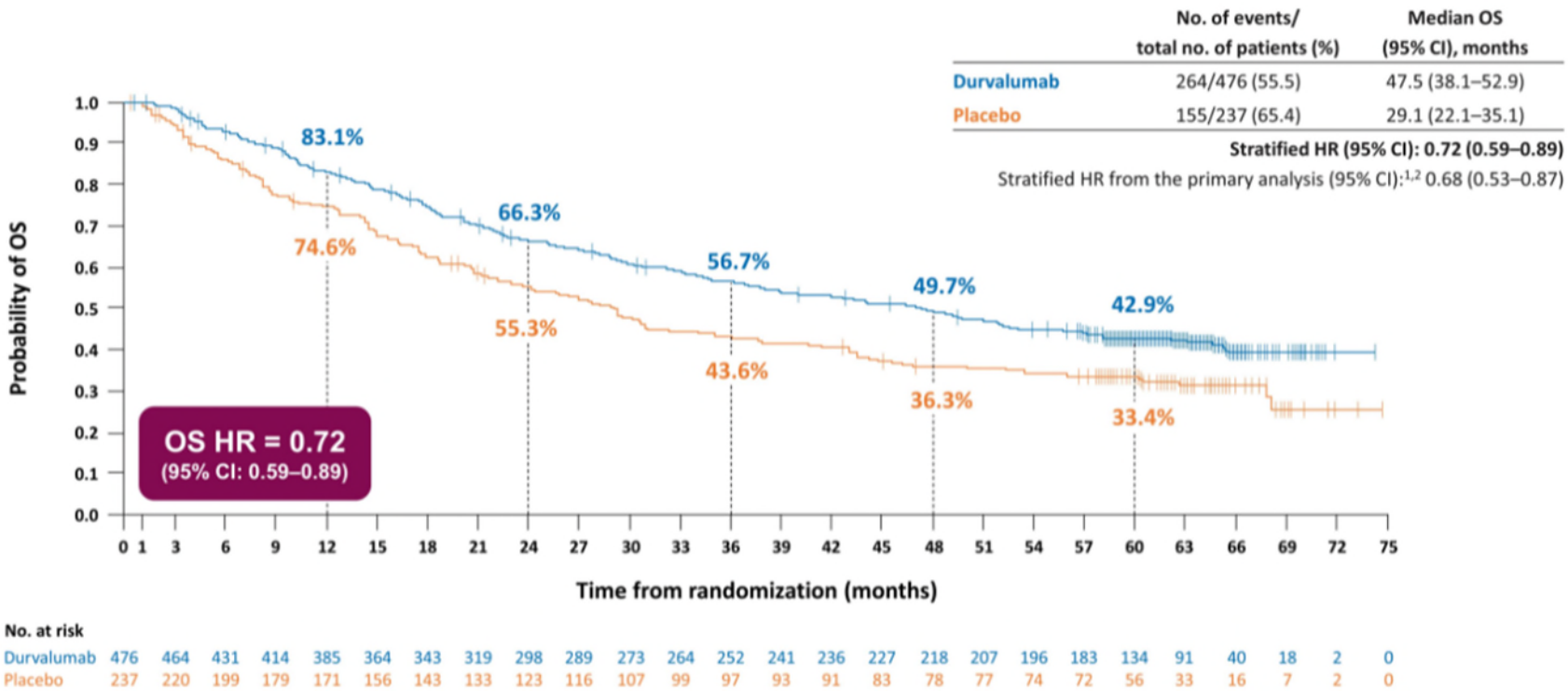
EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Discuss barriers to accessing advanced lung cancer therapies and clinical trials.*
- *Encourage self-reflection to reduce bias in clinical decision-making.*

5 yr PACIFIC Overall Survival Data

Updated OS (ITT)



CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival

Data cutoff: 11 January 2021 (median follow-up: all patients, 34.2 months [range, 0.2–74.7]; censored patients, 61.6 months [range, 0.4–74.7]).

1. Antonia SJ, et al. New Engl J Med 2018;379:2342–50; 2. European Medicines Agency. Durvalumab (Imfinzi). Summary of product characteristics 2020. Available from: https://www.ema.europa.eu/en/documents/product-information/imfinzi-epar-product-information_en.pdf 5. [Accessed April 2021]

Spigel DR et al. 2021 ASCO Annual Meeting. Abstract 8511. Spigel DR et al. *J Clin Oncol*. 2022;40(12):1301-1311.

Chemoradiation and Immunotherapy in Frail Populations: PACIFIC 6

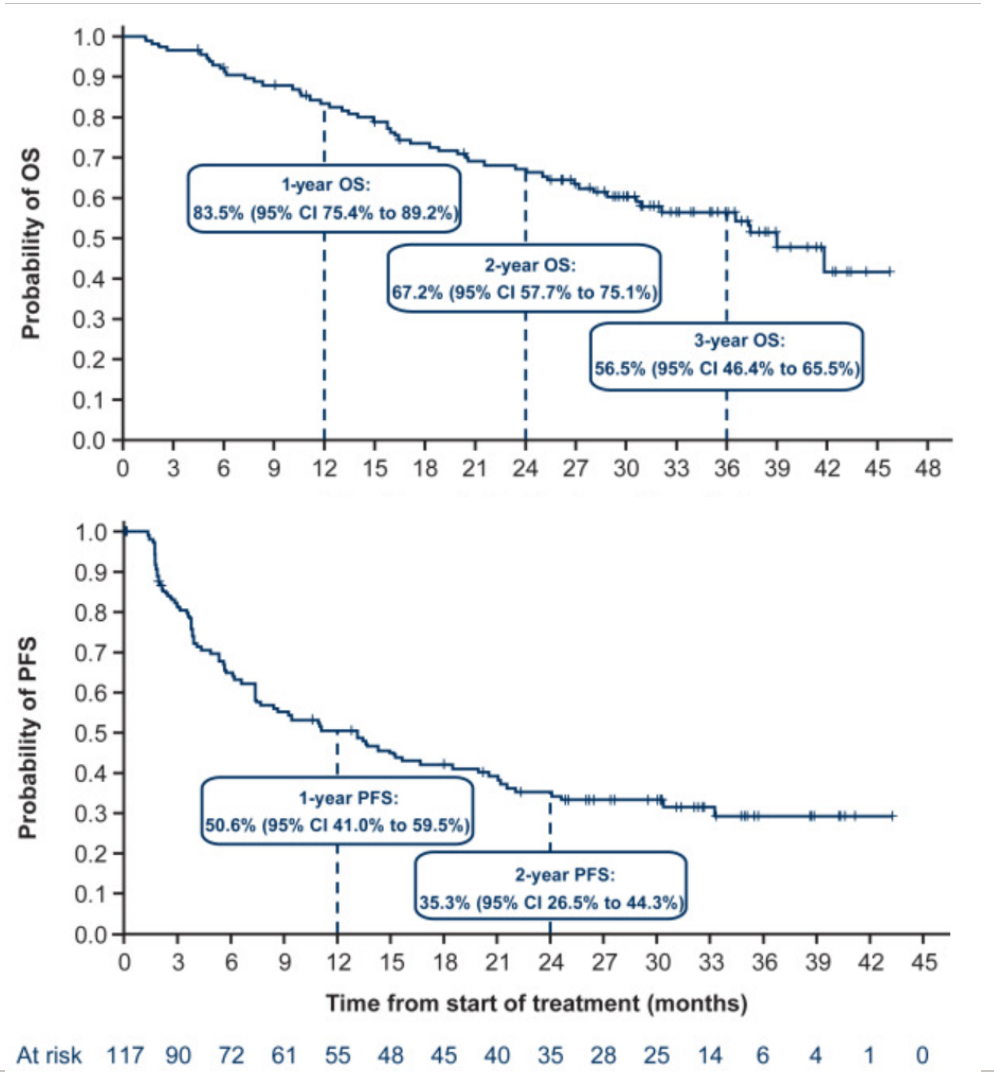
The phase II PACIFIC-6 (NCT03693300) trial evaluated durvalumab after sequential CRT in patients with unresectable stage III NSCLC.

The primary endpoint was safety; PFS and OS were secondary endpoints.

At final analysis, 27.4% of patients had grade 3/4 AEs and 6.0% had grade 3/4 AEs considered possibly related to treatment.

Durvalumab after sequential CRT showed encouraging efficacy, with a median OS of 39.0 months and a median PFS of 13.1 months.

Durvalumab after sequential CRT was well tolerated and may be an alternative strategy in this setting when concurrent CRT is not feasible.



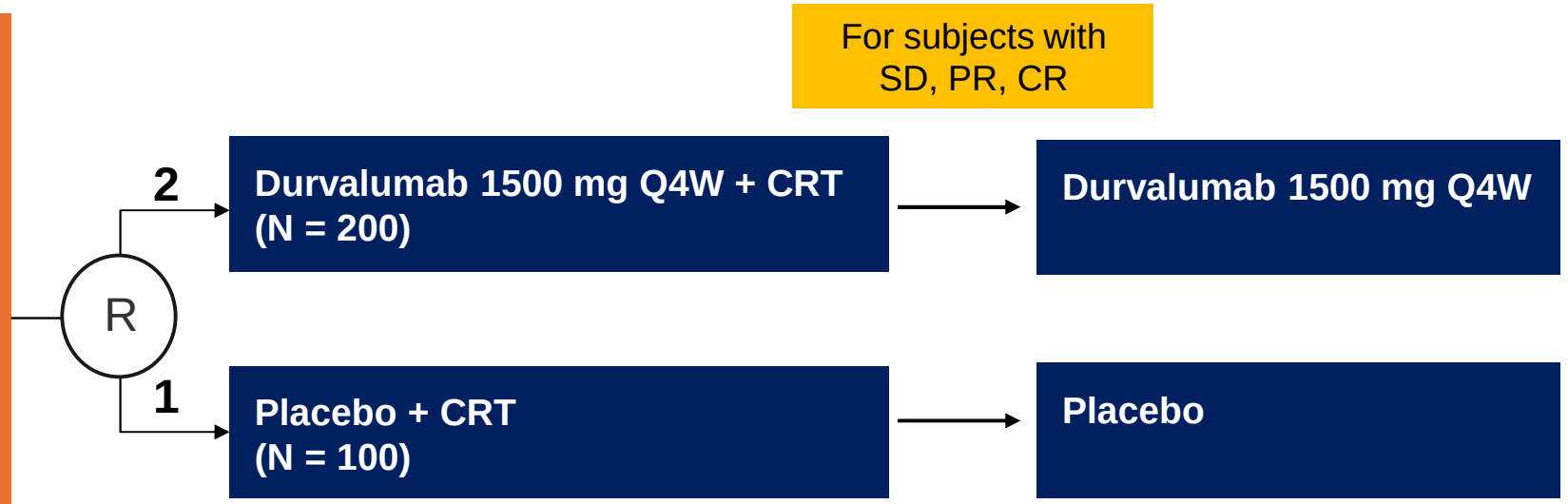
Garrasino et al, JTO 2022

PACIFIC-2: Study Design

Study Population

- Patients with unresectable, Stage III NSCLC
- All-comers (PD-L1 expression-agnostic)
- ECOG PS 0-1

Randomised N = 300 patients



- Early IDMC safety assessment in first 15 and 60 TOTAL subjects (CRT+28 days)
- In Japan, assessment after first 9 TOTAL subjects (CRT+28 days)

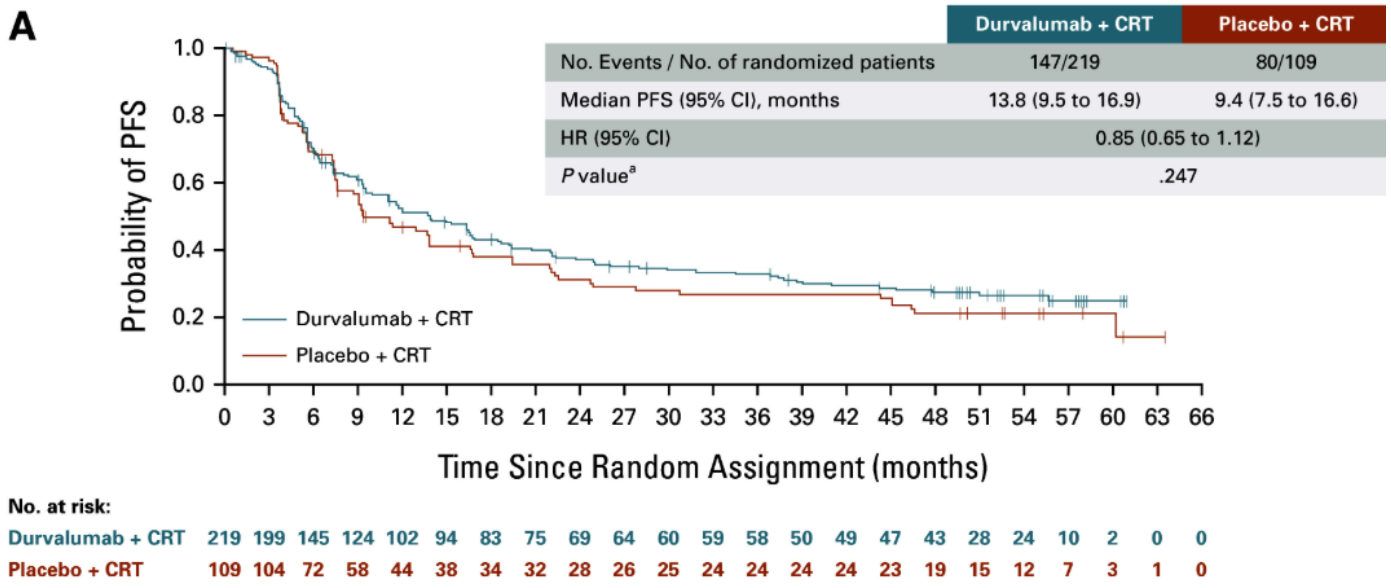
Stratification

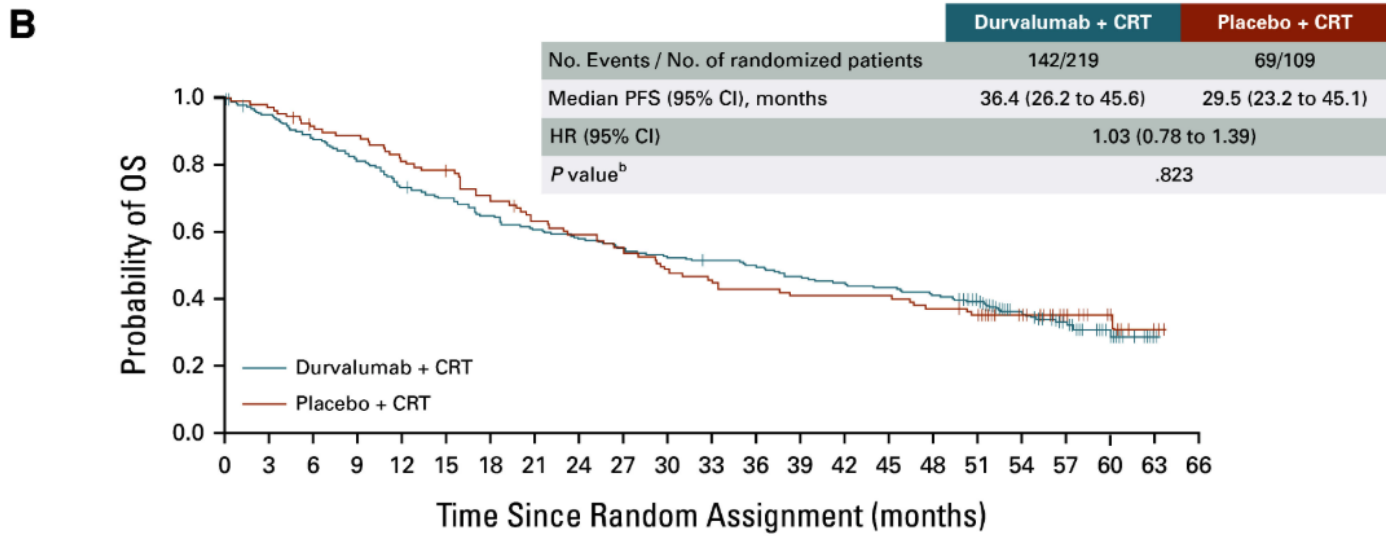
- Age (≤65, >65)
- Stage (IIIA vs IIIB/C)

- **Primary Endpoints: ORR, PFS**
- **Key Secondary Endpoints:** OS, OS24
- **Treat to progression**

PACIFIC 2

88% of pts on Durva completed CRT, 90% on placebo
>90% of pts receiving CRT received protocol prescribed RT (>57 Gy)
High grade pneumonitis 4.6% in durva vs. 5.6% placebo



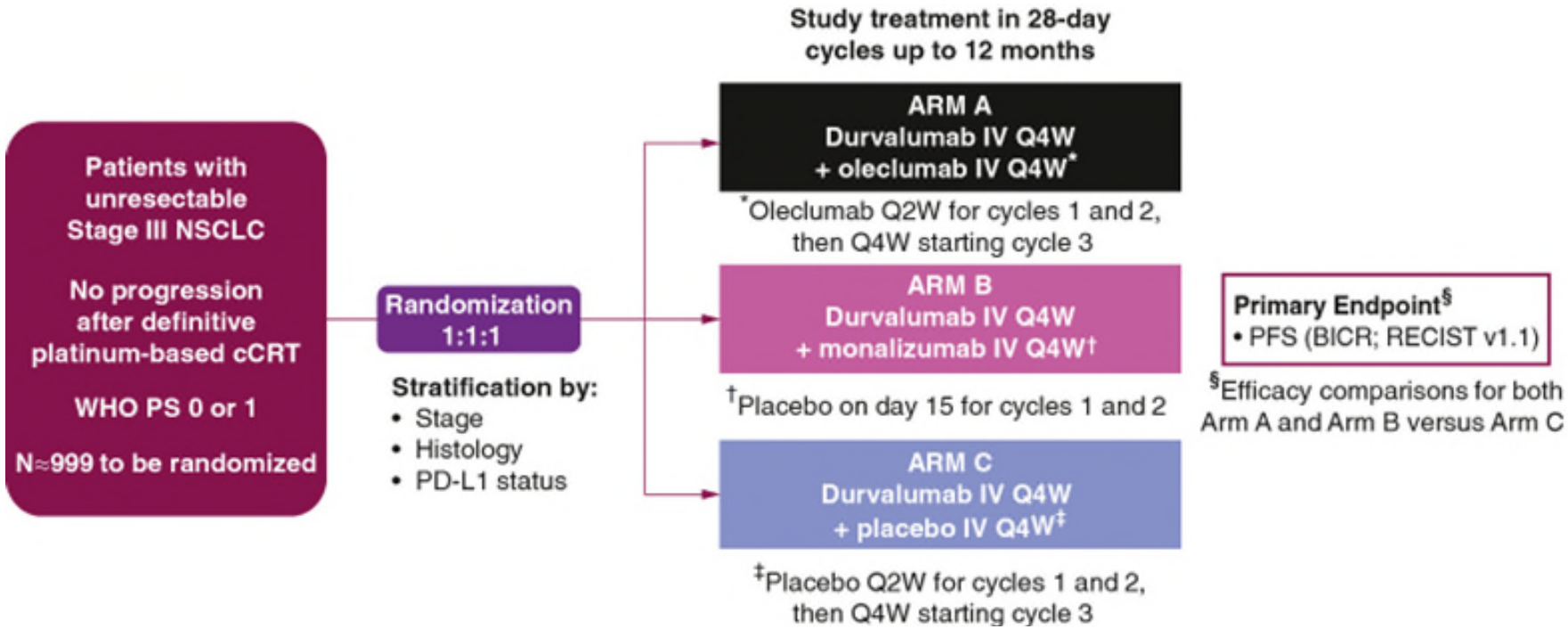


Bradley et al, JCO 2025

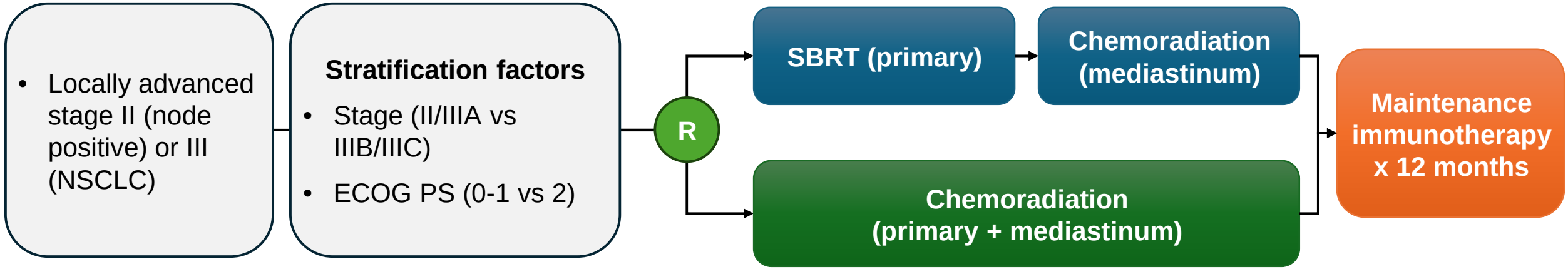
PACIFIC 9: NCT03822351

Oleclumab is a monoclonal antibody that blocks CD73, reducing extracellular adenosine which acts as an immunosuppresant

NKG2A is a receptor on T cells and natural killer (NK) cells that can inhibit T cell and NK cell effector function when it binds to HLA-E; **monalizumab** is a monoclonal antibody that binds to NKG2A

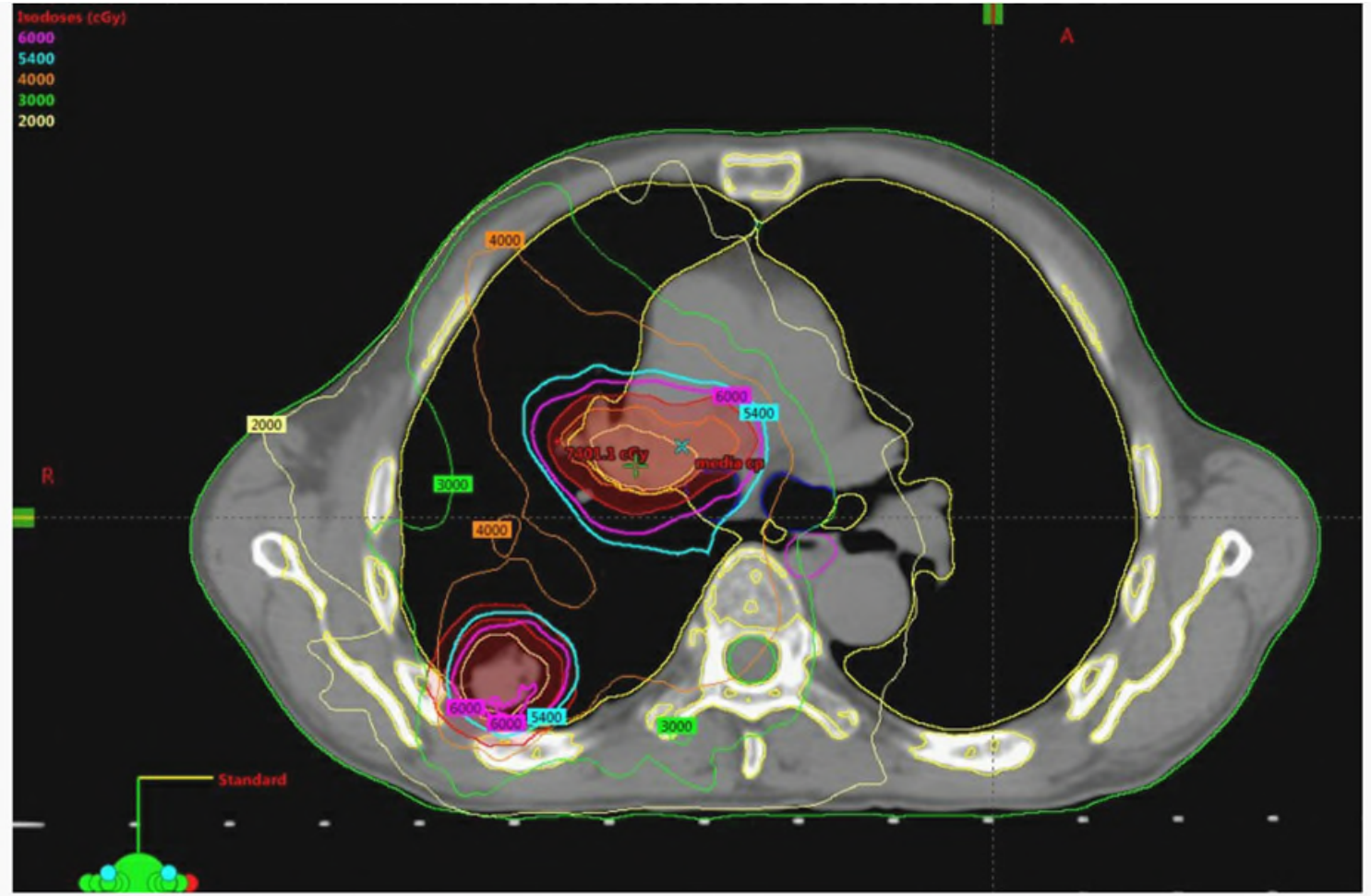


NRG Oncology LU008



- Primary endpoints: OS and PFS
- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 month
- Experimental arm: SBRT to the primary (standard BED ≥100 Gy dose regimen) → chemoradiation to mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
  - **SBRT to primary tumor**
    - 3 fractions to 54 Gy (BED10 of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED10 of 112.5 Gy) [peripheral or central]
    - 5 fractions to 50 Gy (BED10 of 100 Gy) [central] or to 60 Gy (BED10 of 132 Gy) [peripheral or central]

NRG LU008: SBRT to Primary



- Total volume of lung receiving 40 Gy = 332 cc (compared with 590 cc, 44% reduction)
- Total volume of lung receiving 40 Gy = 922 cc (compared with 1,300 cc, 29% reduction)
- Total volume of lung receiving 10 Gy = 2,168 cc (compared with 2,360, 8% reduction)

Is it time to readdress the paradigm of upfront concurrent chemoradiotherapy in LA-NSCLC?

- Prior studies (e.g. CALGB[1]) failed to demonstrate a benefit for induction chemotherapy followed by chemoradiotherapy
- However, chemoimmunotherapy is much more effective than chemotherapy in resectable (neoadjuvant) and advanced disease
- Current Standard of Care
  - Resectable Stage III: Chemoimmunotherapy → surgery → immunotherapy
  - Unresectable Stage III: Chemoradiation→ durvalumab
- Benefits to the Induction approach for Unresectable Stage III NSCLC
  - Early introduction of highly effective systemic treatment
  - Potential reduction in toxicity
  - Faster treatment start
  - Optimizes both treatments

1. Vokes EE, Herndon JE, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol Off J Am Soc Clin Oncol*. 2002;20(20):4191-4198. doi:10.1200/JCO.2002.03.054

Induction Strategy in Stage III Unresectable NSCLC?

Summary of studies of neoadjuvant chemoimmunotherapy followed by chemoradiotherapy in unresectable stage III NSCLC

Study	N	Arms	1-yr PFS	1-yr OS
APOLO	38	ChemoIO→ CRT→ IO	68.4	86.8
GASTO-1091	264	ChemoIO→ CRT→ IO ChemoIO→ CRT→ obs	72.6 52.5	Not reported
InTRist	52	IO+ chemo→ CRT→ IO Chemo→ CRT→ IO	85.6 54.5	Not reported

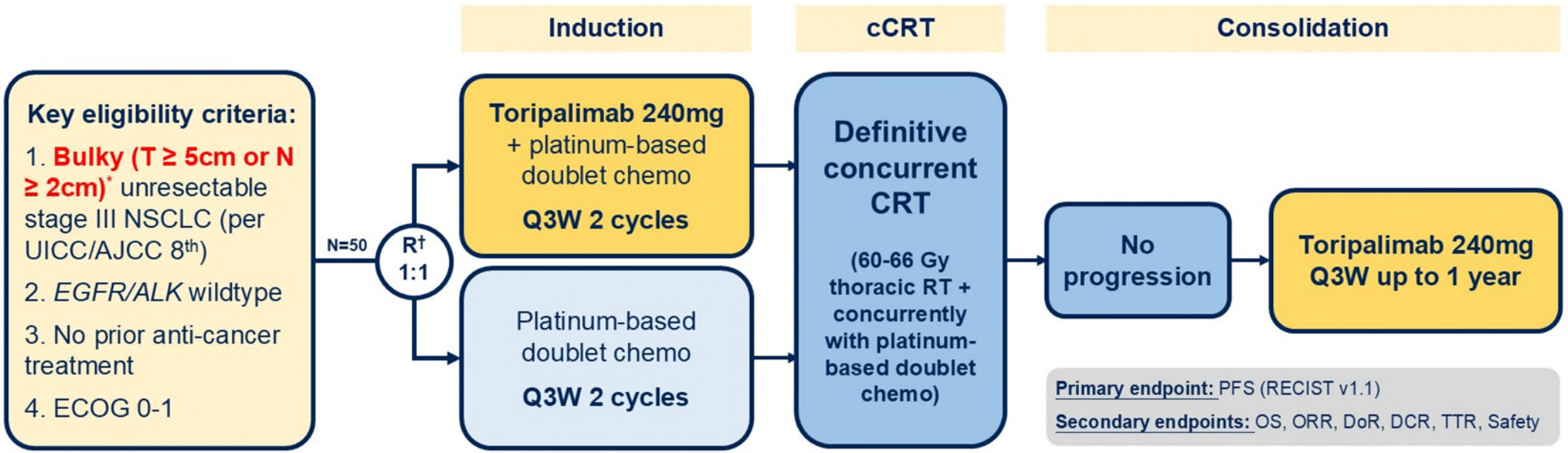
Provencio M, Campos B, Guirado M, et al. OA12.05 APOLO: Phase II Trial of Induction Chemo-Immunotherapy Plus Chemoradiotherapy and Maintenance Immunotherapy in Stage III NSCLC. *J Thorac Oncol*. 2024;19(10):S37. doi:10.1016/j.jtho.2024.09.067

Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *N Engl J Med*. 2017;377(20):1919-1929. doi:10.1056/NEJMoa1709937

Liu H, Qiu B, Zhao Y, et al. A phase II randomized trial evaluating consolidative nivolumab in locally advanced non-small cell lung cancer post neoadjuvant chemotherapy plus nivolumab and concurrent chemoradiotherapy (GASTO-1091). *J Clin Oncol*. 2024;42(16_suppl):8008-8008. doi:10.1200/JCO.2024.42.16_suppl.8008

InTRist study design

- **InTRist (NCT05888402): A randomized, single-center, Phase II trial**



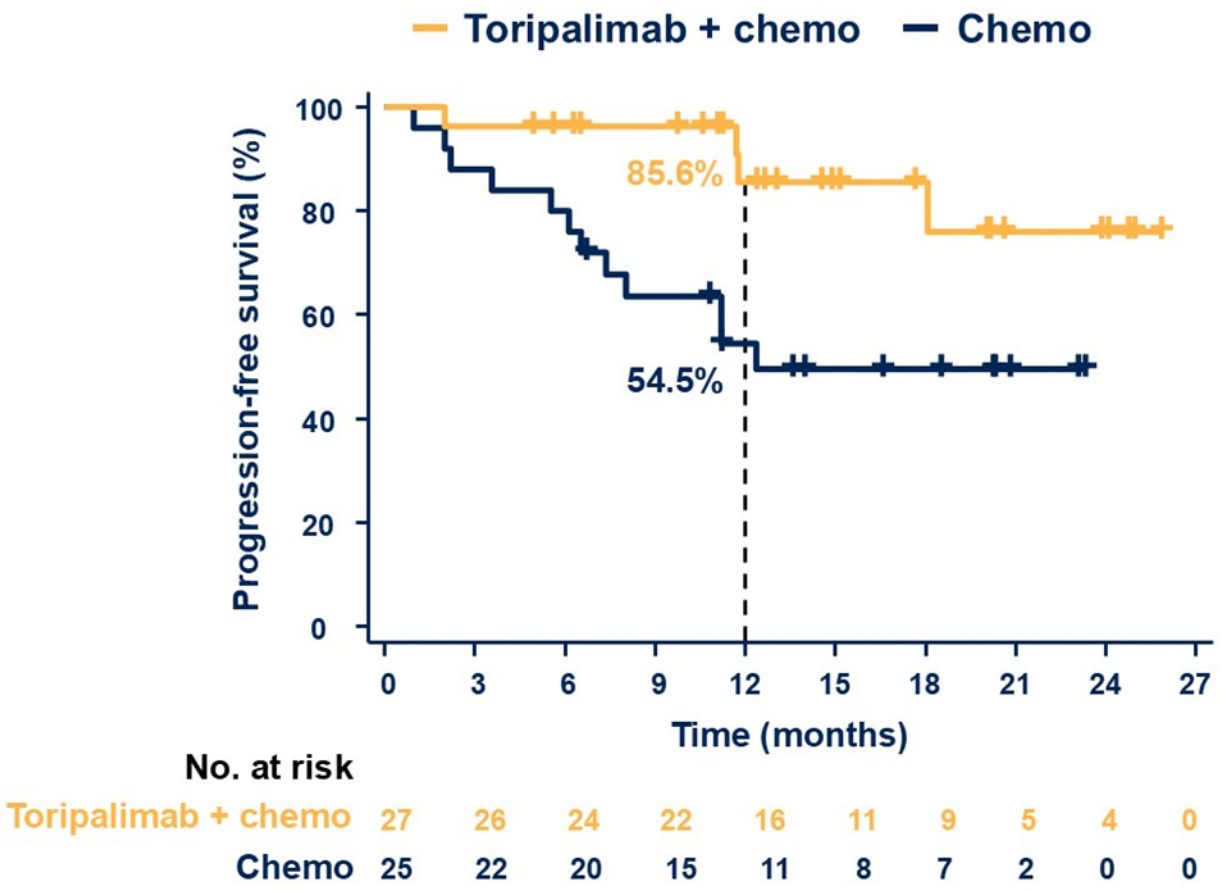
* Primary tumor ≥5 cm in the greatest dimension, or metastatic lymph nodes ≥2 cm in the shortest diameter
† Stratification factor: squamous vs non-squamous

cCRT, concurrent CRT; RT, radiotherapy; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DoR, duration of response; DCR, disease control rate; TTR, time to response

Wang et al. *J Clin Oncol* **43**, 8012-8012(2025).

InTRist Study

Primary endpoint: PFS



	Toripalimab + chemo	Chemo
Median PFS, mo (95% CI)	NR (NR-NR)	12.4 (8.0-NR)
1-yr PFS, % (95% CI)	85.6 (71.6-100.0)	54.5 (37.7-78.7)
HR (95% CI)	0.26 (0.08-0.81)	
Log-rank *P*	0.012	

Median follow-up 14.7 months

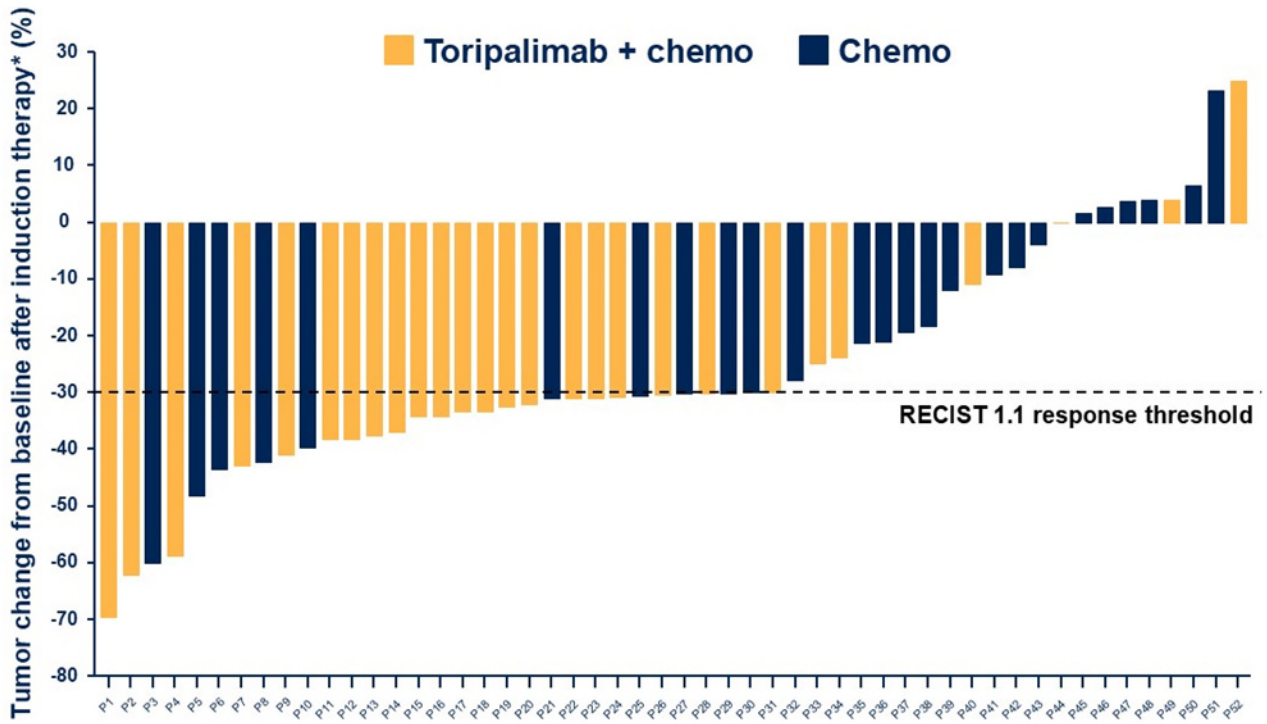
Data cutoff date: March 6th, 2025

Wang et al. *J Clin Oncol* **43**, 8012-8012(2025).

InTRist Study

Efficacy after induction therapy

	Toripalimab + chemo (n=27)	Chemo (n=25)	*P*†
Objective Response Rate	77.8%	40.0%	0.006
Disease Control Rate	96.3%	92.0%	0.945

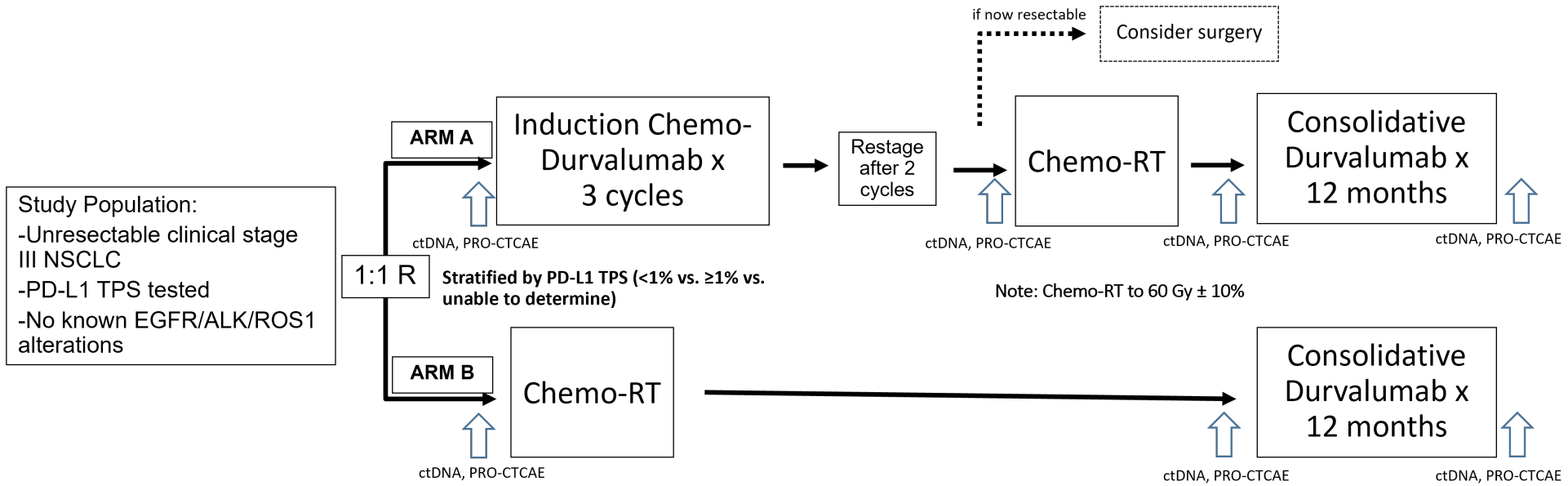


* The percentage change in tumor size was calculated according to the RECIST v1.1 criteria
† *P* value was calculated by Chi-square test or Yates' correction

Data cutoff date: March 6th, 2025

Wang et al. *J Clin Oncol* **43**, 8012-8012(2025).

SWOG S2608-SIMON: Schema



SWOG S2608-SIMON: Endpoints/Statistics

Primary endpoint: **Overall survival**

Secondary endpoints: **Progression-free survival, Patient-reported toxicity** (4 PRO-CTCAE measurements); RT dosimetry metrics; overall response rate (when appropriate); percentage of patients completing RT; locoregional progression rate; distant metastasis rate; percentage of patients undergoing surgery rather than chemo-RT

Exploratory endpoints: **ctDNA modulation** (at least 3-4 ctDNA measurements)

Design	Primary Endpoint	Target HR	Type I Error	Power	Required # Events	Accrual Time	Follow-up Time	Required Sample Size
Phase III	OS	0.72	0.025	80.9%	320	27 mo	48 mo	**504** (560 considering 10% ineligibility rate)

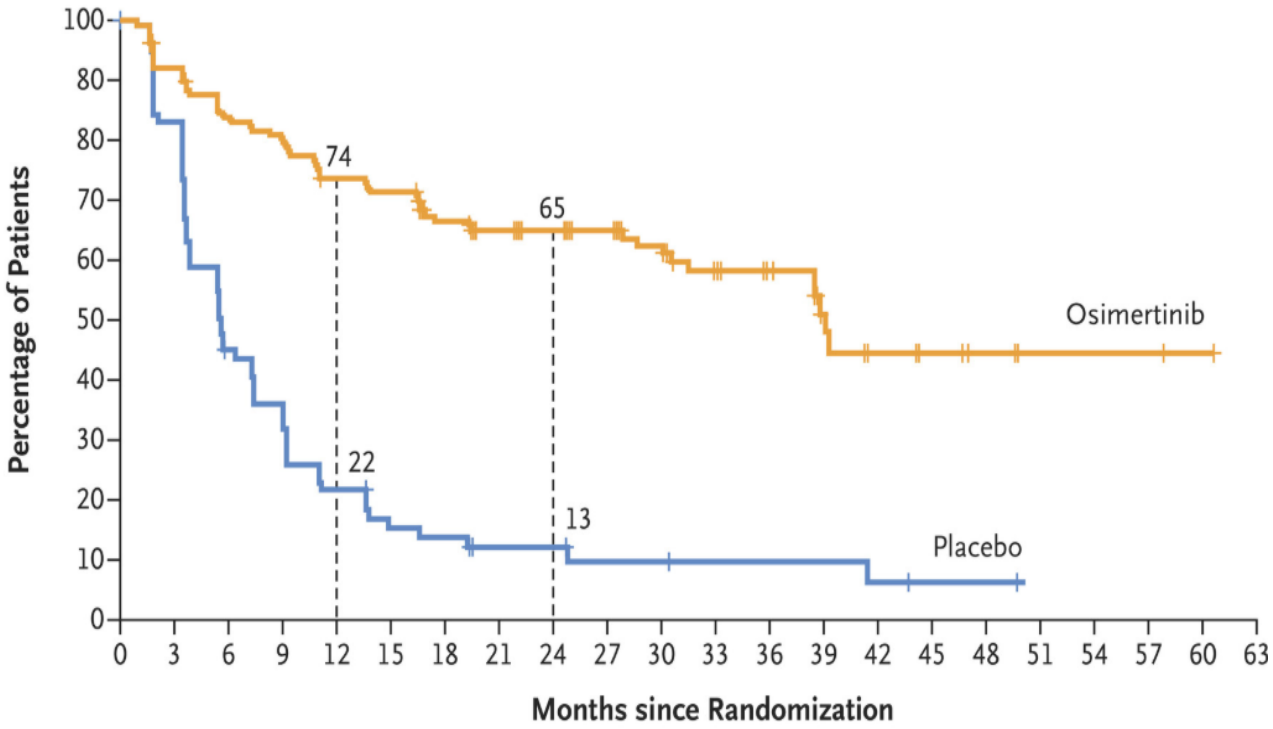
City of Hope®

EGFR Mutated, Unresectable NSCLC

LAURA

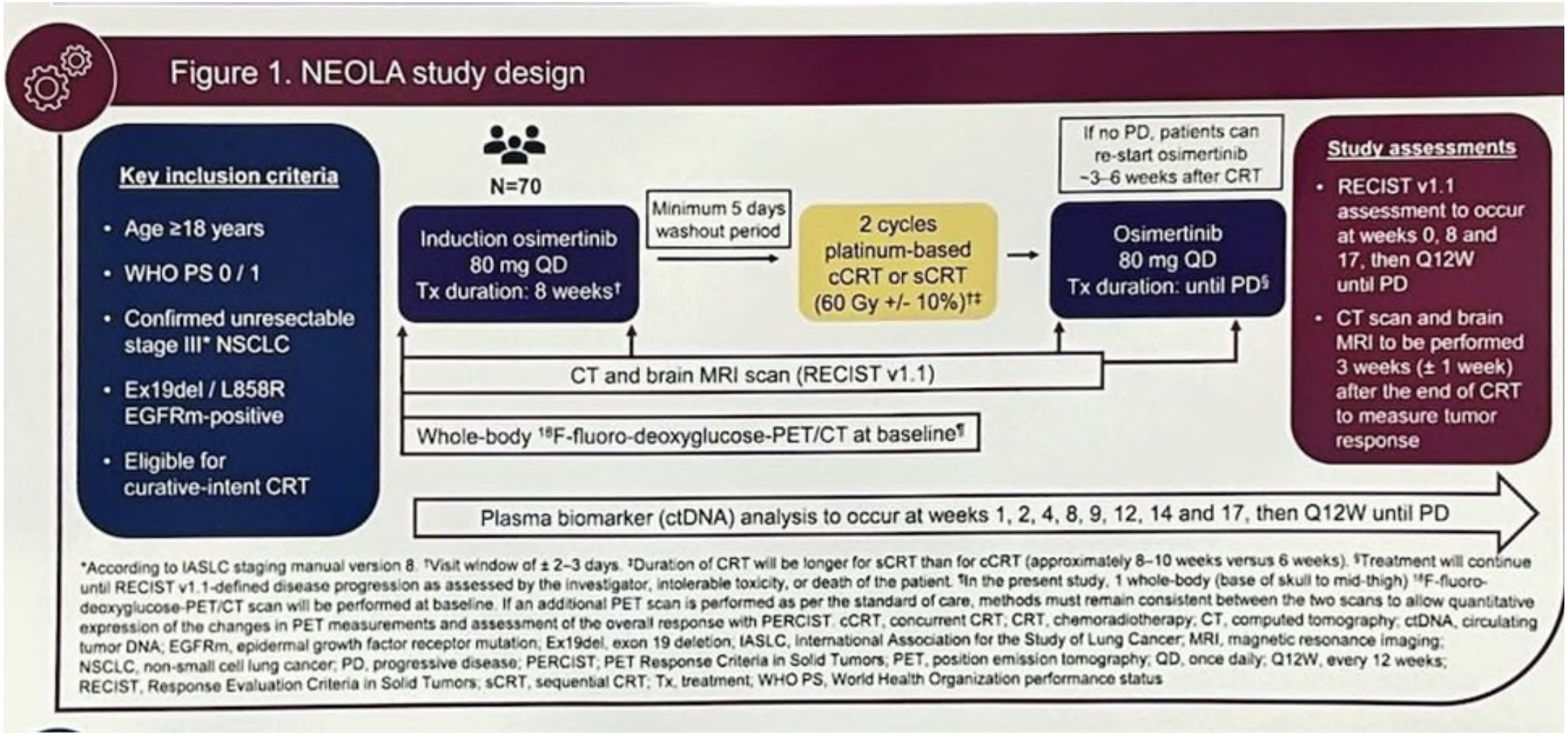
- Adjuvant Osimertinib improve PFS in patients with stage III **unresectable EGFR mutated non-small cell lung cancer (NSCLC) after chemoradiation[1,2]**

- Concerns remain about design and generalizability
  - Lack of mandated staging with PET/CT
  - Inclusion of patients with baseline brain metastases[3]
  - Lack of radiation QA or standardization
  - Indefinite duration of TKI



1. Lu S et al, *N Eng J Med* 2024
2. Yu J et al. *J Thor Oncol* 2024;19(10):S6-S7
3. Lu S et al., *Ann Oncol* 2024

NEOLA



Adero et al, WCLC 2024

SORT: A Randomized Phase II Study of **S**equencing **O**simertinib, **R**adiation, and Chemo**t**herapy in Stage III NSCLC with activating EGFR mutations.

NRG-LU013

Eligibility
Unresectable Stage III NSCLC
EGFR Mutation (Del19 or L858R)
ECOG PS 0-2

↓

RANDOMIZE 1:1
N = 240

→

ARM 1 (Control)
Standard of Care

INDUCTION	→	CONCURRENT CHEMORADIATION	→	MAINTENANCE
None		Chemotherapy (physician choice)* + Radiation 60 Gy / 30 fractions		Osimertinib 80 mg daily until progression or intolerable side effects

ARM 2 (Experimental)
Induction Strategy

INDUCTION (~6 weeks)	→	CONCURRENT CHEMORADIATION	→	MAINTENANCE
Carboplatin AUC=5 Day 1 Pemetrexed 500 mg/m^2 Day 1 Osimertinib 80 mg daily Q3W × 2 cycles		Chemotherapy (physician choice)* + Radiation 60 Gy / 30 fractions ***Osimertinib HELD***		Osimertinib 80 mg daily until progression or intolerable side effects

Study Design
Primary Endpoint: Progression-Free Survival | **Secondary Endpoints:** Overall Survival, Safety, Patterns of Failure | **Statistical Design:** HR=0.64,

*Control arm chemo options: Carboplatin/Pemetrexed, Cisplatin/Pemetrexed, Cisplatin/Etoposide, or Carboplatin/Paclitaxel

Conclusions

- Outcomes for unresectable stage III NSCLC are improving
  - CRT + consolidation durvalumab yields significant survival improvements
  - Ongoing studies evaluating adding agents to durva in consolidation
  - RT improvement → NRG LU008 incorporating SBRT into unresectable disease

- Next wave of innovation may focus on induction therapies, challenging traditional paradigm of concurrent CRT
  - Most effective therapy upfront, reducing RT treatment volumes and toxicity?