NRG-LU004: Phase I study of AcceleRated vs. Conventionally fractionated radiotHerapy with durvalumab in PD-L1 high expressing nON-small cell lung cancer (**ARCHON-1**)

- **Hypothesis:** It is safe to combine radiotherapy alone (especially accelerated hypofractionated radiotherapy) with durvalumab concurrently and in maintenance in PD-L1 high locally-advanced NSCLC

Rationale Replacing Chemo With Immunotherapy

- Concurrent chemo-radiation was done at one point to improve on the terrible outcomes of radiation alone
- But, no consolidation chemo nor consolidation/maintenance targeted therapy trials in an unselected population have shown a survival benefit
- Current standard of care remains concurrent chemo-radiation followed by 1 year immunotherapy
- Concurrent chemo regimens do not achieve systemic therapy dosing and their main benefit may be to provide radiosensitization, with significant toxicities
- Ongoing studies demonstrate that immunotherapy can be a radiosensitizer but also have systemic effects, potentially even better in select patients (PD-L1 Hi)

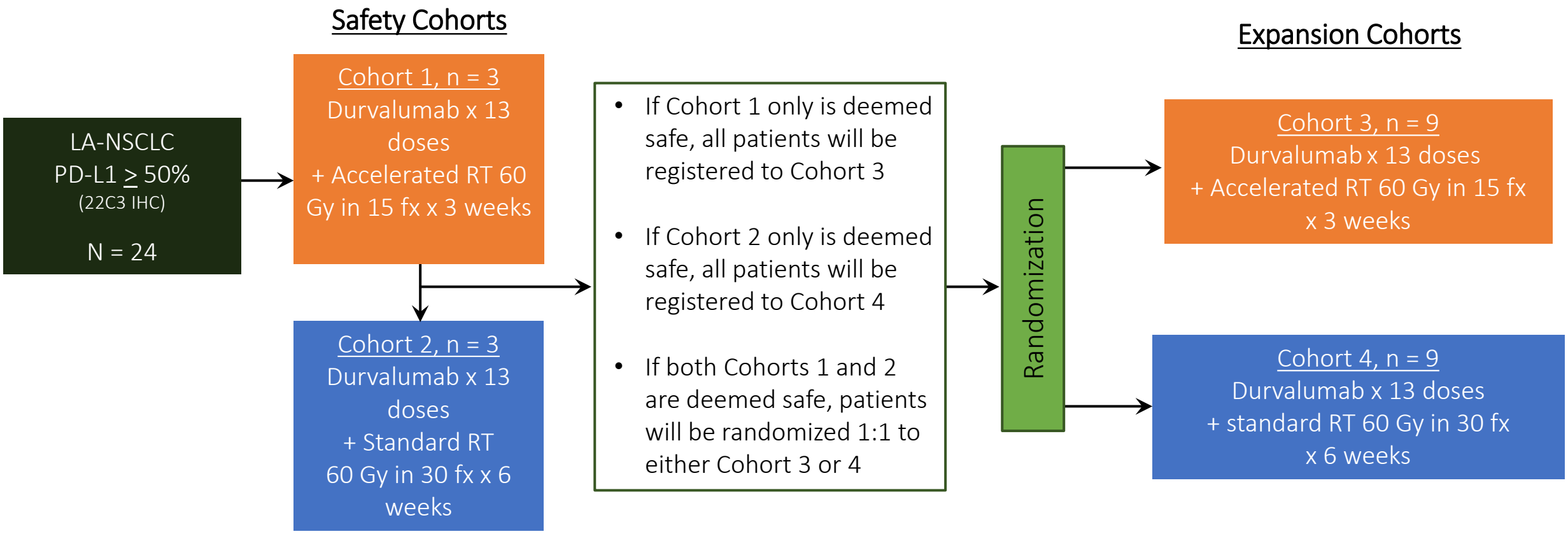
- **Replacing chemo is in-line with AZ strategic development** (confirmed with US and Global leads)

Replacing Chemotherapy With Immunotherapy Trials

Trial	NCT	Phase of Trial	N	NSCLC Stage	Type of Radiation	Systemic Therapy	Biomarker Eligibility Requirement
NRG LU004	03801902	I	24	IIA to IIIC	Accelerated hypofractionated and conventional fractionated	Durvalumab	PD-L1 IHC ≥ 50%
SPRINT	03523702	II	63	II to III	Conventional	PD-L1 IHC ≥ 50% receives Pembrolizumab while < 50% receives concurrent chemotherapy	PD-L1 IHC status
MDACC	04013542	I	20	II to III	Conventional	Nivolumab-Ipilimumab	None
Poor PS Trials							
Cleveland Medical Center	03818776	I	27	IIA to IIIC unsuitable for concurrent chemo-radiation	Proton beam (60 or 69 cGy)	Durvalumab	None
PARIS	03245177	I	25	III unsuitable for concurrent chemo-radiation	Conventional	Pembrolizumab	None

- ClinicalTrials.gov. NCT03801902; ClinicalTrials.gov. NCT03523702; ClinicalTrials.gov. NCT03818776; ClinicalTrials.gov. NCT03245177.

NRG-LU004: Phase I Trial of Accelerated or Conventionally Fractionated Radiotherapy Combined With MEDI4736 (durvalumab) in PD-L1 High Locally Advanced Non-Small Cell Lung Cancer (NSCLC) (ARCHON-1)



Primary: safety of adding durvalumab to 2 schedules of RT (60 Gy in 30 fx or 15 fx)
Secondary: feasibility, toxicities, PFS
Exploratory: tumor tissue/blood biomarkers, microbiome, TMB, PD-L1 IHC

- Durvalumab begins 2 weeks (day -14) before RT (+/- 48 hours) and is given 1500 mg IV Q4 weeks.
- ClinicalTrials.gov. NCT03801902.

Endpoints

Safety and Feasibility of durvalumab + RT in two flavors (accelerated RT vs conventional RT)

Primary endpoint: treatment related serious adverse events assessed using CTCAE v5.0

DLT observation period:

- ACRT + durva = 90 days from start of RT
- Standard RT + durva = 8 weeks from start of RT

DLT definition:

- Grade 4-5 non hematologic AEs within DLT window, significant dose delays, or permanent discontinuation of study drug if causatively related to drug

To move to phase II, treatment arm must be both “safe” and “feasible”

Safety: In the first part of study, if 0-1 of 6 evaluable pts develop any safety event after RT, then the regimen will be deemed safe, and that arm will continue to second part of study and enroll 6 additional pts

For each arm, after completing the entire study, if <=3 of the 12 evaluable pts experience a safety event, then the treatment will be considered **“safe” or “tolerable”**

Feasibility: Based on percentage of pts who received **at least 80%** of the planned dose of durvalumab during the first 8 weeks after durva. If 80% of the pts (10 of 12 per arm) receive at least 80% of the planned dose is considered to be **“feasible**

LU004 status

Activated: January 4, 2019

Suspended: January 22, 2020 (Cohort 1)

Reopened: January 22, 2020 (Cohort 2)

Suspended: April 13, 2020 (Cohort 2)

Reopened: July 16, 2020 (Cohorts 3 and 4)

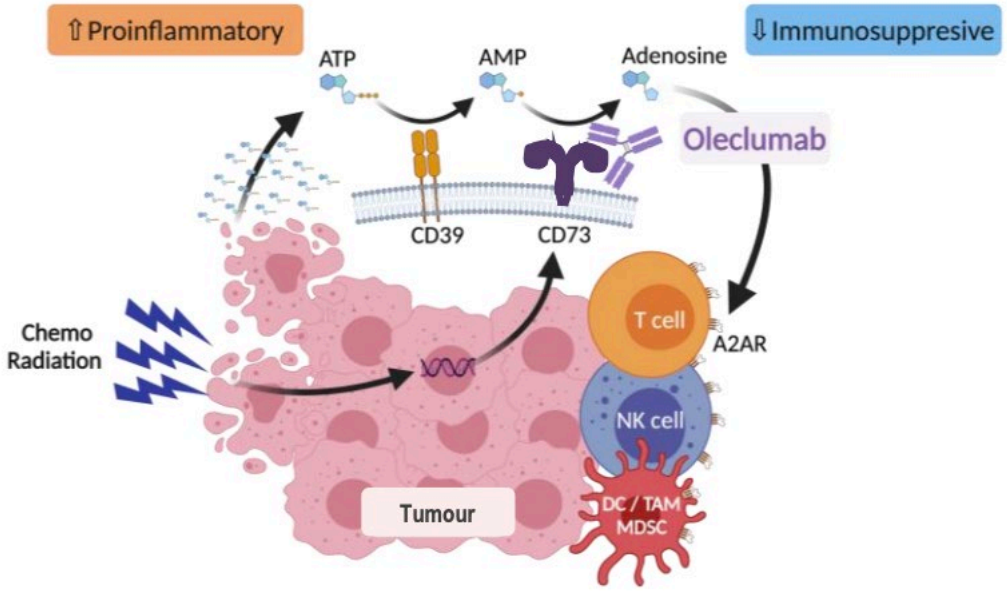
Closed: June 21, 2021 (Study)

Summary of safety of LU004

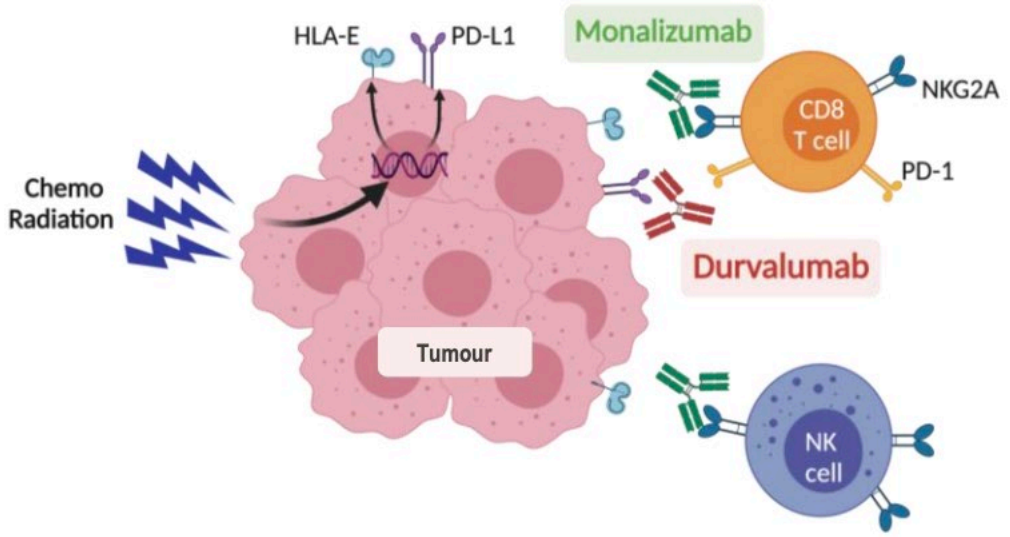
- Treatment with RT and durva was safe and well tolerated during and after treatment
- Toxicities were low (lower than what we see with chemoradiation)
- The reasons why 3 out of the 12 pts in the conventional RT + durva arm didn’t get second dose of durva had NOTHING to do with feasibility of combining durva with radiation, but patients had viral hepatitis reactivation, pneumonia and hemoptysis that were NOT related to treatment
- Efficacy results will be presented after two years of follow up

COAST (Combination Platform Study in Unresectable Stage III NSCLC; NCT03822351)

- Phase 2 study of durvalumab alone or combined with the anti-CD73 mAb oleclumab or anti-NKG2A mAb monalizumab as consolidation therapy



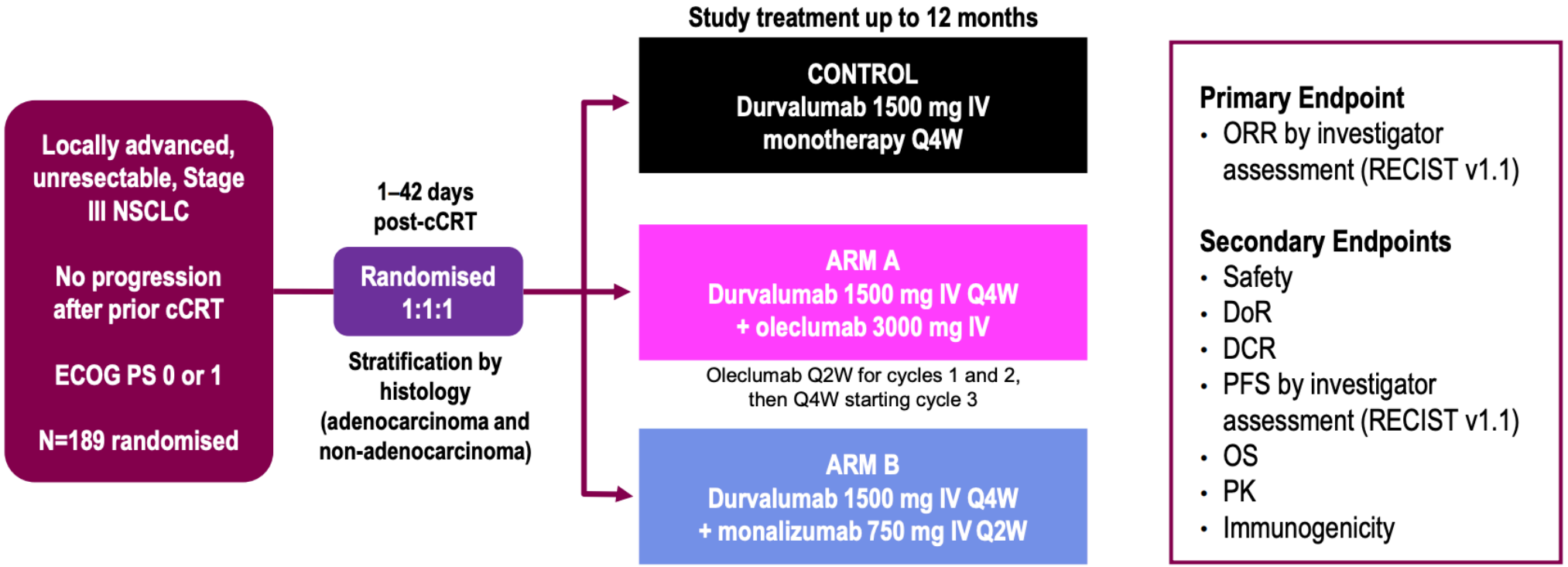
Oleclumab, anti-CD73,
Reduces extracellular adenosine production
Promotes antitumor immunity



Monalizumab blocks NKG2A
to reduce inhibition of NK and
CD8+ T cells

- mAb, monoclonal antibody.
Martinez-Marti A, et al. J Clin Oncol. 2021;39(15_suppl):LBA42.

COAST: Phase 2



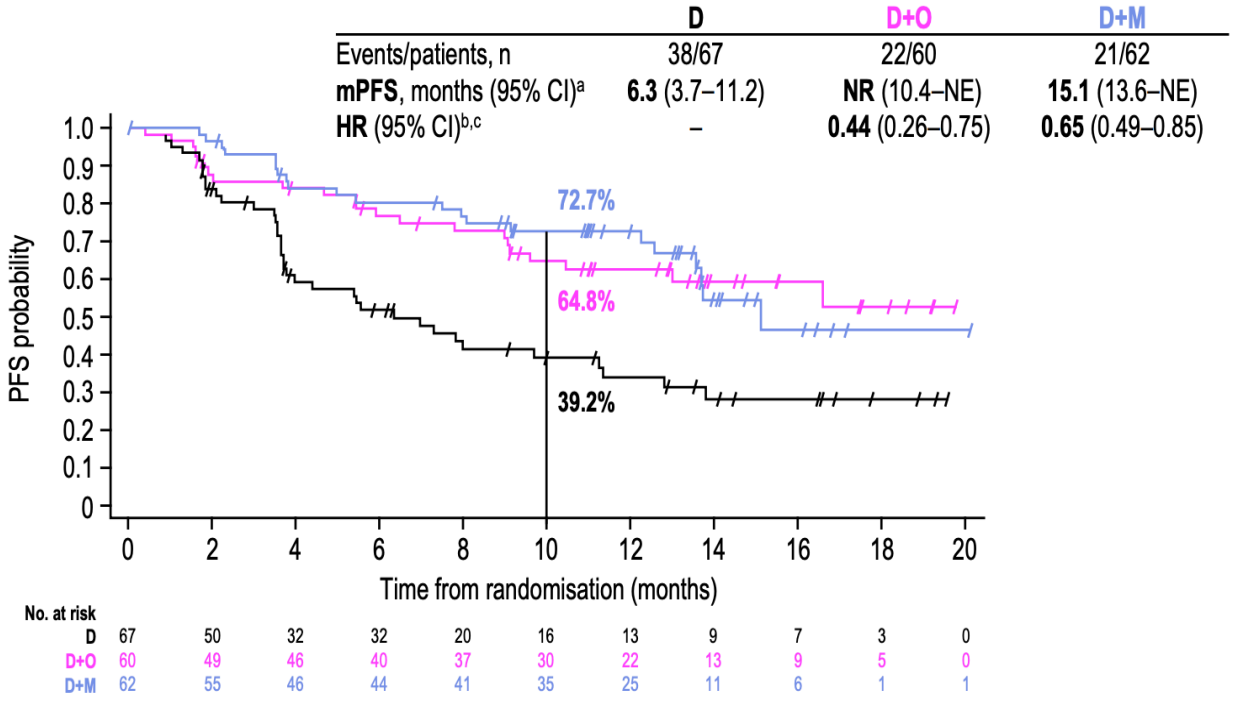
- A planned sample size of 60 patients per arm was designed to provide acceptable precision in estimating antitumor activities in an early phase setting
- Between Jan 2019 and Jul 2020, 189 patients were randomized of whom 186 received D (n = 66), D+O (n = 59) or D+M (n = 61)

- D, durvalumab; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; M, monalizumab; O, oleclumab; PK, pharmacokinetics.
Martinez-Marti A, et al J Clin Oncol. 2021;39(15_suppl):LBA42.

COAST Results Favor D+O and D+M for PFS With No Significant Increase in Toxicity

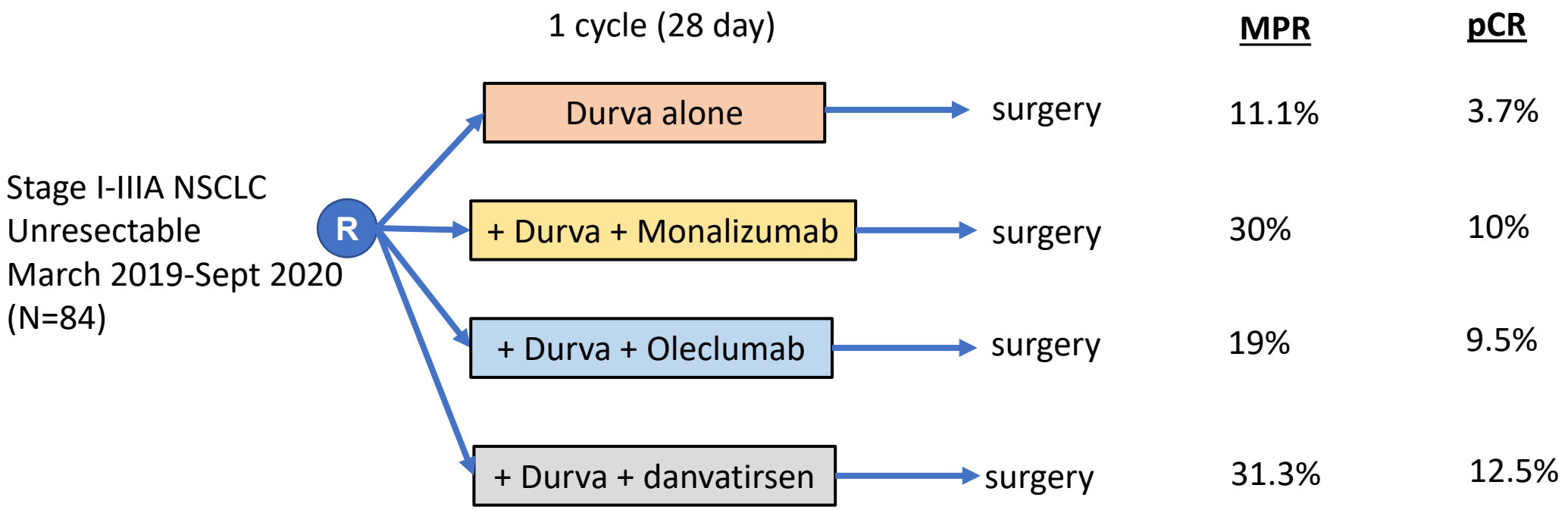
Antitumor activity	D (n = 67)	D+O (n = 60)	D+M (n = 62)
Confirmed ORR	17.9	30	35.5
DCR 16 weeks	58.2	81.7	77.4
Median DoR (months)	NR	12.9	NR
mPFS	6.3	NR	15.1
HR	-	0.44	0.65

Incidence, n (%)	D (n = 66)	D+O (n = 59)	D+M (n = 61)
Any TEAEs	65 (98.5)	57 (96.6)	61 (100)
Grade 3 TEAEs	26 (39.4)	24 (40.7)	17 (27.9)
Study drug-related AEs	49 (74.2)	46 (78.0)	50 (82.0)
Study drug-related SAEs	6 (9.1)	7 (11.9)	5 (8.2)
AEs leading to discontinuation	11 (16.7)	9 (15.3)	9 (14.8)
Deaths*,†	7 (10.6)	4 (6.8)	3 (4.9)



- *All reported deaths within 90 days post-last dose, regardless of relationship to study drug; †In total, 4 deaths were related to study drug, 2 (pneumonitis and radiation pneumonitis) in the D arm, 1 (pneumonitis) in the D+O arm, and 1 (myocardial infarction) in the D+M arm.
- Martinez-Marti A, et al J Clin Oncol. 2021;39(15_suppl):LBA42.

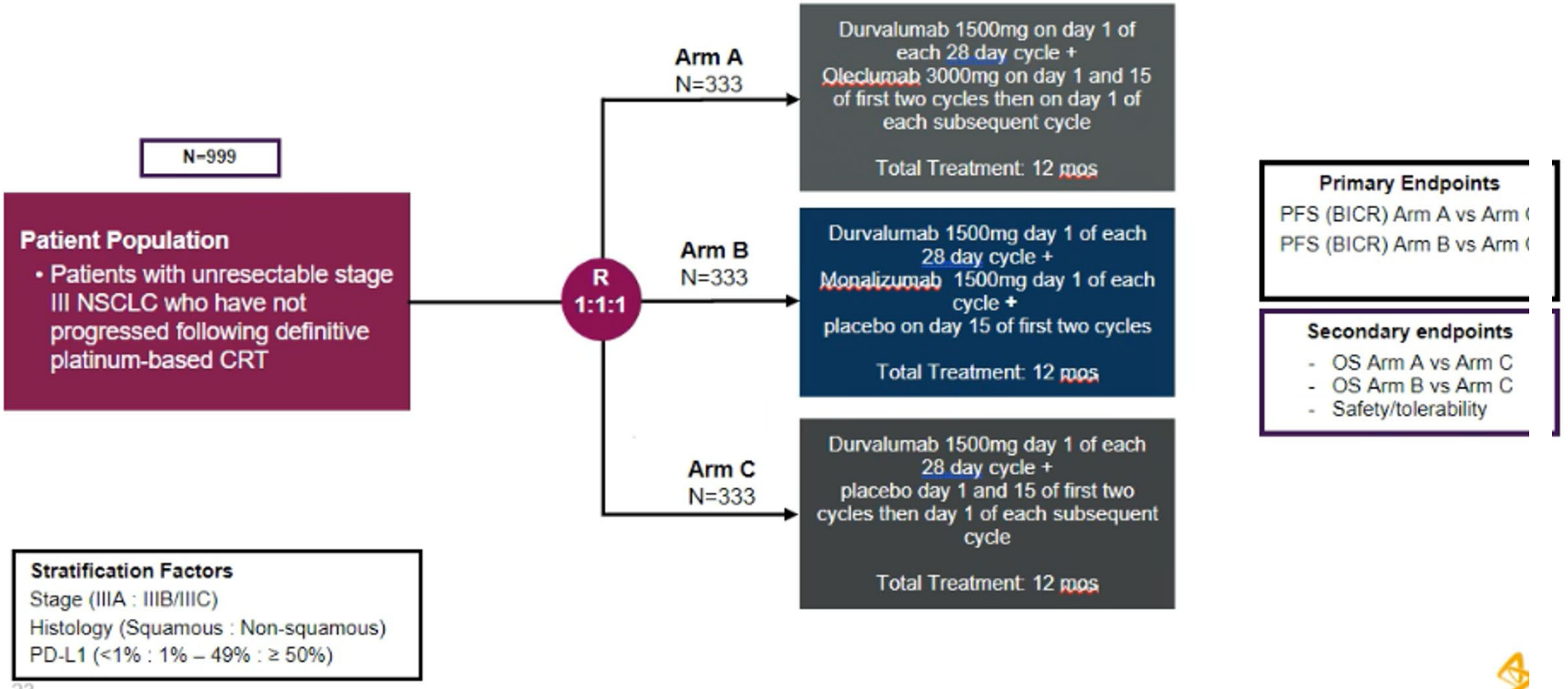
NeoCoast-1: Tina Cascone AACR 2022



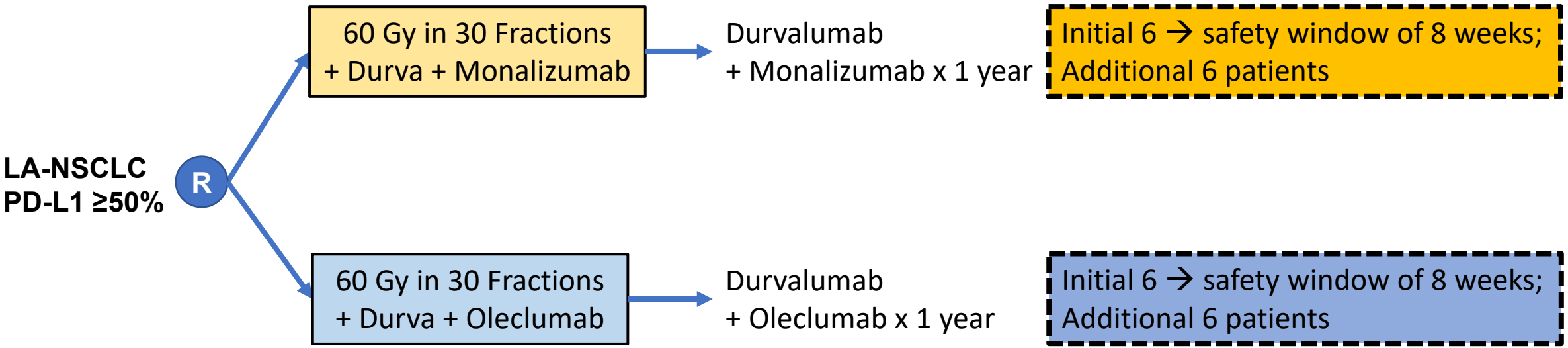
Aligning with AZ strategy in future development

PACIFIC- 9 Study design

Phase III, double-blind, multicenter international study of durvalumab + oleclumab and durvalumab + monalizumab for the treatment of patients who have not progressed following concurrent chemoradiation treatment for locally-advanced, stage III, unresectable NSCLC.



CTEP approved amendment to LU004



Planned approach

LU004 amendment w/ two added cohorts (N=24)

LA-NSCLC
PD-L1 ≥50%

R

60 Gy in 30 Fractions + Durva + Monalizumab → Durvalumab + Monalizumab x 1 year (N=12)

60 Gy in 30 Fractions + Durva + Oleclumab → Durvalumab + Oleclumab x 1 year (N=12)

Followed by proposal to be approved by NRG RSC and TMSC submission

Randomized Phase 2/3

LA-NSCLC
PD-L1 ≥50%

R

60 Gy in 30 Fractions + Chemo → Durvalumab x 1 year — Control "PACIFIC arm"

60 Gy in 30 Fractions + Durva + Oleclumab → Durvalumab + Olec x 1 year — Experimental "triple combo" Oleclumab

60 Gy in 30 Fractions + Durva + Monalizumab → Durvalumab + Mona x 1 year — Experimental "triple combo" Monalizumab