NRG Oncology-Japan Meeting 2023 Summer
呼吸器領域　試験紹介

埼玉医科大学国際医療センター
呼吸器内科
各務　博

NSCLC trials

Locally advanced NSCLC

RTOG-1308 Photon CRT **vs** Proton CRT

LU004 TRT 60Gy+Durva+Monalizumab **vs** TRT 60Gy+Durva+Oleclumab

NRG-LU008 CRT 60Gy→Durva **vs** SBRT (primary)+CRT(mediastinum)→Durva

Early stage NSCLC

PACIFIC 4/RTOG 3515 SBRT+Durva q4w x 24 m **vs** SBRT+Placebo

SWOG/NRG S1914 SBRT (Day43-64) +Atezo q3w x 8 cycles **vs** SBRT

Limited metastatic NSCLC

薬物治療 4コース→no PD and limited meta (SBRT±surgery可能)

NRG-LU002 Maintenance Cx **vs** SBRT ± surgery followed by Cx

Brain Metastases from Lung cancer

NRG-CC009	SCLC new Brain meta	HA-WBRT **vs** SRS
CCTG CE.7	NSCLC new Brain meta	
NRG BN009	brain meta after SRS recurrence	
NRG BN012	NSCLC brain meta	post-ope SRS **vs** pre-ope SRS

NSCLC以外

LD-SCLC

NRG-LU005　CRT **vs** CRT+atezolizumab　**日本 34+3 /45**

ED-SCLC

NRG-LU007　Cx+atezo → atezo **vs** Cx+atezo → ５箇所までのRT+atezo

Mesothelioma

NRG-LU006　Pleurectomy/Decorication and CDDP+Pemetrexed

Adjuvant Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) **vs** BSC

Original LU004 schema: Durva alone

REGISTRATION

- Treatment naïve, unresectable LA-NSCLC (stage II-III) or locally advanced recurrent disease from prior surgery
- PD-L1 expression using Dako 22C3 IHC ≥50%
- PS 0-1
- **No chemotherapy**
- Eligible to receive immunotherapy

INITIAL SAFETY SCHEDULES (PART 1)

Cohort 1, n=6
Durvalumab q4 weeks x 13 doses
+ ACRT 60 Gy in 15 fx x 3 weeks
(Mandatory hold of 90 days after RT)

AND

Cohort 2, n=6
Durvalumab q4 weeks x 13 doses
+ standard RT 60 Gy in 30 fx x 6 weeks
(Mandatory hold of 60 days after RT)

EXPANSION COHORTS

•If Cohort 1 only is deemed safe, all patients will be registered to Cohort 3.

•If Cohort 2 only is deemed safe, all patients will be registered to Cohort 4

•If both Cohorts 1 and 2 are deemed safe, patients will be randomized to either Cohort 3 or 4

INDIVIDUAL OR RANDOMIZED COHORTS (PART 2)

Cohort 3, n=6
MEDI4736 (durvalumab) q4 weeks x 13 doses
+ ACRT 60 Gy in 15 fx x 3 weeks

AND/OR

Cohort 4, n=6
MEDI4736 (durvalumab) q4 weeks x 13 doses
+ standard RT 60 Gy in 30 fx x 6 weeks

Completed Accrual Sept 2021

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Phase II COAST trial

Locally advanced, unresectable, Stage III NSCLC

No progression after prior cCRT

ECOG PS 0 or 1

N=189 randomised

1–42 days post-cCRT

Randomised 1:1:1

Stratification by histology (adenocarcinoma and non-adenocarcinoma)

Study treatment up to 12 months

CONTROL
Durvalumab 1500 mg IV monotherapy Q4W

ARM A
Durvalumab 1500 mg IV Q4W + oleclumab 3000 mg IV

Oleclumab Q2W for cycles 1 and 2, then Q4W starting cycle 3

ARM B
Durvalumab 1500 mg IV Q4W + monalizumab 750 mg IV Q2W

Primary Endpoint
- ORR by investigator assessment (RECIST v1.1)

Secondary Endpoints
- Safety
- DoR
- DCR
- PFS by investigator assessment (RECIST v1.1)
- OS
- PK
- Immunogenicity

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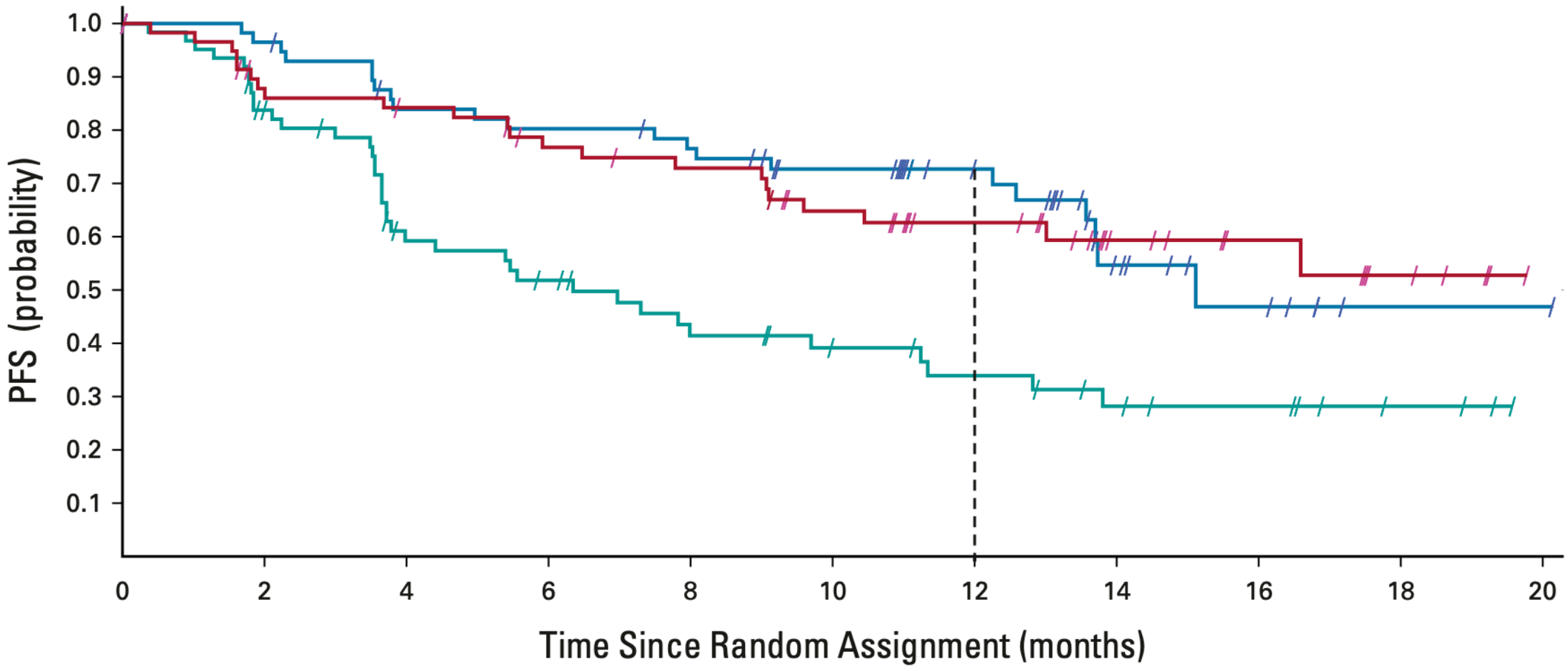
Monalizumab: 抗NKG2A抗体

NKG2Aは、主に腫瘍組織に浸潤しているnatural killer（NK）細胞やT細胞に発現し、CD94と複合体を形成することにより、腫瘍細胞が発現しているhuman leukocyte antigen-E（HLA-E）に結合します。すなわち、がん細胞は、自らが発現するHLA-EをNK細胞やT細胞のNKG2A/CD94に結合させることで、これらの免疫細胞からの攻撃を免れています。

Oleclumab: 抗CD73抗体

CD73は、免疫抑制性のアデノシンの生成を促進して腫瘍微小環境中へ放出させ、免疫活性を低下させます。CD73の阻害によりT細胞活性を刺激する可能性が示唆されています。

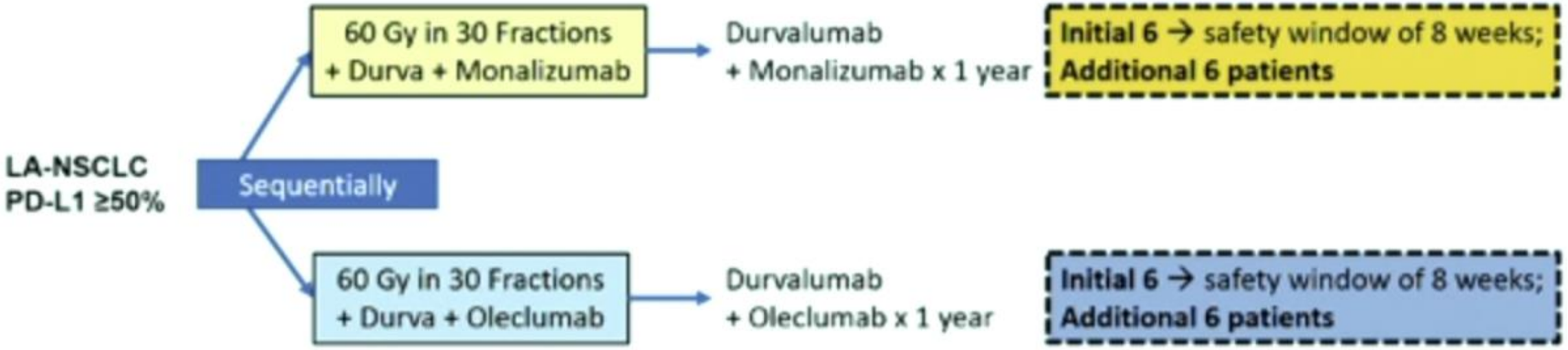
Treatment Arm	No. of Events/ Total No. of Patients (%)	Median PFS, Months (95% CI)[a]	12-Month PFS Rate, % (95% CI)	HR, % (95% CI)[b,c]
Durvalumab + monalizumab	21/62 (33.9)	15.1 (13.6 to NE)	72.7 (58.8 to 82.6)	0.42 (0.24 to 0.72)
Durvalumab + oleclumab	22/60 (36.7)	NR (10.4 to NE)	62.6 (48.1 to 74.2)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



No. at risk:

Durvalumab + monalizumab	62	55	46	44	41	35	25	11	6	1	1
Durvalumab + oleclumab	60	49	46	40	37	30	22	13	9	5	0
Durvalumab	67	50	32	27	20	16	13	9	7	3	0

Amended LU004: D+O or D+M



- CTEP approved 7/11/23
- cIRB review 7/18/23

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Endpoints

Primary endpoint: Safety of durvalumab in combination with RT alone or with RT and monalizumab or oleclumab

Secondary endpoints

- Feasibility of durvalumab in combination with RT alone or with RT and monalizumab or oleclumab
- Adverse events, as measured by CTCAE v 5.0
- Progression free survival, according to RECIST guidelines

Exploratory endpoints

- Progression free survival, according to irRC guidelines
- Immune parameter changes during treatment

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LU008 - Phase III Prospective Randomized Trial of Primary Lung Tumor Stereotactic Body Radiation Therapy Followed by Concurrent Mediastinal Chemoradiation for Locally-Advanced Non-Small Cell Lung Cancer

Charles B. Simone, II, MD

July 22, 2023

@NRGOnc NRG Oncology

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Hypotheses

- As opposed to delivering SBRT as a boost, replacing conventionally fractionated radiotherapy with SBRT to the primary tumor followed by concurrent chemoradiation to the mediastinum will:
  - Be well-tolerated and associated with lower rates of radiation pneumonitis due to increase conformity with SBRT and less lung irradiate between the primary tumor and the mediastinum
  - Improve local control that will drive an improvement in progression-free survival and overall survival

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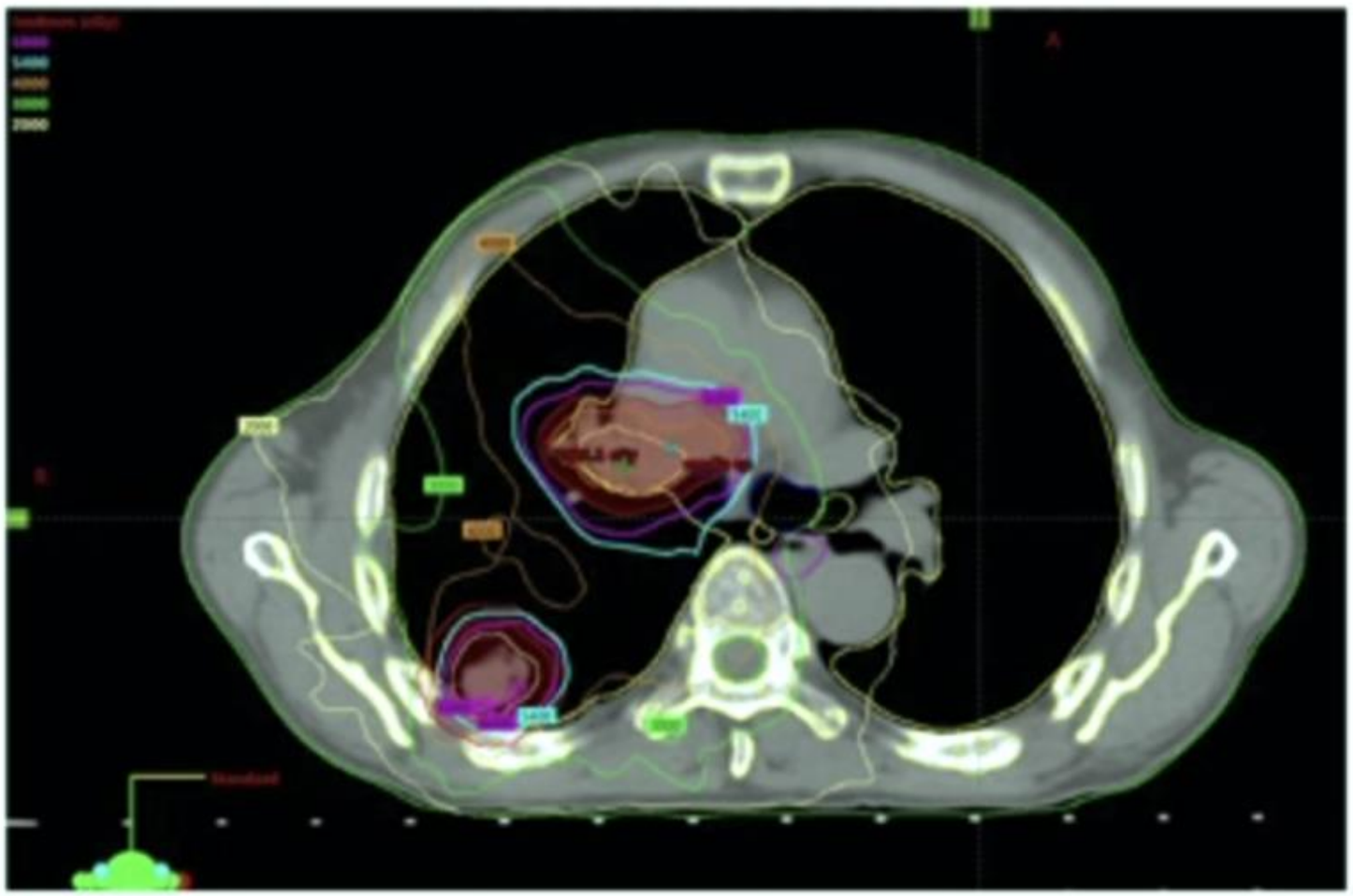
Representative Case Example



Total volume of lung receiving 40 Gy= 332 cc (compared to 590 cc, 44% reduction)
Total volume of lung receiving 20 Gy=922 cc (compared to1300 cc, 29% reduction)
Total volume of lung receiving 10 Gy=2168 cc (compared to 2360, 8% reduction)

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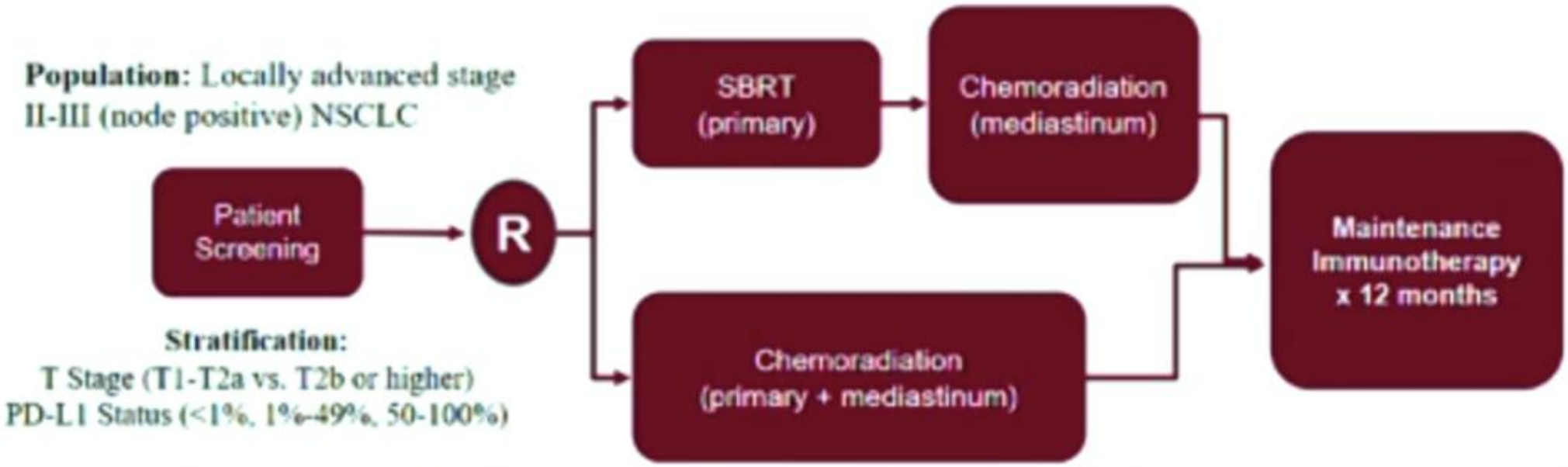
LU008 Schema: Phase III



- Control arm: chemoradiation to the primary and mediastinal disease (60 Gy/2 Gy) → immunotherapy maintenance x 12 months
- 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 (BED_{10} of 151.2 Gy) [peripheral]
    - 4 fractions to 50 Gy (BED_{10} of 112.5 Gy) [peripheral]
    - 5 fractions to 50 Gy (BED_{10} of 100 Gy) [peripheral or central]
  - Radiation to involved hilar/mediastinal lymph nodes: 2 Gy x 30 fx to 60 Gy, IMRT or proton therapy
  - Concurrent chemotherapy: carboplatin + paclitaxel, cisplatin + etoposide, cisplatin + pemetrexed, or carboplatin + pemetrexed
  - Maintenance immunotherapy: durvalumab x 12 months [if durvalumab is NOT given, carbo/paclitaxel pts receive 2 cycles of consolidation]

Highly Pragmatic Trial

- Most pragmatic thoracic NCTN trial
  - No lab cutoffs (discretion of med onc)
  - No diagnosis, CT chest, MRI brain, lab, or PFT time windows
    - PET within 60 days
  - Allows ECOG 2
  - Allows EGFR/ALK/ROS1 patients (do not need to administer durva)
  - Allows other malignancies if not thought to interfere with safety/efficacy analysis
  - Allows protons or photons
- RTOG 1308 (Q1 2024) and EA5181 (Q4 2023) are both approaching accrual completion, no other competing large locally advanced NSCLC trials across the entire NTCN
- Please open and accrue!!

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