IASLC 2023 World Conference on Lung Cancer

SEPTEMBER 9-12, 2023 | SINGAPORE

# Best of WCLC 2023 Session I: Radiation in early-stage & metastatic NSCLC

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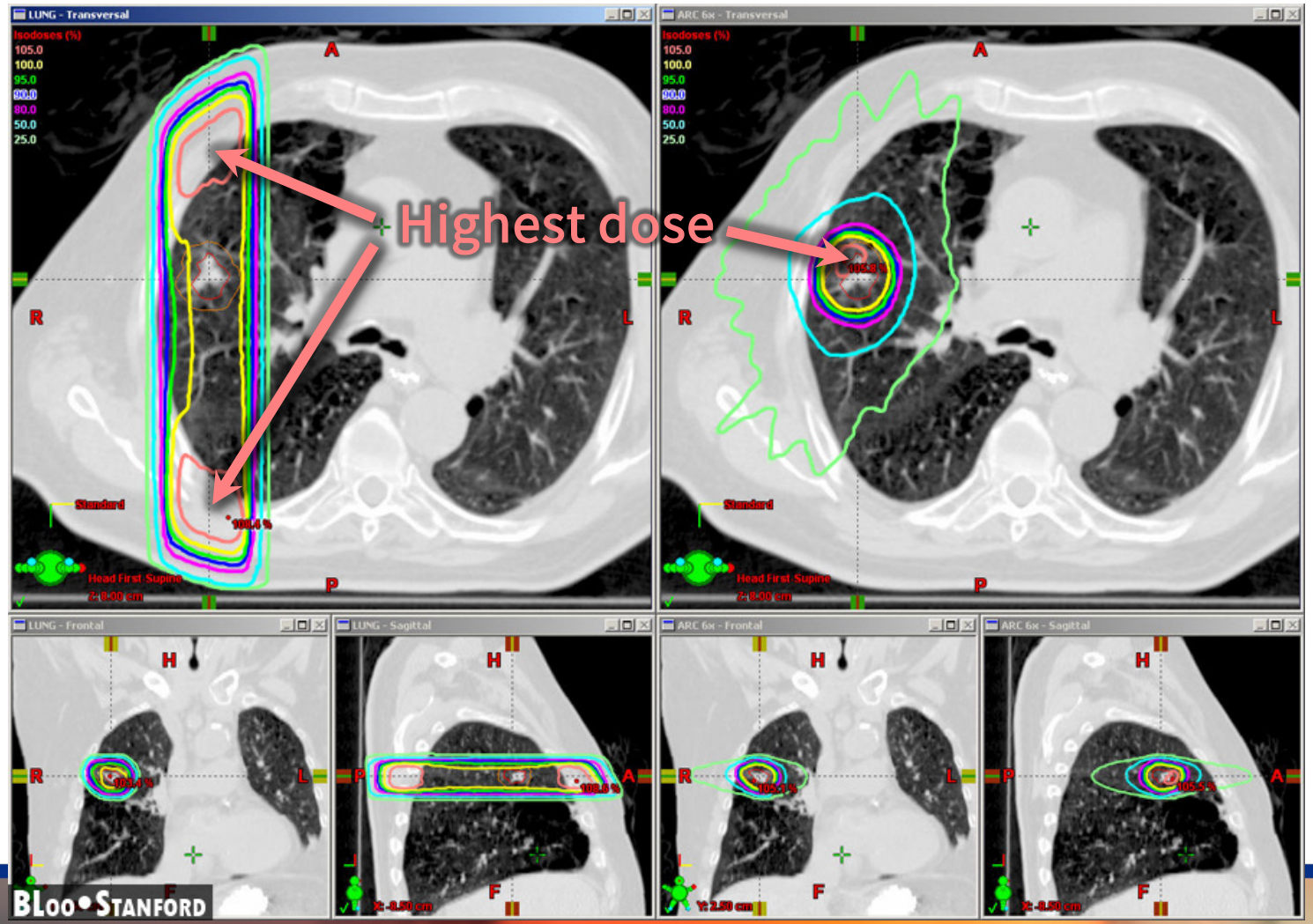
Stanford University School of Medicine

@BLoo_LT_SABR

San Francisco, Sept 30, 2023

# Conventional *vs.* SABR dose distribution



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# Stereotactic Ablative Radiotherapy With or Without Immunotherapy for Early-Stage or Isolated Lung Parenchymal Recurrent Node-Negative NSCLC: An Open-Label, Randomized, Phase 2 Trial

## I-SABR Study

**Chang JY, Lin SH, Dong DL, Liao ZX, Gandhi S, Gay CM, Zhang JJ, Chun SG, Elamin YY, Frank FV, Blumenschein G, Cascone T, Le XN, Pozadzides JV, Tsao A, Verma V, Welsh J, Chen AB, Altan M, Mehran RJ, Vaporciyan AA, Swisher SG, Balter PA, Fujimoto J, Wistuba II, Feng L, Lee JJ and Heymach JV**

**The University of Texas MD Anderson Cancer Center**
**Houston, TX 77025**
**USA**

## Inclusion criteria:

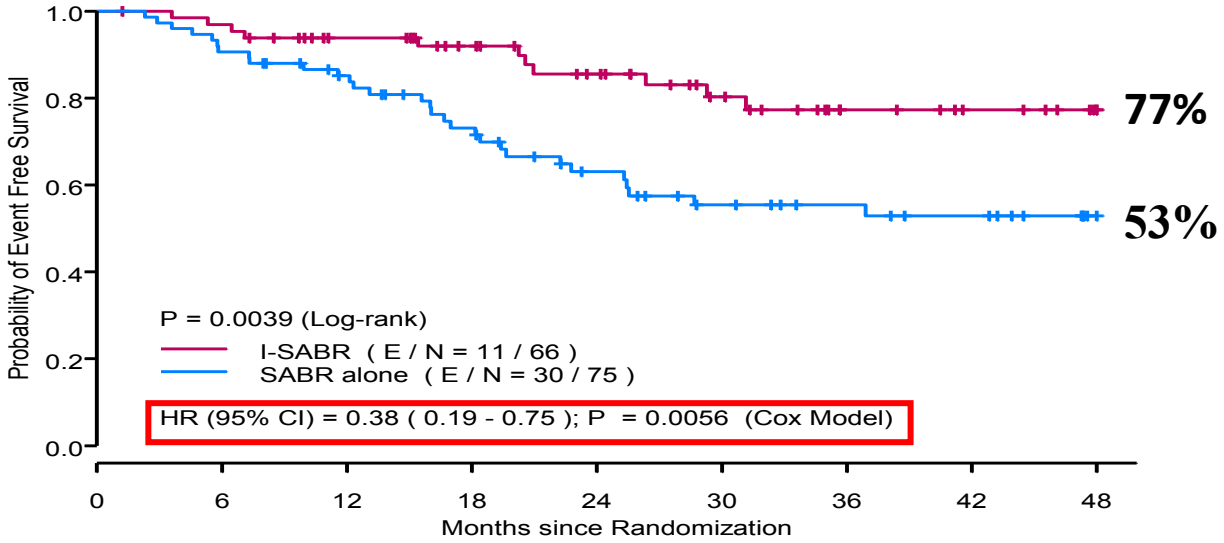
- >18 y/o, ECOG 0-2
- Biopsy confirmed NSCLC
- IA-IB (tumor size ≤4 cm, N0M0), stage IIA (≤5 cm, N0M0), or stage IIB (>5 cm & ≤7 cm, N0M0), including multiple primary tumors
- Isolated lung-parenchymal recurrent or persistent NSCLC suitable for SABR.

## Exclusion criteria:

- Tumor size >7 cm; Ultra-central lesion within 5 mm of any critical structures
- Not suitable for SABR
- Ongoing pneumonia
- Lymph node involvement or distant metastasis
- Previous immunotherapy or inability to tolerate immunotherapy.

# Primary endpoint: EFS per protocol and ITT

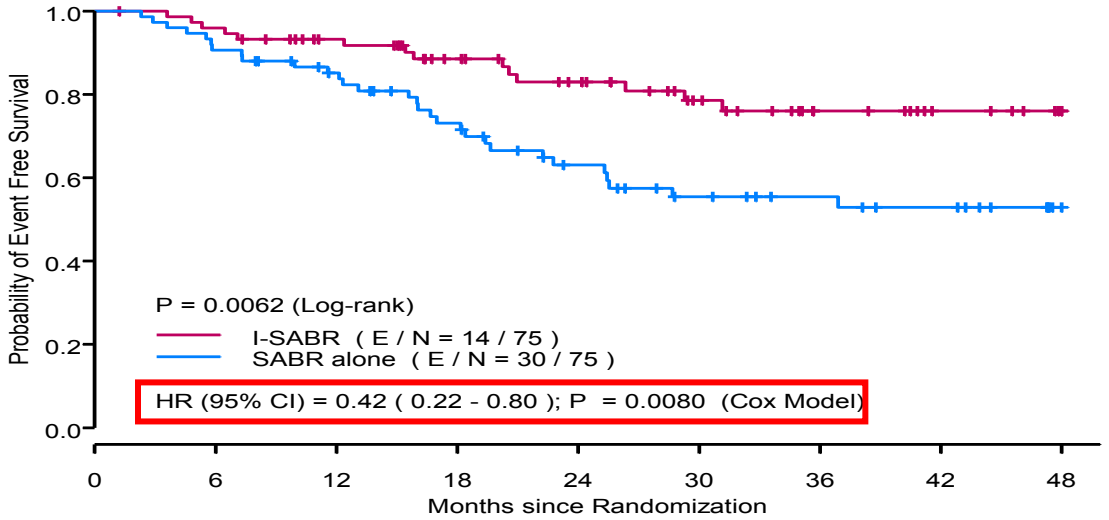
## Per protocol




No. at Risk (No. of Event)

| | | | | | |
|---|---|---|---|---|---|
| I-SABR | 66 ( 0 ) | 54 ( 4 ) | 38 ( 4 ) | 18 ( 3 ) | 7 ( 0 ) |
| SABR | 75 ( 0 ) | 59 ( 11 ) | 34 ( 14 ) | 22 ( 4 ) | 11 ( 1 ) |

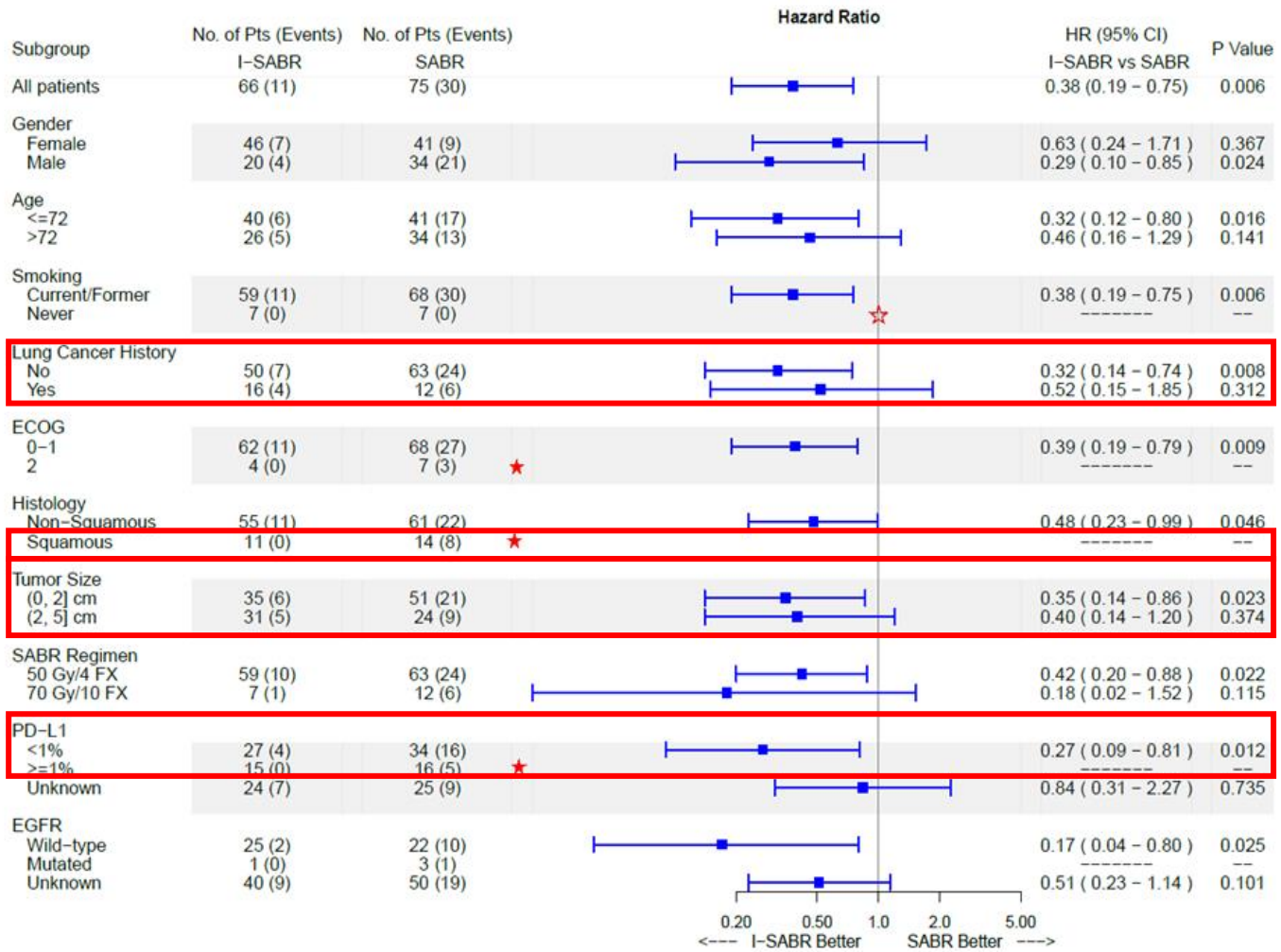
## Per ITT




No. at Risk (No. of Event)

| | | | | | |
|---|---|---|---|---|---|
| I-SABR | 75 ( 0 ) | 62 ( 5 ) | 43 ( 6 ) | 22 ( 3 ) | 9 ( 0 ) |
| SABR | 75 ( 0 ) | 59 ( 11 ) | 34 ( 14 ) | 22 ( 4 ) | 11 ( 1 ) |

# Subgroup analysis



## Toxicity

| | Grade 2 | | Grade 3 | |
|---|---|---|---|---|
| | SABR | I-SABR | SABR | I-SABR |
| Acute kidney injury | .. | .. | .. | 1 |
| Adrenal insufficiency | .. | .. | .. | 1 |
| Anorexia | 1 | .. | .. | .. |
| Arthralgia | .. | 2 | .. | .. |
| Blurred vision | .. | 1 | .. | .. |
| Conjunctivitis | .. | .. | .. | 1 |
| Diarrhoea | .. | 1 | .. | .. |
| Dyspnoea | .. | .. | .. | 1 |
| Fatigue | 1 | 7 | .. | 2 |
| Hyperthyroidism | .. | 1 | .. | 1 |
| Hypoxia | .. | .. | .. | 1 |
| Hepatitis (acute) | .. | .. | .. | 1 |
| Myalgia | .. | 1 | .. | .. |
| Oral mucositis | .. | 1 | .. | .. |
| Oral dysesthesia | .. | 1 | .. | .. |
| Pneumonia (infectious) | .. | .. | .. | 1 |
| Pneumonitis | 1 | 2 | .. | .. |
| Pruritus | .. | 2 | .. | .. |
| Rash | .. | 2 | .. | 1 |
| Xeroophthalmia | .. | 1 | .. | .. |
| Xerostomia | .. | 1 | .. | .. |

Data are number of events. No grade 4–5 adverse events occurred.
I-SABR=stereotactic ablative radiotherapy with immunotherapy.
SABR=stereotactic ablative radiotherapy.

*Table 2:* **Grade 2 or higher adverse events possibly, probably, or definitively related to therapy**

## Pattern of failure

| Event | I-SABR (n=66) | SABR (n=75) |
|---|---|---|
| Local Failure Only | 0 (0%) | 7 (9.3%) |
| Regional Failure Only | 4 (6.1%) | 2 (2.7%) |
| Distant Metastasis Only | 2 (3.0%) | 3 (4.0%) |
| Local + Regional Failure | 0 (0%) | 0 (0%) |
| Local + Distant Failure | 0 (0%) | 2 (2.7%) |
| Local + Regional + Distant Failure | 0 (0%) | 1 (1.3%) |
| Regional + Distant Failure | 0 (0%) | 5 (6.7%) |
| Second Primary Lung Cancer | 2 (3.0%) | 6 (8.0%) |
| Any Local Failure | 0 (0%) | 10 (13.3%) |
| Any Regional Failure | 4 (6.1%) | 8 (10.7%) |
| Any Distant Failure | 2 (3.0%) | 12 (16.0%) |
| Any Death | 4 (6.1%) | 9 (12.0%) |
| Any Recurrence and/or Death Event | 8 (12.1%) | 27 (36.0%) |
| No Relapse or Death | 58 (87.9%) | 48 (64.0%) |

**RT in-field failure**
**I-SABR: 0%**
**SABR: 1%**

# Conclusions:

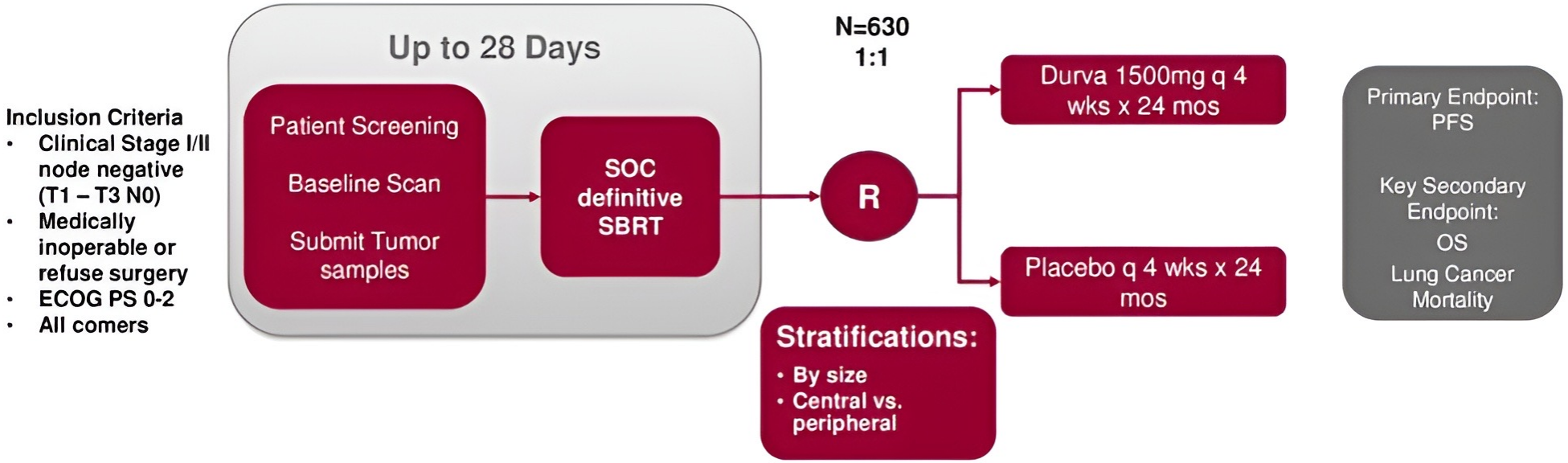
**1. Compared with SABR alone, I-SABR significantly improved event-free survival at 4 years in people with early-stage treatment-naive or lung parenchymal recurrent node-negative NSCLC, with tolerable toxicity.**

**2. I-SABR could be a treatment option in these participants. Phase III randomized study is needed to establish the SOC.**

THE LANCET

•PMID: 37478883
• DOI: 10.1016/S0140-6736(23)01384-3

# PACIFIC 4 / RTOG 3515 Schema




Additional Key points

- NSCLC proven by histology / cytology
- Tissue submission mandated – core preferred but will accept FNA samples for translational analysis
- SOC SBRT taking place during screening. SBRT planning can occur before study enrollment
- Randomization within **7 days of completion of SOC SBRT**

# Stanford individualized SABR (iSABR)

## Phase II tumor volume/location/histology adapted dosing

**A** Small tumor (≤10 $cm^3$)

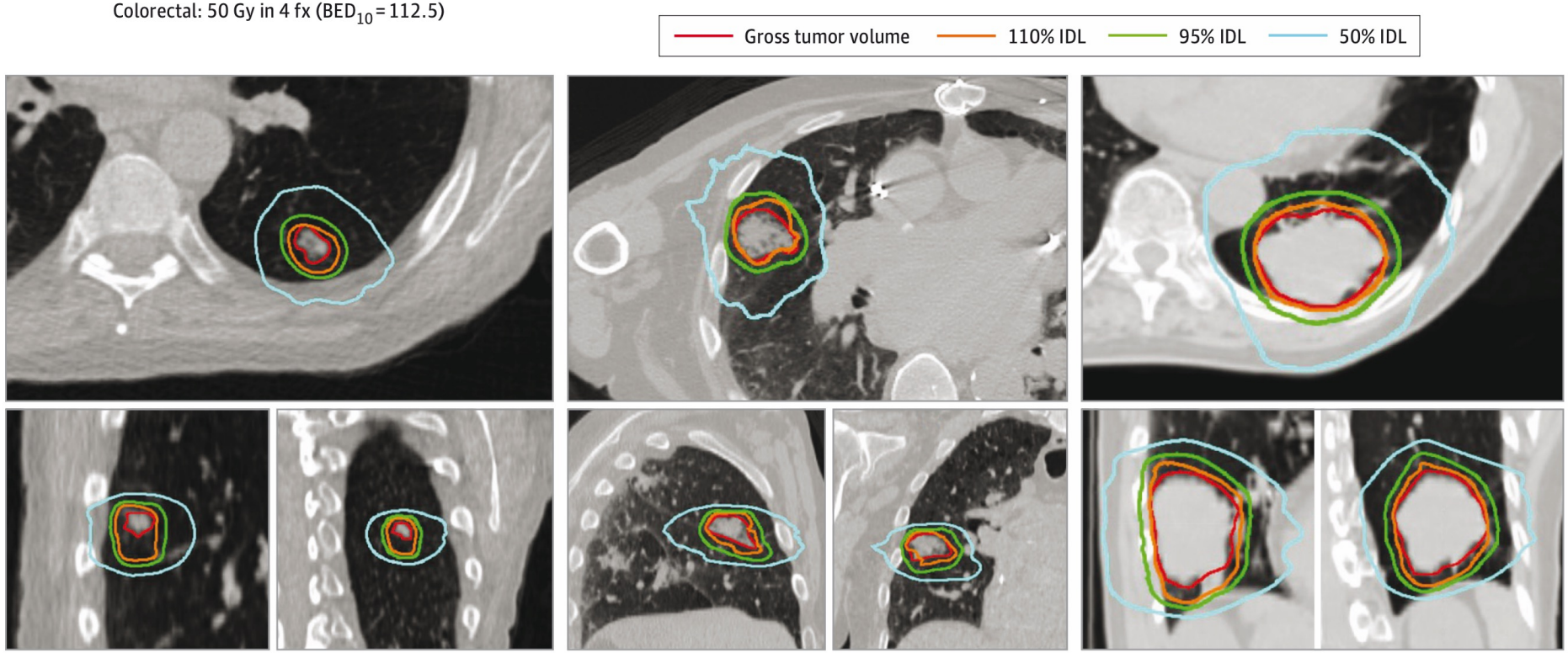
Peripheral: 25 Gy in 1 fx ($BED_{10}$=87.5)
Central: 40 Gy in 4 fx ($BED_{10}$=80)
Colorectal: 50 Gy in 4 fx ($BED_{10}$=112.5)

**B** Medium tumor (>10 $cm^3$ and ≤30 $cm^3$)

Peripheral: 50 Gy in 4 fx ($BED_{10}$=112.5)
Central: 50 Gy in 4 fx ($BED_{10}$=112.5)

**C** Large tumor (>30 $cm^3$)

Peripheral: 54 Gy in 3 fx ($BED_{10}$=151.2)
Central: 60 Gy in 8 fx ($BED_{10}$=105)




N = 217 pts, 285 tumors

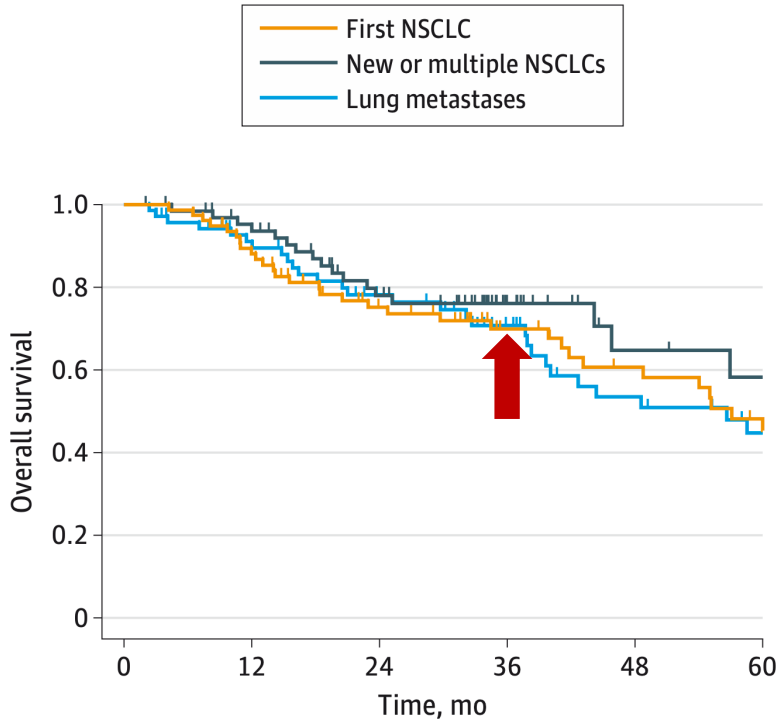
Gensheimer *JAMA Oncol* 2023

# Stanford individualized SABR (iSABR)

## Phase II tumor volume/location/histology adapted dosing

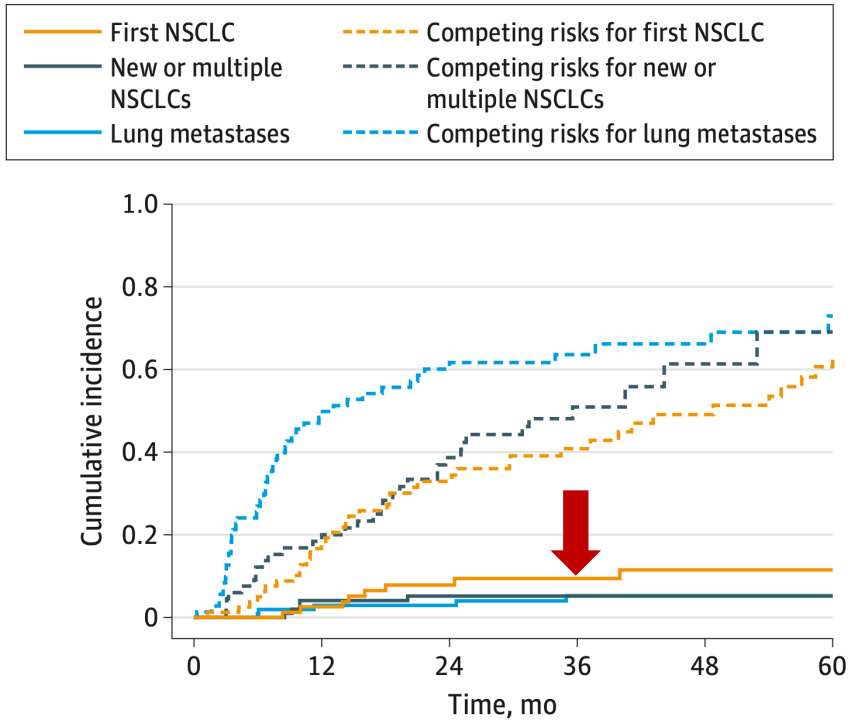
**N =**
**217 pts,**
**285 tumors**

**A** Overall survival, per patient




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| First NSCLC | 79 | 66 | 48 | 33 | 26 | 18 |
| New or multiple NSCLCs | 67 | 60 | 44 | 24 | 12 | 10 |
| Lung metastases | 71 | 59 | 45 | 34 | 22 | 15 |

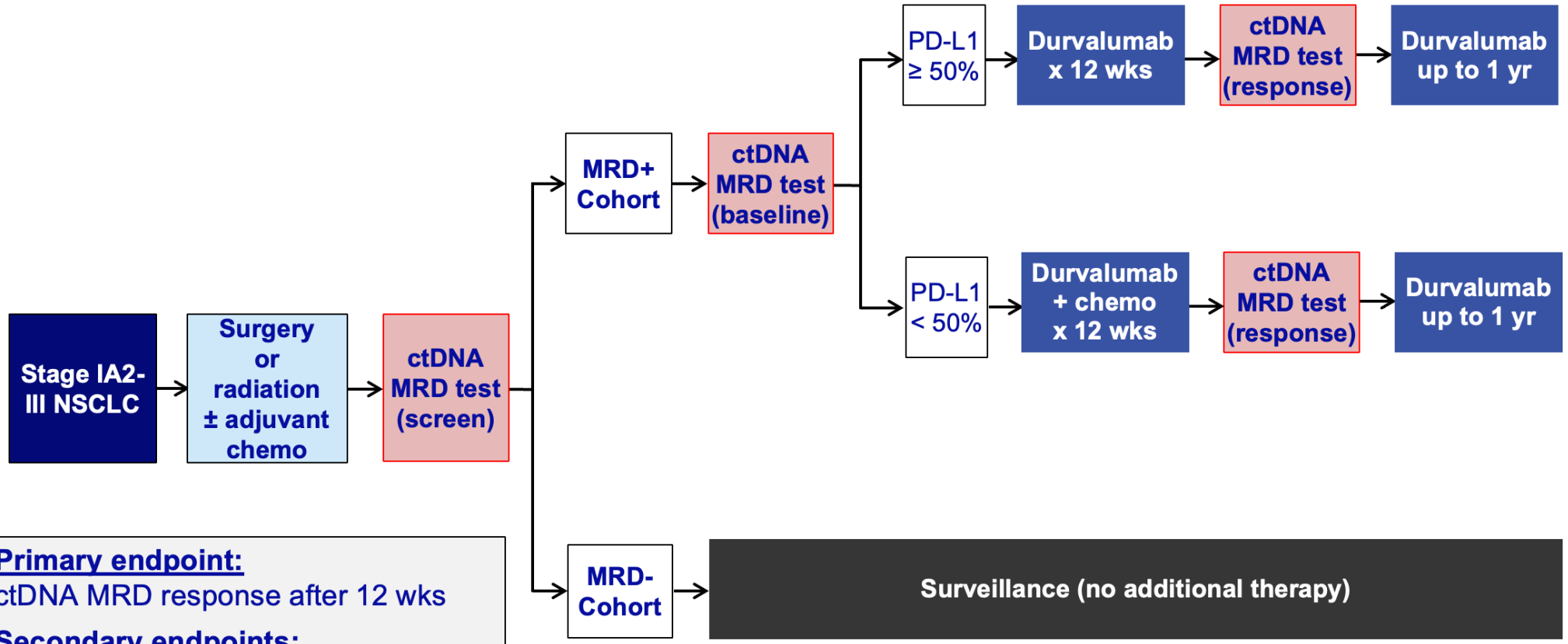
**C** Treated-tumor recurrence, per tumor




| No. at risk | | | | | | |
|---|---|---|---|---|---|---|
| First NSCLC | 79 | 61 | 38 | 25 | 19 | 14 |
| New or multiple NSCLCs | 103 | 77 | 55 | 24 | 13 | 11 |
| Lung metastases | 103 | 69 | 46 | 27 | 15 | 13 |

Gensheimer *JAMA Oncol* 2023

# Adjuvant ctDNA-Adapted Personalized Treatment in Early Stage NSCLC (ADAPT-E) Trial




**Primary endpoint:**
ctDNA MRD response after 12 wks

**Secondary endpoints:**
- Disease-free survival (DFS)
- Overall survival (OS)
- Safety

ctDNA MRD assay: Roche AVENIO Surveillance Panel



PIs: J. Neal & M. Diehn (NCT04585477)

# BRIGHTSTAR

## Local Consolidative Therapy and Brigatinib in Treating Patients With Stage IV or Recurrent Non-small Cell Lung Cancer

TKI-naïve ALK+ advanced NSCLC

**Key inclusion criteria:**

- ≥ 18 years
- Documented ALK rearrangement (tissue or liquid biopsy)
- TKI naïve or first-line Brigatinib within ≤ 8 weeks of enrollment
- At least one site of residual disease for LCT
- ECOG PS ≤2

Enrollment Window
**Brigatinib** x8 weeks

CT/PET
Brain MRI

non-PD

**Brigatinib**
Until PD

**Local Consolidative Therapy**

- If < 3 active sites of disease then LCT to all sites
- If > 3 active sites of disease then LCT to sites at physician discretion

- Brigatinib until disease progression or unacceptable toxicity.
- Primary objective is safety and tolerability of Brigatinib with LCT.
- Secondary objectives include PFS, OS and TTP on non-LCT lesions. PFS calculated from brigatinib initiation.
- Exploratory objectives include utility of pre-treatment, pre-LCT and post-LCT liquid biopsy assessment as a prognostic and predictive biomarker

| LCT modality | N (%) |
|---|---|
| Radiation | 27 (79%) |
| Surgery | 3 (9%) |
| Surgery and radiation | 2 (6%) |
| No LCT amenable residual disease | 1 (3%) |
| Withdrew consent | 1 (3%) |
| **Extent of LCT** | **N (%)** |
| Complete | 20 (62%) |
| Partial | 12 (48%) |

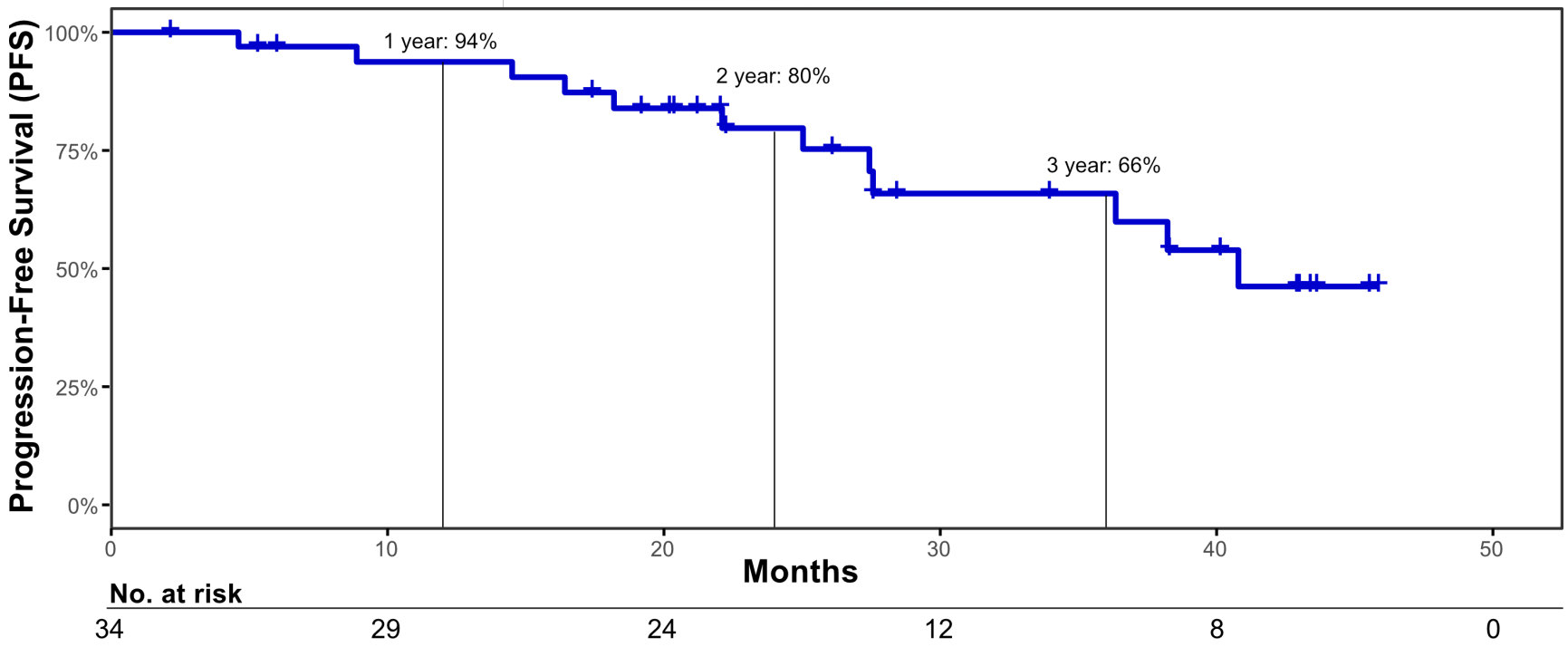
32/34 patients successfully completed planned LCT

| Number of metastases at baseline | |
|---|---|
| ≤3 | 6 (18%) |
| >3 | 28 (82%) |

## Grade (G) ≥3 LCT related adverse events

| Adverse event | N |
|---|---|
| G4 bronchopulmonary hemorrhage | 1 |
| G3 anemia | 1 |
| G3 pneumonitis | 1 |
| G3 esophagitis | 1 |
| G3 vomiting | 1 |
| G3 nausea | 1 |

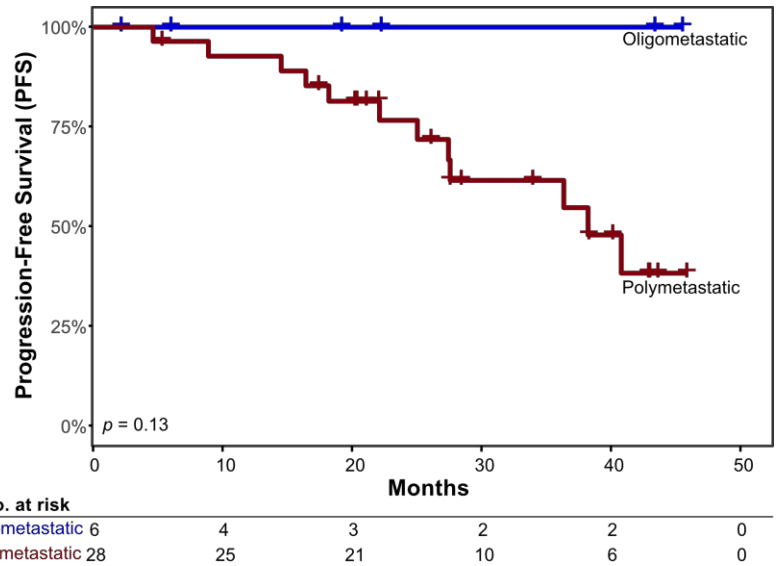
There were no grade 5 events related to LCT



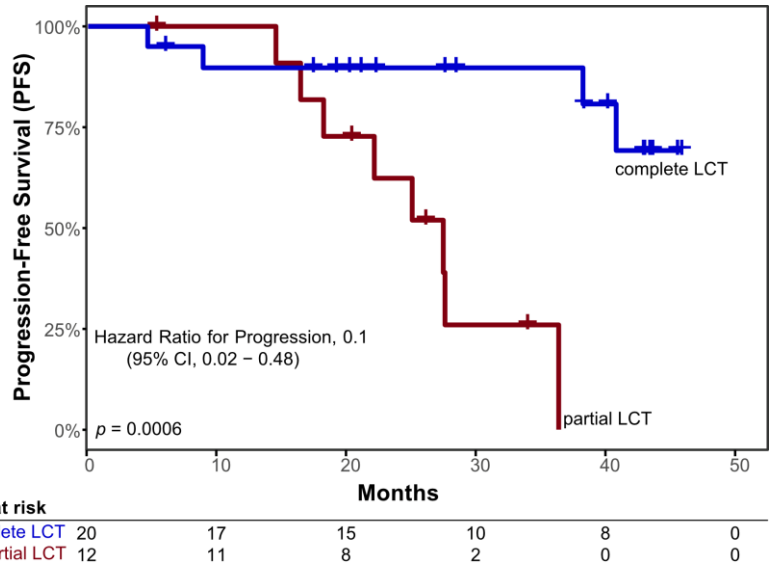

| PFS Rate | BrightStar | ALTA 1L* (first line single agent brigatinib) |
|---|---|---|
| **1-yr** | 94% | 80% |
| **2-yr** | 76% | 56% |
| **3-yr** | 66% | 47% |

# Predictors of outcome

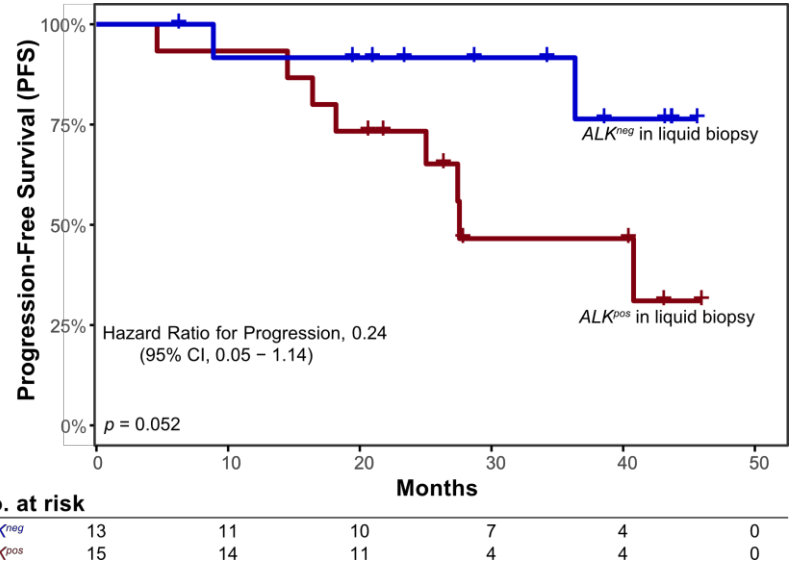
## No of mets at baseline




## Extent of LCT




## ALK status in plasma at baseline




LCT to all sites of residual disease and negative ALK status in plasma at baseline were associated with better outcomes

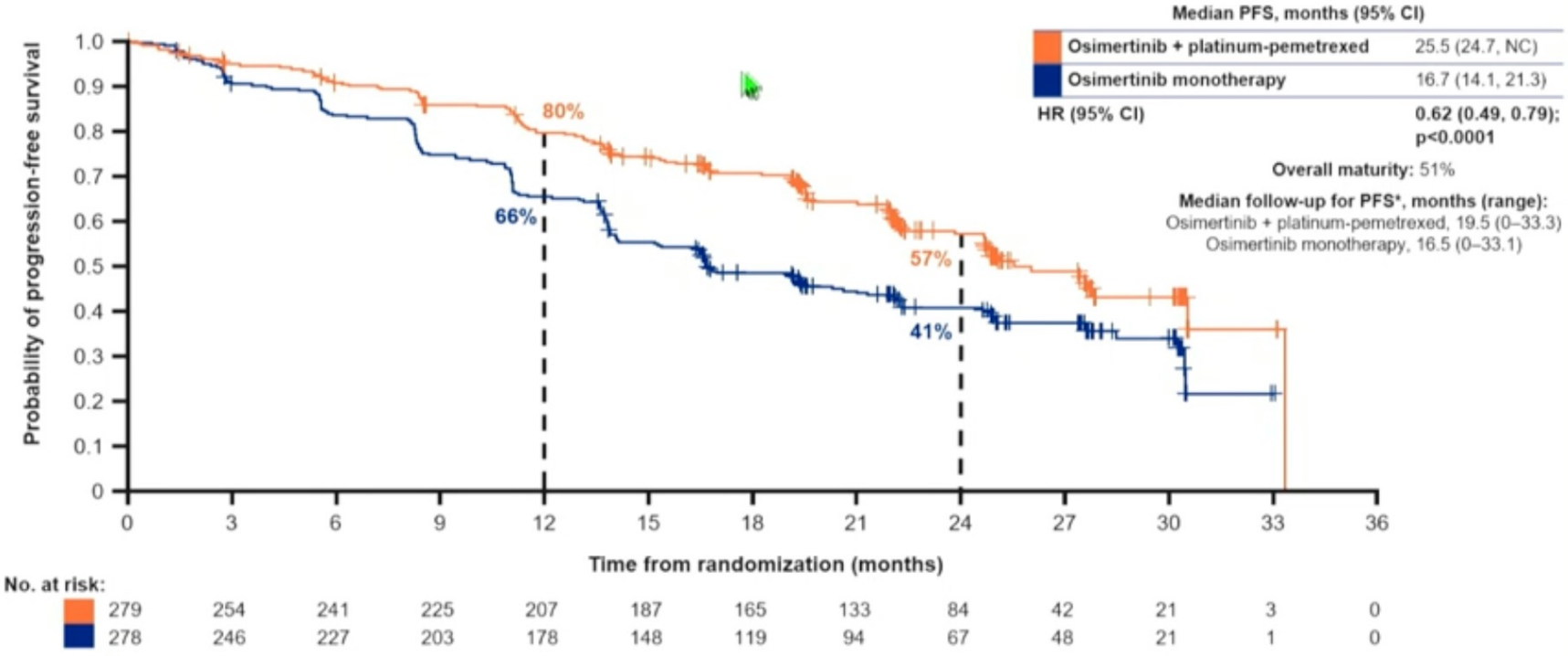
# Conclusion

- Brigatinib with LCT is safe in patients with ALK-rearranged advanced NSCLC.
- Brigatinib with LCT yielded promising outcomes when compared to historical outcomes: 3-year PFS rate was 66% in Brightstar compared to 47% in the brigatinib arm of ALTA-1L.
- Complete LCT, baseline ALK plasma negativity, and lower post-induction volume, but not number of metastases at baseline (oligo vs poly) were associated with increased benefit for LCT.
- A randomized trial (BrightStar-2) is planned to compare two intensifications strategies, LCT and chemotherapy, with brigatinib alone as first line therapy for ALK+ NSCLC.

# FLAURA2 Phase III osi ± chemo

## Progression-free survival per investigator

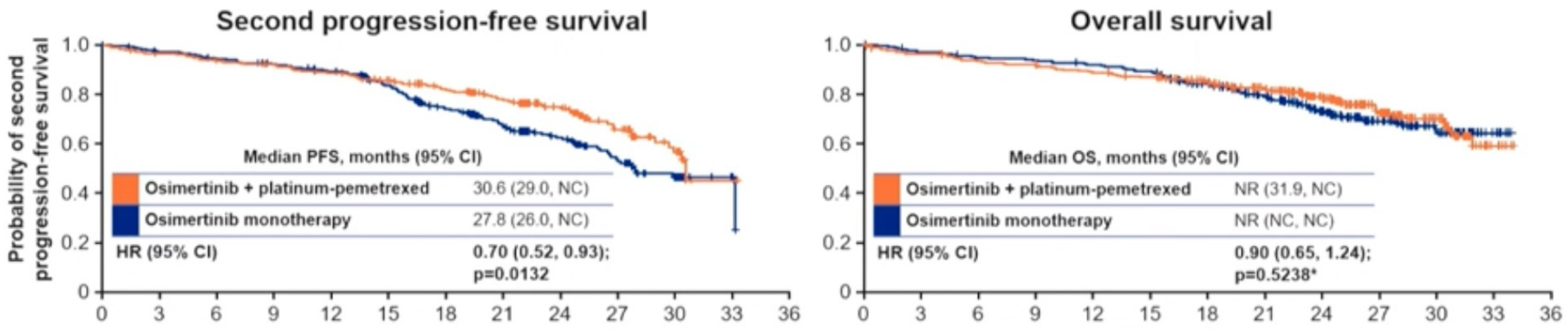
- Median PFS was improved by ~8.8 months with osimertinib plus platinum-pemetrexed vs osimertinib monotherapy




Data cut-off: 03 April 2023
*In all patients
CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

# FLAURA2 Phase III osi ± chemo

## PFS2 and interim analysis of OS




No. at risk:

| | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 279 | 263 | 254 | 247 | 236 | 220 | 194 | 158 | 107 | 54 | 26 | 3 | 0 | 279 | 267 | 258 | 253 | 244 | 237 | 219 | 191 | 139 | 84 | 46 | 7 | 0 |
| | 278 | 265 | 255 | 246 | 232 | 206 | 166 | 130 | 90 | 58 | 26 | 3 | 0 | 278 | 267 | 260 | 257 | 251 | 244 | 214 | 185 | 133 | 85 | 46 | 10 | 0 |

- PFS2 and OS were immature at this interim analysis (34% and 27% data maturity, respectively)
- At DCO, 57 / 123 patients (46%) in the osimertinib plus platinum-pemetrexed arm and 91 / 151 patients (60%) in the osimertinib monotherapy arm received any subsequent anti-cancer treatment†
  - In both arms, cytotoxic chemotherapy was the most common subsequent anti-cancer treatment (33% and 54% in the combination and monotherapy arms, respectively)†

Data cut-off: 03 April 2023

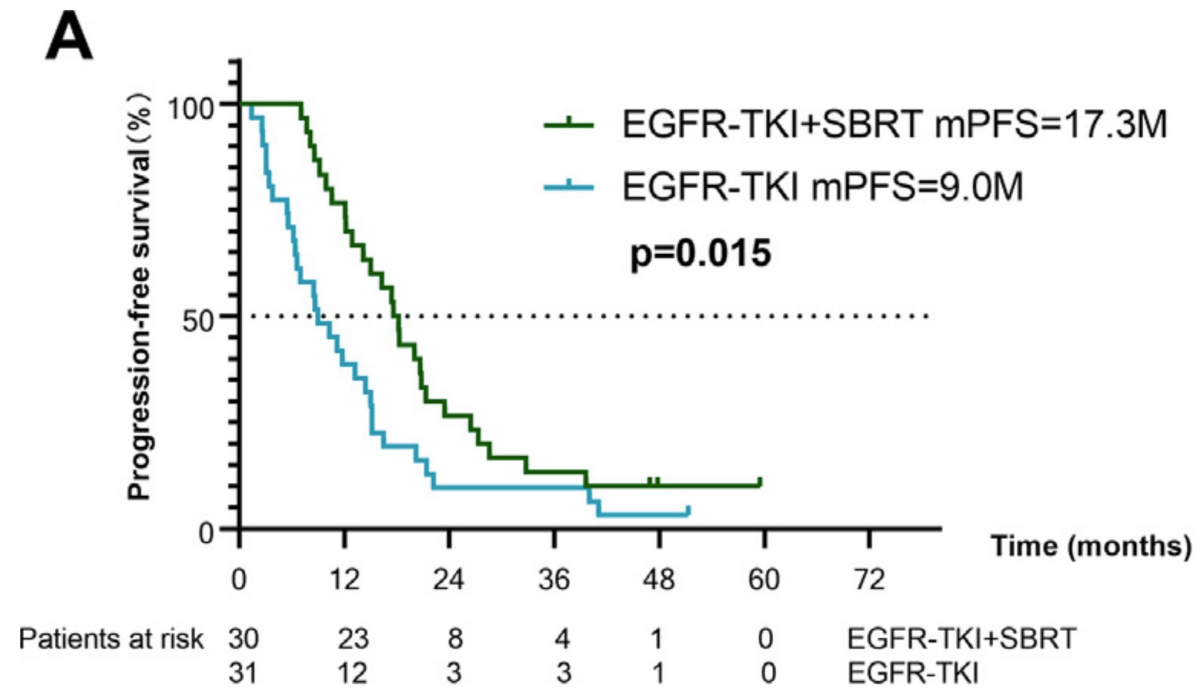
*Significance level is p-value <0.00158 at this interim for OS; †Subsequent anti-cancer treatments included those with a start date after the date of the last dose of study treatment; patients could have received more than one subsequent anti-cancer treatment, and percentages of patients by treatment type are calculated from the number of patients who discontinued randomized study treatment

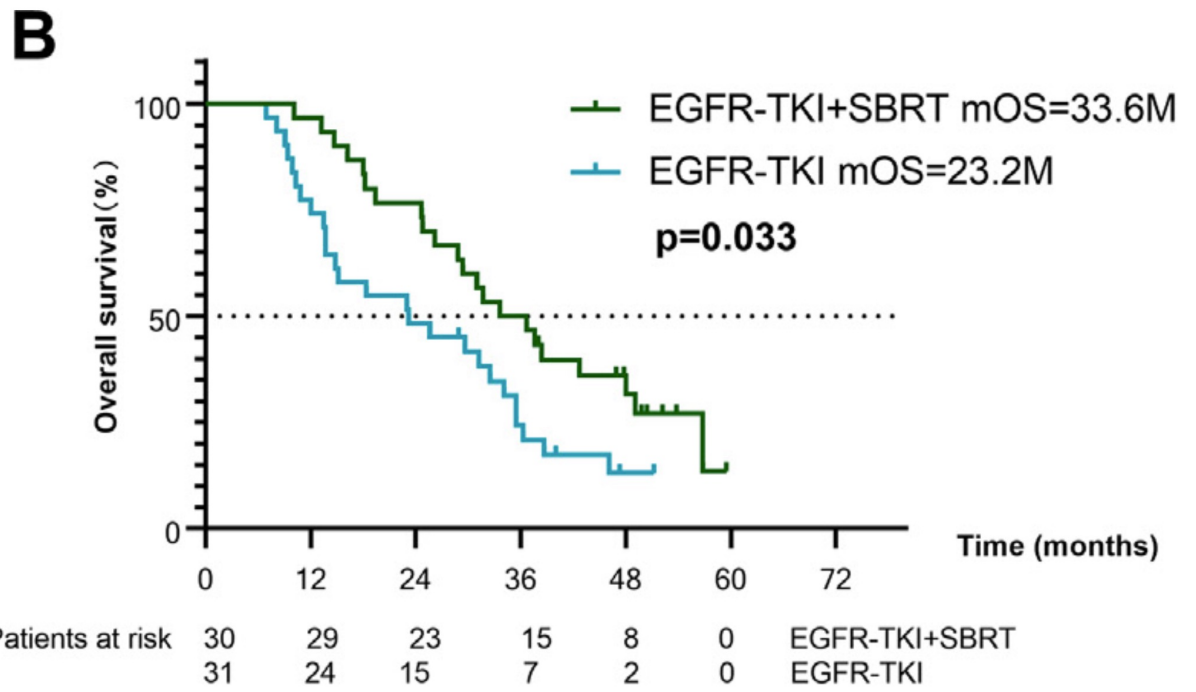
CI, confidence interval; DCO, data cut-off; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival; PFS, progression-free survival; PFS2, second progression-free survival

# Radical RT for oligometastatic cancer

## Wuhan: Phase IIR TKI ± SABR* for synchronous oligometastatic EGFRm

*after 3 mo PR/SD on TKI



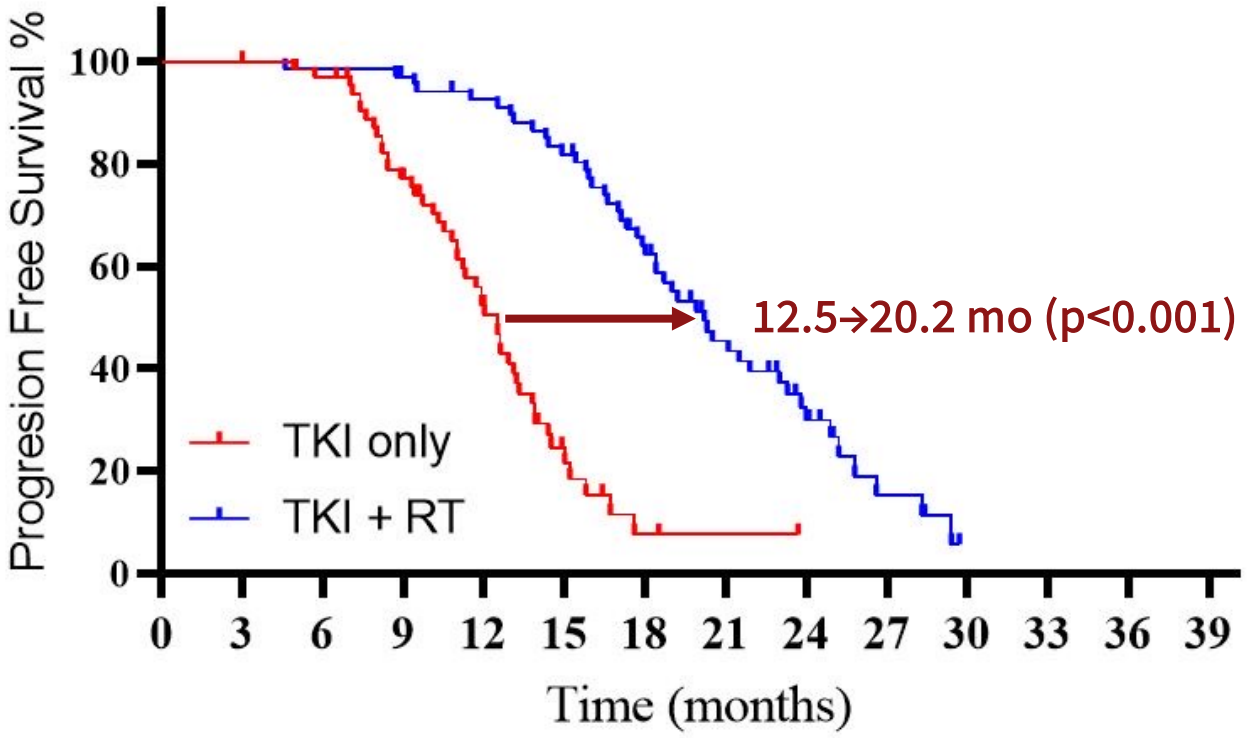




Peng *Radiother Oncol* 2023

# Radical RT for oligometastatic cancer

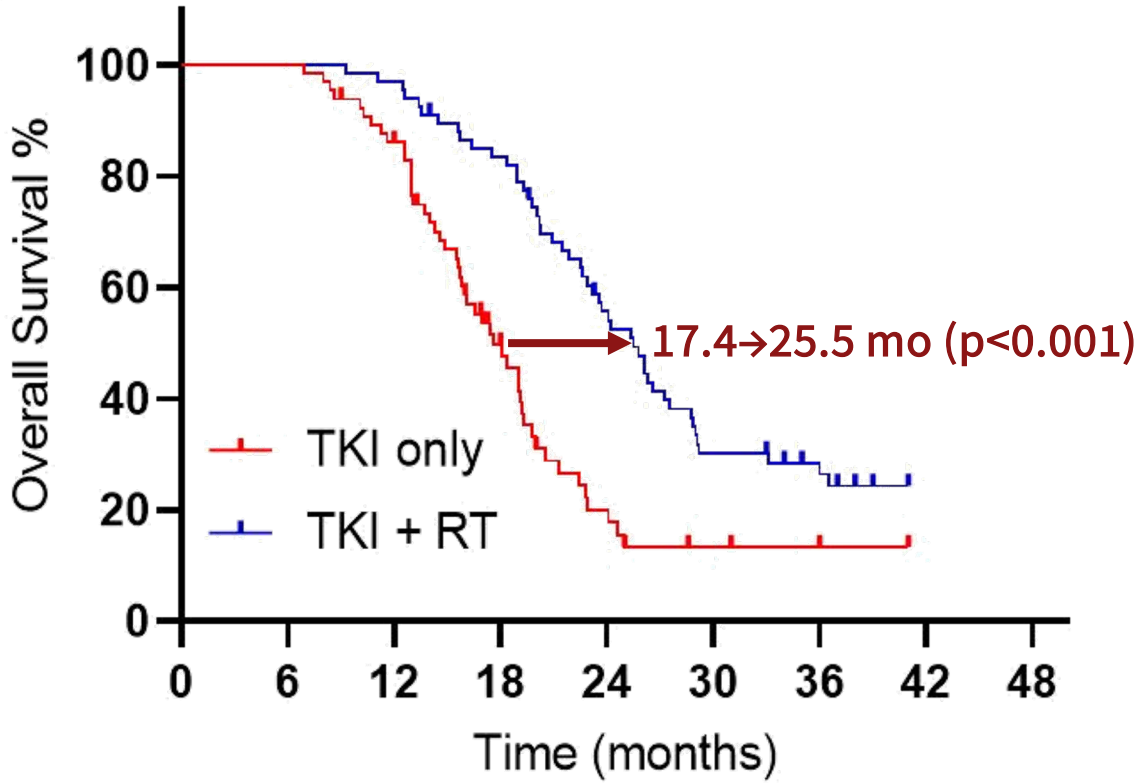
## SINDAS: Phase III TKI ± up front SABR for synchronous oligometastatic EGFRm

Figure 2




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| TKI only | 65 | 65 | 62 | 48 | 28 | 8 | 3 | 2 | 1 | 0 | 0 |
| TKI + RT | 68 | 67 | 67 | 65 | 60 | 51 | 37 | 22 | 12 | 5 | 1 |

Figure 3




| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TKI only | 65 | 65 | 55 | 26 | 9 | 5 | 3 | 2 |
| TKI + RT | 68 | 68 | 66 | 56 | 36 | 20 | 14 | 9 |

Wang *JNCI* 2022

# Take-home points

- SABR with immune checkpoint inhibition may provide one of the most promising improvements in therapeutic index for early lung cancer to date
- Individualization of therapy may be a way to optimize outcomes further
- Increasing evidence that local therapies, particularly RT/SABR, can improve PFS & OS in selected patients with metastatic lung cancer, and should be considered more broadly