Abstracts of Interest

- Chang JY *et al*. Artificial Intelligence-Based Model for Personalized Immunotherapy in Patients with Early-Stage NSCLC Treated with Stereotactic Ablative Radiotherapy: I-SABR SELECT (OA 13.05)

- Le Rouex PY *et al*. Prediction of health-related quality-of-life results after lung Stereotactic Body Radiotherapy using dose-volume parameters from functional mapping on Gallium-68 perfusion PET/CT (poster 424)

iSABR Trial: Phase 2 Randomized Trial

- Randomized phase 2 comparison of SABR alone versus SABR followed by 4 cycles nivolumab for early stage inoperable or parenchymal recurrence of NSCLC

- SABR was 50 Gy in 4 fractions (peripheral) or 70 Gy in 10 fractions (central)

- 156 patients randomized

- Powered to detect a 23% difference in 4-year event free survival

- Median FU time was 33 months

Chang JY et al. Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncology 2023

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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 (PI: Joe Chang)

I-SABR:
Killed cancer cells as tumor-specific vaccine in situ
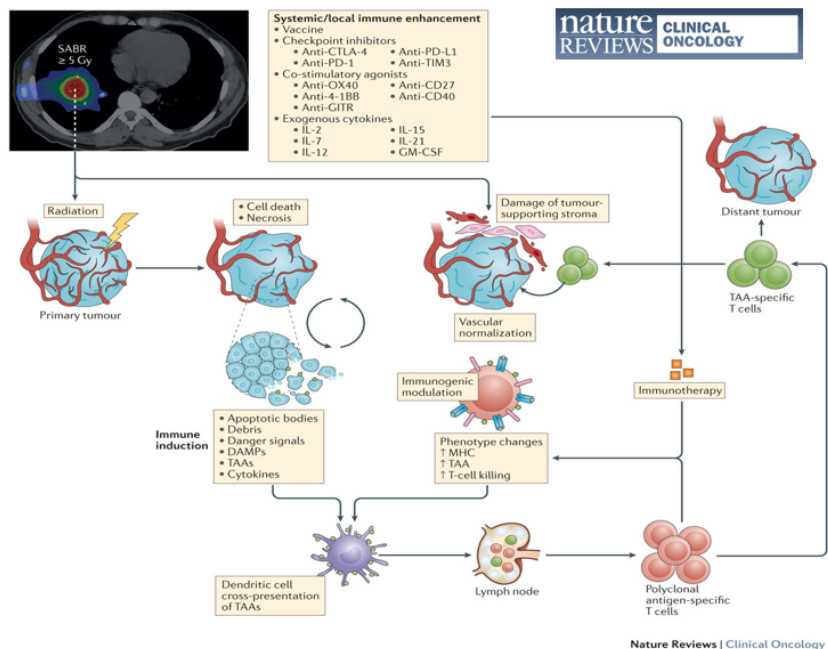
Schema

Bernstein/Chang et al:
Nature Reviews Clin Onc 2016

Staging:
Histologic confirmed
Diagnostic CT
PET/CT of lungs,
   mediastinum,
   adrenals
Brain MRI or CT
   (if indicated)
Invasive mediastinal
   staging (if indicated)
Pulmonary function tests
Lab tests

Stratification by:
Performance status
   (0–1 vs. 2)
Tumor size
   (≤3 cm vs. 3.1–5 cm vs. 5.1–7 cm)
Histology
   (squamous vs. non-squamous)
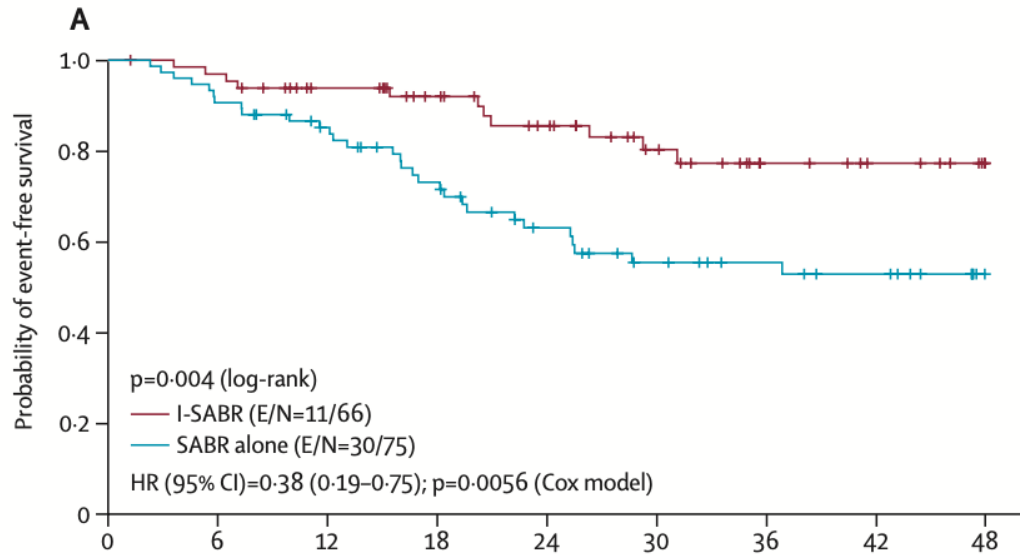Lung cancer history
   (stage I vs. recurrence)

Randomized

SABR Only
50 Gy in 4 fx
OR
70 Gy in 10 fx

I-SABR
Nivo (480 mg) same day or 36 H 1st fx
SABR: 50 Gy in 4 fx OR 70 Gy in 10 fx
Nivo q4wk for 12 weeks
(4 doses total)

Follow-up:
H&P, labs, CT q3mo for 2 years
PET/CT at 9 months
PFT, EKG at 12 months
Collect tissues, blood/stool before, during and after TX
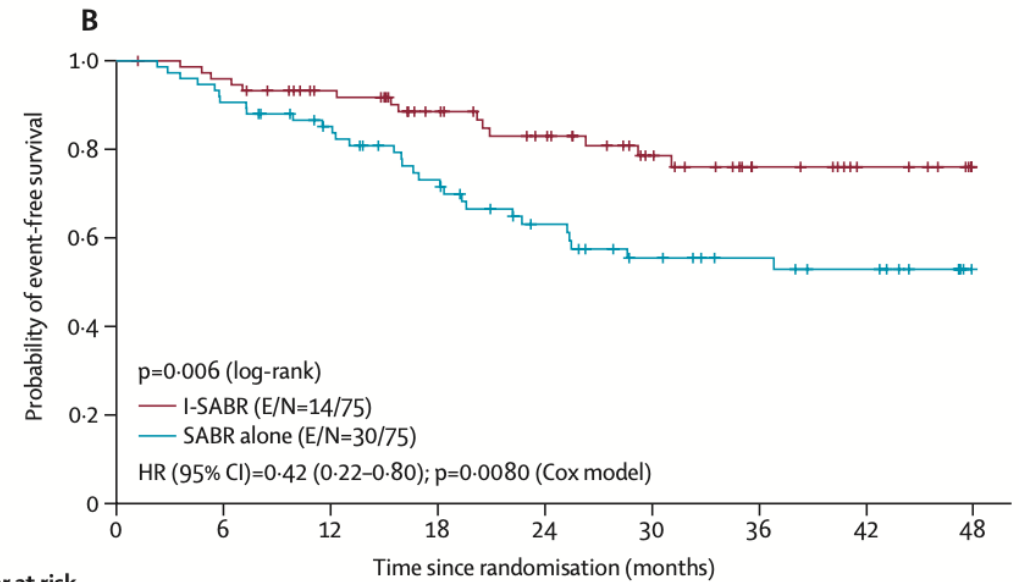Image-based radiomic modeling

Chang and Heymach et al: Lancet 402:871-881, 2023

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iSABR Trial Results

Per Protocol Analysis

Intention to Treat Analysis

Chang JY et al. Stereotactic ablative radiotherapy with or without immunotherapy for early-stage or isolated lung parenchymal recurrent node-negative non-small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncology 2023
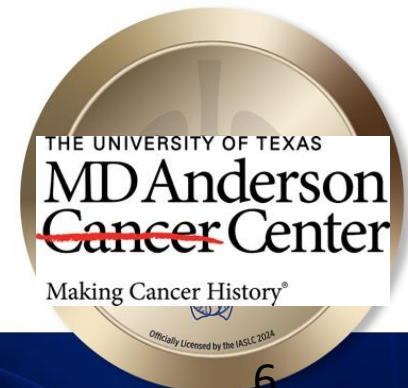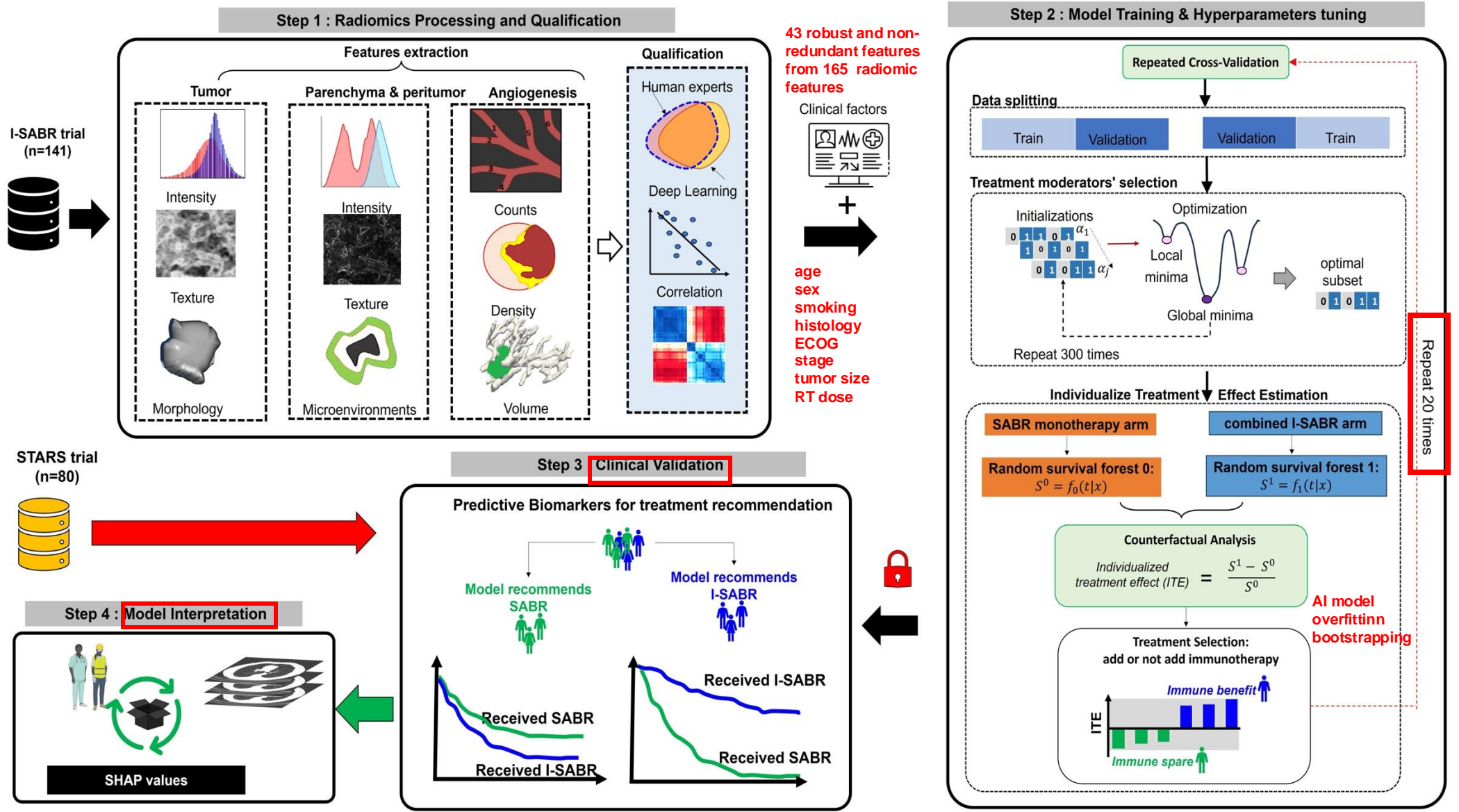
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2024

Artificial Intelligence-Based Model for Personalized Immunotherapy in Patients with Early-Stage NSCLC Treated with Stereotactic Ablative Radiotherapy:

I-SABR SELECT

Joe Y. Chang, MD, PhD, ASTRO, FACR
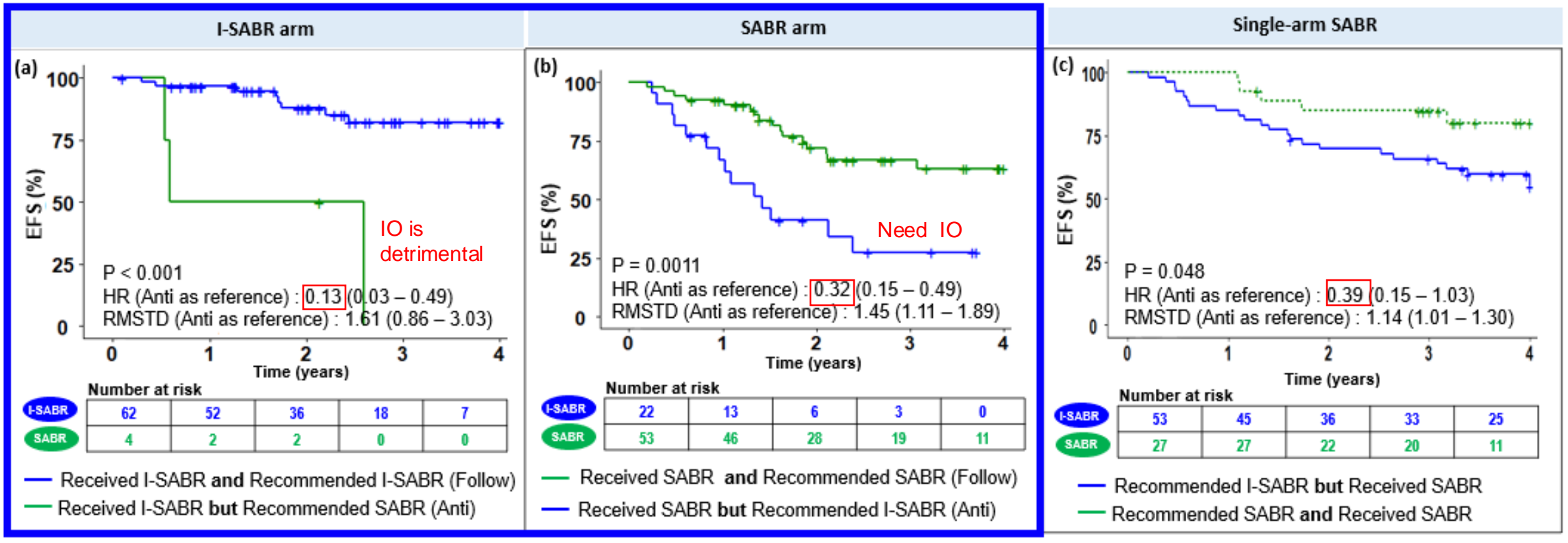University of Texas MD Anderson Cancer Center

Design

Step 1 : Radiomics Processing and Qualification

I-SABR trial (n=141)

Features extraction

Tumor
- Intensity
- Texture
- Morphology

Parenchyma & peritumor
- Intensity
- Texture
- Microenvironments

Angiogenesis
- Counts
- Density
- Volume

Qualification
- Human experts
- Deep Learning
- Correlation

43 robust and non-redundant features from 165 radiomic features

Clinical factors

**age
sex
smoking
histology
ECOG
stage
tumor size
RT dose**

Step 2 : Model Training & Hyperparameters tuning

Repeated Cross-Validation

Data splitting

| Train | Validation | Validation | Train |

Treatment moderators' selection

Initializations α_1 ... α_j

Optimization
- Local minima
- Global minima

optimal subset

Repeat 300 times

Repeat 20 times

Individualize Treatment Effect Estimation

SABR monotherapy arm → Random survival forest 0: $S^0 = f_0(t|x)$

combined I-SABR arm → Random survival forest 1: $S^1 = f_1(t|x)$

Counterfactual Analysis

Individualized treatment effect (ITE) $= \dfrac{S^1 - S^0}{S^0}$

AI model overfittinn bootstrapping

Treatment Selection: add or not add immunotherapy

ITE — Immune benefit / Immune spare

Step 3   Clinical Validation

STARS trial (n=80)

Predictive Biomarkers for treatment recommendation

Model recommends SABR

Model recommends I-SABR

Received SABR / Received I-SABR

Received I-SABR / Received SABR

Step 4 : Model Interpretation

SHAP values

Swarm intelligence to pinpoint potential effect modifiers

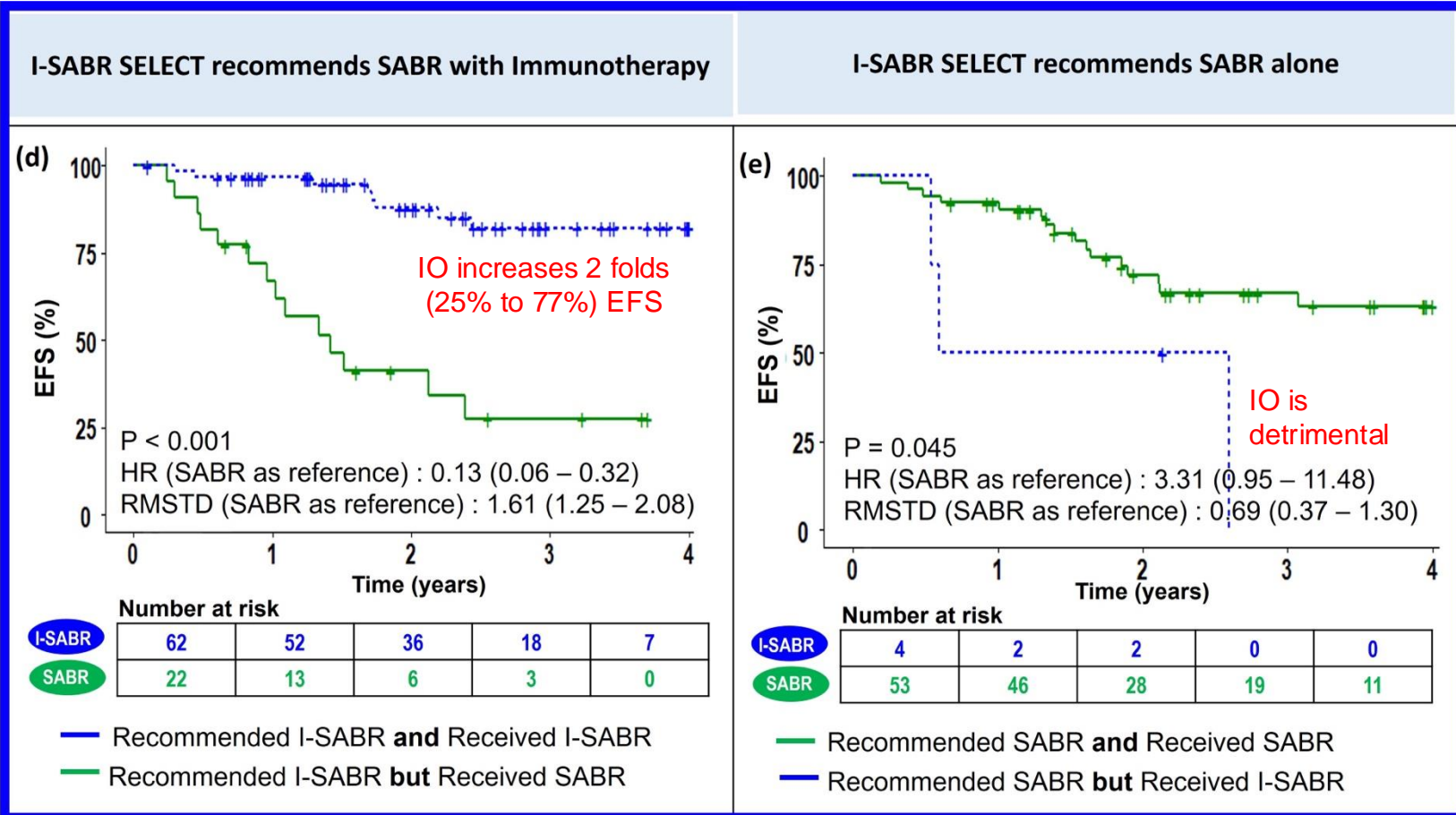# I-SABR vs SABR cohorts (follow vs Anti-recommendation)

Phase-II I-SABR Trial

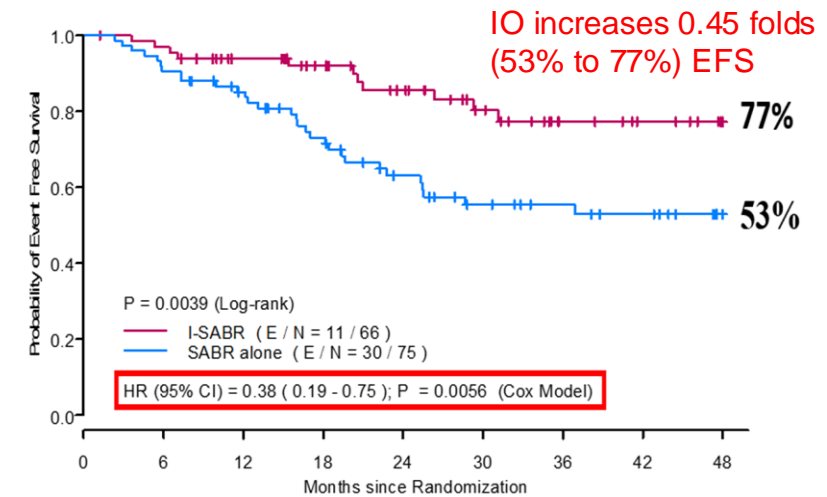**STARS Trial**
(Chang et al: Lancet Oncology 22:1488, 2021)

Follow vs Anti-recommendation in all pts in I-SABR Trial

I-SABR SELECT recommends SABR with Immunotherapy

IO increases 2 folds (25% to 77%) EFS

P < 0.001
HR (SABR as reference) : 0.13 (0.06 – 0.32)
RMSTD (SABR as reference) : 1.61 (1.25 – 2.08)

Number at risk

I-SABR	62	52	36	18	7
SABR	22	13	6	3	0

— Recommended I-SABR **and** Received I-SABR
— Recommended I-SABR **but** Received SABR

I-SABR SELECT recommends SABR alone

IO is detrimental

P = 0.045
HR (SABR as reference) : 3.31 (0.95 – 11.48)
RMSTD (SABR as reference) : 0.69 (0.37 – 1.30)

Number at risk

I-SABR	4	2	2	0	0
SABR	53	46	28	19	11

— Recommended SABR **and** Received SABR
— Recommended SABR **but** Received I-SABR

Chang and Heymach et al: I-SABR
Lancet 402:871-881, 2023

Per protocol

IO increases 0.45 folds (53% to 77%) EFS

77%

53%

P = 0.0039 (Log-rank)
— I-SABR (E / N = 11 / 66)
— SABR alone (E / N = 30 / 75)

HR (95% CI) = 0.38 (0.19 - 0.75); P = 0.0056 (Cox Model)

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)

How does this fit into existing landscape?

- 3 separate randomized phase 3 trials conducted to test hypothesis that adding IO to SABR improves outcomes in early stage, medically inoperable NSCLC

Randomized Phase 3 Trials with SABR + Immunotherapy for Early-Stage NSCLC

Study	Drug	Timing	Duration ICI	Primary Endpoint	N	Outcome
PACIFIC 4	Durvalumab	Concurrent and Adjuvant (first 100 pts adjuvant only)	Up to 24 months	PFS	630	Awaiting results, no interim analysis yet
S1914	Atezolizumab	Neoadjuvant, concurrent and adjuvant	Up to 6 months	OS	480	**Closed early after interim analysis for futility**
KEYNOTE 867	Pembrolizumab	Concurrent and Adjuvant	Up to 12 months	OS and EFS	530	**Closed early after interim analysis for futility**

Why was iSABR positive while two randomized phase 3 trials appear to be negative?

- Patient population differences?
  - Included parenchymal recurrences, which were excluded in phase 3 trials
  - Patient selection decisions at a single institution
- IO started after SABR?
- Shorter duration IO?
- Different checkpoint inhibitor?
- Imbalances between arms in a randomized phase 2 by chance?

- Can a selection model such as iSABR select help explain why these trials were negative?

Prediction of health-related quality-of-life results after lung Stereotactic Body Radiotherapy using dose-volume parameters from functional mapping on Gallium-68 perfusion PET/CT

Pierre-Yves Le Roux, D Bourhis, F Pinot, M Hamya, G Goasduff, F Blanc-Béguin, S Hennebicq, M Mauguen, K kerleguer, U Schick, M Consigny, O Pradier, G Le Gal, PY Salaun, V Bourbonne, F Lucia

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Functional Lung Avoidance Radiotherapy

- Preferentially voids higher functioning lung regions identified through various imaging modalities while directing dose toward lower and non-functioning lung regions

- Hypothesized to reduce lung toxicity

- Range of imaging modalities used to identify functional lung regions
  - 4DCT ventilation imaging
  - ^{3}He MRI
  - Gallium-68 ventilation and perfusion PET/CT
  - Hyperpolarized Xenon-129 MRI
  - SPECT/CT
  - DCE-MRI

- Balance between accuracy of imaging technique to identify functional lung, and availability/cost

Lung SBRT

- Standard lung SBRT planning :

  ➢ Dose constraints on the anatomical lung delineated on CT

  ➢ Simplistically assumes that the lungs are functionally homogeneous

- Regional distribution of pulmonary function is heterogeneous
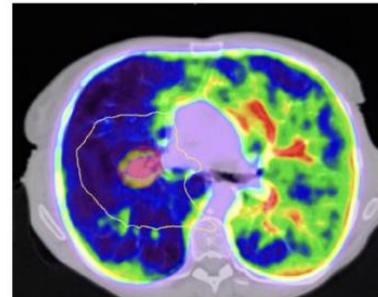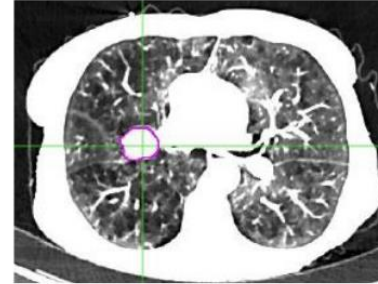
Functional lung avoidance planning

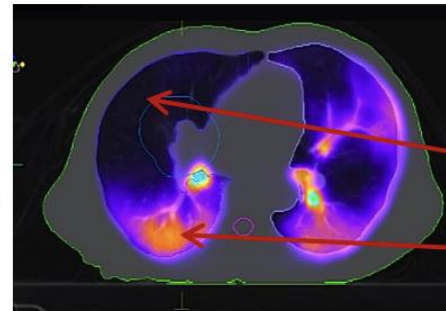➢ personalizing RT treatment planning to individuals' lung functional distribution

Lucia F, Diagnostics 2023

PEGASUS trial
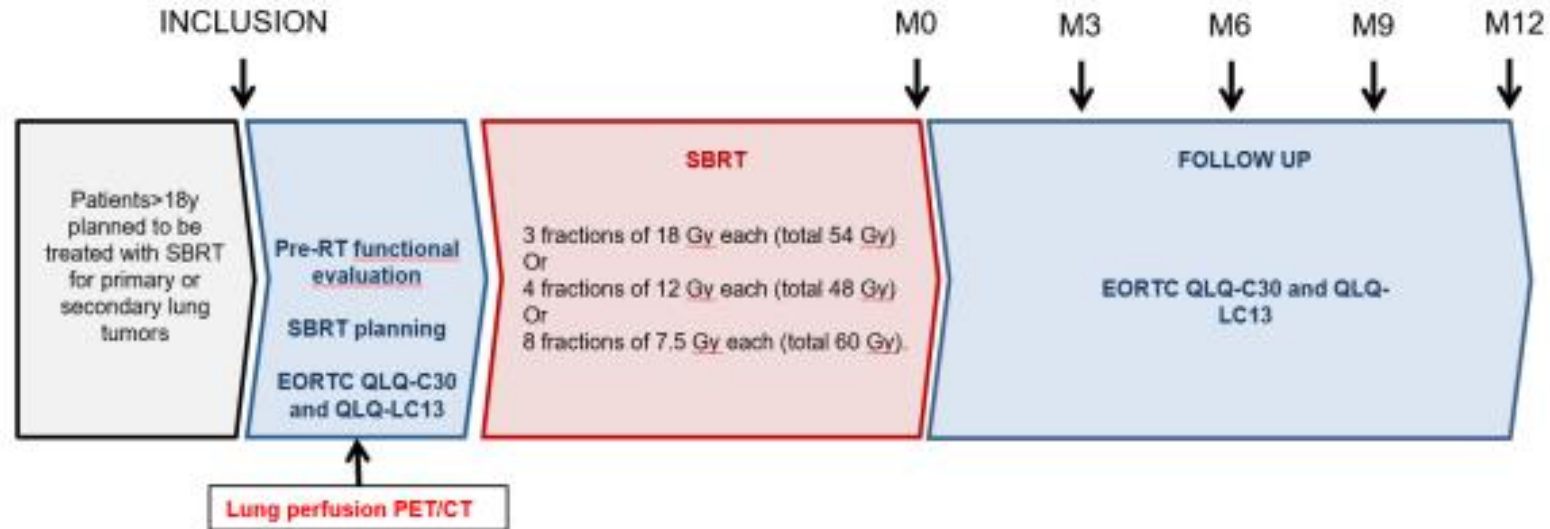
Primary endpoint:

- **baseline-to-early change** (between 1 month and 3 month) and **baseline-to-late change** (between 6 month and 12 month) in the QLQ-C30 **global health status (GHS)/quality-of-life (QoL) score** and in the **deterioration of the dyspnea (patient-reported lung toxicity)**

Results

Comparison of dosimetric parameters in patients with and without impairement of dyspnea

Early change

		Total (N= 39)	No (N= 33)	Yes (N= 6)	P
MLD AV		2.9 [2.1, 3.8]	2.9 [2.0, 3.7]	2.5 [2.3, 4.5]	0.75
MLD LVF		2.7 [1.2, 4.6]	2.8 [1.2, 4.8]	2.3 [1.1, 3.0]	0.48
MLD FV50%		3.0 [1.6, 4.2]	2.8 [1.3, 4.1]	4.8 [4.1, 5.9]	<0.0001
MLD FV70%		3.1 [1.8, 3.9]	2.7 [1.8, 3.8]	4.0 [3.6, 5.1]	0.02
MLD FV90%		2.9 [1.8, 3.7]	2.8 [1.7, 3.5]	3.1 [2.9, 4.9]	0.18

Late change

		Total (N= 22)	No (N= 19)	Yes (N= 3)	P
MLD AV		2.9 [2.3, 4.0]	2.9 [2.3, 4.0]	2.9 [2.5, 3.7]	1.0
MLD LVF		3.6 [1.6, 4.8]	3.8 [2.3, 5.0]	1.3 [1.0, 2.5]	0.19
MLD FV50%		2.9 [1.3, 4.0]	2.4 [1.1, 3.4]	4.1 [3.9, 4.1]	0.03
MLD FV70%		2.8 [1.9, 3.9]	2.6 [1.8, 3.8]	3.8 [3.4, 4.1]	0.02
MLD FV90%		2.8 [2.2, 3.8]	2.8 [2.0, 3.8]	3.3 [2.9, 4.0]	0.11

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Results

Comparison of dosimetric parameters in patients with and without impairement of quality of life/Global health status

Early change

		Total (N= 39)	No (N= 26)	Yes (N= 13)	P
MLD AV		2.9 [2.1, 3.8]	2.9 [1.9, 3.6]	2.9 [2.4, 4.4]	0.47
MLD LVF		2.7 [1.2, 4.6]	2.9 [1.9, 5.0]	1.4 [0.8, 3.2]	0.19
MLD FV50%		3.0 [1.6, 4.2]	2.1 [1.1, 3.1]	4.2 [4.1, 5.5]	<0.0001
MLD FV70%		3.1 [1.8, 3.9]	2.1 [1.5, 3.5]	3.9 [3.5, 4.4]	<0.0001
MLD FV90%		2.9 [1.8, 3.7]	2.4 [1.5, 3.5]	3.3 [2.8, 4.6]	0.03

Late change

		Total (N= 22)	No (N= 15)	Yes (N= 7)	P
MLD AV		2.9 [2.3, 4.0]	2.9 [2.3, 4.4]	2.9 [2.3, 3.3]	0.53
MLD LVF		3.6 [1.6, 4.8]	4.3 [2.7, 5.0]	1.4 [1.0, 3.5]	0.11
MLD FV50%		2.9 [1.3, 4.0]	1.6 [1.00, 3.0]	4.1 [3.4, 4.2]	0.01
MLD FV70%		2.8 [1.9, 3.9]	2.5 [1.5, 3.2]	3.8 [3.0, 4.1]	0.08
MLD FV90%		2.8 [2.2, 3.8]	2.6 [1.9, 4.0]	3.2 [2.7, 3.3]	0.21

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Functional Lung Avoidance Trials- Completed

Study	Design	N	Imaging technique	Primary endpoint	Outcomes
FLAIR trial Yaremko et al (IJROBP 2022)	Randomized, masked design	31 enrolled, 27 randomized	³He MRI	Change in FACT-L LCS score	No difference in FACT-L LCS score
Vinogradskiy Y et al (IJROBP 2022)	Single arm phase II	67	4DCT ventilation imaging	Rate of grade ≥2 pneumonitis	14.9% grade ≥2 pneumonitis
Yamamoto et al (IJROBP 2018 & WCLC 2022)	Single arm pilot study	34	4DCT ventilation imaging	grade ≥3 adverse events	4.2% grade≥3 pneumonitis 12.5% grade≥3 esophagitis
PEGASUS Trial (WCLC 2024)	Single arm phase II	60	Gallium68-MMA perfusion PET/CT	QLQ-C30 QOL	Dose to FL associated with decreased QOL

Functional Lung Avoidance Trials- Not yet reported

Study	Design	N	Imaging technique	Primary endpoint
Peter MacCallum (NCT03569072)	Single arm feasibility study	20	Gallium-68 ventilation and perfusion PET/CT	Technical feasibility
National Taiwan University (NCT03077854)	Single arm, blinded trial	64	4DCT ventilation imaging	Pulmonary QOL at 3 months post-RT
University of Pennsylvania (NCT05302817)	Phase 1 single arm	20	Hyperpolarized Xenon-129 MRI	Adverse events related to xenon
University of Washington (NCT02773238)	Single arm phase II	56	SPECT/CT	Overall survival (trial also involves dose escalation)
Dana-Farber (NCT01799135)	Pilot	6	DCE-MRI	Feasibility
University of Wisconsin (NCT02843568)	Randomized	139	4DCT ventilation imaging	Pulmonary function based on tissue elasticity
University of Aarhus (NCT01745484)	Single arm	71	SPECT	Grade 2 pneumonitis
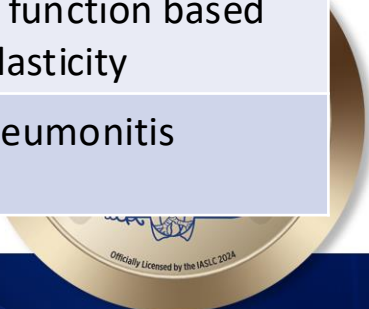
PEGASUS-2

Functional lung avoidance planning guided by lung perfusion PET/CT versus anatomical planning for lung stereotactic body radiotherapy:
a double blinded, multicenter, randomized, controlled trial.

Summary

- Intriguing deep learning model based on phase 2 iSABR trial suggests patient selection may be critical when adding IO to SABR in early stage disease

- However, role of immunotherapy in early stage medically inoperable NSCLC in question after early closure of 2 separate phase 3 trials

- Functional lung avoidance planning is an intriguing approach to reduce lung toxicity from thoracic radiation

- Randomized phase 3 trials and broader availability of the needed technologies are required