TTF FIELDS FOR THE THORACIC ONCOLOGIST

Joshua Sabari, MD

NYU Langone Health Perlmutter Cancer Center

April 19, 2024

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TEXAS LUNG CANCER CONFERENCE
AUSTIN 2024

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TTF FIELDS FOR DUMMIES

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Outline

- Technology
  - MOA
- Trials
  - LUNAR
    - Subsets
  - B36
  - LUNAR-2
  - METIS
  - STELLAR

Leal T et al LBA9005 ASCO 2023

Neuro-Oncology

Neuro-Oncology 18(3), 303–305, 2016
doi:10.1093/neuonc/now012

TTFields: where does all the skepticism come from?

Wolfgang Wick

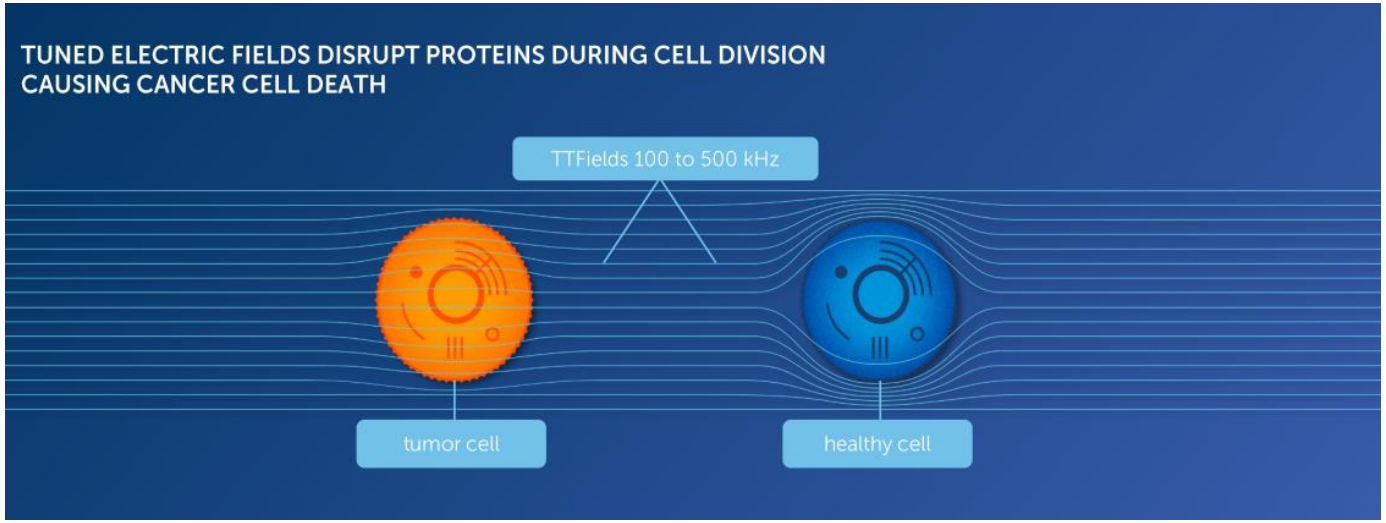
Neurology Clinic, University of Heidelberg and Clinical Cooperation Unit (CCU) Neurooncology, German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany (W.W.)

Corresponding Author: Wolfgang Wick, MD, Neurology Clinic & National Centre for Tumour Disease, University of Heidelberg, Im Neuenheimer Feld 400, D-69120 Heidelberg, Germany (wolfgang.wick@med.uni-heidelberg.de).

Neuro Oncol 2016 Mar: 18(3):303-305

Tumor Treating Fields (TTF)

- Alternating electric fields can be tuned to different frequencies
  - 100 – 500 kHz
- Different cancer types respond to different frequencies (kHz) and intensities (V/cm)



- **MOA:**
  - Disrupt cell division (Antimitotic)
  - Changes to electrical potential across tumor cell membranes lead to influx of Ca2+ ions and subsequent abnormal spindle formation and apoptosis
  - Aberrant mitosis leads to aneuploidy
  - Increased ER stress and “immunogenic” cell death

1. Bomzon Z. et al. *Academic Press.* 2022.
2. Karanam NK et al. *Int J RadiatBiol*. 2021;97(8):1044–1054.
3. Kirson ED et al. *Proc Natl AcadSci U S A*. 2007;104(24):10152–10157.
4. Mun EJ et al. *Clin Cancer Res.* 2018;24(2):266–275.
5. Giladi M et al. *SciRep.* 2015;5:18046.

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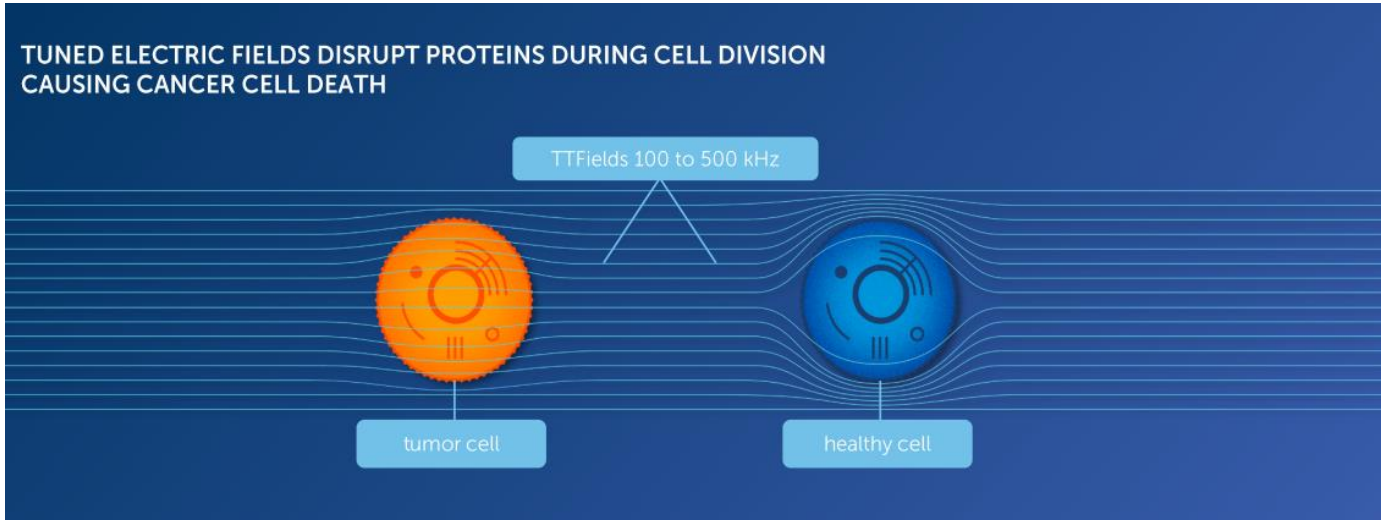

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Unanswered Questions:

- Lack of clear mechanism in human systems/multiple tissue interfaces

1. Single agent efficacy? Always studied in combination with SOC
2. Lack of blinded/sham control data
3. Time on therapy
4. Cost/Access

1. Bomzon Z. et al. *Academic Press.* 2022.
2. Karanam NK et al. *Int J RadiatBiol.* 2021;97(8):1044–1054.
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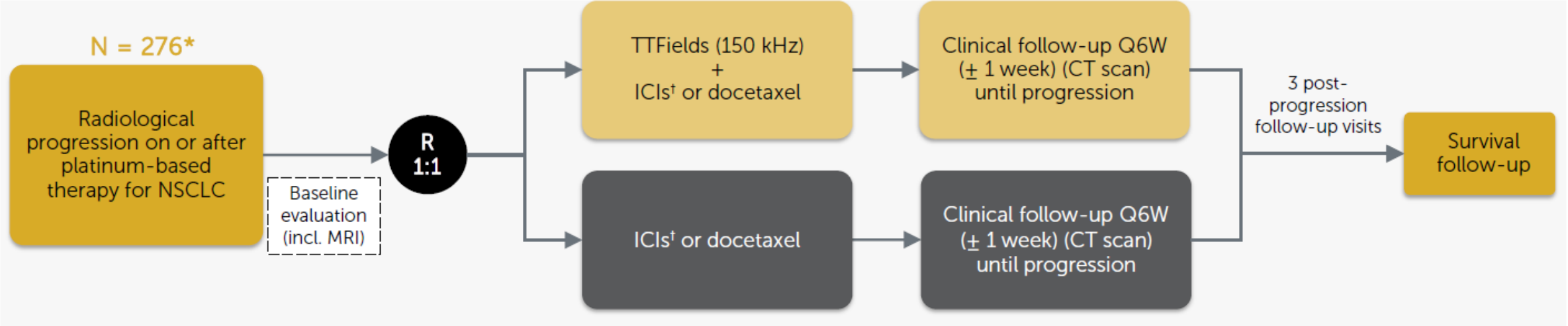
LUNAR: Phase III Randomized Open Label Study of TTF Therapy Concurrent with ICI or Docetaxel in Stage IV NSCLC following progression on or after platinum based therapies



Primary	Key Secondary	Other Secondary
• OS with TTFields + SOC vs SOC alone	• OS in ICI-treated subgroup • OS in docetaxel-treated subgroup	• PFS • ORR • PFS/OS by histology

Data Cut: November 26, 2022

Leal T et al LBA9005 ASCO 2023

LUNAR: Phase III Randomized Open Label Study of TTF Therapy Concurrent with ICI or Docetaxel in Stage IV NSCLC following progression on or after platinum based therapies

Novocure Announces Update on Phase 3 Pivotal LUNAR Trial of Tumor Treating Fields in Non-Small Cell Lung Cancer

April 13, 2021

Pre-specified interim analysis concluded with favorable recommendation to continue the LUNAR trial

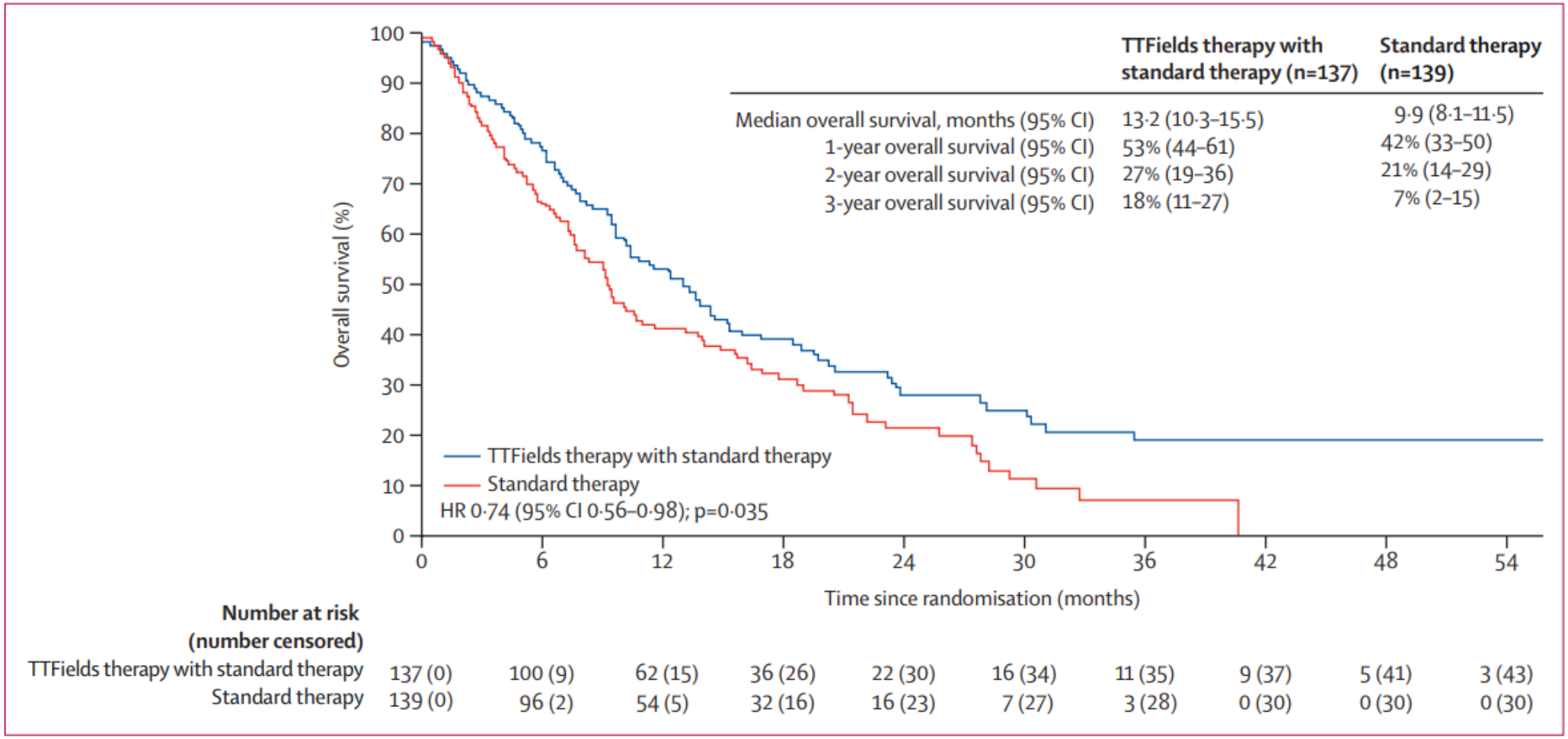
DMC stated accrual to 534 patients is likely unnecessary and possibly unethical for patients randomized to control arm and recommended a shortened trial

ST. HELIER, Jersey–(BUSINESS WIRE)–Novocure (NASDAQ: NVCR) today announced an update regarding its phase 3 pivotal LUNAR trial of Tumor Treating Fields (TTFields) in stage 4 non-small cell lung cancer (NSCLC) following platinum failure. Following a routine review of the study by an independent data monitoring committee (DMC), Novocure was informed that the pre-specified interim analysis for the LUNAR trial would be accelerated given the length of accrual and the number of events observed, to date. The interim analysis included data from 210 patients accrued to the LUNAR trial through February 2021. After review of the interim analysis report, the DMC concluded that the LUNAR trial should continue with no evidence of increased systemic toxicity.

- March 2021 planned interim analysis: DMC recommended a reduced patient accrual (534–276 patients) and follow-up (18–12 months) would be sufficient to evaluate endpoints while retaining statistical power

Leal T et al LBA9005 ASCO 2023 ; Press Release https://www.businesswire.com/news/home/20210413005428/en/ Accessed 4/16/24

LUNAR: Overall Survival in the IIT Population



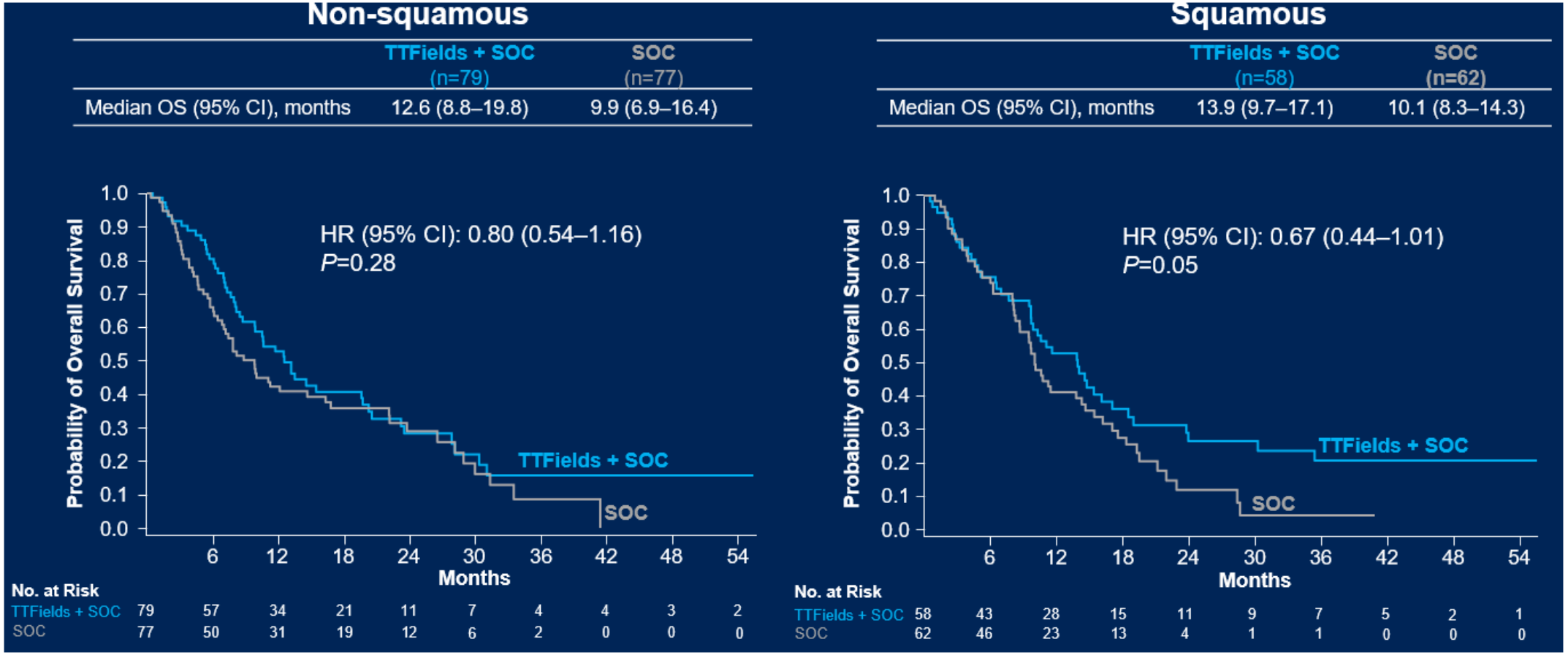
	TTFields therapy with standard therapy (n=137)	Standard therapy (n=139)
Median overall survival, months (95% CI)	13·2 (10·3–15·5)	9·9 (8·1–11·5)
1-year overall survival (95% CI)	53% (44–61)	42% (33–50)
2-year overall survival (95% CI)	27% (19–36)	21% (14–29)
3-year overall survival (95% CI)	18% (11–27)	7% (2–15)

Number at risk (number censored)										
TTFields therapy with standard therapy	137 (0)	100 (9)	62 (15)	36 (26)	22 (30)	16 (34)	11 (35)	9 (37)	5 (41)	3 (43)
Standard therapy	139 (0)	96 (2)	54 (5)	32 (16)	16 (23)	7 (27)	3 (28)	0 (30)	0 (30)	0 (30)

Leal T et al Lancet Oncol 2023; 24:1002-17

LUNAR Subgroups

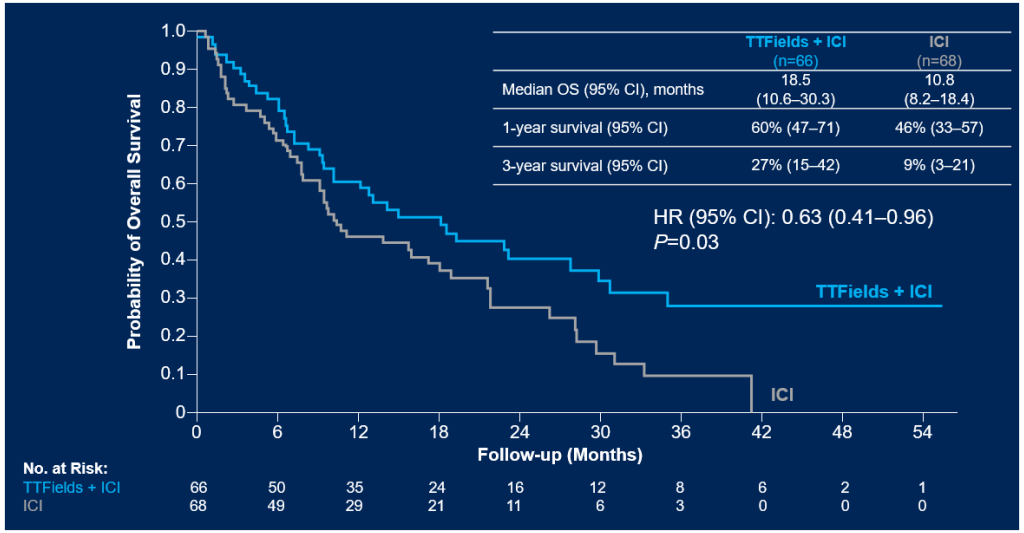
OS by histology:



Leal T et al LBA9005 ASCO 2023

LUNAR Subgroups

OS in the ICI treated group:



	TTFields + ICI (n=66)	ICI (n=68)
Median OS (95% CI), months	18.5 (10.6–30.3)	10.8 (8.2–18.4)
1-year survival (95% CI)	60% (47–71)	46% (33–57)
3-year survival (95% CI)	27% (15–42)	9% (3–21)

Leal T et al LBA9005 ASCO 2023

LUNAR Subgroups

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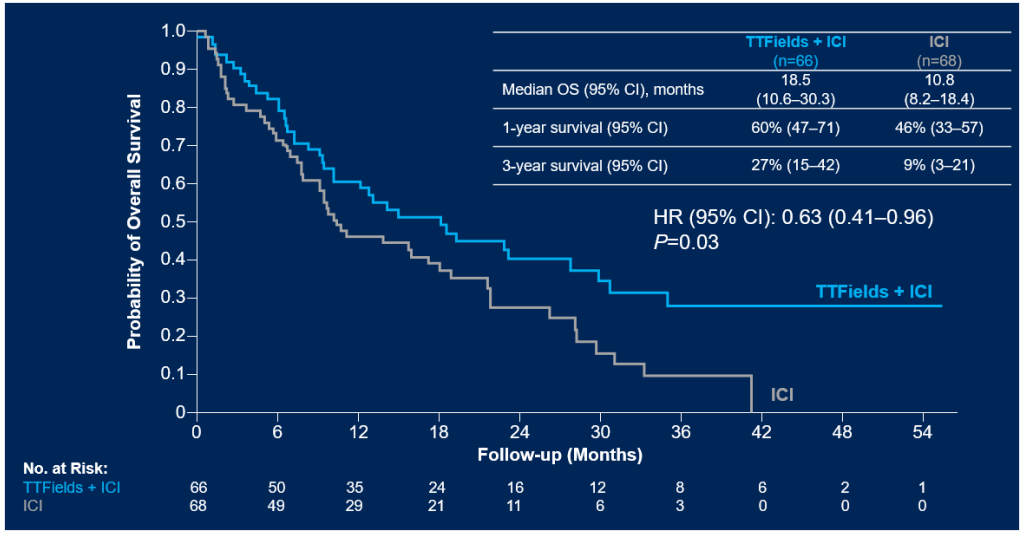

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	TTFields + ICI (n=66)	ICI (n=68)
Prior ICI, yes	2%	3%
PD-L1 (TPS)		
<1%	18%	24%
1–49%	26%	27%
≥50%	8%	12%
Unknown	49%	38%

Leal T et al LBA9005 ASCO 2023; Leal T et al IASCL WCLC 2023

LUNAR Subgroups

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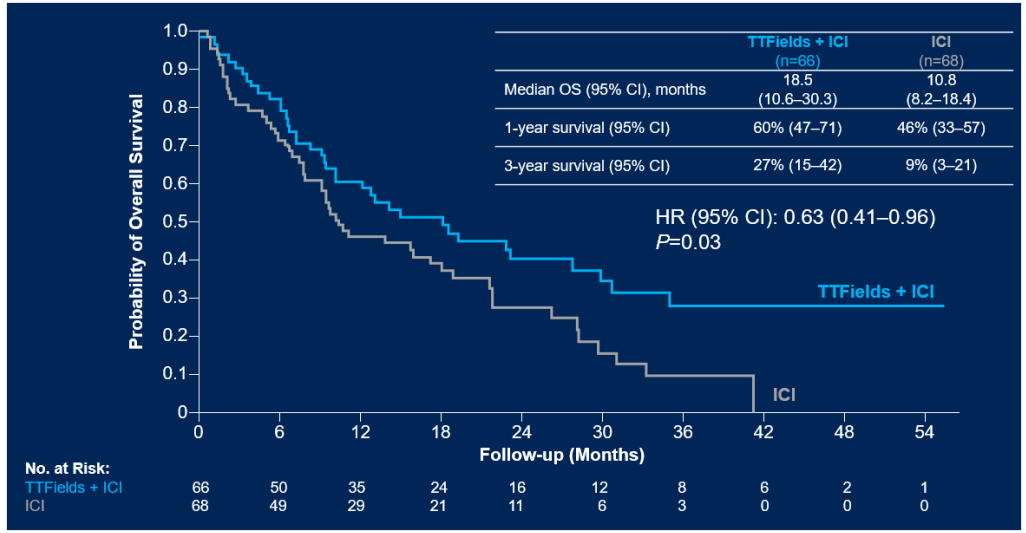

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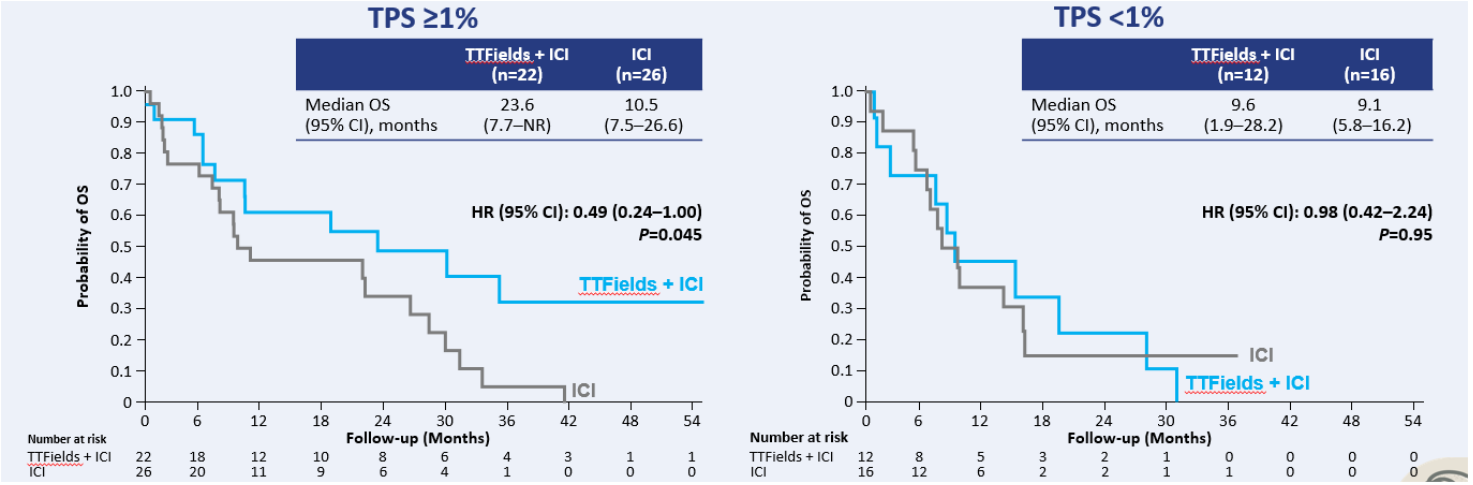
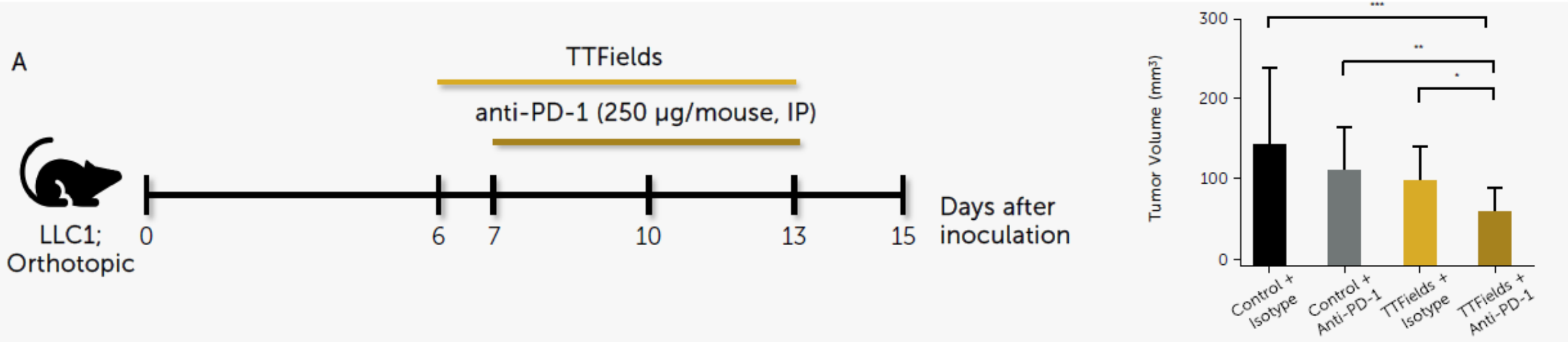
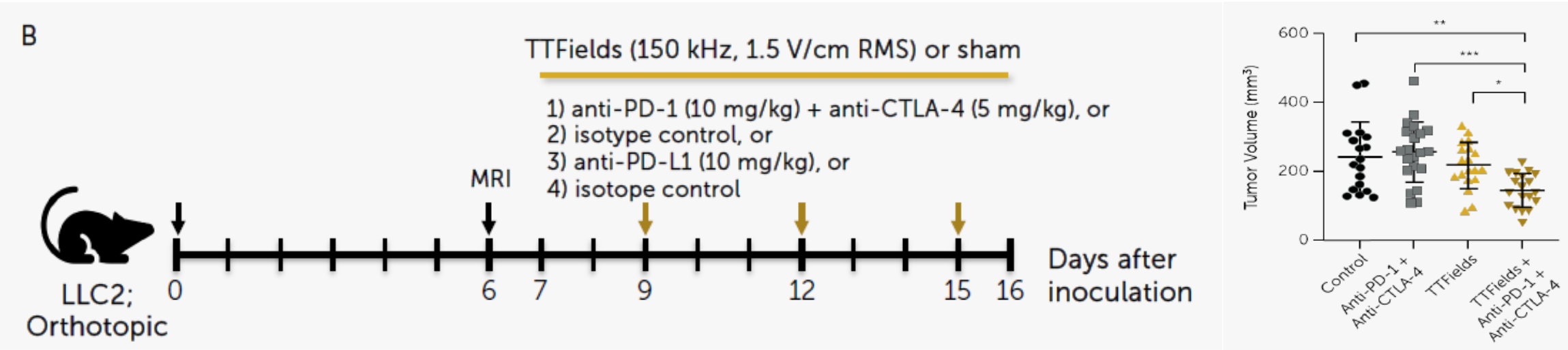


Leal T et al LBA9005 ASCO 2023; Leal T et al IASCL WCLC 2023

TTFields + Immune Checkpoint Inhibitors in vivo





1. Voloshin T et al. *Cancer Immunol Immunother*. 2020;69(7):1191–1204.
2. BarsheshetYet al.*Int J Mol Sci*. 2022;23(22):140

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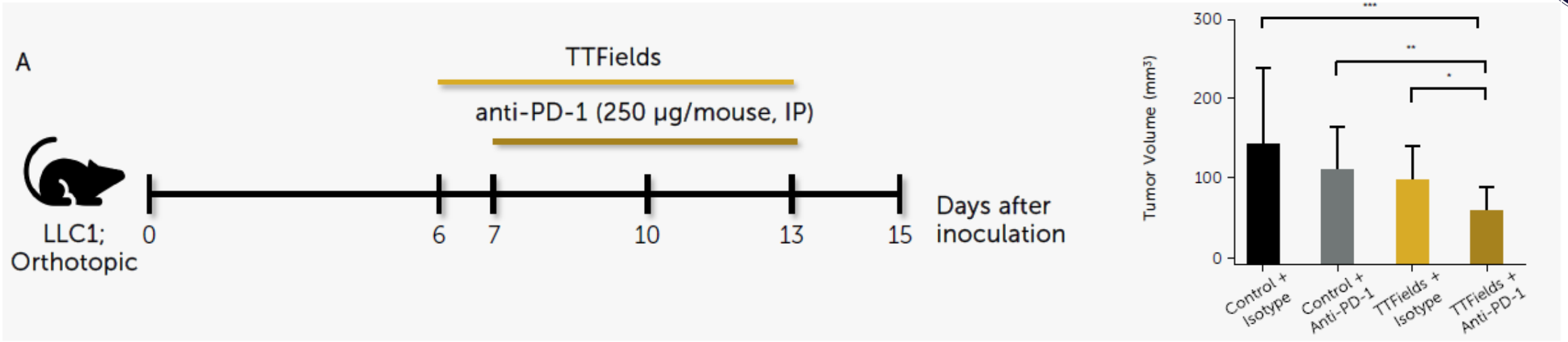
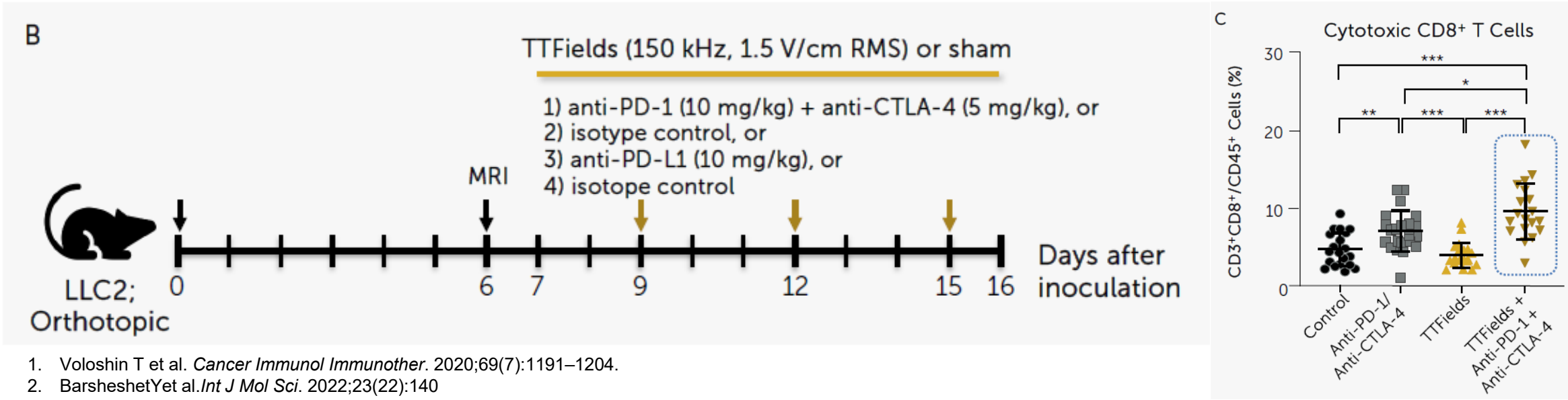
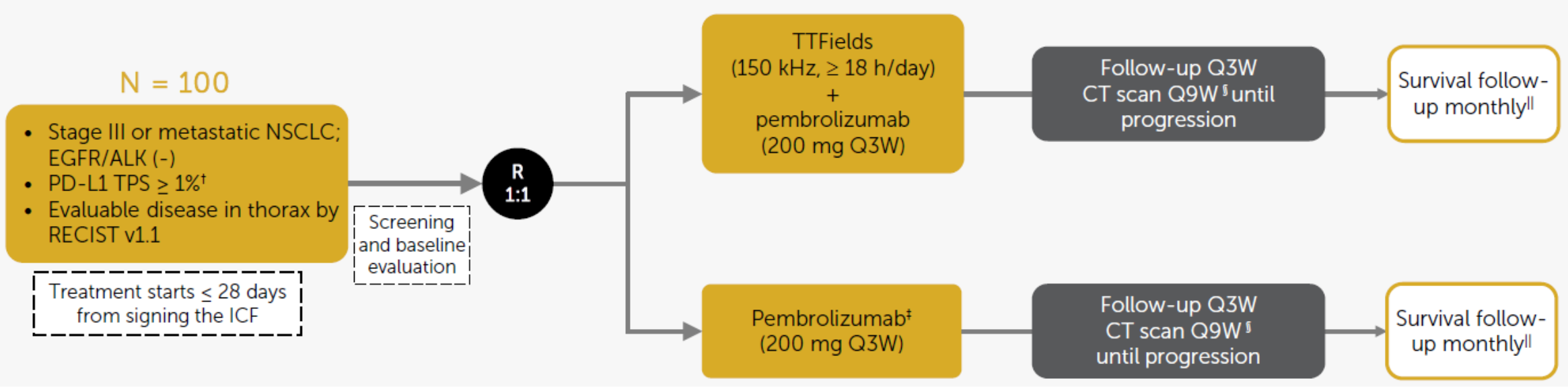




1. Voloshin T et al. *Cancer Immunol Immunother*. 2020;69(7):1191–1204.
2. BarsheshetYet al.*Int J Mol Sci*. 2022;23(22):140

KEYNOTE B36: A Pilot, Randomized, Open-Label Study of TTFields 150 kHz in combination with Pembrolizumab in 1L advanced or metastatic NSCLC

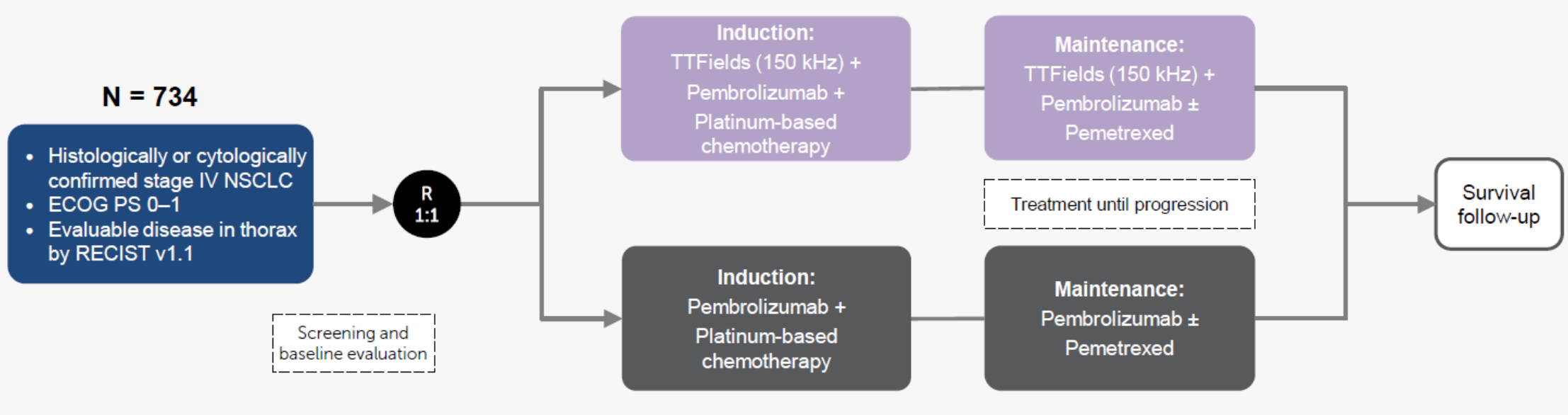


Primary completion date: July 2024

- Stratification:
  - PD-L1: TPS 1-49% vs TPS ≥ 50%;
  - Histology: Squamous vs Non-squamous
- Endpoints:
  - Primary – PFS
  - Secondary – OS, DOR, DCR, ORR, Safety
  - Exploratory – ORR, OS, and PFS by PD-L1 expression

Clinicaltrials.gov NCT04892472 Accessed 4/16/24

LUNAR -2: Randomized Phase III Study in 1L setting advanced metastatic NSCLC

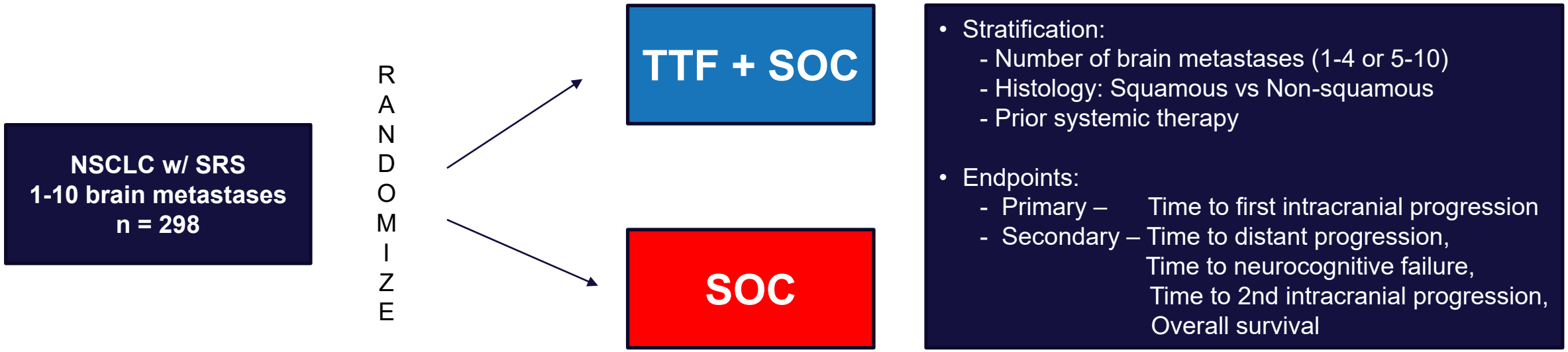


Primary completion date: October 2028

- Stratification:
  - PD-L1: TPS <1% vs 1-49% vs TPS ≥ 50%;
  - Histology: Squamous vs Non-squamous
  - Prior ICI Y/N
- Endpoints:
  - Primary – OS and PFS
  - Secondary – OS, and PFS by PD-L1 expression and histology

Clinicaltrials.gov NCT06216301 Accessed 4/16/24

METIS: Open-label, Randomized Study of Radiosurgery With or Without Tumor Treating Fields (TTFields) for 1-10 Brain Metastases From NSCLC



Mehta MP et al TPS9106 ASCO 2017 NCT02831959 Clinicaltrials.gov accessed 4/16/24

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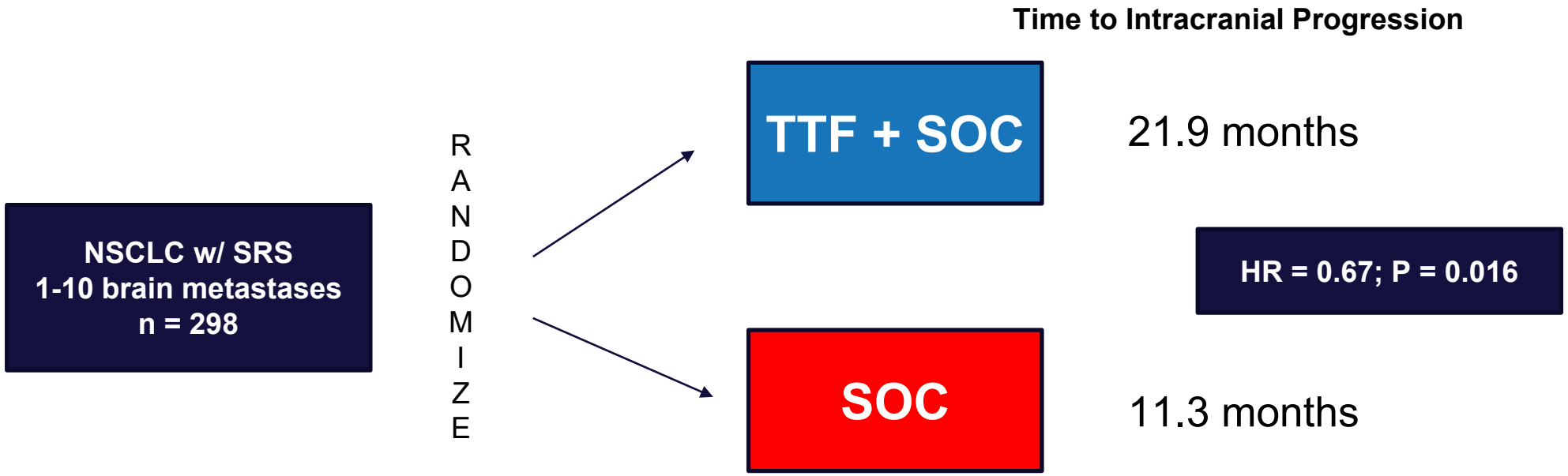

Median TTFields therapy treatment duration was 16 weeks
Median usage was 67%

Novocure Press Release 3/27/24 Accessed 4/16/24

Conclusions/Opinions

- TTFields is an interesting modality of therapy
  - Doesn't fit our artificial construct of: surgery, radiation, systemic therapy
  - Novel MOA, need further translation and clinical data

- Can this be personalized?
  - Alternating electrical fields can be tuned to different frequencies (100 – 500 kHz, most lung studies performed at 150 kHz)
  - Different cancer types respond to different frequencies (kHz) and intensities (V/cm)

- Need current/relevant data to guide management decisions
  - LUNAR trial: 3 month improvement in OS ITT (HR 0.74, p = 0.035); 8 month improvement in mOS for TTF + ICI (HR 0.62, p = 0.030)
  - B36 ongoing; need to enroll patients in LUNAR-2
  - Do we need randomized/sham controlled trials?
  - Patient selection; subgroups (mutation profile, PD-L1, disease location vs systemic immune response)

- What harm is there to the patient?
  - Well tolerated safety profile – most come AE dermatitis G1/2, no G4/5 AEs; time on therapy 18 hours/day; median device usage (15 weeks ICI; 13 weeks docetaxel in LUNAR)
  - Cost/Access