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Fondazione Policlinico Universitario Agostino Gemelli IRCCS
Università Cattolica del Sacro Cuore

C-ART
Advanced Radiation Therapy



Primary radiation therapy for stage IV cancer combined with new drugs

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Rome (Italy), October 18, 2026

Outline



- Biological rationale
- Available clinical evidence
- Patient selection
- Treatment delivery
- Future directions

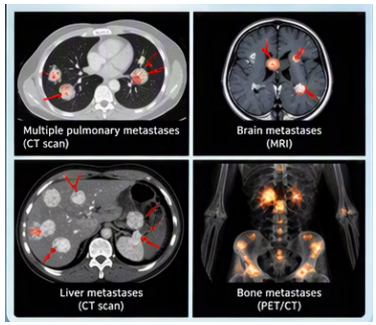
Disclosures



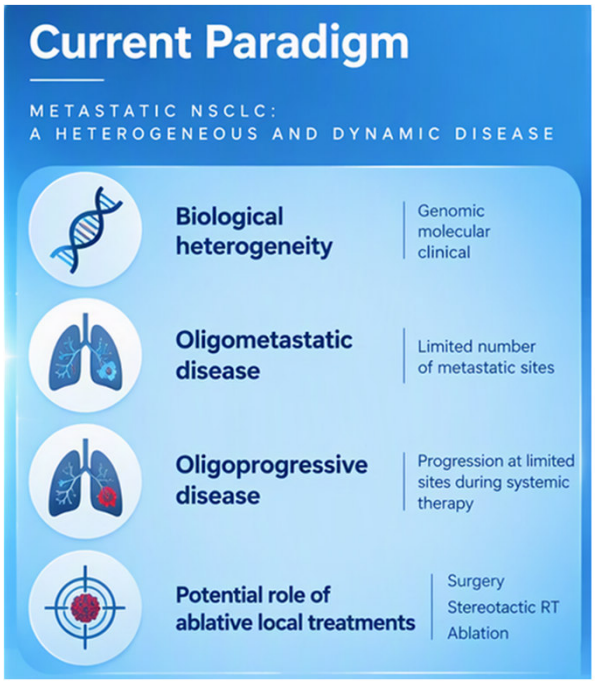
- Lecture in a company's organized public meeting: AstraZeneca, MSD, Pfizer
- Research supports: (Sub)investigator in trials (institutional financial support or clinical trials) sponsored by AstraZeneca, Merck Sharp & Dohme LLC

The paradigm shift

Stage IV NSCLC is no longer one disease







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The paradigm shift

What is the role of **local control** of the primary tumor when systemic therapy is highly effective?

- **Systemic therapy** → controls microscopic/distant disease
- **Radiotherapy** → controls macroscopic disease



Potential benefits

Durable intrathoracic control

Prevention of local complications

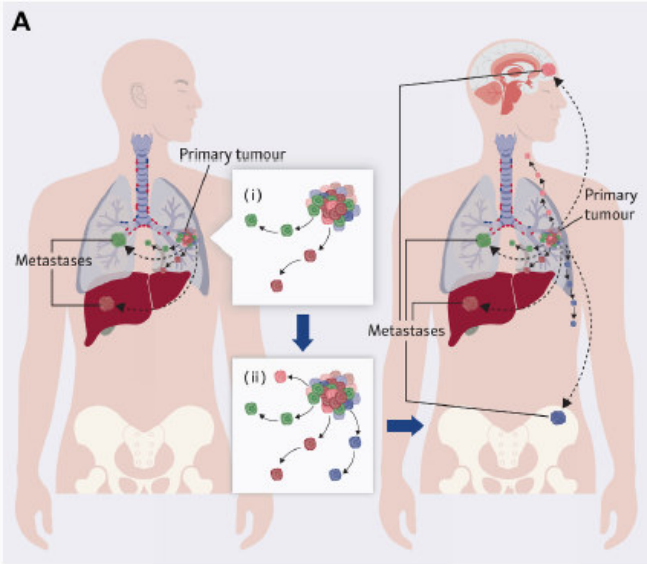
Reduction of symptom burden

Improved progression-free survival

Potential overall survival benefit

The biological rationale

Why **local therapy** in metastatic disease?



The primary tumor may no longer be just a symptom-producing lesion; it may be a source of future progression

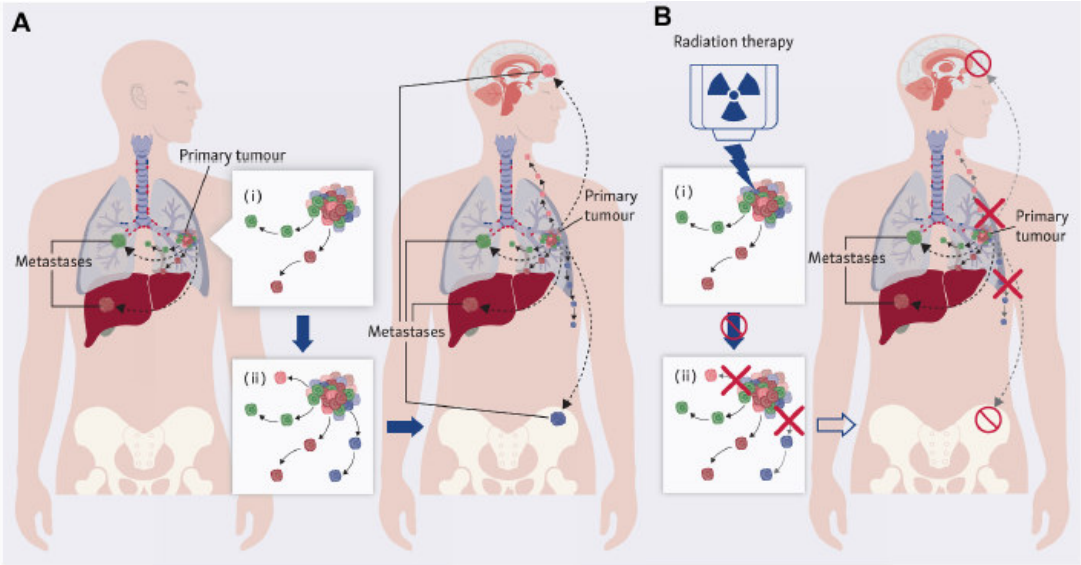
Potential mechanisms:

- Persistent source of *viable tumor cells*
- Intratumoral *heterogeneity*
- *Subclonal* evolution
- Acquisition of *resistance*
- Continuous metastatic *seeding*

McMahon RA, Lee tal. *J Thorac Oncol* 2026;21:103643
Al Bakir M, Huebner A, et. al TRACERx *Nature*. 2023; 616:534-542

The biological rationale

Why **local therapy** in metastatic disease?



Radiotherapy **can:**

- Cytoreductive potential
- Immunomodulatory effect:
  - Release tumor antigens
  - Increase T-cell infiltration
  - Enhance antigen presentation
  - Modify the tumor microenvironment

Potential systemic effects:

- Limiting distant metastasis spread
- Immune priming
- Abscopal responses
- Delay emergence of resistant clones

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McMahon RA, Lee tal. *J Thorac Oncol* 2026;21:103643
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First evidence: the oligoMets proof-of-concept

Trial	N	Population	RT/LCT	PFS	OS
Iyengar 2018	29	≤5 lesions	SABR + maintenance vs maintenance	9.7 vs 3.5 mo	exploratory
Gomez 2019	49	≤3 mets, non-PD after systemic therapy	LCT vs MT/O	14.2 vs 4.4 mo	41.2 vs 17.0 mo
SABR-COMET	99	1–5 mets, multiple primaries	SABR + SOC vs SOC	-	42.3% vs 17.7% 5-y OS

Modified from McMahon RA, Lee tal. *J Thorac Oncol* 2026;21:103643

First evidence: the oligoMets proof-of-concept

original report

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

Daniel R. Gomez, MD[1]; Chad Tang, MD[1]; Jianjun Zhang, MD, PhD[1]; George R. Blumenschein Jr, MD[1]; Mike Hernandez, MS[1]; J. Jack Lee, PhD[1]; Rong Ye, MS[1]; David A. Palma, MD, PhD[2]; Alexander V. Louie, PhD, MSc[2]; D. Ross Camidge, MD, PhD[3]; Robert C. Doebele, MD, PhD[3]; Ferdinandos Skoulidis, MD, PhD[1]; Laurie E. Gaspar, MD[3]; James W. Welsh, MD[1]; Don L. Gibbons, MD[1]; Jose A. Karam, MD[1]; Brian D. Kavanagh, MD, MPH[3]; Anne S. Tsao, MD[1]; Boris Sepesi, MD[1]; Stephen G. Swisher, MD[1]; and John V. Heymach, MD, PhD[1]

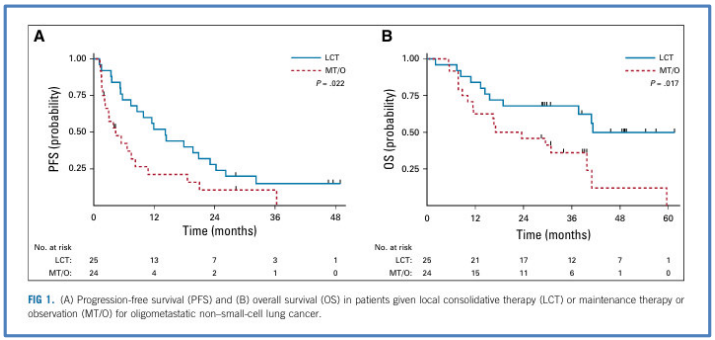


FIG 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non–small-cell lung cancer.

Phase II Randomized Trial

Patients:

Stage IV NSCLC
≤3 metastatic sites
No progression after first-line systemic therapy

Randomization:

- Maintenance/observation
- Local consolidative therapy

Results
Median PFS
- 14.2 vs 4.4 months

Median OS
- 41.2 vs 17 months

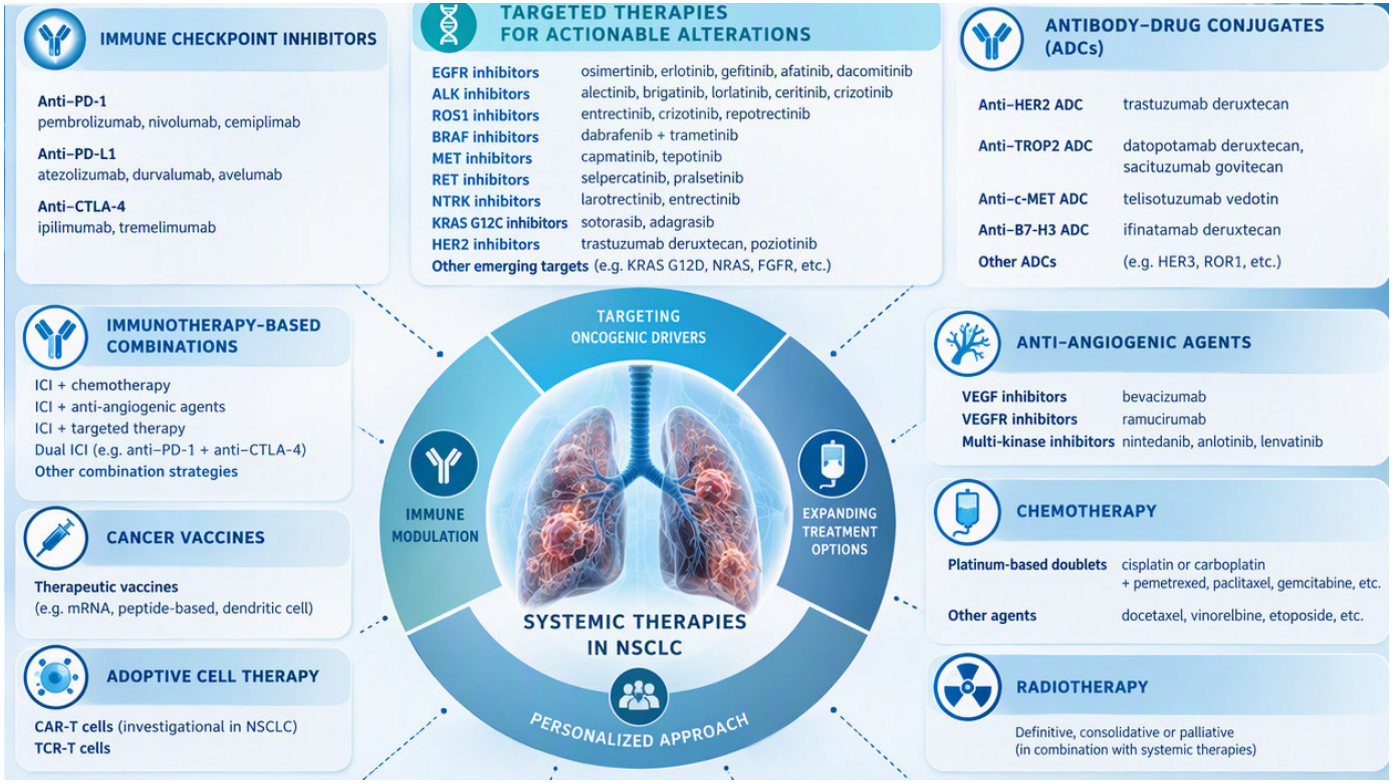
Key result

Aggressive local treatment improved survival

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The sistemic therapy revolution

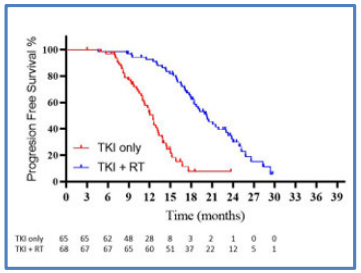


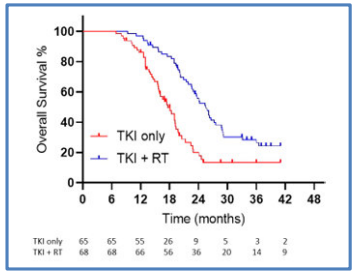
EGFR-mutated NSCLC: the strongest evidence

JNCI: Journal of the National Cancer Institute, 2023, 115(6), 742–748
https://doi.org/10.1093/jnci/djac015
Advance Access Publication Date: 30 January 2022
Article

Randomized Trial of First-Line Tyrosine Kinase Inhibitor With or Without Radiotherapy for Synchronous Oligometastatic *EGFR*-Mutated Non-Small Cell Lung Cancer

Xiao-Shan Wang, MD,[1,†] Yi-Feng Bai, MD,[1,†] Vivek Verma, MD,[2] Rui-Lian Yu, MD,[1] Wei Tian, MS,[1] Rui Ao, MD,[1] Ying Deng, MD,[1] Xue-Qiang Zhu, MD,[1] Hao Liu, MD,[1] Hai-Xia Pan, MD,[1] Lan Yang, MD,[1] Han-Song Bai, MD,[3] Xing Luo, MD,[3] Yan Guo, MS,[3] Ming-Xiu Zhou, MD,[3] Yue-Mei Sun, MD,[4] Zi-Can Zhang, MD,[4] Si-Min Li, MD,[3,5] Xue Cheng, MD,[3] Bang-Xian Tan, MD,[3] Liang-Fu Han, MD,[6] Ying-Yi Liu, MD,[7] Kai Zhang, MD,[8] Fan-Xin Zeng, PD,[9] Lin Jia, MD,[10] Xin-Bao Hao, MD,[11] You-Yu Wang, MD,[1] Gang Feng, MD,[1] Ke Xie, MD,[1] You Lu, MD,[12] Ming Zeng, MD, PhD[1,*]





Upfront RT added to TKI therapy improved PFS and OS in patients with EGFRm synchronous oligometastatic NSCLC, with an acceptable safety profile.

Main Limitations

- **Small, highly selected population:** strict eligibility criteria and no brain metastases → limited generalizability
- **Outdated systemic therapy:** only **1st-generation EGFR-TKIs** were used
- **Treatment heterogeneity:** RT dose, planning and follow-up imaging were not fully standardized; subsequent therapies were also not aligned with current practice.

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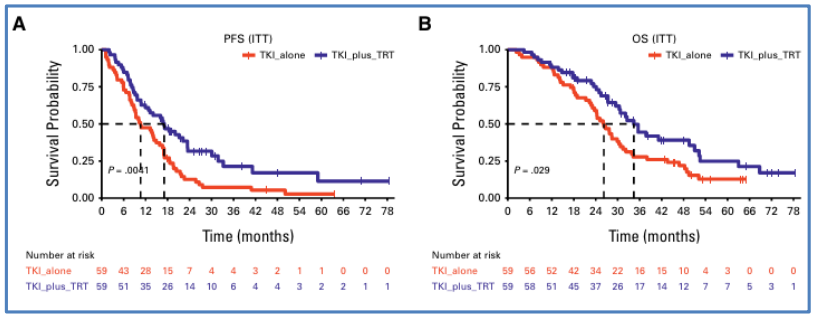
EGFR-mutated NSCLC: the strongest evidence

Original Reports | Thoracic Oncology

Thoracic Radiotherapy Improves the Survival in Patients With *EGFR*-Mutated Oligo-Organ Metastatic Non–Small Cell Lung Cancer Treated With Epidermal Growth Factor Receptor–Tyrosine Kinase Inhibitors: A Multicenter, Randomized, Controlled, Phase III Trial

Hongfu Sun, MD[1]; Minghao Li, MD[2]; Wei Huang, MD[1]; Jian Zhang, MD[3]; Shihong Wei, MD[4]; Yongjing Yang, MD[5]; Zhongtang Wang, MD[1]; Shucheng Ye, MD[5]; Heyi Gong, MD[3]; Yaowen Zhang, MD[7]; Jie Li, MD[8]; Haixia Song, MD[4]; Lifang Wang, MD[3]; Xiangming Chen, BS[9]; Haiqun Lin, MD[10]; Gaofeng Ding, MD[11]; Hongwei Li, MS[8]; Anping Zheng, MD[7]; Xuezhen Ma, MD[12]; ShaoShui Chen, MD[13]; Liping Liu, MD[14]; Kaixian Zhang, MD[15]; Chengrui Fu, MD[1]; Wenzhi Liu, MD[16]; Jing Wang, PhD[8]; Xiaqin Zhang, MS[8]; Tingting Liu, MS[1]; Dan Han, MD[1]; Qian Zhao, MD[1]; Peipei Wu, MD[14]; Qianqian Yuan, MD[15]; LiJun Tian, MD[13]; Ping Zhang, MD[8]; Xueqin Wu, MD[8]; Fei Chen, MD[8]; Zicheng Zhang, MD[16]; and Baosheng Li, MD[1]

DOI https://doi.org/10.1200/JCO.23.02075



Definitive local treatment may be biologically relevant in selected EGFR-mutant disease, but treatment intensity and toxicity remain critical.

Main Limitations

- **Small selected population:** → limited generalizability
- **Outdated systemic therapy:** only **1st-generation EGFR-TKIs** were used (icotinib)

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EGFR-mutated NSCLC: the strongest evidence

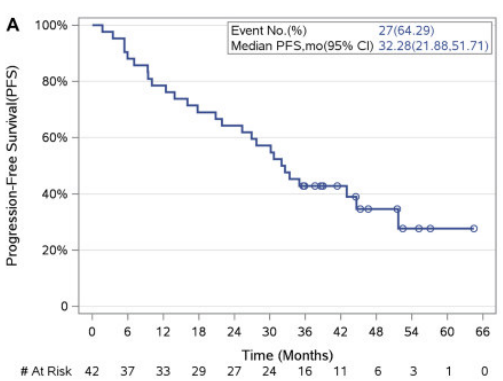
Osimertinib plus consolidative radiotherapy for advanced *EGFR* mutant non-small cell lung cancer: a multicentre, single-arm, phase 2 trial

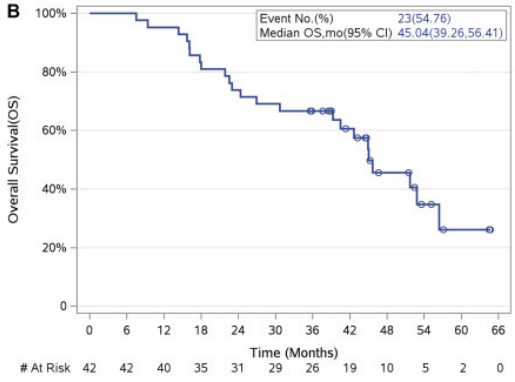
Sagus Sampath,[a,g] Sawsan Rashdan,[b,c,g] Puneeth Iyengar,[c,d,h] Townes A. Mickel,[d] Song Zhang,[c,e] Chul Ahn,[c,e] Ang Gao,[c,e] Jonathan E. Dowell,[b,c] Yuanyuan Zhang,[c,d] Kenneth D. Westover,[c,d] Suzanne M. Cole,[b,c] Arya Amini,[a] Adam Rock,[f] Erminia Massarelli,[f,i] Marianna Koczywas,[f] and David E. Gerber[b,c,e,*]

[a]Department of Radiation Oncology, City of Hope National Medical Center, Duarte, CA, USA
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[d]Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX, USA
[e]Peter O'Donnell Jr. School of Public Health, University of Texas Southwestern Medical Center, Dallas, TX, USA
[f]Department of Medical Oncology, City of Hope National Medical Center, Duarte, CA, USA

Multicentre, single-arm phase 2 trial

- **42 patients** with previously untreated stage IV EGFRm NSCLC
- No restriction on number or site of metastases
- Consolidative RT to residual disease: **up to 6 sites/organs;** 32 patients (76%) received consolidative RT





Early consolidative RT after initial osimertinib response appears feasible, well tolerated and associated with prolonged disease control

Promising, *hypothesis-generating evidence*—but a randomised trial is required to determine the incremental benefit of consolidative RT over osimertinib alone.

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EGFR-mutated NSCLC: the strongest evidence

NorthStar: A phase II randomized study of osimertinib (OSI) with or without local consolidative therapy (LCT) for metastatic EGFR-mutant non-small cell lung cancer (NSCLC)

- **Median PFS:** 25.4 vs 17.0 months **HR 0.60 (95% CI 0.40–0.92); P=0.02**
- Grade ≥3 adverse events: **29% vs 16%**, with no unexpected safety signals

A secondary analysis focused on refining **patient selection** by evaluating predictors of benefit and patterns of recurrence.

LCT modalities were RT alone, 33 (59%); RT + surgery, 6 (11%); surgery alone, 17 (30%)
76% of pts continued Osi during RT



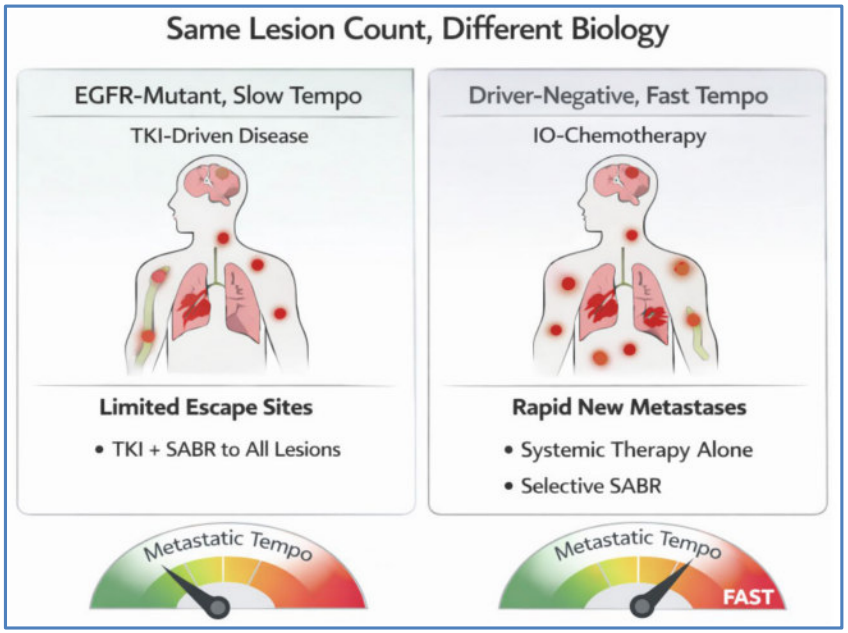
- Clearance of thoracic nodal disease and pleural effusion following Osi emerged as potential predictors of benefit from LCT
- Failures after LCT were predominantly distant, occurring outside the RT field and most commonly at new metastatic sites.
- Higher radiation dose (BED ≥75 Gy) was associated with significantly improved outcomes

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Elamin, et al. ESMO Congress 2025. LBA72
Gandhi, et al. ESMO open 11, 2026

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What about Non-AGA NSCLC?



Driver-negative / non-AGA NSCLC :

Modern systemic therapy:

Platinum chemotherapy + immunotherapy or immunotherapy-based combinations

The role of radical RT and optimal timing of irradiation of the primary tumor in stage IV NSCLC remains *uncertain*

Paucity of high quality randomized control trials

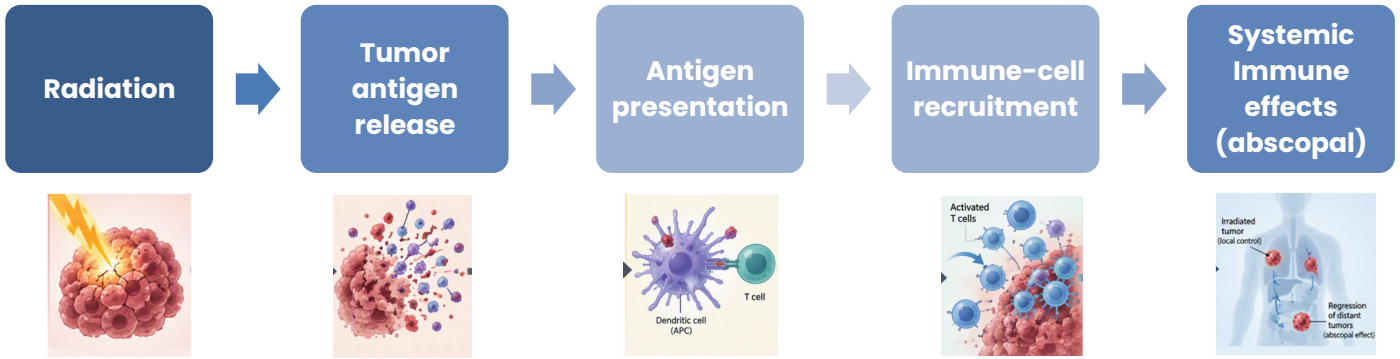
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O'Dwyer N, Palma DA. *BMJ Oncology* 2026;5:e001052. doi:10.1136/bmjonc-2025-001052

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Radiotherapy + Immunotherapy: synergy or hype?

The biological rationale is compelling



RT + ICI→ *Biological synergy ≠ proven clinical benefit*

Radiotherapy + Immunotherapy



Study	ICI	Design	RT Approach	Main Findings	Clinical Relevance
KEYNOTE-001 (Shaverdian et al., 2017)	Pembrolizumab	Secondary analysis	Prior thoracic/extrathoracic RT	Prior RT associated with longer PFS and OS compared with no prior RT	First clinical evidence of RT-immunotherapy synergy
PEMBRO-RT (Theelen et al., 2019)	Pembrolizumab	Randomized phase II	SBRT 24 Gy/3 fx before pembrolizumab	Improved ORR (36% vs 18%); numerical improvements in PFS and OS	First randomized signal supporting RT + PD-1 blockade
MD Anderson Trial (Welsh et al., 2020)	Pembrolizumab	Randomized phase I/II	Concurrent SBRT or hypofractionated RT	Safe combination; exploratory benefit particularly in PD-L1-low disease	Suggested RT may overcome primary resistance
PEMBRO-RT + MDACC Pooled Analysis (Theelen et al., 2021)	Pembrolizumab	Pooled randomized analysis	SBRT/HypoRT	Higher ORR, PFS and OS with RT + pembrolizumab	Strongest prospective evidence for radio-immunotherapy synergy
NIVORAD (2023)	Nivolumab	Randomized phase II	SBRT + nivolumab vs nivolumab	Did not meet primary endpoint; acceptable safety profile	Confirmed feasibility but limited efficacy signal
FORMENTI et al (2018)	Ipilimumab	Phase I/II	Multisite SBRT	Demonstrated systemic immune activation and abscopal responses in a subset of patients	Proof-of-concept for immunogenic effects of RT
Durvalumab + RT (phase I/II studies)	Durvalumab	Early-phase metastatic studies	SBRT or hypofractionated RT	Safe combination with evidence of immune activation; efficacy signals remain exploratory	Biological rationale later reinforced by PACIFIC in stage III disease

Radiotherapy + Immunotherapy

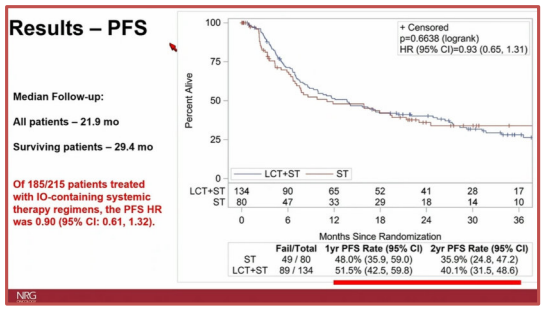
NRG-LU002: Randomized phase II/III trial of maintenance systemic therapy versus local consolidative therapy (LCT) plus maintenance systemic therapy for limited metastatic non-small cell lung cancer (NSCLC)

Patients :

- ≤3 extracranial metastases
- no progression after first-line systemic therapy (~90% received immunotherapy-based treatment)

Randomization:

Systemic therapy
Systemic therapy + LCT (radiation and/or surgery)



Overall PFS Hazard Ratio (HR) was 0.93 (p = 0.66)
Overall OS Hazard Ratio (HR) was 1.05

Grade ≥3 pneumonitis 1% vs 10%

Key result

Routine use of LCT after modern immunotherapy-based systemic therapy is not supported, and future applications will require better biological patient selection and toxicity reduction.

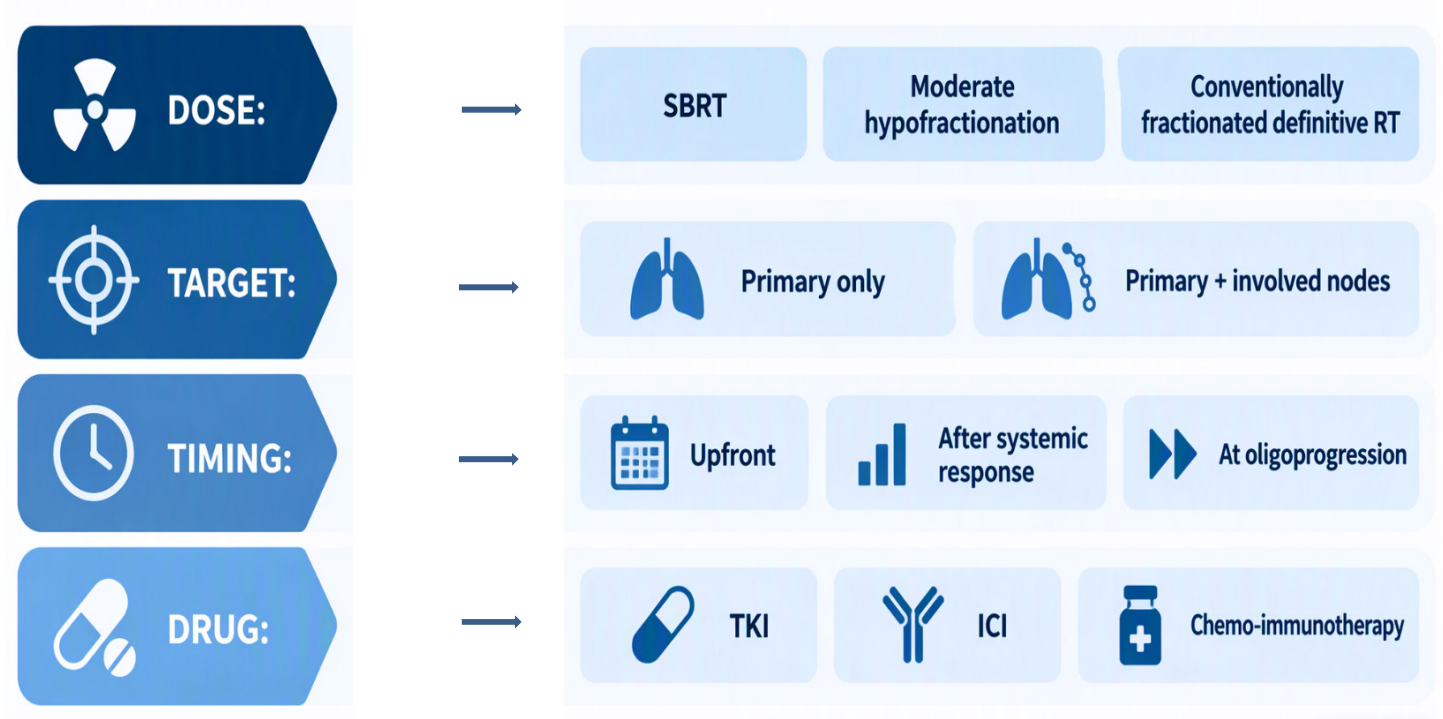
Iyengar P, Hu C, Gomez DR, et al. J Clin Oncol. 2024;42(16_suppl):8506.
Modified from ASCO 2024

Patient selection

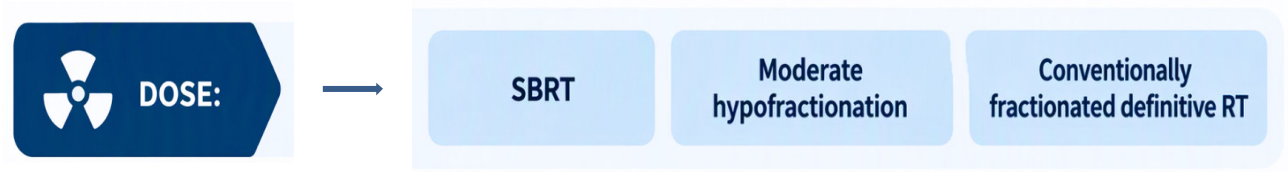


Clinical scenario	*Main question*
Widespread stage IV	Is RT purely palliative?
Oligometastatic	Can we eradicate all visible disease?
Oligopersistent after systemic therapy	Should we consolidate residual?
Oligoprogressive	Can RT prolong benefit from systemic therapy?
EGFR/ALK driven	Should we treat thoracic residual disease despite excellent response?

How should we irradiate the primary?



How should we irradiate the primary?

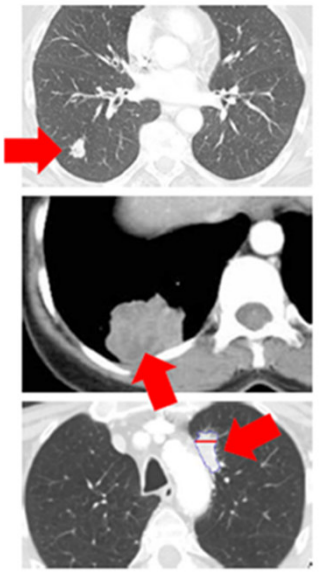


Peripheral small primary → SBRT (es. 54 Gy/3 fx, 48–50 Gy/4 fx, 50–55 Gy/5 fx)

Central / ultracentral → more fractionated SBRT/hypofractionation

Bulky primary / mediastinal nodes → conventional or moderately hypofractionated RT

Large thoracic volume → consider systemic therapy first and reassess

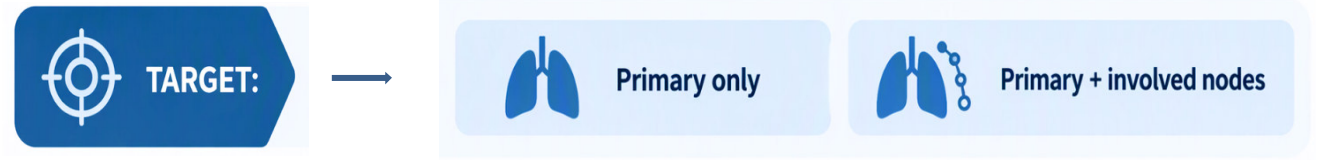


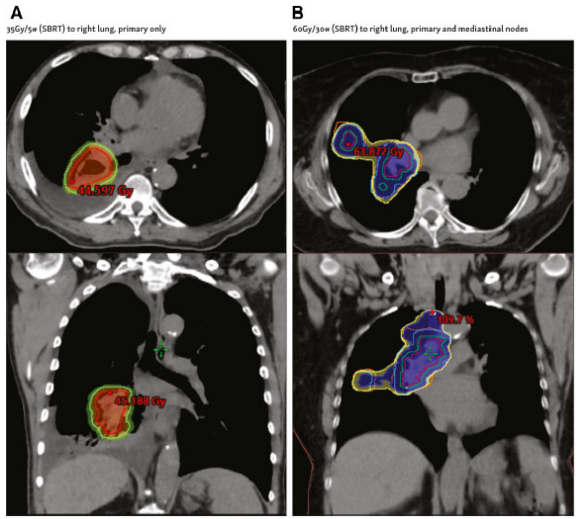
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RISK ADAPTED STRATEGIES

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How should we irradiate the primary?



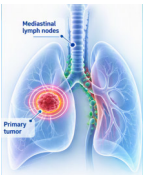


Include Mediastinal Nodes :

✓ Improve locoregional control
✓ Prevent compression of vessels or esophagus

Spare Draining Lymph Nodes:

✓ Preserve antitumor immune function
✓ Limit radiation-induced lymphopenia
✓ Potentially support immunotherapy activity



Clinical Trade-off:

nodal sparing may complicate future thoracic or mediastinal re-irradiation.

CURRENT EVIDENCE

No established standard: nodal-volume selection remains largely clinician-dependent.

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McMahon RA, Lee tal. *J Thorac Oncol* 2026;21:103643

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How should we irradiate the primary?





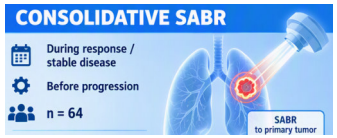
Consolidative vs Salvage SABR to the Primary Tumor in Stage IV NSCLC

Sun et al., Frontiers in Oncology 2026

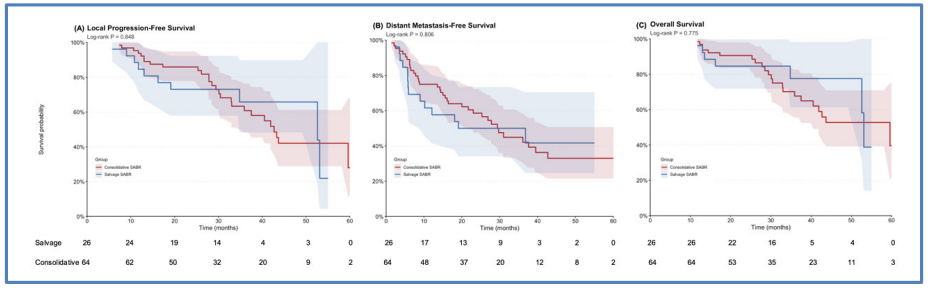
The optimal timing of primary tumor SABR in metastatic NSCLC remains uncertain.

Study Design
Retrospective analysis of 90 patients with stage IV NSCLC
Median follow-up: 38.8 months

Endpoint	Consolidative SABR	Salvage SABR
1-year LPFS	93.8%	84.6%
1-year DMFS	75.0%	61.5%
1-year OS	96.2%	77.6%







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Comparable results with analogous safety profiles

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How should we irradiate the primary?



- Although NOT addressing the use of radical RT to the primary tumor specifically, consesus recommendations from the EORTC-ESTRO OligoCare consortium provide guidance on the integration of systemic therapies

- Given the natural history of AGA and non-AGA lung cancers it is possible that NO universally «optimal» combinational startegy exists

- Treatment approaches may need to be tailored to individual biology, disease burden and patiets-specific factors

McMahon RA, Lee tal. *J Thorac Oncol* 2026;21:103643
Kroeze SGC, Pavic M, et al *Lancet Oncol*. 202; 24:e12e-e132

IASLC Consensus Recommendation

Timing of primary RT

- **Early RT** after induction systemic therapy
- Particularly promising in patients with **AGA**

⚠ **Still unclear**

Optimal timing in patients without AGA

Dose&Volumes

- **Higher RT** doses may improve outcomes
- Fractionation should be **tailored** to tumor location

⚠ **Still unclear**

Elective omission of involved lymph nodes to enhance IT efficacy

Integration

- Treatment **coordination** to avoid delays, interruption
- **Pneumonitis** risk appears additive rather than synergistic

⚠ **Still unclear**

Careful assessment when combining multiple treatment modalities

MULTIDISCIPLINARY DISCUSSION

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Modified from McMahon RA, Lee tal. *J Thorac Oncol* 2026;21:103643

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On-going trials

Trial Name	Phase	Patients (no.)	Actionable Mutations	Randomized	Primary Radiation Dose(s)	Primary Tumour (RT)	Other Metastasis (RT)	RT Timing	Systemic Therapy	Completion Date	Trial ID
NIRVANA-Lung	III	460	No	Yes	18Gy/3#	Yes	Yes	Upfront	Chemotherapy Immunotherapy	Dec-26	NCT03774732
PRIME-Lung	I	40	No	Yes	36Gy/12# 40Gy/15# 35-50Gy/5#	Yes	No	Upfront	Chemotherapy Immunotherapy	Mar-26	NCT05222087
PRIME-Lung	III	420	No	Yes	36Gy/12# 40Gy/15# 35-50Gy/5#	Yes	No	Upfront	Chemotherapy Immunotherapy	Jan-29	NCT07135882
TOURIST (PRINCE)	III	472	No	Yes	36Gy/12# 39Gy/13#	Yes	No	Upfront	Chemotherapy Immunotherapy	Dec-27	ISRCTN17123858
DRO2301	II	48	No	No	Not Stated	Yes	No	Upfront or within 6 months	Chemotherapy Immunotherapy	Feb-29	NCT06262321
MARS	III	162	No	Yes	36Gy/12#	Yes	No	3 Mo post Chemo/IO	Chemotherapy Immunotherapy	Feb-26	NCT04530708
salVage	III	128	Yes	Yes	Surgery or Radiotherapy (SBRT)	Yes	Yes	Patients responding post 3 cycles of SoC systemic therapy	Targeted therapy or Chemo/IO	Nov-27	NCT06114108
CHESS	II	96	No	No	Surgery or Radiotherapy 60-66Gy/30-33#	Yes	Yes	Patients responding post 3 mo of systemic therapy	Chemotherapy Immunotherapy	Dec-26	NCT03965468
HALT	II	113	Yes	Yes	SBRT: Site Dependant	Yes (not mandated)	Yes	Oligoprogression	TKI	Dec-26	ISRCTN53398136

RT, radiotherapy; SBRT, stereotactic body radiotherapy; SoC, standard of care; TKI, tyrosine kinase inhibitor.

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McMahon RA, Lee tal. *J Thorac Oncol* 2026;21:103643

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Take-home messagges



1. Stage IV NSCLC is no longer one disease.
2. Systemic therapy has changed the value proposition of local control.
3. In selected oligometastatic patients, comprehensive local therapy improves PFS and may improve OS.
4. The strongest evidence for treating the primary specifically is emerging in molecularly selected populations — particularly EGFR-mutated oligo-disease.
5. The future is not “the same RT for everyone”; it is biology-driven, response-adapted, multidisciplinary local therapy.

*“The question is no longer whether we can irradiate the primary tumor. The question is **which patient** has enough life expectancy, enough disease control and enough favorable biology to make local control clinically meaningful.”*

Thank you for your attention!



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