Consolidation RT in metastatic disease without oncogenic driver

Dr. Amelia Insa, *Hospital Clínico Univ. de Valencia*

CONFLICTO DE INTERESES

- ***Consultorías: Roche, Astra Zéneca, Janssen, Takeda, BeOne***
- ***Gastos de Congresos: Pfizer, Takeda, Roche, Janssen, MSD***
- ***Sesiones divulgativas: Roche, Regeneron, Janssen, Astra Zéneca***

Introduction

Local therapy, especially radiation, has historically been used for palliation in advanced NSCLC.

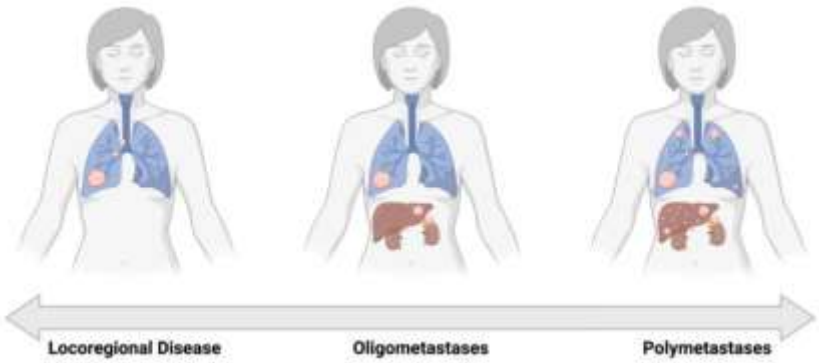
Immunotherapy has transformed the treatment landscape of advanced NSCLC without actionable driver mutations.

Is it appropriate to aim to cure systemic disease with local treatments such as radiotherapy?

- ***Not in widespread metastatic disease.***

- *But **yes, in carefully selected biological subgroups**—particularly **oligometastatic NSCLC**—local ablative therapy (especially RT) combined with systemic treatment can **modify the natural history of the disease** and may even achieve **long-term, potentially curative outcomes** in a subset of patients.*

The oligometastatic (OMD) concept



From biological aspect

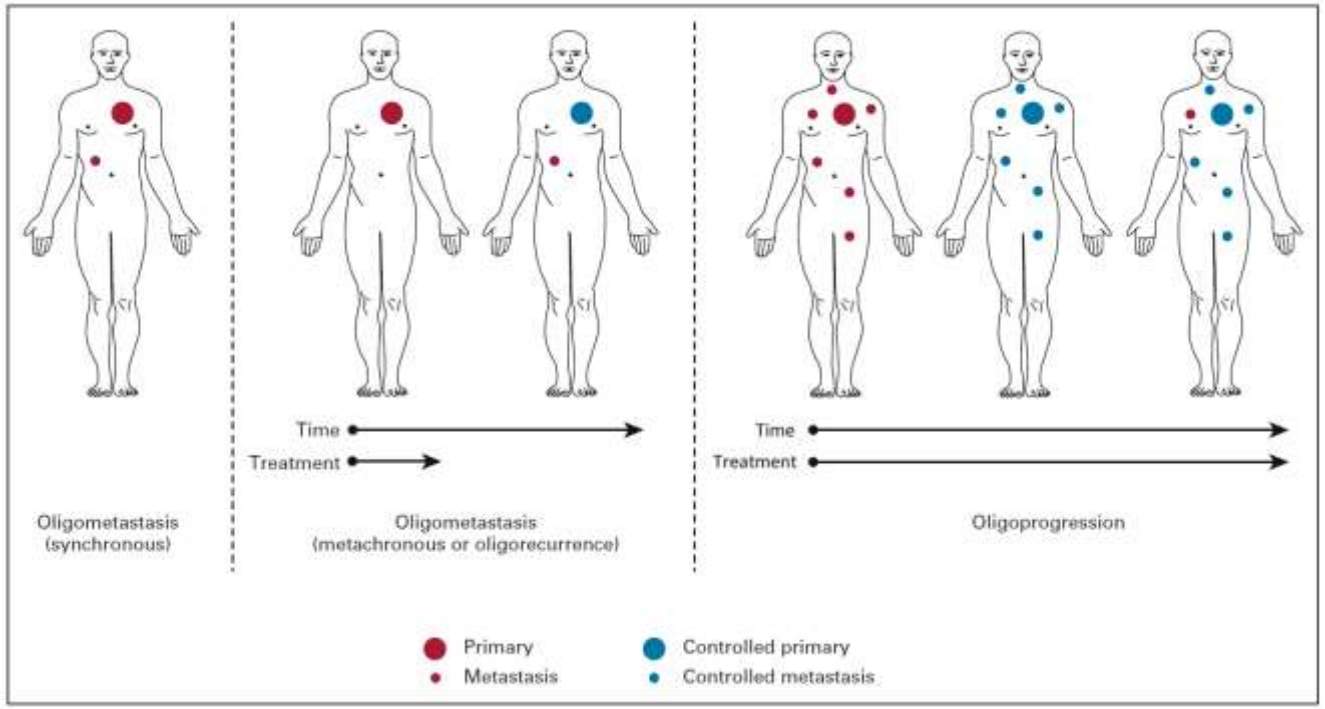
tumor with limited metastatic capacity, which is intermediate between a localized tumor and a widely metastatic tumor.

From quantitative aspect

both the number of metastatic sites and the number of organs are limited.

From treatment aspect

a type of advanced cancer with potential for cure.



A consensus from Thoracic Experts (EORTC)

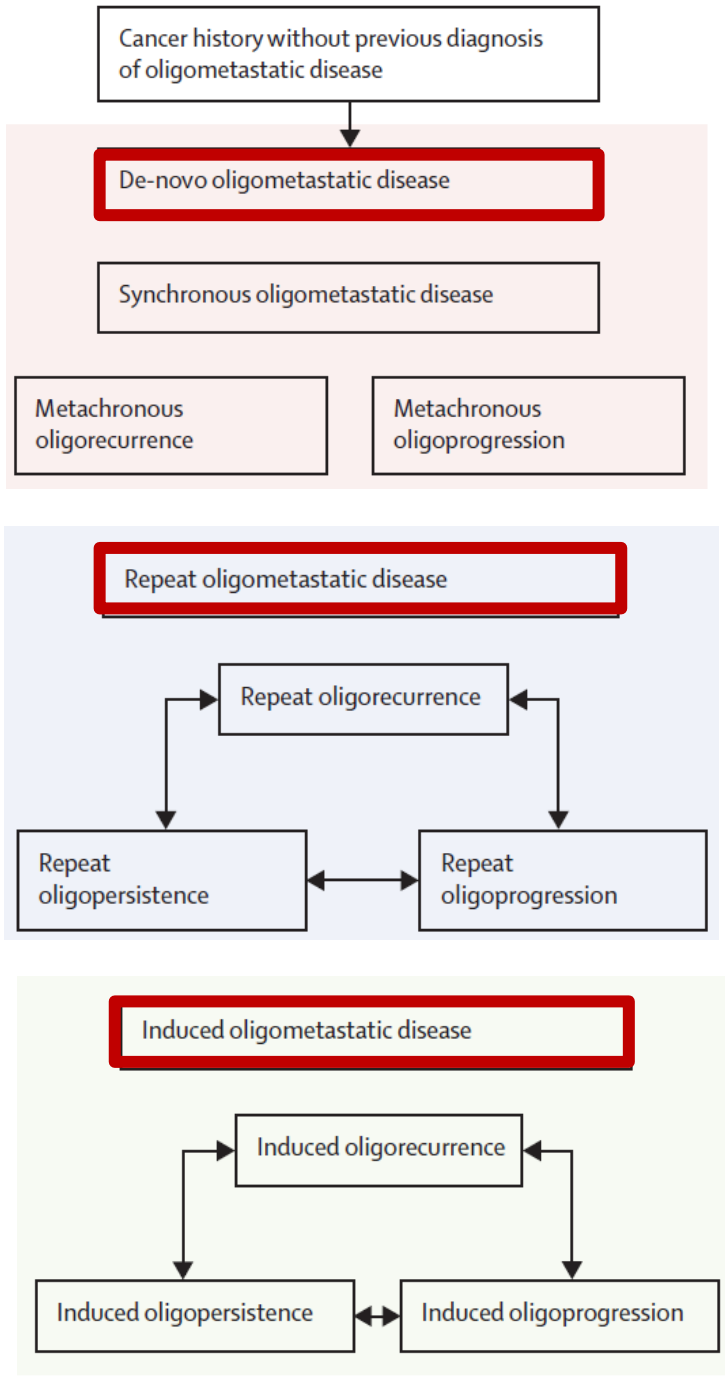
- ✓ *Radical treatment with acceptable toxicity*
- ✓ *Max 5 mets and 3 organs (Diffuse serosal and bone marrow mets excluded)*
- ✓ *Mediastinal lymph node is considered local disease (should be taken into account for radical treatment)*
- ✓ *Recommended staging: PET-CT, MR-brain*
- ✓ *Pathologic confirmation in single M1*

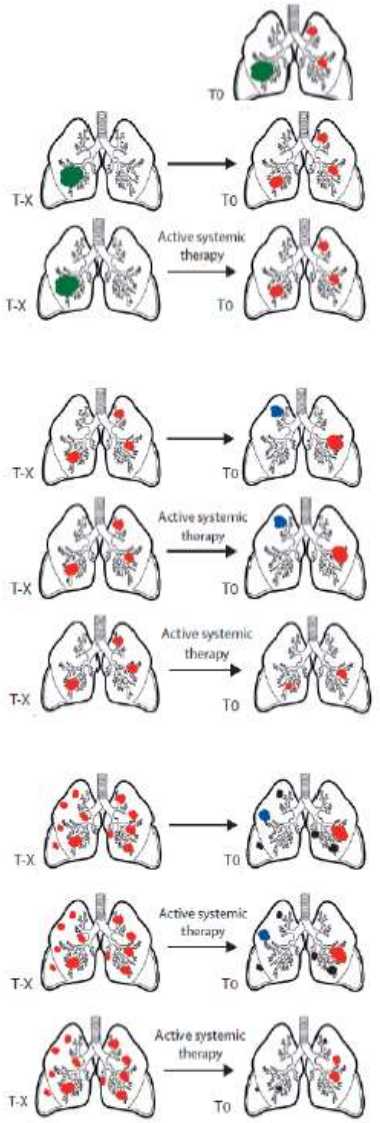
Jasper, JCO, 2022
Levy, WCLC, 2018

EORTC/ESTRO Consensus

- One patient might develop several and different states of oligometastatic disease throughout the course of disease.
- Transition from one oligometastatic state to another is not necessarily associated with a worsening of the prognosis.

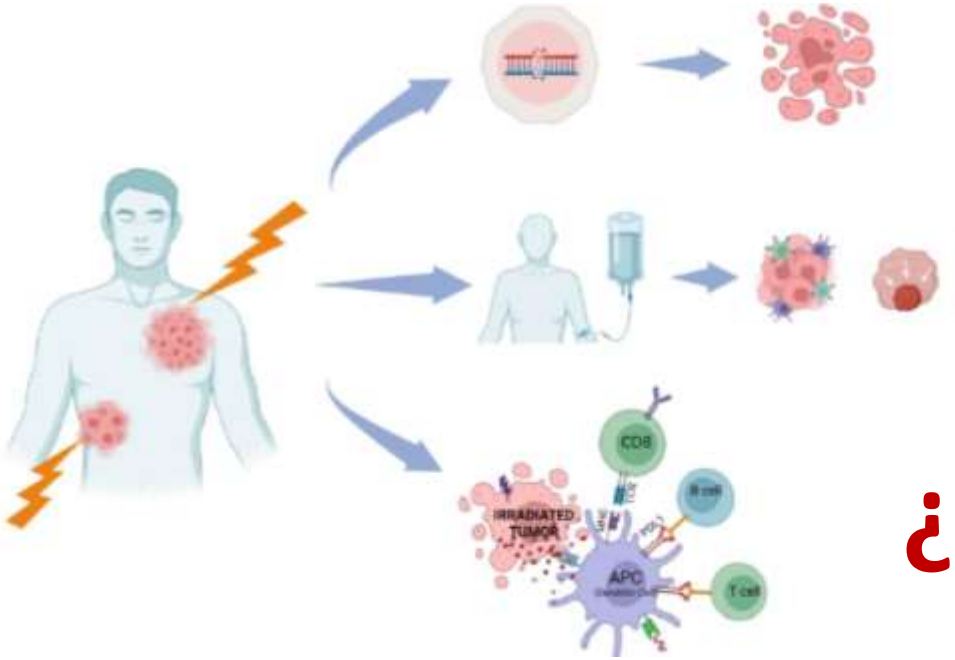
Patients with metachronous OMD and no nodal involvement had the most favorable OS.





Guckenberger, Lancet Oncol, 2020
Wilmann, Radiother Oncol. 2022

Goals and Purposes of SBRT of OMD/OPD



Achieving "cure" – eradicating all known sites of disease

Oligorecurrence/ de Novo oligometastatic

Allowing the continuation of systemic therapy

Oligoprogression/Oligopersistence
Deeper overall response

¿?

Enhancing immune and "out-of-field" response

Abscopal effect

Tsai, WCLC 2025

The role of RT seems to be better established in driver-positive advanced NSCLC.

Prospective Trials of Consolidative RT in EGFR+ NSCLC

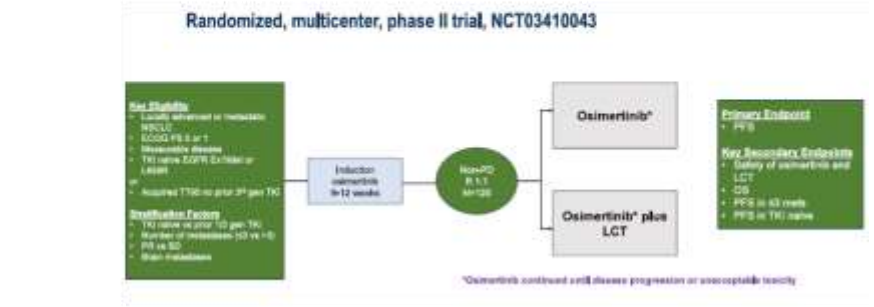
1st Author	Region	Design	n	Patient Selection	Time to RT	TKI	RT site	Outcome
Zhou[1]	China	**Ph 2,** Single-arm	64	**Oligometastatic, 61%**	4 mos	3G EGFR TKI	94% 1-2 sites, primary 37%	mPFS 29.9 mo
Sampath[2]	USA	**Ph 2,** Single-arm	32/42	**Polymetastatic**	2 mos	3G EGFR TKI	67% 1-2 sites, primary 60%	mPFS 32.3 mo
Keane[3]	USA	**Ph 2,** Single-arm	27	**Polymetastatic**	6 mos	59% late gen TKI	primary 93%	mPFS 23.4 mo
Peng[4]	China	**Ph 2,** Randomized	61	**Oligometastatic** 52% 1 met organ	3 mos	1G EGFR TKI	Primary 83%, met 57%	mPFS 17.6 v 9 mo (p=0.02)
NROG-002[5]	China	**Ph 3,** Randomized	118	**Oligomet** (≤3 organs), But 36% >10 total mets	2 weeks	1G EGFR TKI	Primary tumor and thoracic LN	mPFS 17.1 v. 10.6 mo, (p=0.004) mOS 34.4 vs. 26.2 mo (p = 0.029)

1. Zhou Y, et al. eClinicalMedicine 2024;76: 102853; 2. Sampath, et al. eClinicalMedicine 2025;87: 103435; 3. Keane, et al. Int J Radiat Oncol Biol Phys. 2025 Mar 15;121(4):975-979.; 4. Peng P, et al. Radiother Oncol. 2023 Jul;184:109681; 5. Sun, et al. JCO 2025.

Piotrowska Z, ESMO, 2025

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)

NorthStar Trial



Elamin, Y, ESMO, 2025

What is the role of RT in driver-negative advanced NSCLC?

First Clinical trials

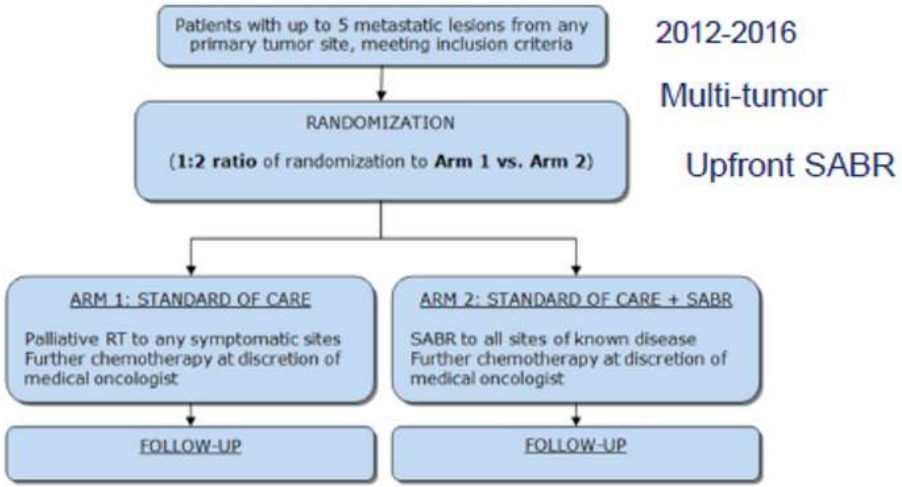
- ***Oligometastatic disease: using systemic treatment concomitante with LAT or as an induction to create an oligometastatic status.***

- ***Oligoprogression during systemic therapy.***

Clinical trials in oligometastatic disease: upfront SABR

Palma et al[12] (SABR-COMET)	II	One to five metastases (all histologies)	99	SOC	SABR + SOC	PFS 11.6 *v* 5.4 months ($P = .001$) Initial OS 41 *v* 28 months ($P = .090$, $\alpha = .20$) Long-term 5-year OS 42.3% *v* 17.7% ($P = .006$)	SABR: 29% G2+ and 4.5% G5 Control: 9% G2+, no G5

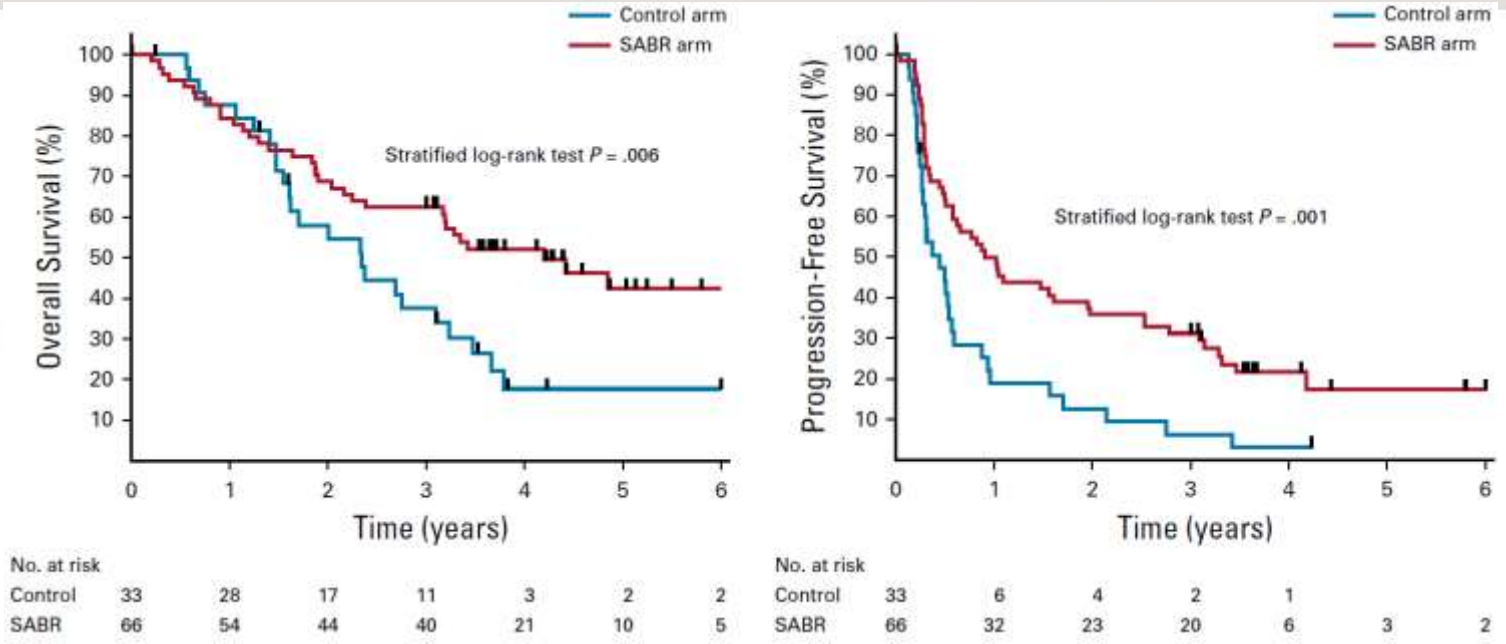
Site of original primary tumor		
Breast	5 (15)	13 (20)
Colorectal	9 (27)	9 (14)
Lung	6 (18)	12 (18)
Prostate	2 (6)	14 (21)
Other	11 (33)	18 (27)



2012-2016

Multi-tumor

Upfront SABR

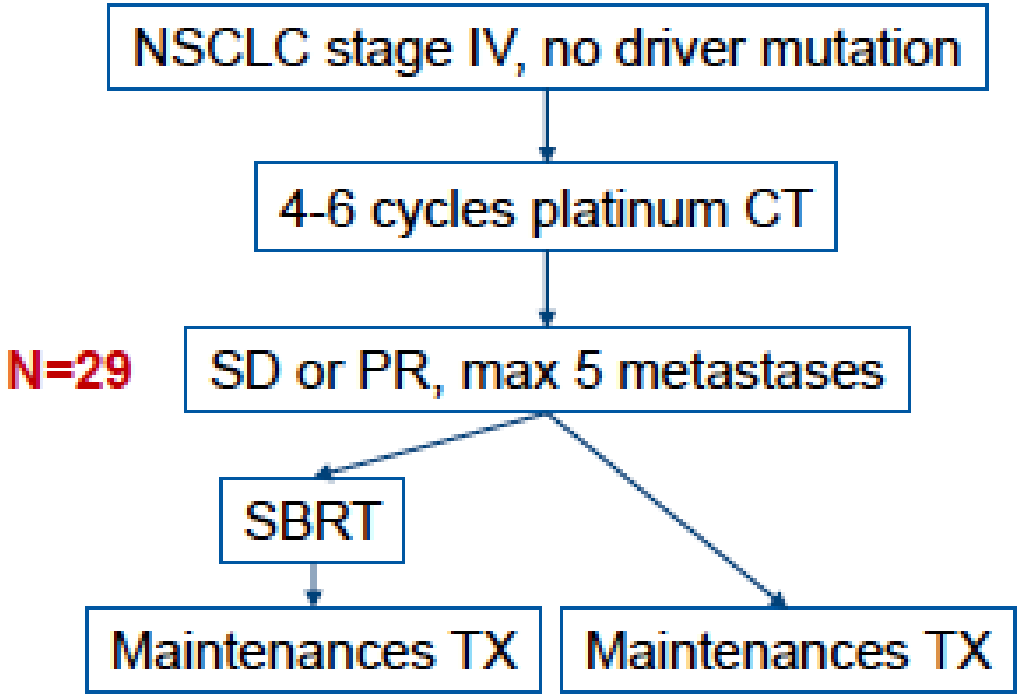


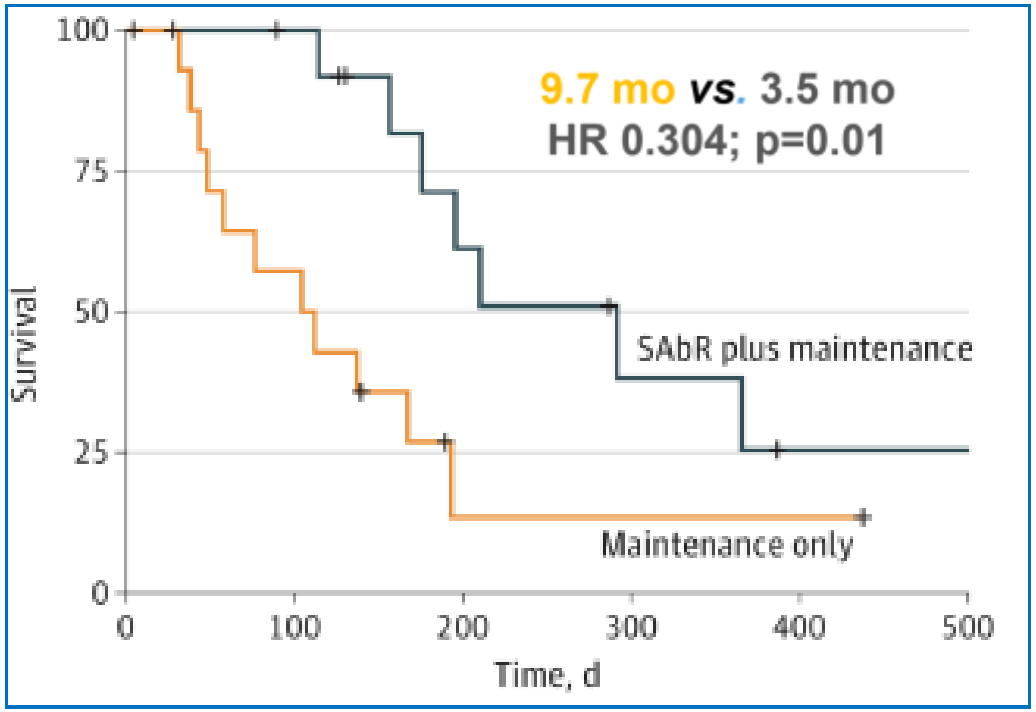
Eight-year OS was 27.2% in the SABR arm versus 13.6% in the control arm (hazard ratio, 0.50; 95% confidence interval, 0.30-0.84; P = .008)

Jasper, JCO, 2022, Palma, JCO 2020,
Harrow, Int J Radiat Oncol Biol Phys, 2022

Clinical trials in oligometastatic disease: systemic tto to create OMD

Iyengar et al[4]	II	One to five metastases after first-line chemotherapy	29	Maintenance chemotherapy	Radical tx of primary plus SABR plus maintenance chemotherapy	PFS 9.7 *v* 3.5 months ($P = .01$)	SABR: 29% G3, no G4-5 Control: 20% G3-4, no G5





Median sites of disease 3 (2-6)
Intrathoracic sites were the most common locations of treatment for SBRT

Jasper, JCO 2022,
Iyengar, JAMA ONCOL, 2017

Clinical trials in oligometastatic disease: systemic tto to create OMD

Gomez et al[13]	II	One to three metastases after first-line chemotherapy	49	Maintenance therapy or observation	Radical tx of primary plus SABR or surgery	PFS 14.2 *v* 4.4 months ($P = .022$) OS 41.2 *v* 17.0 months ($P = .017$)	SABR: 20% G3, no G4-5 Control: 8% G3, no G4-5

Gomez Lancet Oncol 2016

Stage IV NSCLC

4-6 cycles platinum CT
min. 3 months TKI

N=49 NSCLC max. 3 metastases

Local Tx

Maintenances TX | Maintenances TX

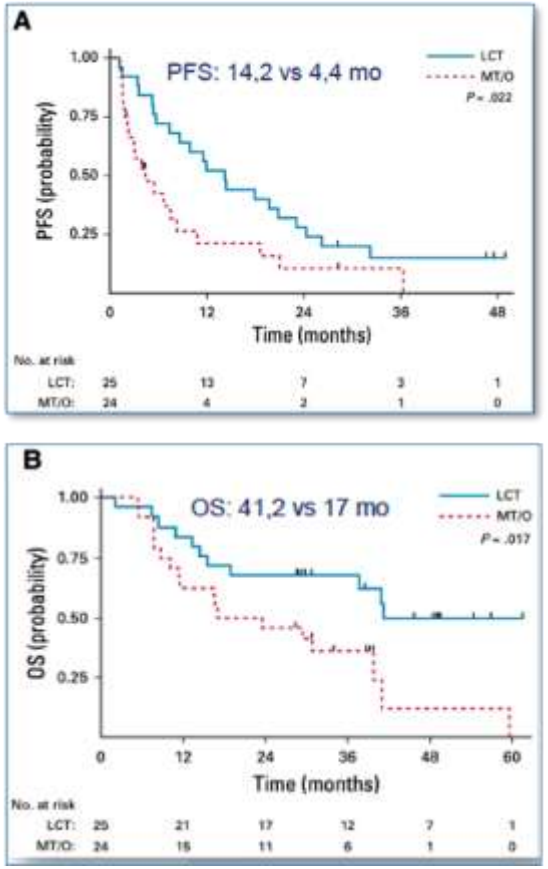
N = 25 N = 24

Local consolidative therapy used

- Hypofractionated RT or SABR in 48%
- Surgery and RT for 24%
- Chemo-RT for 8%
- Hypofractionated RT and CT-RT for 12%
- Surgery only for 4%

CNS metastases 28%,
Metachronous 6%
Synchronous 94%

EGFR+ 12%, ALK 8% (LCT)



Jasper, JCO, 2022
Gómez, JCO, 2016, 2019

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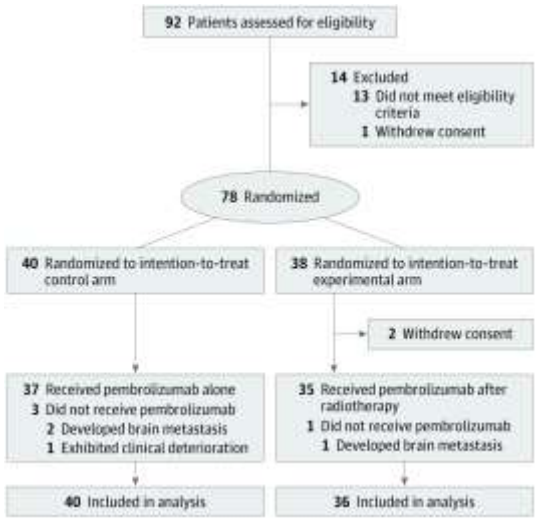
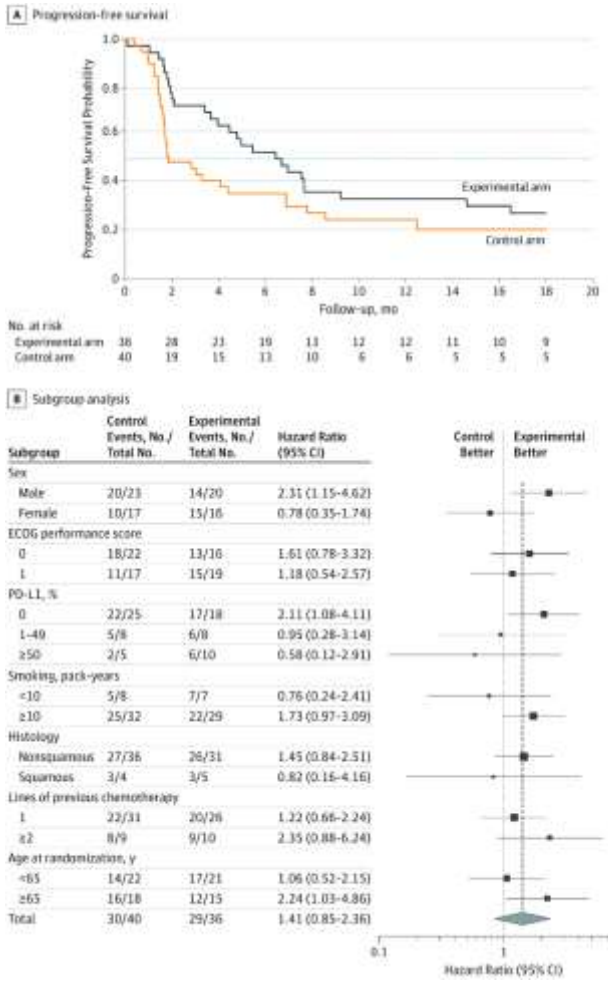
Limitation: None of these trials incorporated immunotherapy

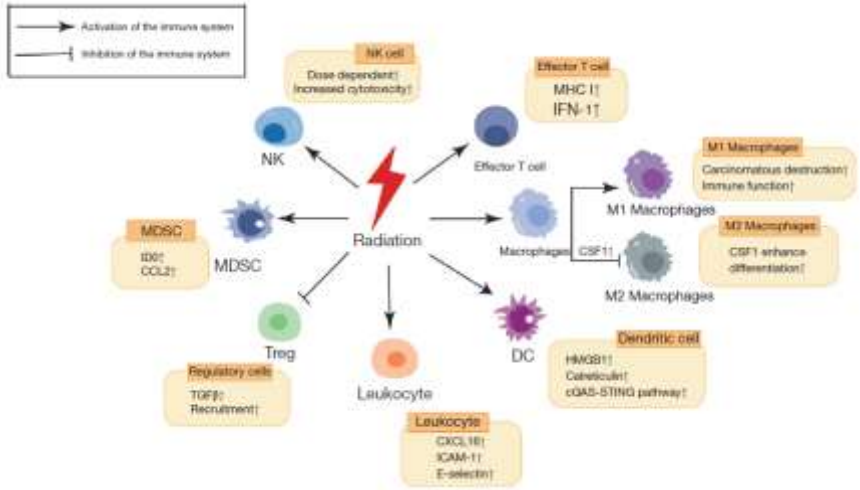
Jasper, JCO, 2022

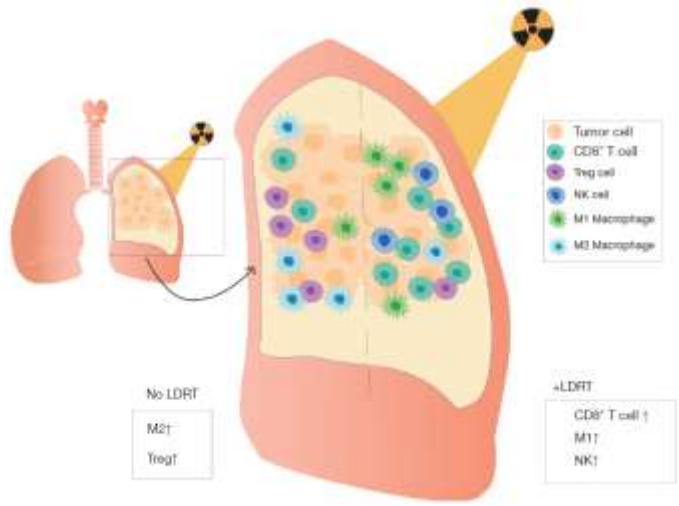
Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non–Small Cell Lung Cancer: Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial





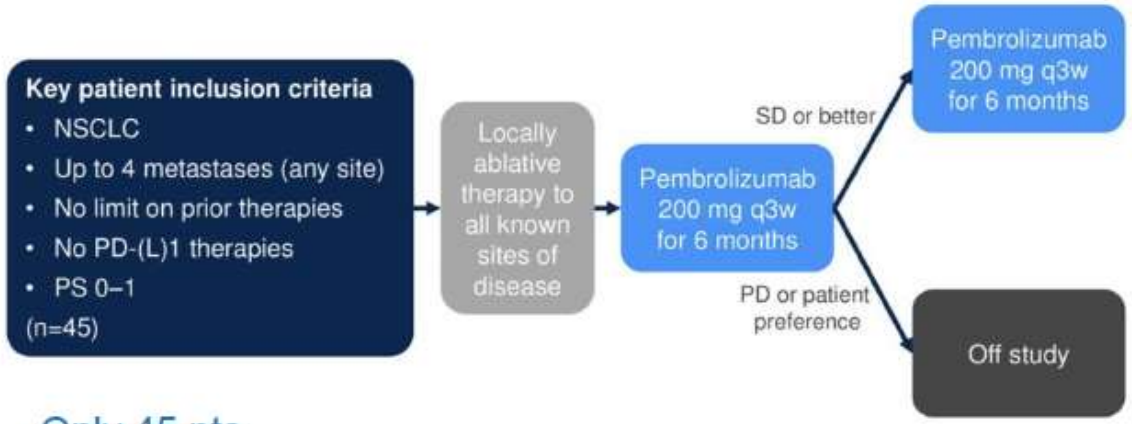
Theelen, JAMA Oncol 2019





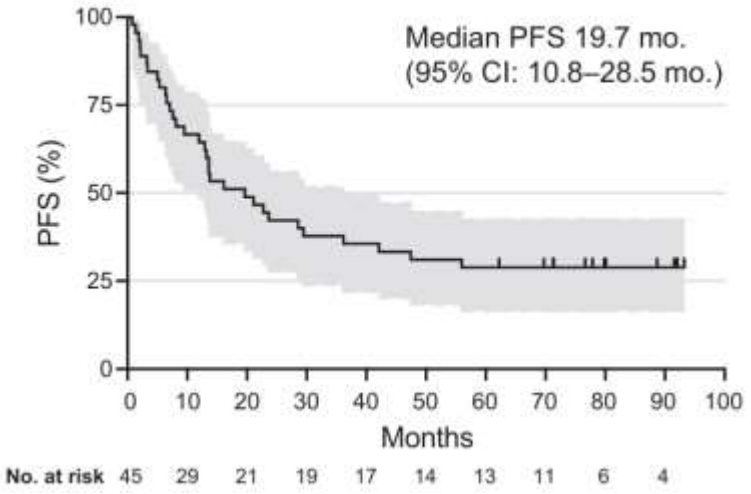
Yang, Transl Lung Cancer Res, 2025

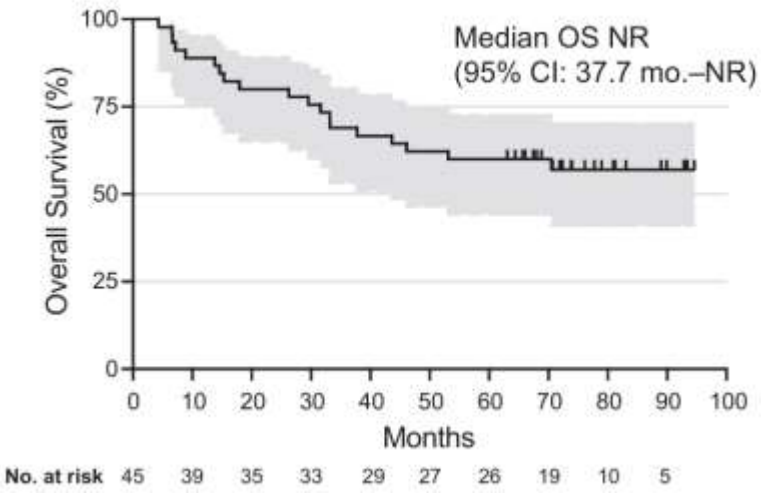
Brief Report: Long-Term Follow-Up of Adjuvant Pembrolizumab After Locally Ablative Therapy for Oligometastatic NSCLC



Only 45 pts

69% metachronous OMD
< 5 mets (2/3 1 met)
54% N0-1
36% brain mets
All EGFR/ALK WT
PD-L1+ 24%

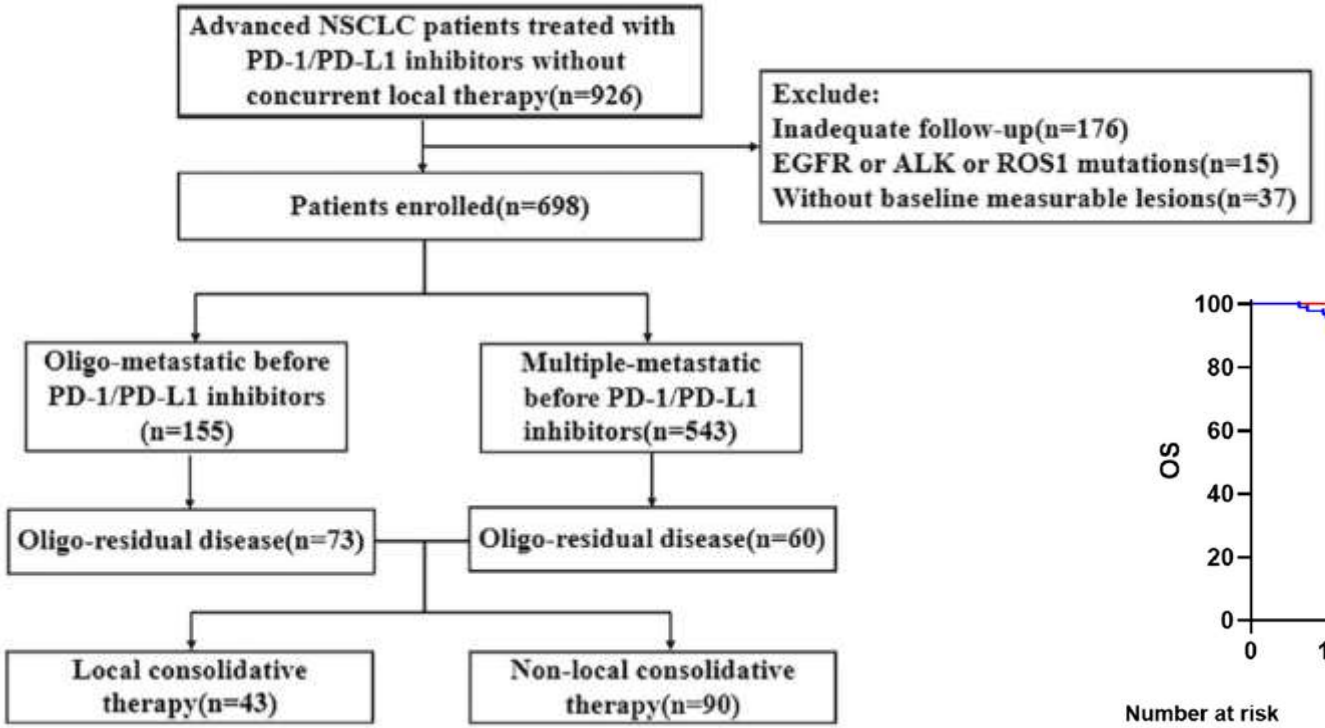




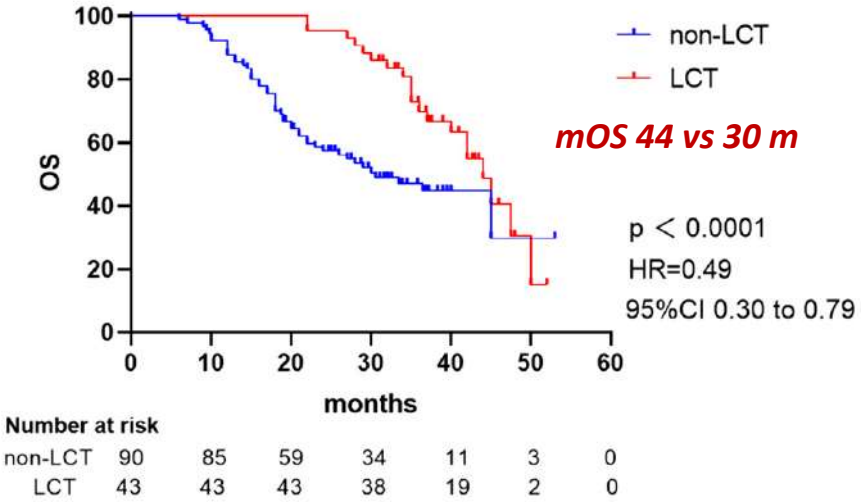
Cantor, JTO Clinical and Research Reports, 2024

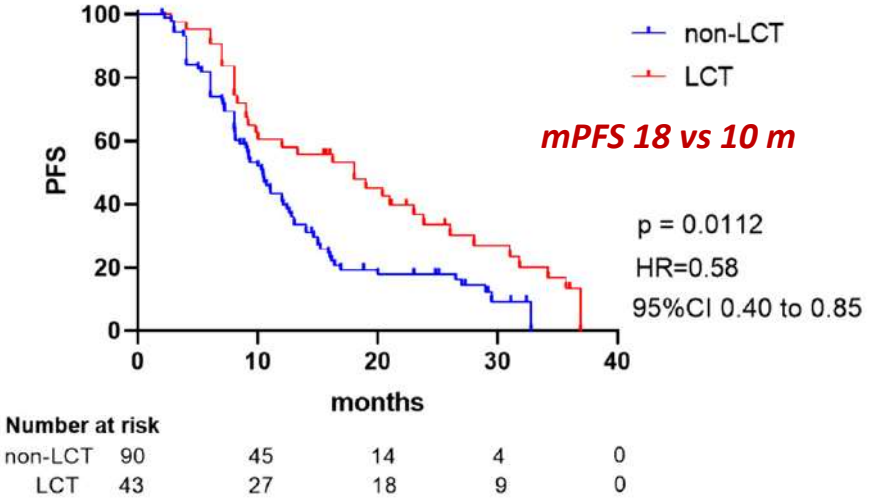
Oligopersistence after PD-L1/PD-L1 therapy

Multicenter retrospective study



Radiation therapy#	39 (90.7)
Radiotherapy type	
Conventional radiotherapy	19 (44.2)
Hypofractionated radiotherapy	14 (32.6)
Stereotactic radiotherapy	10 (23.3)
Radiotherapy organs	
Thoracic radiotherapy	22 (51.2)
Bone radiotherapy	8 (18.6)
Cranial radiotherapy	6 (14.0)
Irradiation to other sites	7 (16.3)

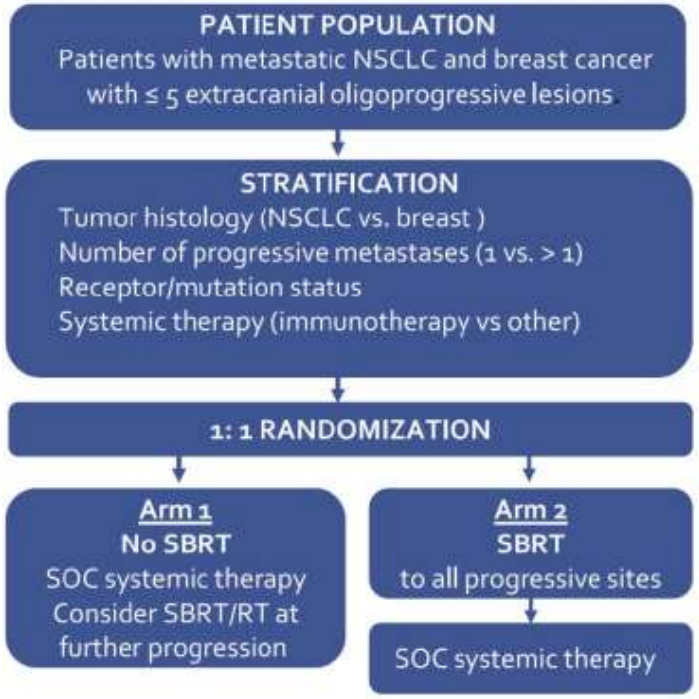




Zhang, Cancer Immunol, Immunotherapy, 2024

Clinical trials for oligoprogression during systemic treatment

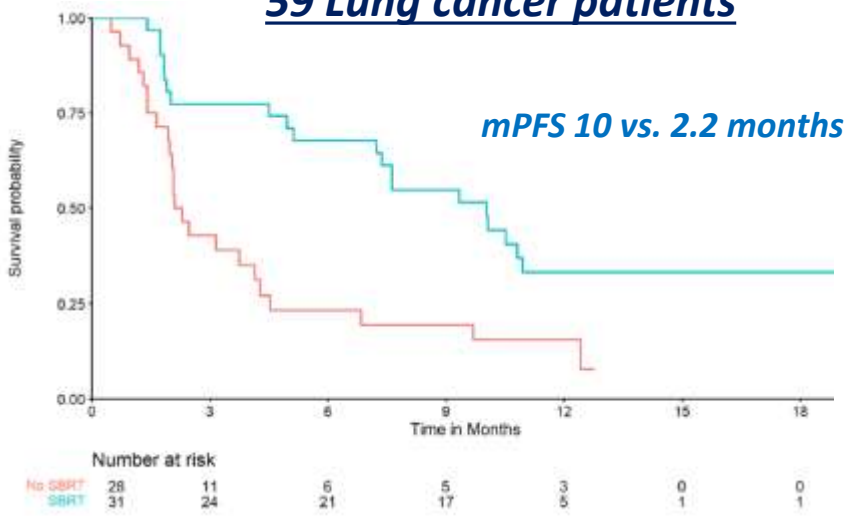
CURB	II	Oligoprogressive NSCLC/breast with ≤5 progressive lesions	106	SBRT + SOC	SOC	PFS	Median PFS: 7.2 vs 3.2m; benefit in NSCLC subgroup	Tsai et al., Lancet, 2023



59 Lung cancer patients

- ✓ ***77-82% : received Immunotherapy***
- ✓ ***71%: 2-5 oligoprogressive lesions***
- ✓ ***84-89% : no driver mutation***

59 Lung cancer patients



In NSCLC, SBRT leads to a reduction in ctDNA (p=0.02), which does not occur with standard of care therapy

Tsai, Lancet 2024

Current phase II/III trials in OMD

ETOP-CHESS

Enrolling Study	Phase	Oligometastatic Definition	Est. Enrollment	Control Arm	Experimental Arm	Primary Outcomes
SARON (NCT02417662)	III	One to three metastases	340	Systemic therapy	Radical tx of primary plus SABR plus systemic therapy	OS
NRG-LU002 (NCT03137771)	II or III	One to three metastases	400	Systemic therapy	Radical tx of primary plus SABR plus systemic therapy	PFS (phase II) OS (phase III)
SABR-COMET-3 (NCT03862911)	III	One to three metastases (all histologies)	297	SOC	SABR + SOC	OS
SABR-COMET-10 (NCT03721341)	III	4-10 metastases (all histologies)	159	SOC	SABR + SOC	OS

Another ongoing phase 2/3 trial (ICARS) including patients with sOMD NSCLC will evaluate PFS and OS after induction systemic treatment and subsequent radical treatment of residual disease followed by cemiplimab maintenance for up to 12 months vs placebo

Guckenberger, Lung cancer 2025

Jasper, JCO, 2022

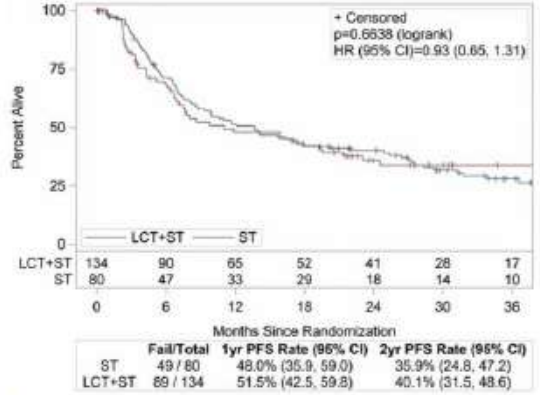
Current phase II/III trials in OMD

NRG-LU002

- largest randomized phase II/III trial conducted to determine if LCT (=radiation and/or surgery) improves survival outcomes in oligometastatic NSCLC
- For 90% of patients enrolled, the study evaluated IO/IO-chemotherapy -/+ LCT in a 1:2 radomization

  10% of patients received cytotoxic chemotherapy only -/+ LCT
- NRG-LU002 was closed to additional enrollment:

Planned interim analysis (216 patients) showed that pre-specified PFS endpoint (HR of 0.83) had not been reached.

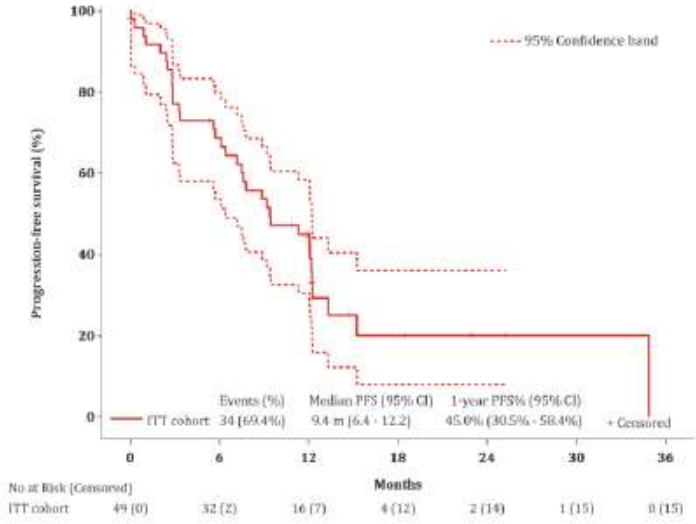


Presented at ASCO 2024

ETOP-CHESS

- Multicenter single arm phase II trial assessing immunotherapy, chemotherapy and stereotactic radiotherapy to metastases followed by definitive surgery or radiotherapy to the primary tumor, in patients with synchronous oligo-metastatic NSCLC

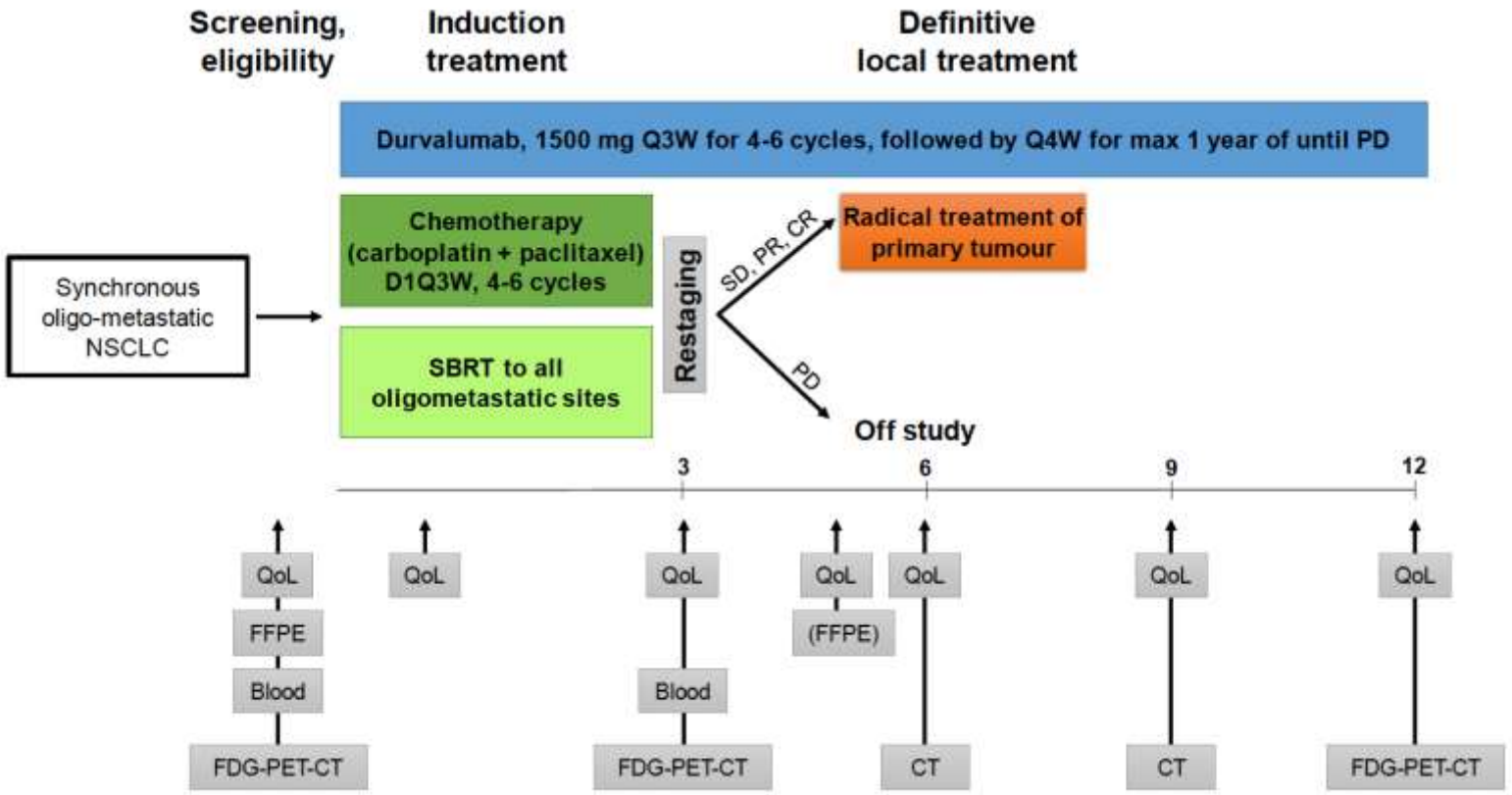
- **Primary endpoint:** one-year PFS, aiming to an improvement from 25% to 50%.
- **PFS: 33%, trial did not meet its primary endpoint.**



Guckenberger et al., Lung Cancer, 2025

ETOP-CHESS

Max 3 met



Exclusion criteria:

- ✓ ***Presence of a driver aberration in the EGFR, ALK, or ROS1 genes,***
- ✓ ***Presence of brain metastases not amenable for RSG or NSG***
- ✓ ***Ineligibility of the primary tumour to definitive local therapy***

The primary endpoint was one-year progression-free survival, aiming to an improvement from 25% to 50%.

Guckenberger, Lung cancer 2025

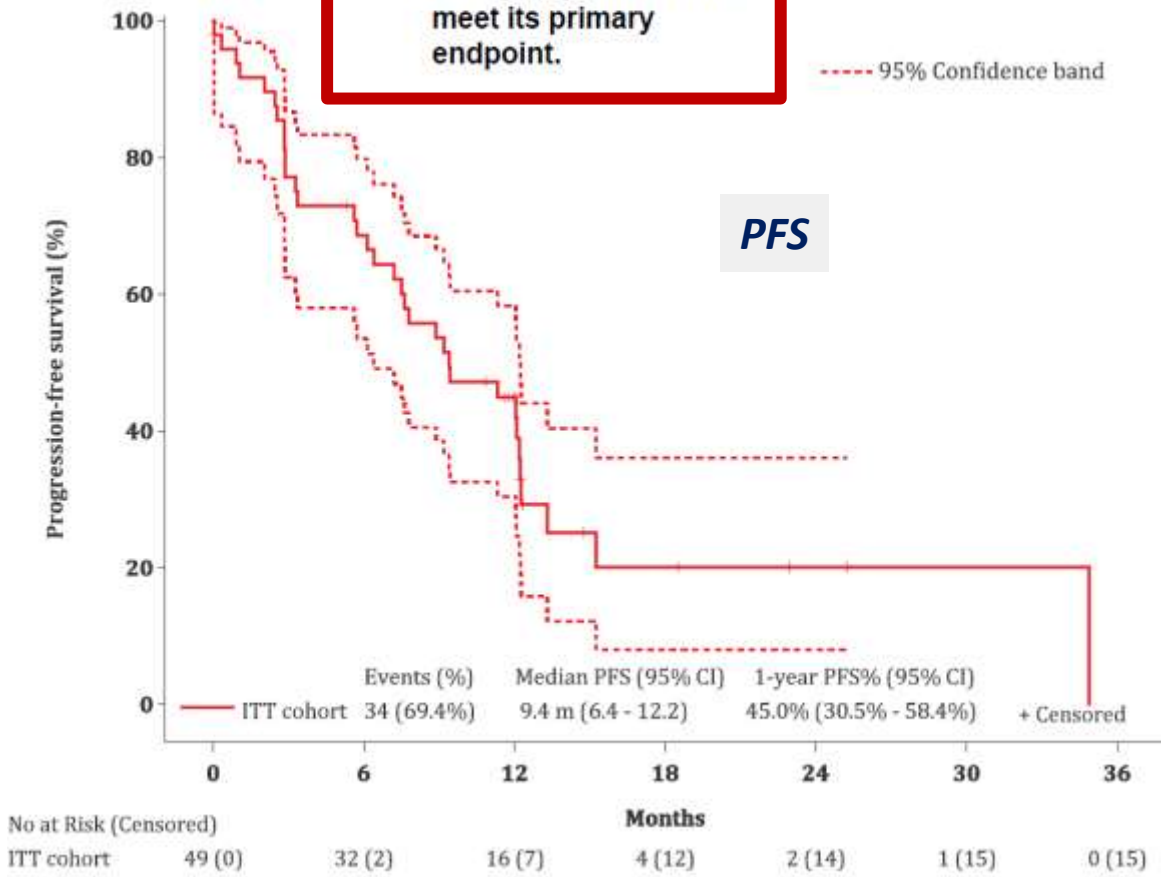
ETOP-CHESS

Negative trial

- **Primary endpoint:** one-year PFS, aiming to an improvement from 25% to 50%.
- **PFS: 33%, trial did not meet its primary endpoint.**

Patient and tumour baseline characteristics.

Characteristic	ITT Cohort (N = 49)
Histology - n (%)	
Adenocarcinoma	29 (59.2)
Squamous	16 (32.7)
Other NSCLC[#]	4 (8.2)
PD-L1 expression — n (%)	
≥1%	20 (40.8)
<1%	16 (32.7)
Missing*	13 (26.5)
No. of oligometastatic lesions at enrolment – n (%)	
1	26 (53.1)
2	15 (30.6)
3	8 (16.3)
Oligometastatic lesion location – n (%)	
Thorax	19 (38.8)
Abdomen	14 (28.6)
Non-spinal bones	14 (28.6)
Brain	4 (8.2)
Pelvis	4 (8.2)
Vertebral column	4 (8.2)
Neck	1 (2.0)
Non-regional lymph nodes	1 (2.0)
Other[$]	2 (4.1)
Brain metastases – n (%)	
Yes	6 (12.2)
No	43 (87.8)



Guckenberger, Lung cancer 2025

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 with metastatic NSCLC having completed at least 4 cycles or courses* of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited metastatic disease (0-3 discrete extracranial sites), all of which must be amenable to SBRT/ radiation +/- Surgery A minimum of one disease site (metastasis or primary) needs to be present after first-line/induction systemic therapy and treatable with local consolidative therapy	**STRATIFY**	**Histology:** Squamous vs. Non-squamous **Systemic Therapy:** Immunotherapy-containing Induction Regimens vs. Cytotoxic Chemotherapy Only Induction Regimens**	**RANDOMIZE**	**Arm 1**: Maintenance systemic therapy alone** **Arm 2:** SBRT/radiation or SBRT/ radiation and Surgery to all sites of metastases (0-3 discrete sites) and/or irradiation (SBRT or hypofractionated RT) of the primary site followed by maintenance systemic therapy. All Arm 2 patients, even if treated with Surgery, must have one site of disease (metastasis or primary) treated with radiation*** If a metastatic site is best treated with hypofractionated radiation, this will be permitted if SBRT or surgery not indicated *** **As noted in Section 5**

NRG-LU002
218 patients
68 sites enrolled
at least 1 pt

2:1 randomization in favor of LCT arm.

Iyengar ASCO, 2024

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)*

PRIMARY OBJECTIVES

- Ph II: Evaluate impact on PFS of adding local consolidative therapy (LCT) to maintenance systemic therapy versus maintenance systemic therapy alone for patients with metastatic NSCLC → no evidence of progression/limited metastatic sites after first-line systemic therapy
- Ph III: Evaluate impact on OS of adding LCT to maintenance systemic therapy versus maintenance systemic therapy alone for patients with metastatic NSCLC → no evidence of progression/limited metastatic sites after first-line systemic therapy

Iyengar ASCO, 2024

Patient or Tumor Characteristic	Maintenance Therapy (n=81)	LCT + Maintenance Therapy (n=134)	Total (n=215)
Histology*			
Non-Squamous cell carcinoma	64 (79.0%)	103 (76.9%)	167 (77.7%)
Squamous cell carcinoma	17 (21.0%)	31 (23.1%)	48 (22.3%)
Systemic Therapy Type*†	(n=75)	(n=129)	(n=204)
Cytotoxic Chemotherapy	8 (10.7%)	11 (8.5%)	19 (9.3%)
Immunotherapy	67 (89.3%)	118 (91.5%)	185 (90.7%)
Number of Lesions			
1	49 (60.5%)	77 (57.5%)	126 (58.6%)
2	20 (24.7%)	37 (27.6%)	57 (26.5%)
3	12 (14.8%)	18 (13.4%)	30 (14.0%)
4	0 (0.0%)	1 (0.7%)	1 (0.5%)
5	0 (0.0%)	1 (0.7%)	1 (0.5%)
Consented to tissue/blood collection			
No	13 (16.0%)	26 (19.4%)	39 (18.1%)
Yes	68 (84.0%)	108 (80.6%)	176 (81.9%)

Iyengar ASCO, 2024

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)*

Negative trial

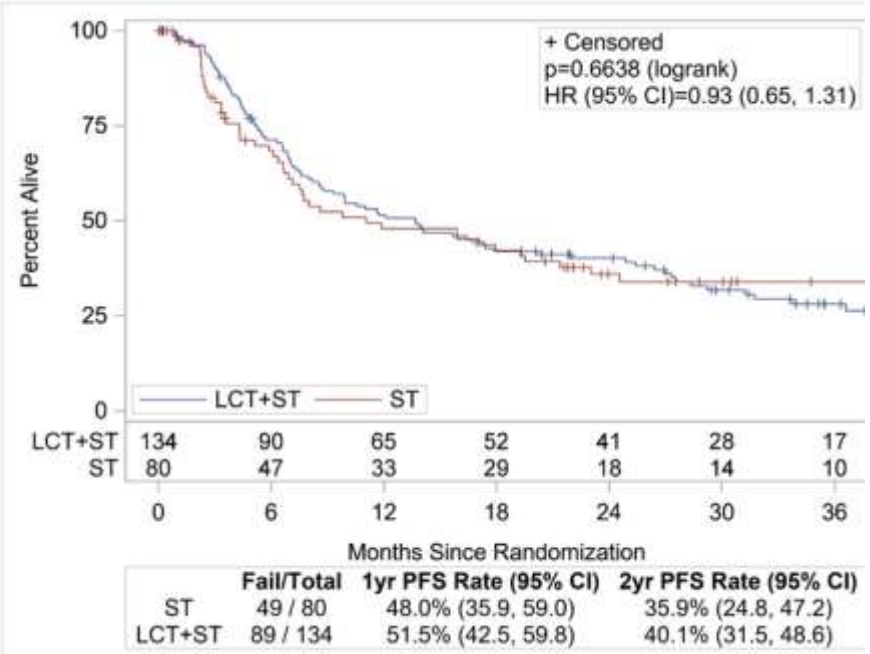
Results – PFS

Median Follow-up:

All patients – 21.9 mo

Surviving patients – 29.4 mo

Of 185/215 patients treated with IO-containing systemic therapy regimens, the PFS HR was 0.90 (95% CI: 0.61, 1.32).



	Fail/Total	1yr PFS Rate (95% CI)	2yr PFS Rate (95% CI)
ST	49 / 80	48.0% (35.9, 59.0)	35.9% (24.8, 47.2)
LCT+ST	89 / 134	51.5% (42.5, 59.8)	40.1% (31.5, 48.6)

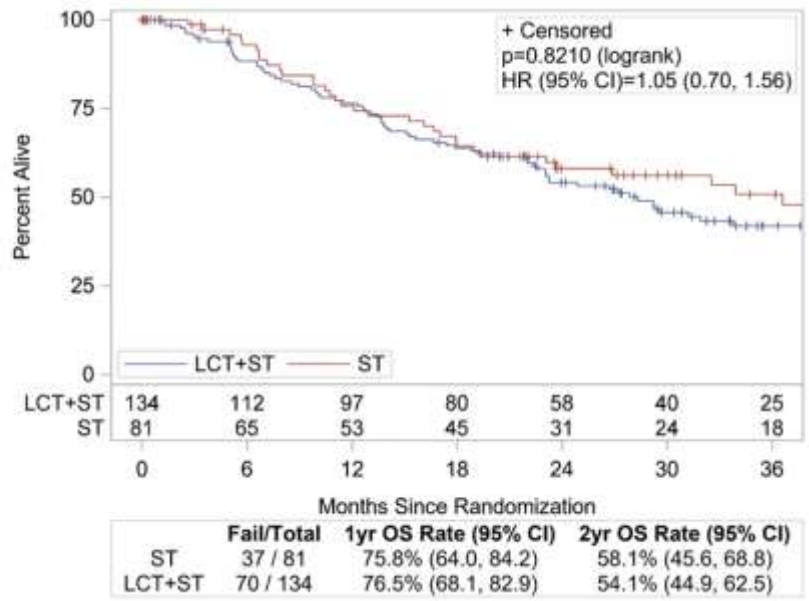
Results – OS

Median Follow-up:

All patients – 21.9 mo

Surviving patients – 29.4 mo

Of 185/215 patients treated with IO-containing systemic therapy regimens, the OS HR remained 1.05 (95% CI: 0.68, 1.63).



	Fail/Total	1yr OS Rate (95% CI)	2yr OS Rate (95% CI)
ST	37 / 81	75.8% (64.0, 84.2)	58.1% (45.6, 68.8)
LCT+ST	70 / 134	76.5% (68.1, 82.9)	54.1% (44.9, 62.5)

- NRG-LU002 was closed to additional enrollment after a planned interim analysis (216 patients enrolled) at the completion of the Ph2 portion of the trial showed that a pre-specified PFS endpoint (HR of 0.83) had not been reached.

- 1-yr and 2-yr PFS and OS rates were not statistically different between arms of the study.
- Patients receiving LCT + maintenance systemic therapy developed more grade 2 or higher toxicities and more grade 3 or higher pneumonitis.

Iyengar ASCO, 2024

“No phase III trial has demonstrated the efficacy of local treatments across the different oligometastatic disease settings.”

Mainly small retrospective studies or exploratory analyses available

Heterogeneous study populations due to lack of a clear definition of OMD

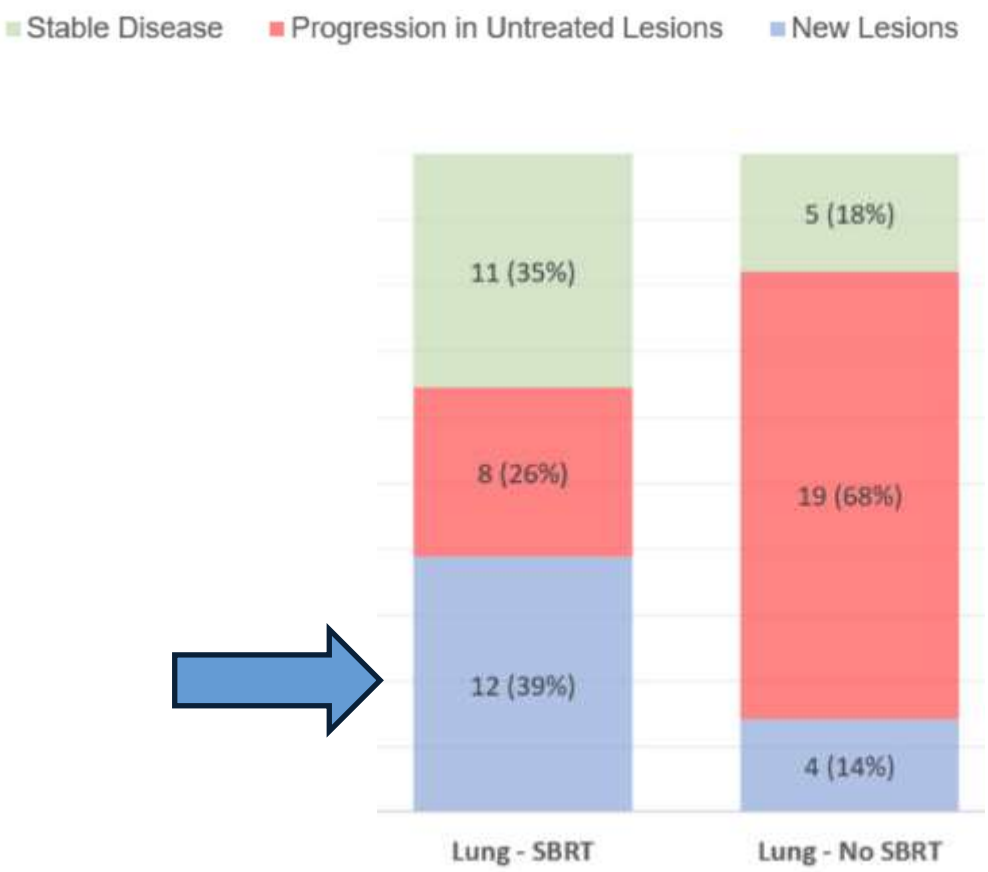
Do We Need to Treat sOMD Differently from Widespread Metastatic Disease?

Current Challenges: better systemic treatments

Neither SABR-COMET nor Gomez et al found a significant improvement in time to new metastases after local ablation, suggesting that micrometastatic disease had seeded in many patients before local ablation of visible Oligometastases.

Overall, more than a quarter of patients had disease progression or died early in the induction phase, with distant disease progression being the most common outcome. (CHESS TRIAL)

CURB



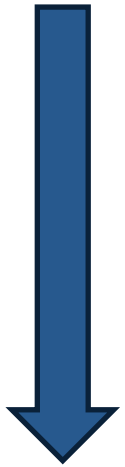
Jasper, JCO, 2022

Tsai, Lancet 2024 *Guckenberger, Lung cancer 2025*

Current Challenges: patient selection

- *As current staging techniques cannot detect potential micrometastases, it seems reasonable to begin with systemic therapy to eliminate these micrometastases and to avoid futile LRT in patients who do not respond to systemic treatment.*

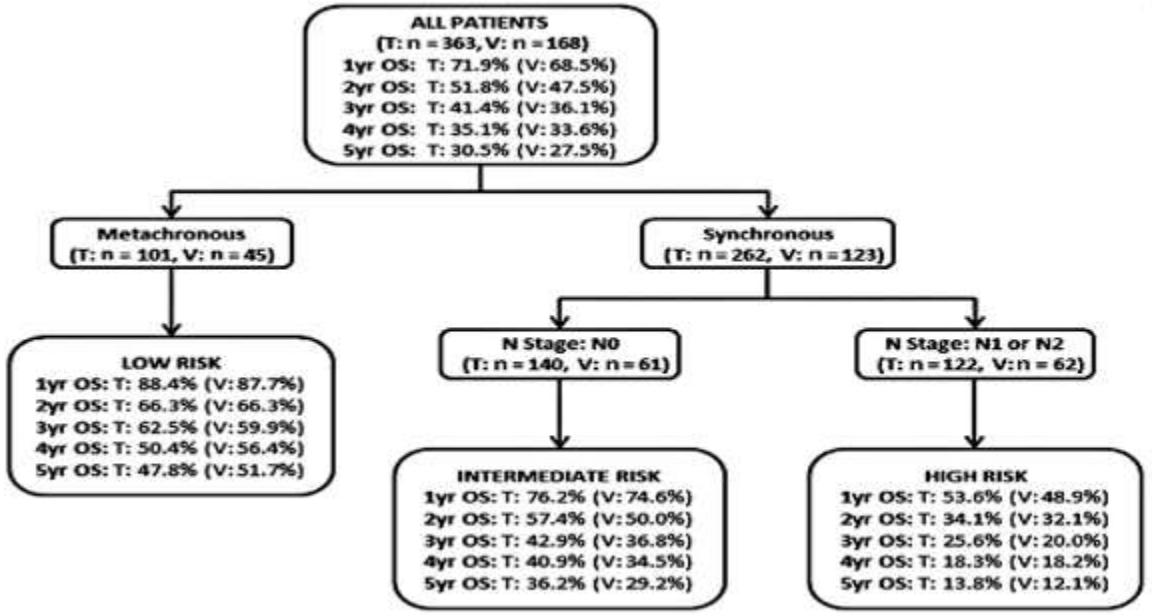
- *The integration of local and systemic therapies in the treatment of OMD requires precise patient selection to maximize therapeutic efficacy and improve clinical outcomes.*



Patient selection

757 oligometatatic NSCLC patients treated with ablative therapy to all sites
457 (75%) syncronous and 148 (25%) metachronous
668 (88%) single metastatic site

	Patient selection	Toxicity risk	Timing
Best candidates	Good performance status Low burden of disease (one oligometastasis) Multiple systemic therapy options	Small lesions Treatment unlikely to cause toxicity (eg, small resection or tumor far from critical structures)	Metachronous oligometastases Responding to systemic therapy
Less favorable	Borderline performance status (eg, ECOG 2) Moderate burden of disease (two to five oligometastases)	Larger lesions Moderate risk of toxicity or impact on organ function	Synchronous oligometastases Overlapping toxicities (eg, immunotherapy and thoracic radiotherapy)
Unfavorable	Poor performance status High burden of disease (> 5 metastases)	Very large lesions High risk of toxicity Comorbidities precluding radiotherapy or surgery	No response to systemic therapy Rapid disease progression



Low-risk | intermediate | High-risk

5y OS 47.8% | **35.2%** | **13.8%**

Jasper, JCO, 2022
Ashworth, Clin Lung Cancer 2014

Patient selection

Positive prognostic factors for OS/PFS in OMD:

• N0 disease	*(Ashworth et al., Frost et al., Opitz et al., Jones et al.)*
• Smaller primary tumor	*(Ashworth et al, Frost et al., Jones et al.)*
• Adenocarcinoma (vs. Other histologies)	*(Ashworth et al., Frost et al., De et al.)*
• Younger age	*(Ashworth et al., Opitz et al.)*
• Fewer metastases (1 vs. >1)	*(Ashworth et al., Frost et al.)*
• Neoadjuvant / perioperative systemic treatment	*(Ashworth et al., Jones et al.)*
• Absence of bone metastases	*(Opitz et al., Rodriguez-Quintero et al.)*
• Disease-free interval >1 year	*(Ashworth et al.)*
• Brain metastases (vs. Extracranial metastases)	*(Ashworth et al.)*
• Good performance score (ECOG)	*(Frost et al.)*
• L0, V0, Pn0	*(Jones et al.)*
• **EGFR mutation**	***(De et al.)***

Ashworth, Lung Cancer 2013, Frost Lung Cancer 2018, Opitz EJCTS 2020, Jones Cancers 2021, De JCO Precis Oncol 2023, Rodriguez-Quintero, J Am Coll Surg 2024, Werner WCLC 2025

Current Challenges: Molecular classification

- *Understanding the biological behavior to each OMD subtype can aid in predicting treatment response and prognosis.*

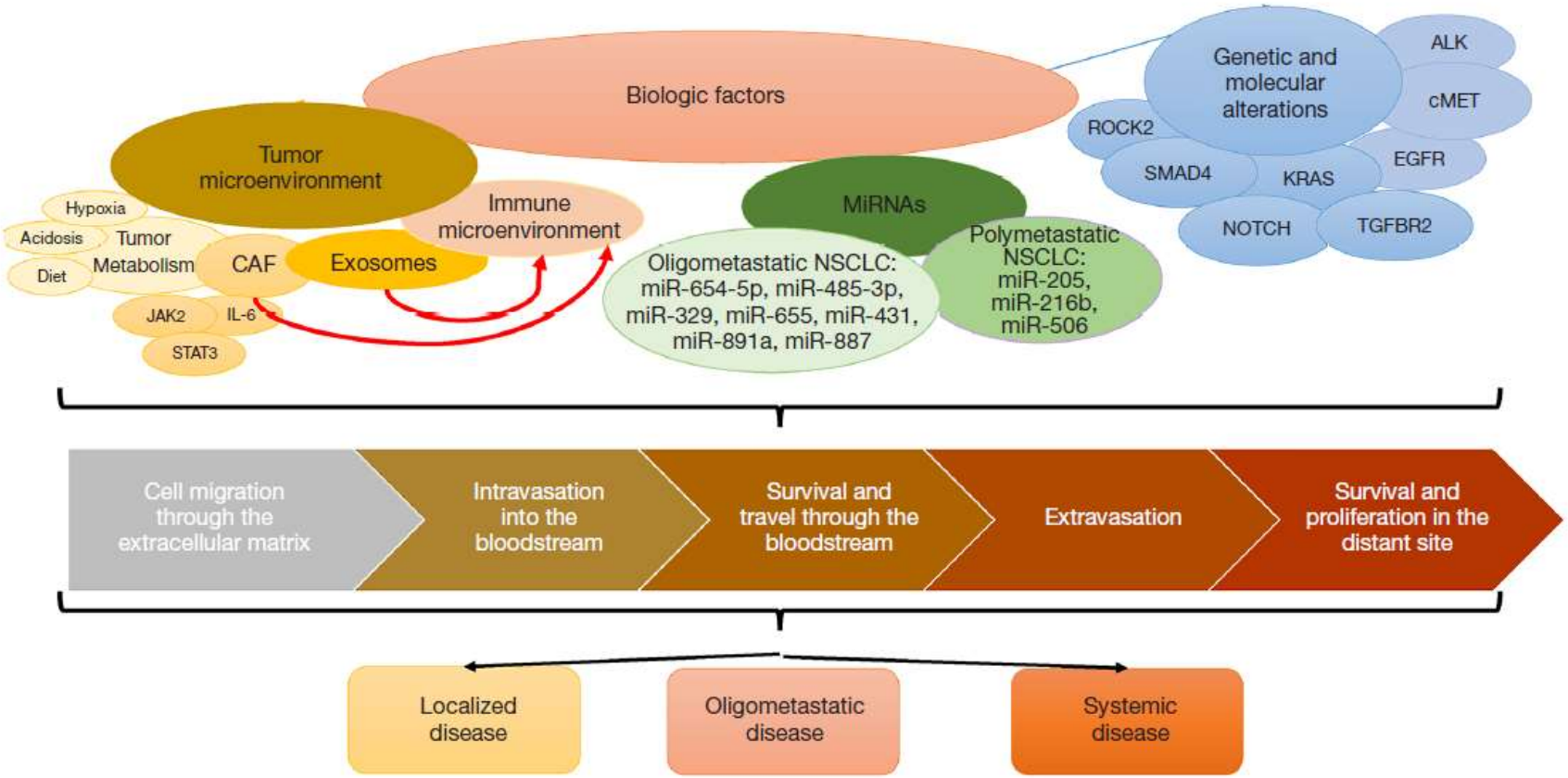
- *Consequently, these subgroups (eg,sOMD,metachronousOMD, oligopersistent disease, and oligoprogressive disease) should be considered distinct clinical entities in the design of future clinical trials.*

- *Biomarker discovery efforts should be tailored to each specific clinical scenario rather than applied broadly across heterogeneous OMD populations.*

Molecular classification

The current gold standard to identify the oligometastatic state is to determine the number of metastatic sites evident on conventional imaging.

However, this definition does not account for tumor markers and genomic signatures, which may strongly influence survival.



	Name	Class of alteration	P-value
Genes Predictive of Oligometastatic Metastatic Disease	ATM JAK2 MAP2K2 NTRK1	SNV/INV* SNV/INV SNV/INV Fusion	0.048 0.058 0.058 0.058
Genes Predictive of Widespread Metastatic Disease	ARID1A CCNE1	SNV/INV SNV/ INV, Amplification	0.097 0.088

Rashdan Transl Lung Cancer Res 2021,
Choi, Front Endocrinol, 2024

Predictors of progression after SBRT

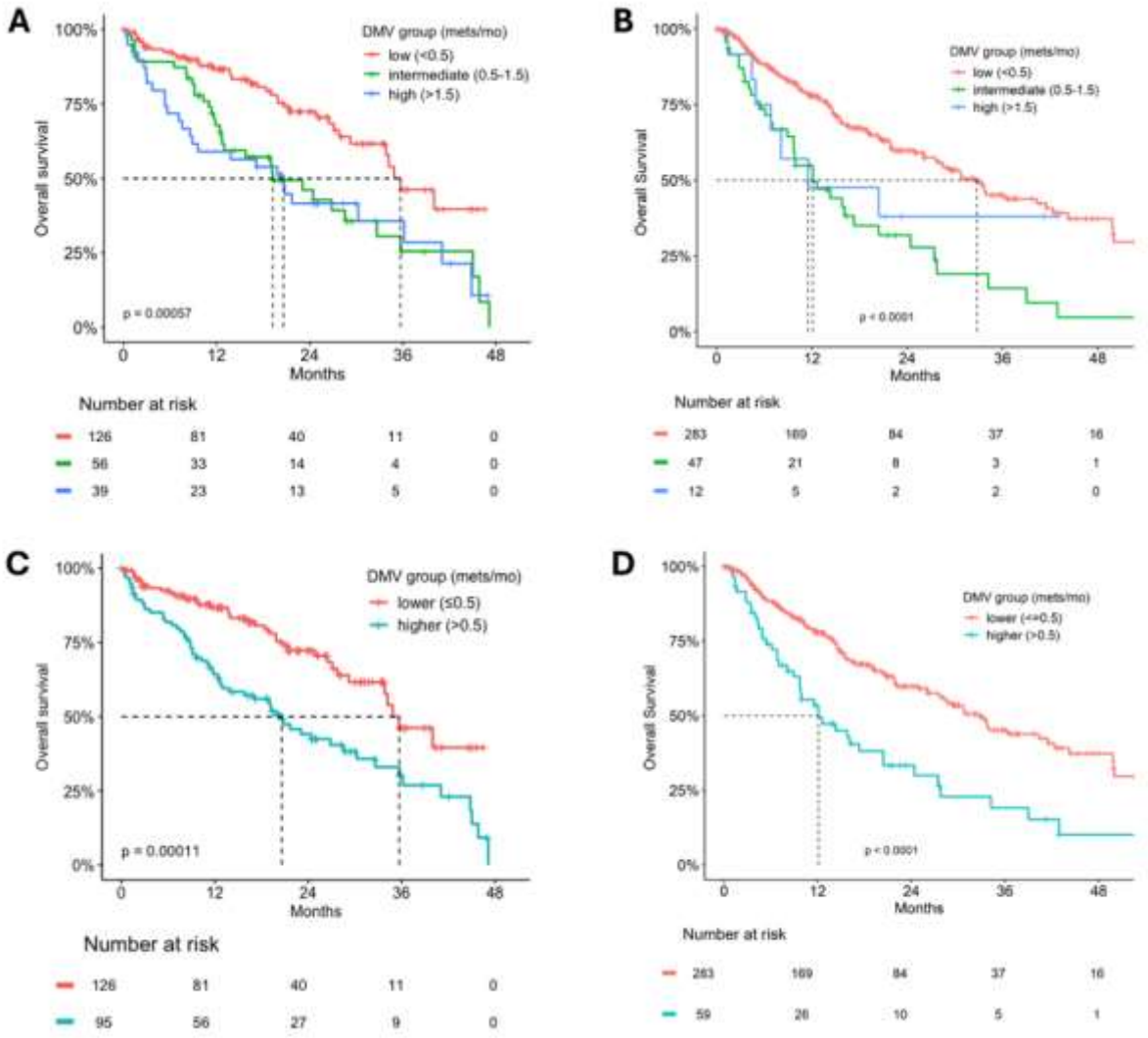
Multinational validation of distant metastasis velocity as a post-progression prognostic score in patients with oligometastatic cancer treated with metastasis-directed stereotactic body radiotherapy

Jonas Willmann [a,b,*], Sarah Baker [c], Hanbo Chen [d], Edward Christopher Dee [e], Eugenia Vlaskou Badra [a], Sebastian M. Christ [a], Michael Mayinger [a], Maiwand Ahmadsei [a], Selma Adilovic [a], Subhadip Das [c], Linden Lechner [c], Wei Liu [c], Mitchell Liu [c], Benjamin Mou [c], Tanya Berrang [c], Devin Schellenberg [c], Scott Tyldesley [c], Darby Erler [d], Puneeth Iyengar [e], Kristin Redmond [f], Umberto Ricardi [g], Matthias Guckenberger [a], Arjun Sahgal [d], Robert Olson [c], Nicolaus Andratschke [a]

European Journal of cancer, 2025

Prospective cohort

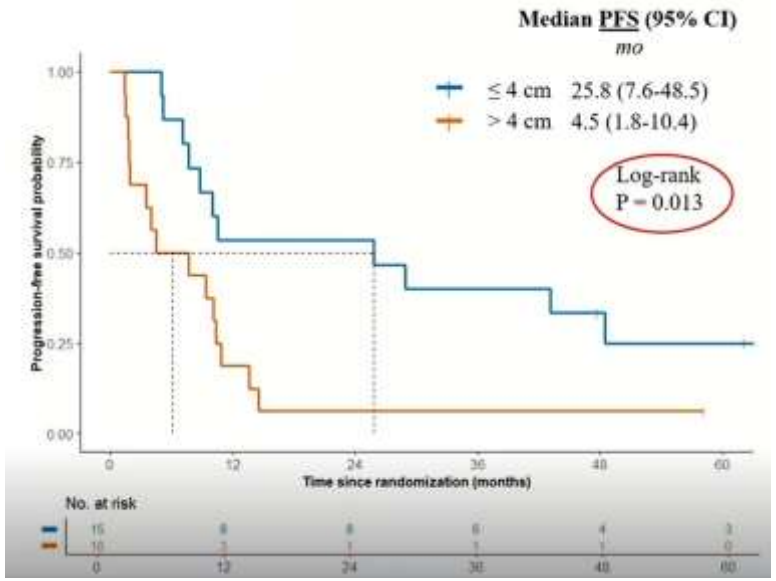
Validation cohort

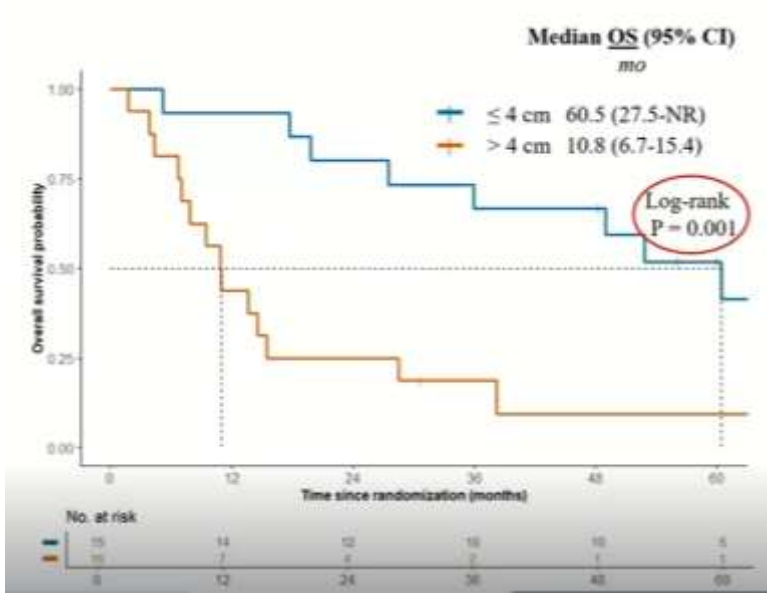


An Analysis of the Randomized Phase II CURB Trial :Tumor Burden Metrics

- *TGL = total number of growing lesions*
- *TNL = total number of lesions*
- *SLD-AL = sum of longest diameters of all lesions*
- *SLD-GL = sum of longest diameters of growing lesions*
- *SLD-SRL = sum of longest diameters of stable/regressing lesions*

Hypothesis: Tumor burden metrics at oligoprogression differ in prognostic value after SBRT





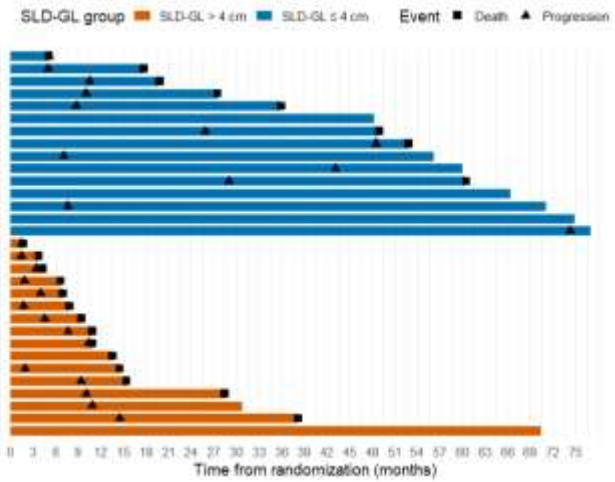
McMillan, WCLC 2025

An Analysis of the Randomized Phase II CURB Trial :Tumor Burden Metrics

	UVA		MVA	
Predictors of **Progression-Free Survival**	HR	p-value	HR	p-value
Prior lines of systemic therapy	1.42 (1.01-1.99)	0.044	1.45 (0.99-2.14)	0.058
SLD-Growing Lesions (reference: ≤4cm)	2.69 (1.20-6.04)	0.016	2.65 (1.16-6.03)	0.021
Liver metastases (reference: no)	2.64 (1.01-6.93)	0.048		0.445

	UVA		MVA	
Predictors of **Overall Survival**	HR	p-value	HR	p-value
ECOG (reference: 0)	2.14 (0.89-5.12)	0.089		0.142
Prior lines of systemic therapy	1.55 (1.07-2.25)	0.020	1.62 (1.08-2.43)	0.021
TGL (reference: 1 lesion)	2.17 (0.90-5.21)	0.085		0.299
SLD-All Lesions (continuous)	1.06 (0.99-1.13)	0.070		0.734
SLD-Growing Lesions (reference: ≤4cm)	4.23 (1.69-10.58)	0.002	1.10 (1.02-1.18)	0.019
Liver metastases (reference: no)	2.71 (0.95-7.72)	0.063		0.857

- SLD-GL ≤ 4 cm → **SBRT + continue** current systemic therapy
- SLD-GL > 4 cm → **SBRT +** consider **switch/intensify** systemic therapy



McMillan, WCLC 2025

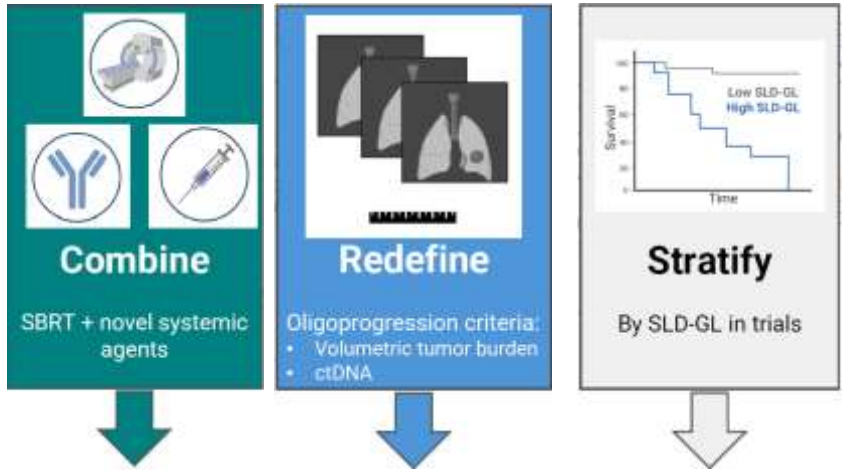
CURB2 Schema

Stratification:

- First-line systemic therapy (ICI alone versus ICI and chemotherapy)
- Number of oligoprogressive lesions (1, 2 versus 3, 4 or 5)
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 versus 2)

Participants with metastatic NSCLC on first-line ICI-based systemic therapy having received at least 3 cycles Restaging studies reveal ≤ 5 extracranial oligoprogressive lesions, all of which must be amenable to SBRT* Oligoprogressive lesions are asymptomatic, not requiring palliative radiotherapy at the time of study enrollment	RANDOMIZATION	→	ARM 1: SBRT/radiotherapy* to all sites of oligoprogression followed by the same first-line SOC systemic therapy	→	Continue with SOC treatment until disease progression**	Follow-up for survival (every 12 weeks)
		→	ARM 2: No SBRT and switch to second-line SOC systemic therapy			
N = 320 participants						

Different stratification factors?



Tsai, WCLC 2025

Conclusions

1. The survival benefit of radiotherapy in the immunotherapy era remains unproven.

Modern data—most notably the NRG-LU002 randomized trial—showed no significant improvement in progression-free or overall survival when adding local radiotherapy to maintenance systemic therapy in synchronous oligometastatic NSCLC

2. Radiotherapy may only benefit a highly selected subgroup of patients.

3. Optimal sequencing of radiotherapy and systemic therapy is unknown.

4. Combining radiotherapy with immunotherapy has theoretical synergy but carries toxicity concerns.

5. Future use of radiotherapy should be biomarker-driven rather than lesion-count-driven.

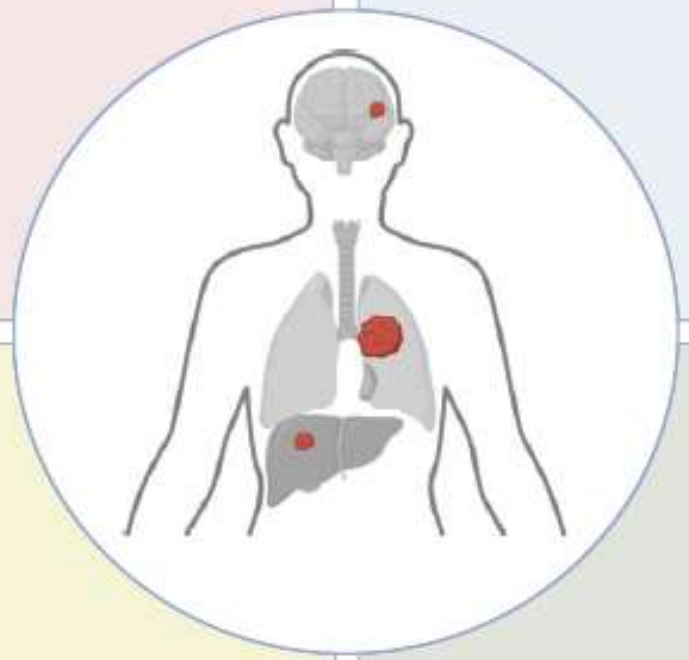
Next Steps

Defining the oligometastatic state

- Probabilistic finding or biological entity
- Radiological or biological diagnosis
- Lesion count or aggressiveness of disease
- Role of organotropism
- Role of micrometastases

Treatment strategies

- Different treatment for oligometastatic and polymetastatic disease
- Sequencing of local and systemic therapy
- Radiotherapy and immunotherapy: synergy or risk of toxic effects



Predicting treatment response

- Identifying true oligometastatic disease before treatment initiation
- Predicting efficacy of systemic therapy
- Role of ctDNA in liquid biopsy, radiomics, and AI

Research and clinical practice

- Lessons learned from negative trials
- Need for biomarker-driven patient selection in clinical trials
- Optimal combination of ICI and local therapy

Jongbloed, JAMA Oncol, 2025

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU

GECP lung cancer research