YUMC Yeungnam University Medical Center

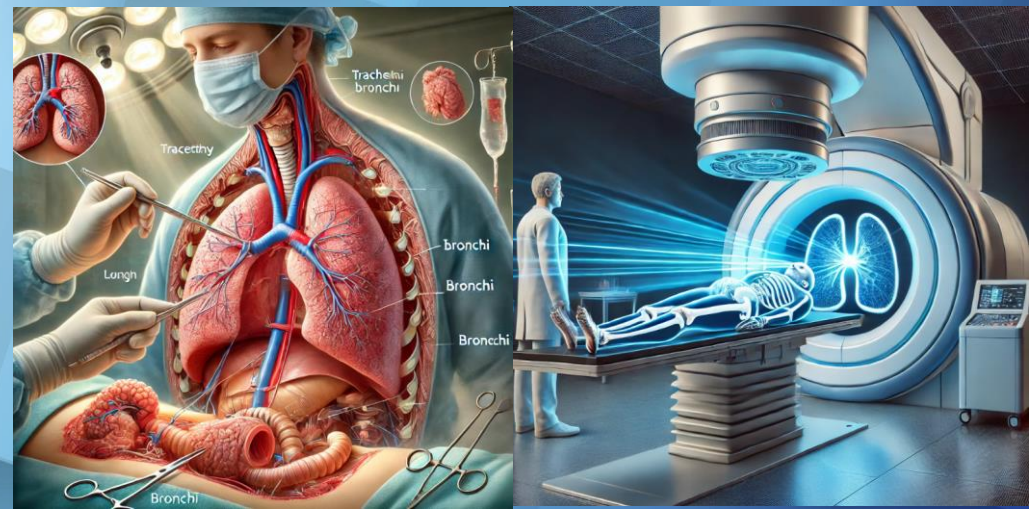
Recent Local Therapy with Targeted Therapy in Advanced NSCLC

2025 동계 분자폐암연구회 임상연구 워크숍

일정 |

장소 |

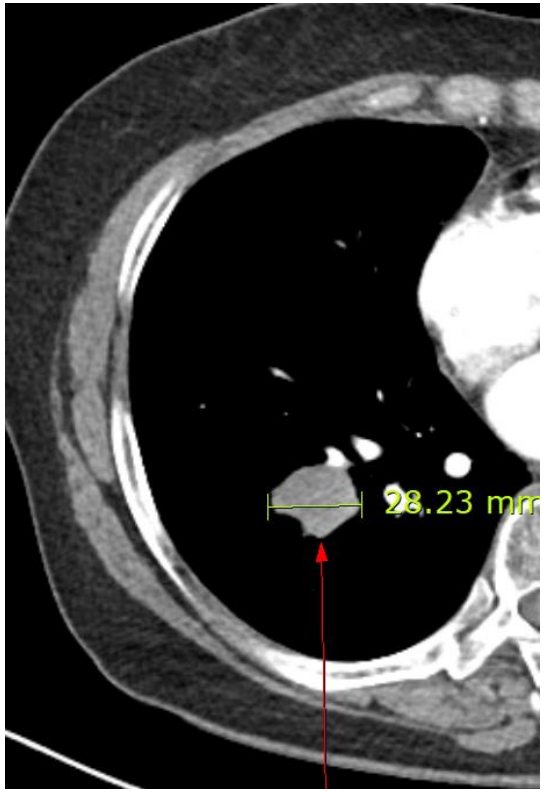
영 남 의 대
안 준 홍

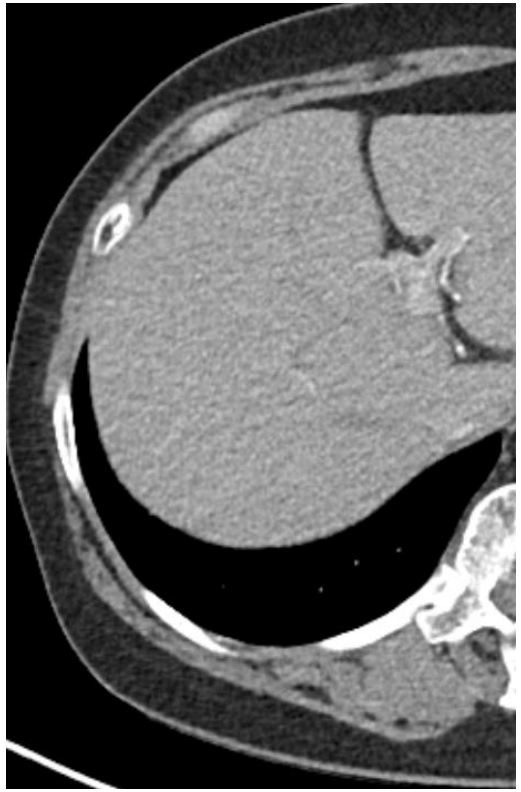


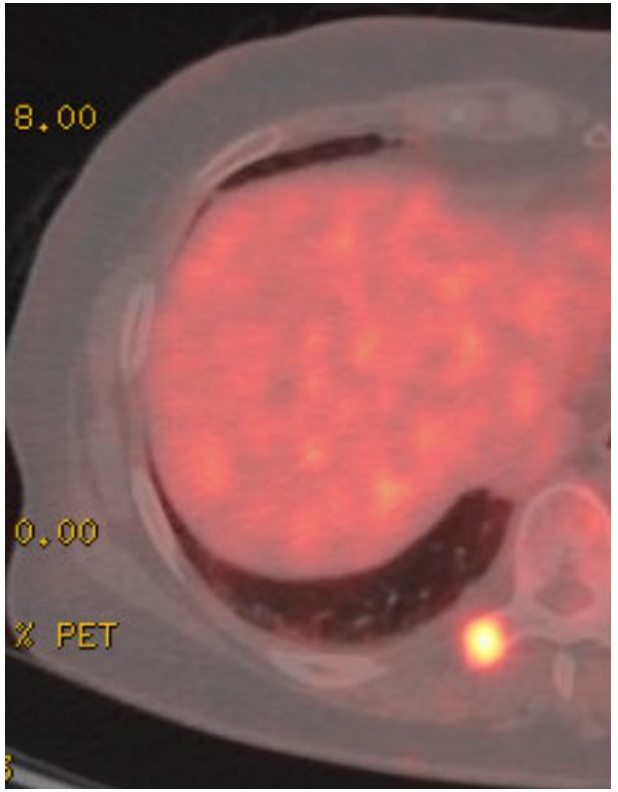
Contents

- Local consolidative therapy (LCT) & Oligometastatic disease (OMD)
- Clinical evidences of LCT
- LCT in oncogene-addicted OMD NSCLC
- Guidelines & Summary

70/F, ADC, RLL, cT1cN0M1b, ALK +, PD-L1: 50% (sp263)





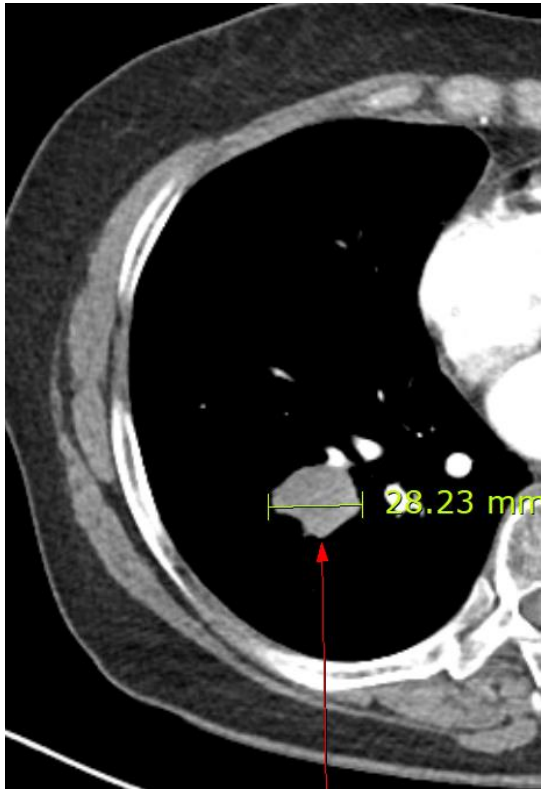


Rt. transverse process of T9 spine

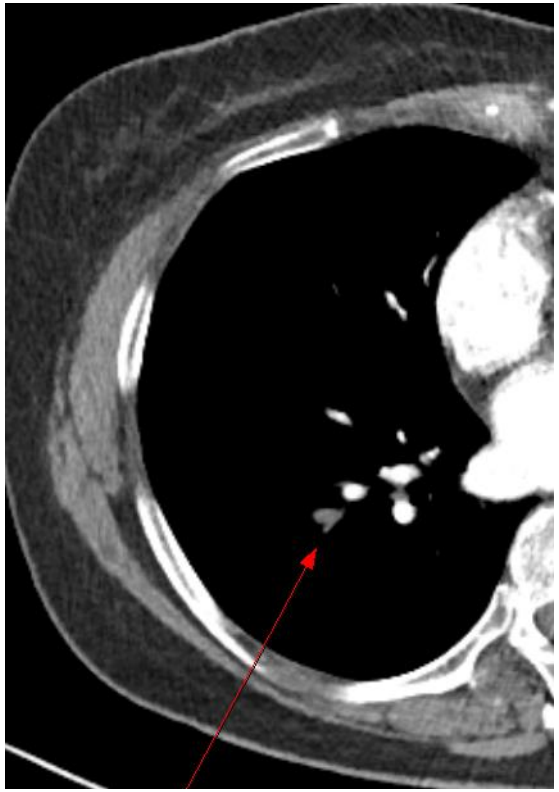
진단과 치료는?

- Synchronous OMD
- Metachronous OMD (Oligorecurrence)
- Oligoprogression

70/F, ADC, RLL, cT1cN0M1b, ALK +, PD-L1: 50% (sp263)



Baseline



1.5M after brigatinib

다학제

진료기간 : 2023-10-04 주치의 : 안준홍 진료과 : 호흡기알레르기내과 [외래]

진료일자 : 20231004

진 료 과 : 호흡기알레르기내과

진료과 소견

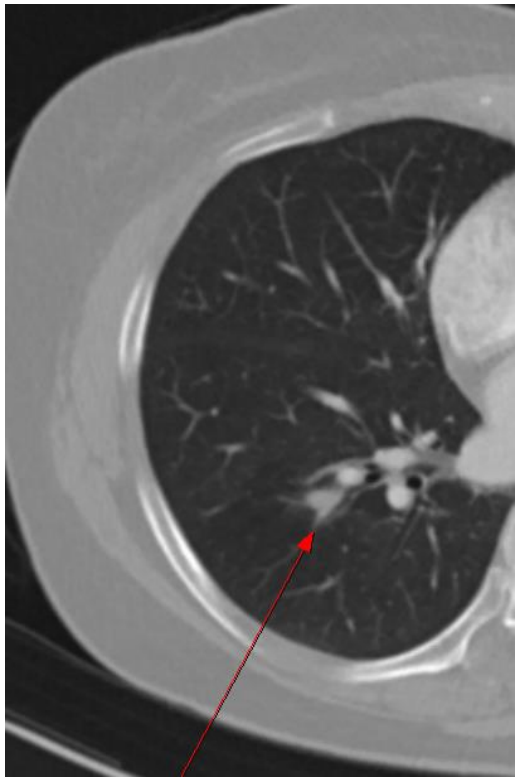
[TR 소견]
NSCLC, Adenoca, RLL, cT1cN0M1b, EGFR/ALK/KRAS (-/+/-),
PD-L1(SP263,50%;SP142,2%;22C3,70%)
M1b : T9 solitary mets
on Brigatinib (2023.8.14-) : PR

* ECOG 0-1

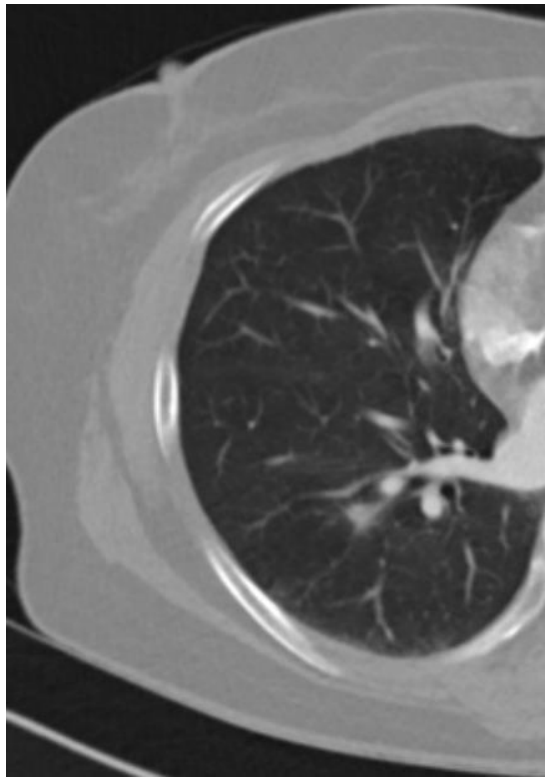
Recommend)
consider SBRT to primary lung mass and T9

RLL, 45Gy, 3fx/T9, 24Gy, 3fx

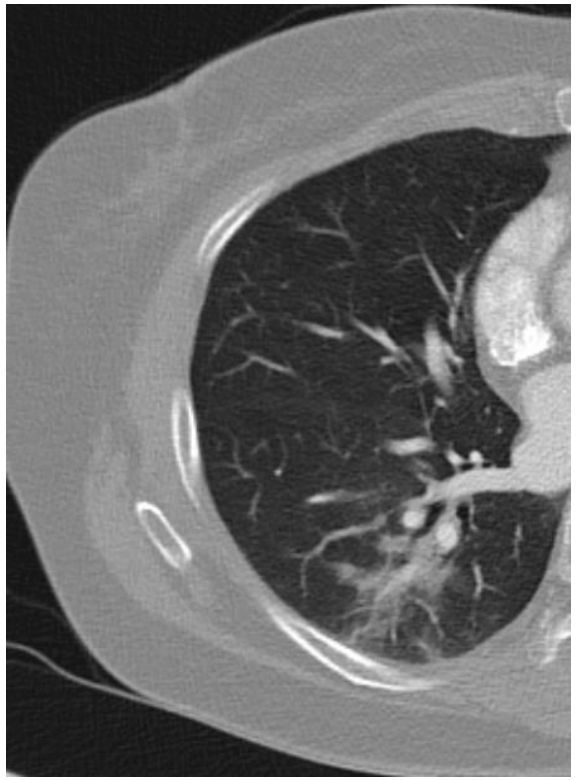
70/F, ADC, RLL, cT1cN0M1b, ALK +, PD-L1: 50% (sp263)



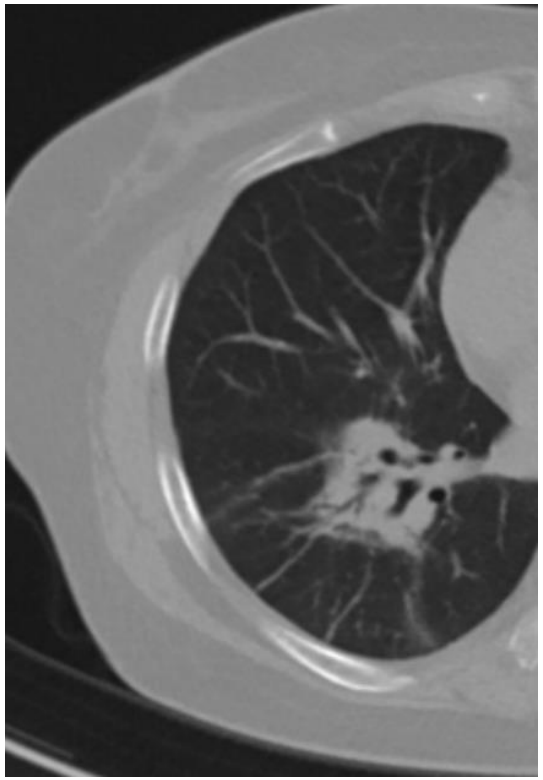
Before SBRT



SBRT 1M

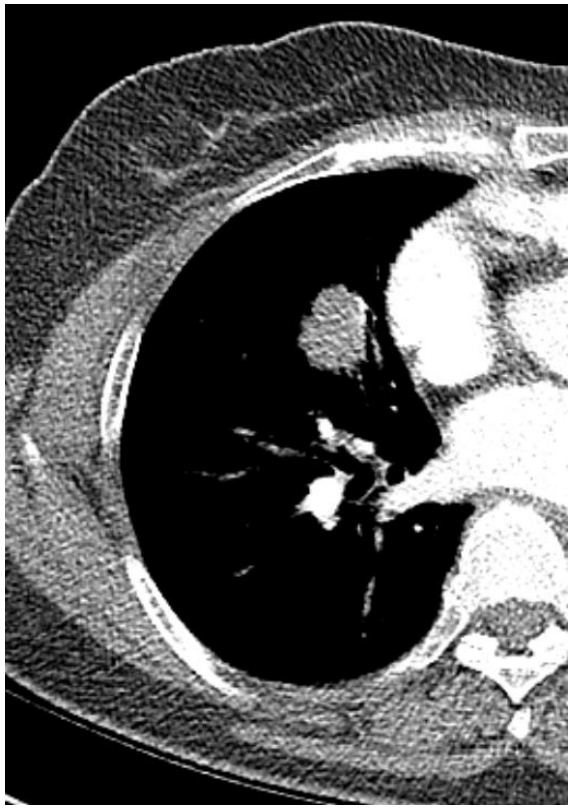


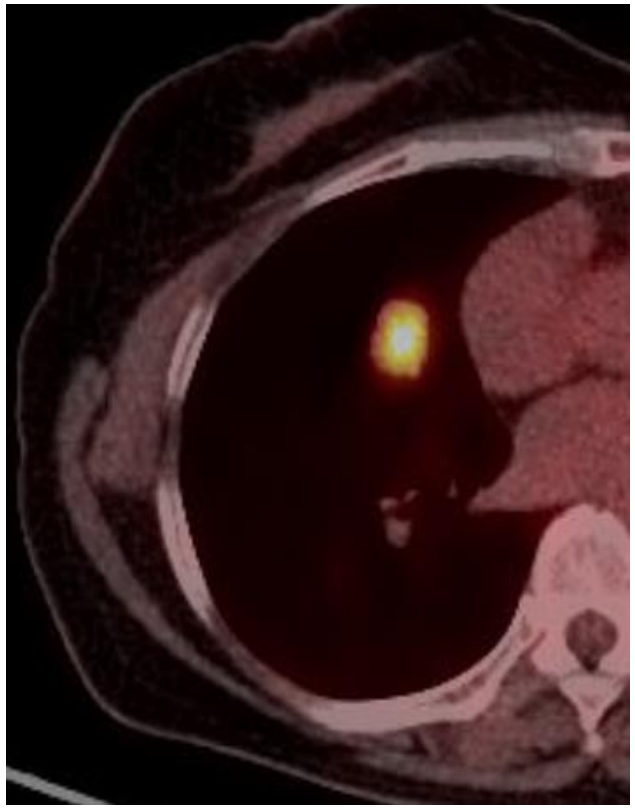
SBRT 3M



SBRT 6M

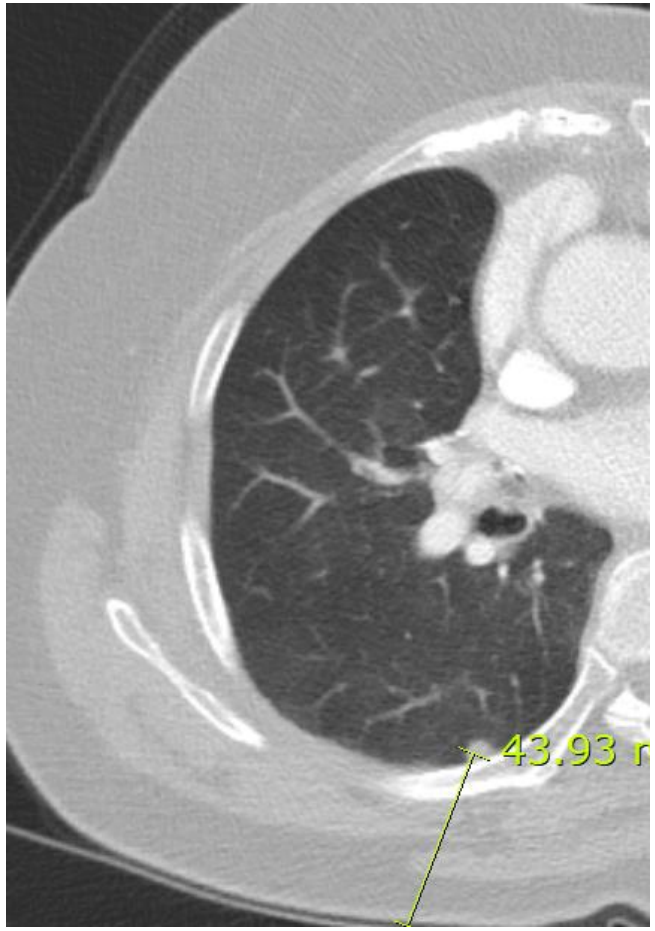
63/F, ADC, RML, pT2aN0M0, 1B, VPI+, ALK +

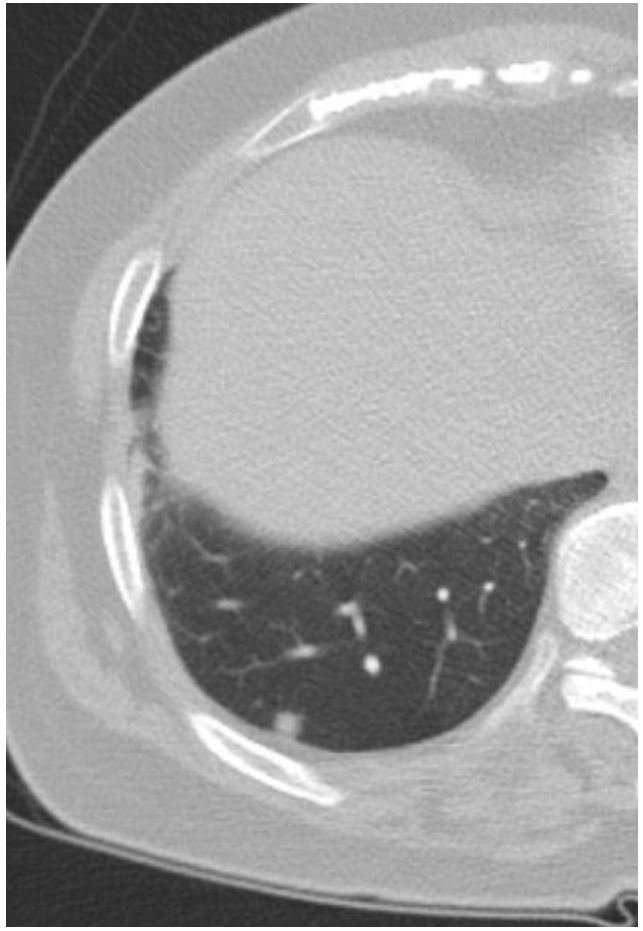


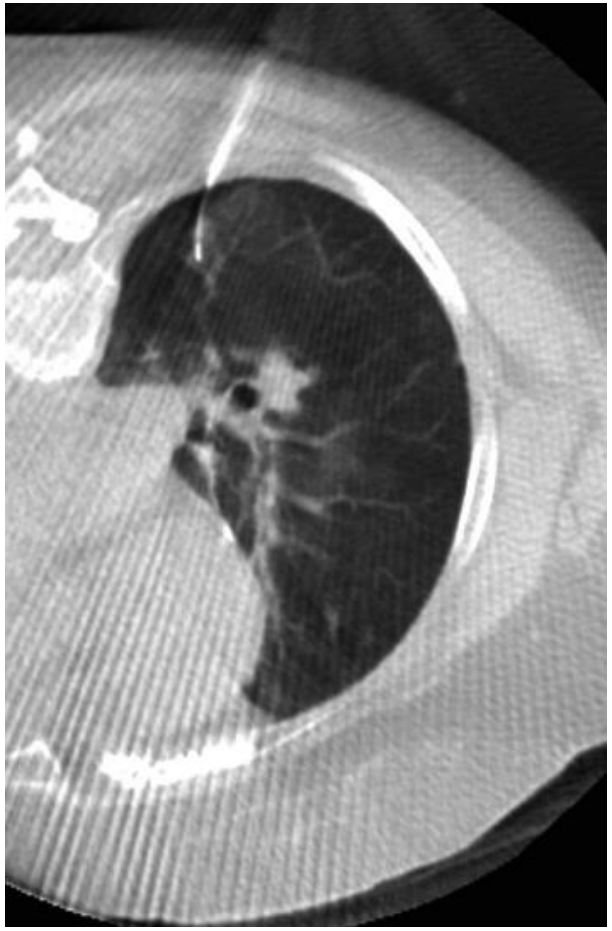


s/p RMLobectomy c MLND (2015)

63/F, ADC, RML, pT2aN0M0, 1B, VPI+, ALK +







Two separate nodules, RLL (2023)
PCNBx: Adenocarcinoma

진단과 치료는?

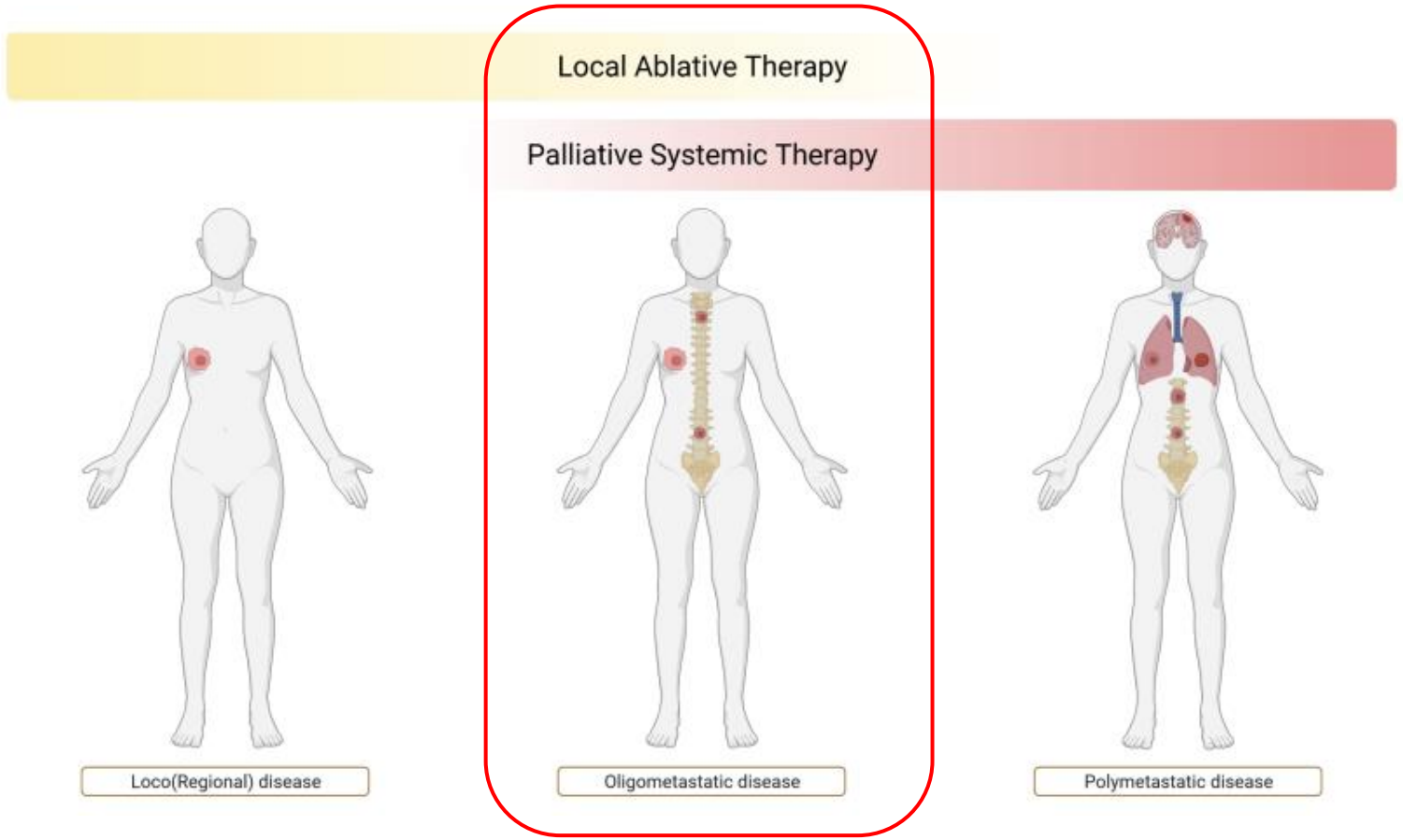
- Synchronous OMD
- Metachronous OMD (Oligorecurrence)
- Oligoprogression

Contents

- Local consolidative therapy (LCT) & Oligometastatic disease (OMD)
- Clinical evidences of LCT
- LCT in oncogene-addicted OMD NSCLC
- Guidelines & Summary

Definition of OMD

Purely localized lesions < OMD < Widely metastatic



J Clin Oncol. 2022 Feb 20;40(6):635-641

Heterogeneity of OMD definition

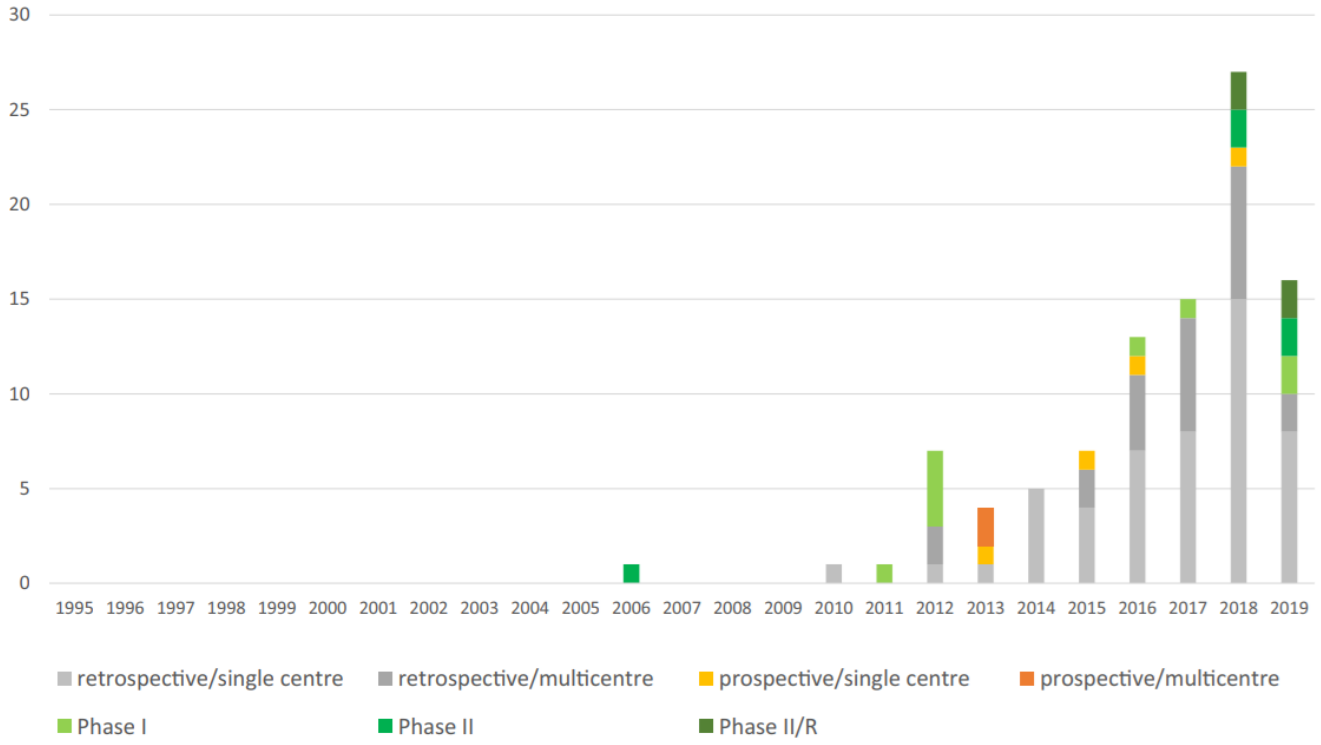


Table 2
OMD definitions used across publications.

Oligometastatic disease (OMD)
Many refer to the original definition of Hellman and Weichselbaum [6]: An intermediate state between local and systemic disease, where radical local treatment of the primary cancer and all metastatic lesions might have a curative potential
+ *Outcome* An intermediate state in which local or treated metastasis control may yield improved systemic control
+ *Disease burden* Limited number of metastases: oligometastatic is defined as a small number of low volume metastases, 5 or less, 3 or less Limited number of sites/regions Single or limited number of organs Limited number of metastases and sites Limited number of distant metastatic regions (typically ≤5) that contain the primary tumor
+ *Disease type* More indolent disease, tumors featuring limited metastatic capacity Specified for certain organ: limited pulmonary dissemination, limited number of nodal recurrences (in prostate cancer; typically, ≤3 or ≤5)
+ *Alternative hypotheses* OMD represents the transition between localized and widespread systemic disease *OR* the clinical manifestation of detectable lesions in a setting of widespread occult disease

Radiother Oncol. 2020;148:157-166

Definition Consensus of OMD

- A maximum of 5 metastases and 3 organs
  - Excludes diffuse serosal (meningeal, pericardial, pleural, mesenteric) metastases
  - Excludes bone marrow involvement
- Pulmonary metastases are counted as a metastatic site
- Mediastinal LN should not count as a metastatic site; mediastinal LN must be considered as regional disease

J Thorac Oncol. 2019 Dec;14(12):2109-2119

Definition of OMD

Consensus

Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document

ESTRO
European SocieTy for Radiotherapy & Oncology

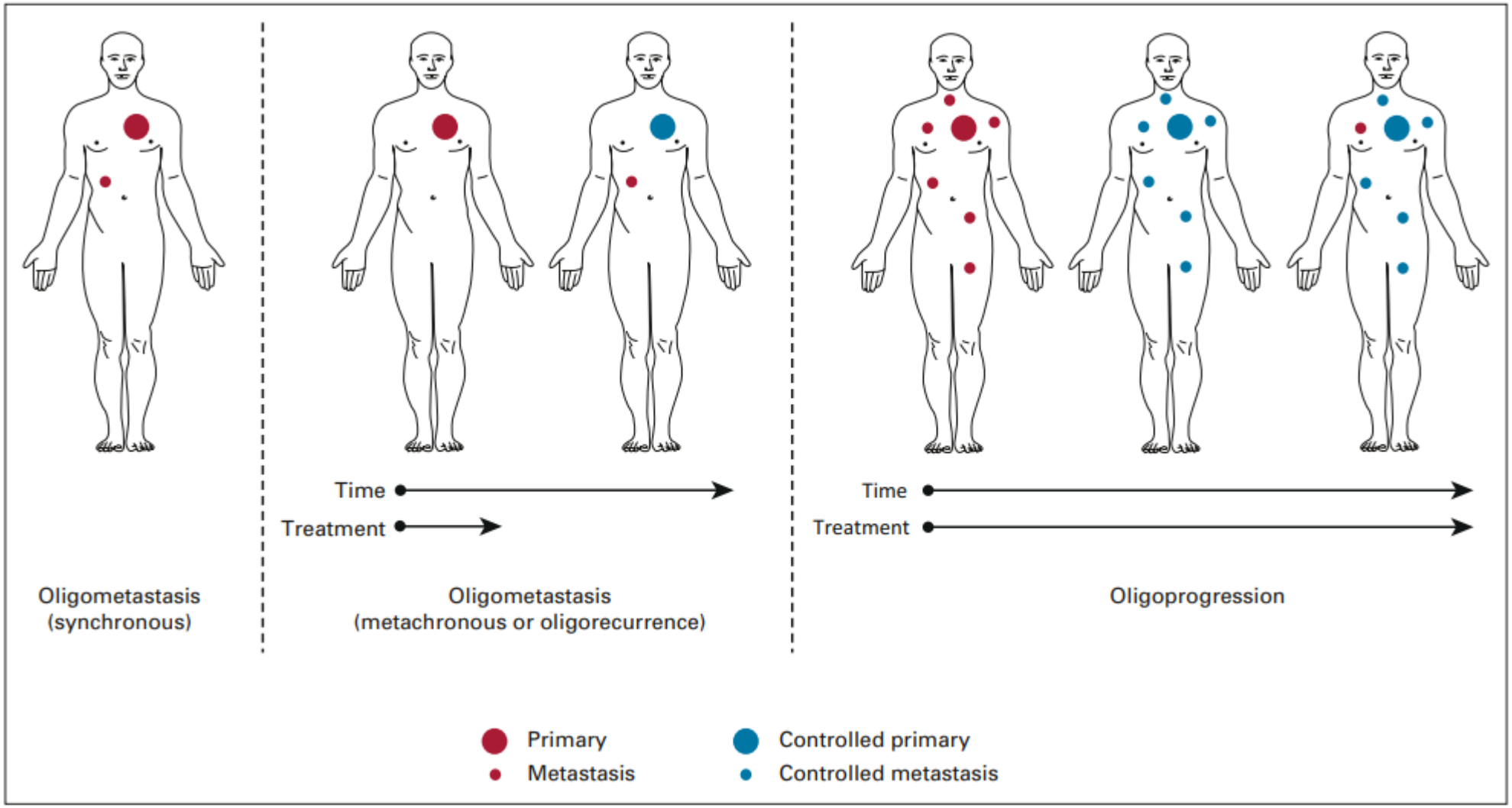
ASTRO
AMERICAN SOCIETY FOR RADIATION ONCOLOGY

OMD can be defined as

- ✓ 1 to 5 metastatic lesions
- ✓ Controlled primary tumor being optional
- ✓ All metastatic sites must be safely treatable

Radiother Oncol. 2020;148:157-166

Classification of OMD



J Clin Oncol. 2022 Feb 20;40(6):635-641

Rationale for LCT in OM NSCLC

- Treatment-resistant malignant cells may serve as a source of subsequent metastatic spread, even in the absence of radiologic PD

→ LCT reduce the burden of treatment-resistant cells

- LCT induce tumor antigen release

→ Enhanced immunosurveillance, antitumor immunity

Contents

- Local consolidative therapy (LCT) & Oligometastatic disease (OMD)
- Clinical evidences of LCT
- LCT in oncogene-addicted OMD NSCLC
- Guidelines & Summary

TABLE 1. Select Randomized Control Trials Using Local Ablative Therapy to Treat Oligometastases in Non–Small-Cell Lung Cancer

Published Study	Phase	Oligometastatic Definition	No.	Control Arm	Experimental Arm	Outcomes	Toxicity
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
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
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

J Clin Oncol. 2022 Feb 20;40(6):635-641

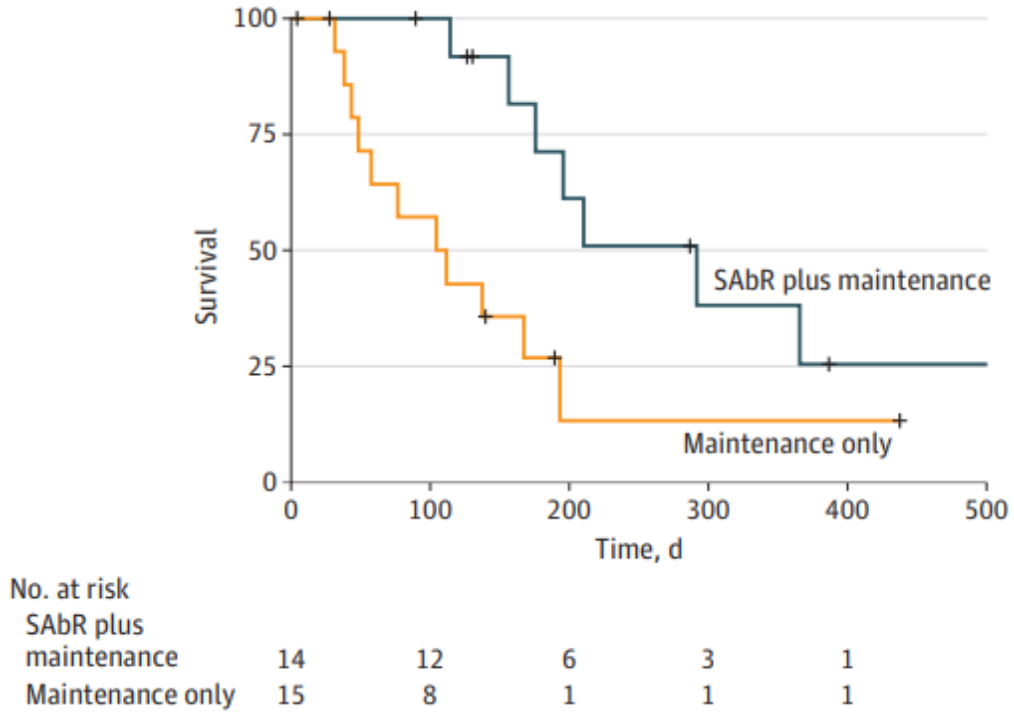
Consolidative Radiotherapy for Limited Metastatic Non–Small-Cell Lung Cancer

A Phase 2 Randomized Clinical Trial

Puneeth Iyengar, MD, PhD; Zabi Wardak, MD; David E. Gerber, MD; Vasu Tumati, MD; Chul Ahn, PhD; Randall S. Hughes, MD; Jonathan E. Dowell, MD; Naga Cheedella, MD; Lucien Nedzi, MD; Kenneth D. Westover, MD, PhD; Suprabha Pulipparacharuvil, PhD; Hak Choy, MD; Robert D. Timmerman, MD

- Prospective phase II RCT
- 29 NSCLC (EGFR, ALK WT)
- Maintenance CTx. alone vs.
  SABR followed by maintenance CTx.
- All primary sites, metastasis were radiated
- sOMD (≤5 metastasis) after 1L CTx.
- PR or SD after induction CTx.

- Toxicity was similar
  (Control 20% G3-4 vs. SABR 29% Gr3)

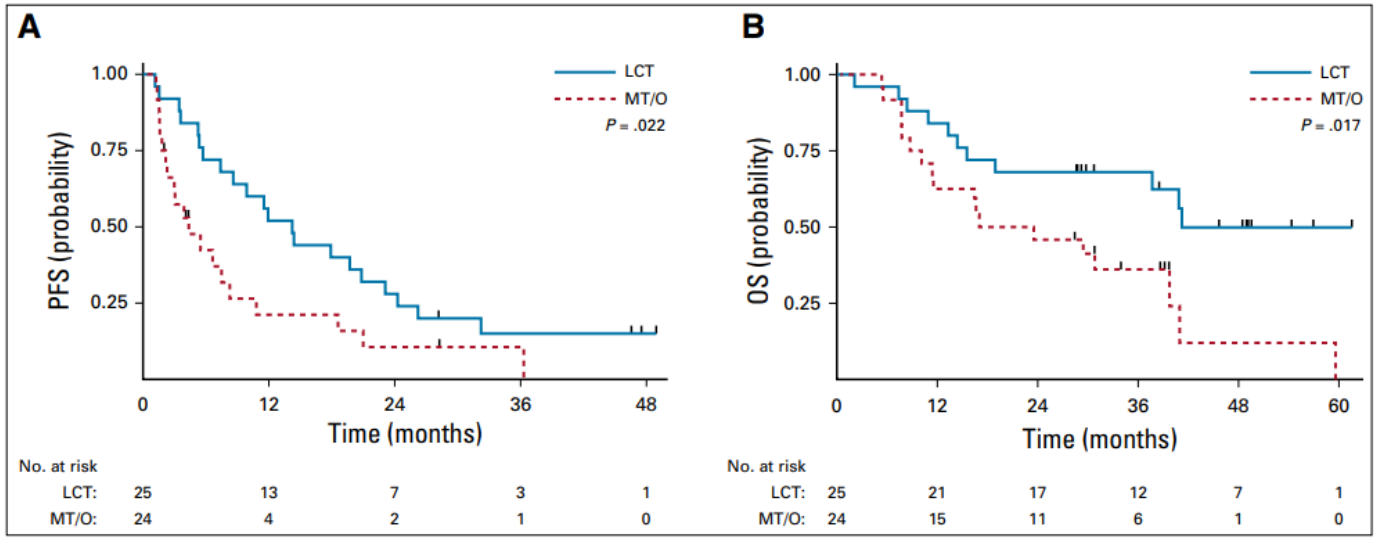


mPFS: 9.7 vs. 3.5 months (HR 0.304, p=0.01)

JAMA Oncol 2018;4(1):e173501

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]



- Prospective phase II RCT
- 49 NSCLC (6 EGFRm, 2 ALKm)
- sOMD (≤3 metastasis) after 1L CTx.
- SOC (≥4C PBC, ≥3M TKI)

- Survival after PD: 37.6 vs 9.4 months
- Toxicity: ≥ Gr3 20% vs 8%, No Gr 4-5

mPFS: 14.2 vs. 4.4 months (p=0.022)

mOS: 41.2 vs. 17.0 months (p=0.034)

Variable	HR	95% CI	P
Treatment			
MO	Ref		
LCT	0.46	(0.21 to 0.99)	.048
No. of metastases			
1	Ref		
2-3	1.50	(0.69 to 3.26)	.310
Mutation status			
None	Ref		
EGFR/EML4ALK	0.15	(0.02 to 1.12)	.065

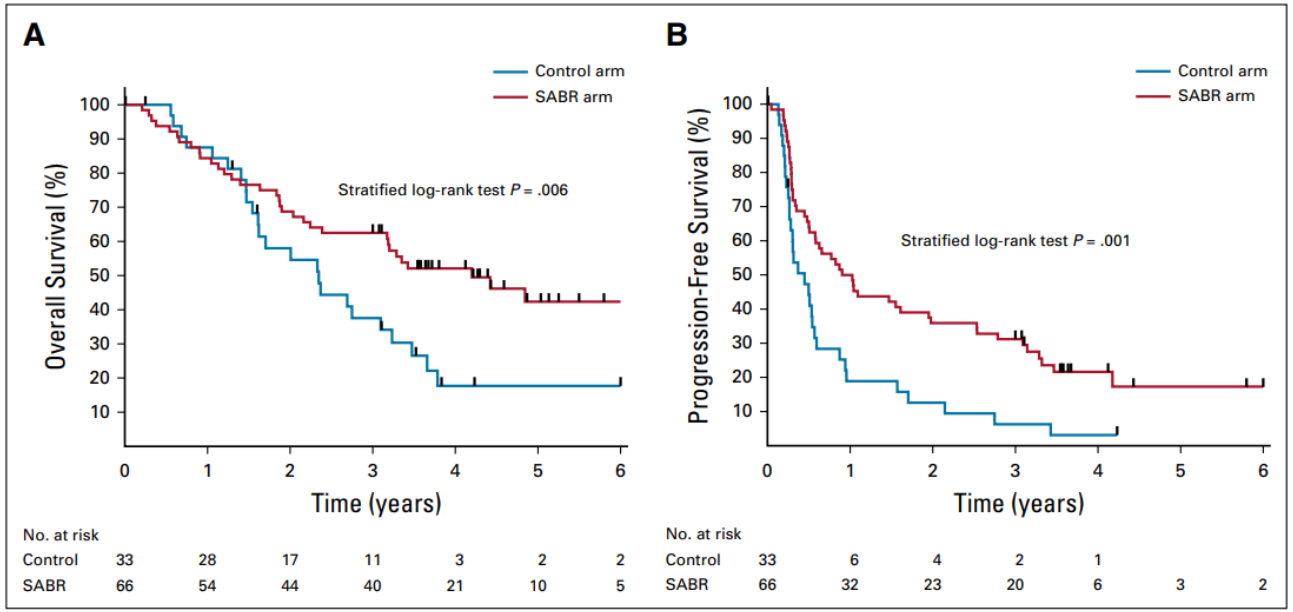
Multivariate Cox model (OS)

Lancet Oncol 2016;17:1672
J Clin Oncol 2019;37:1558

Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of Oligometastatic Cancers: Long-Term Results of the SABR-COMET Phase II Randomized Trial

David A. Palma, MD, PhD[1]; Robert Olson, MD, MSc[2]; Stephen Harrow, MBChB, PhD[3]; Stewart Gaede, PhD[1]; Alexander V. Louie, MD, PhD[4]; Cornelis Haasbeek, MD, PhD[5]; Liam Mulroy, MD[6]; Michael Lock, MD[1]; George B. Rodrigues, MD, PhD[1]; Brian P. Yaremko, MD, PEng[1]; Devin Schellenberg, MD[7]; Belal Ahmad, MD[1]; Sashendra Senthi, MD, PhD[8]; Anand Swaminath, MD[9]; Neil Kopek, MD[10]; Mitchell Liu, MD[11]; Karen Moore, MSc[3]; Suzanne Currie, MSc[3]; Roel Schlijper, MD[2]; Glenn S. Bauman, MD[1]; Joanna Laba, MD[1]; X. Melody Qu, MD, MPH[1]; Andrew Warner, MSc[1]; and Suresh Senan, MBBS, PhD[5]

- Prospective phase II RCT
- 99 multitumor patients, 18 lung cancer
- sOMD (≤5 metastasis)
- Primary tumor had to be controlled before local treatment (at least 3 Mo)
- SOC+SABR vs SOC 2:1 ratio
- Toxicity ≥ Gr2 29% vs 9%, No Gr 3-5



5YR OS: 42.3 vs. 17.7% (p=0.006)

5YR PFS: 17.3 vs. 3.2 % (p=0.001)

J Clin Oncol 2020;38:2830

Table 2. Ongoing Phase III Studies of Local Therapy Versus No Local Therapy for Oligometastatic or Oligoprogressive[a] NSCLC

Trial Name	ClinicalTrials.gov Identifier	Histology	Metastases	Systemic Therapy	Local Therapy	Primary Endpoint
OMEGA	NCT03827577	NSCLC	1–3	Chemotherapy, IO, targeted agents	RT, surgery, RFA	OS
SARON	NCT02417662	NSCLC	1–5	Per physician discretion	RT	OS
NRG LU002	NCT03137771	NSCLC	1–3	Chemotherapy or IO	RT	PFS (phase II), OS (phase III)
CORE	NCT02759783	NSCLC, breast cancer, prostate cancer	1–3	Per physician discretion	RT	PFS
OITROLC	NCT02076477	NSCLC	1–5	Chemotherapy	RT	ORR
SABR-COMET-3	NCT03862911	Mixed	1–3	Per physician discretion	RT	OS
LONESTAR	NCT03391869	NSCLC	1–3 (subset)	Ipilimumab/ nivolumab	RT	OS
HALT	NCT03256981	Oligoprogressive NSCLC with driver mutation	1–3	TKI	RT	PFS

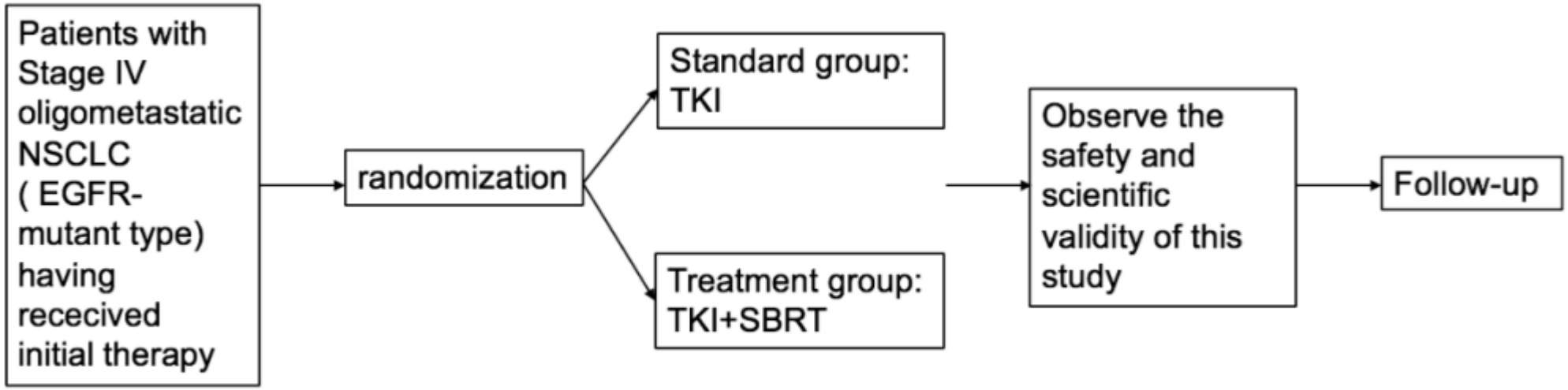
J Natl Compr Canc Netw 2022;20(5):531

Contents

- Local consolidative therapy (LCT) & Oligometastatic disease (OMD)
- Clinical evidences of LCT
- LCT in oncogene-addicted OMD NSCLC
- Guidelines & Summary

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

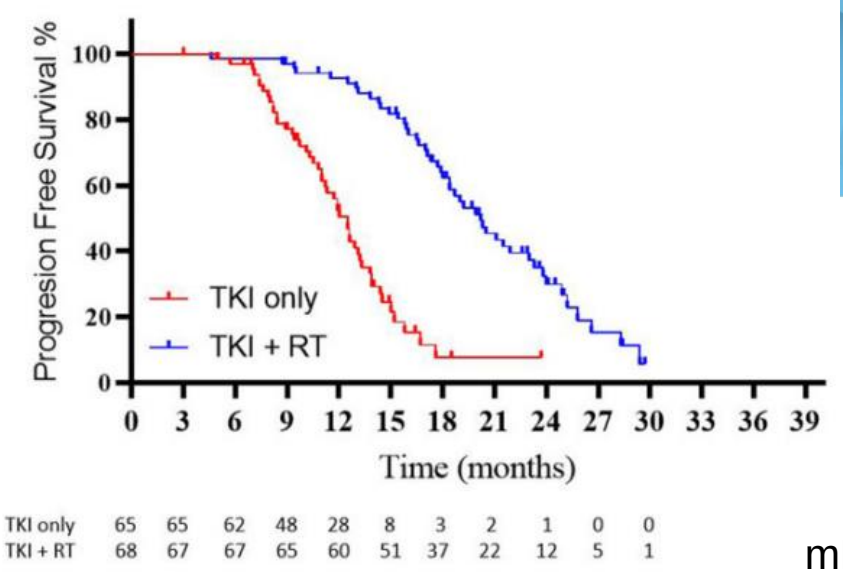
- EGFRm adenocarcinoma
- sOMD (≤5 metastasis, ≤2 lesions in any 1 organ), without BM
- All patients received a 1st G TKI (gefitinib, erlotinib, or icotinib)
- RT: All metastasis + primary tumor/regional LN, 5fx
- Primary endpoint: PFS; Secondary endpoint: OS, Toxicity



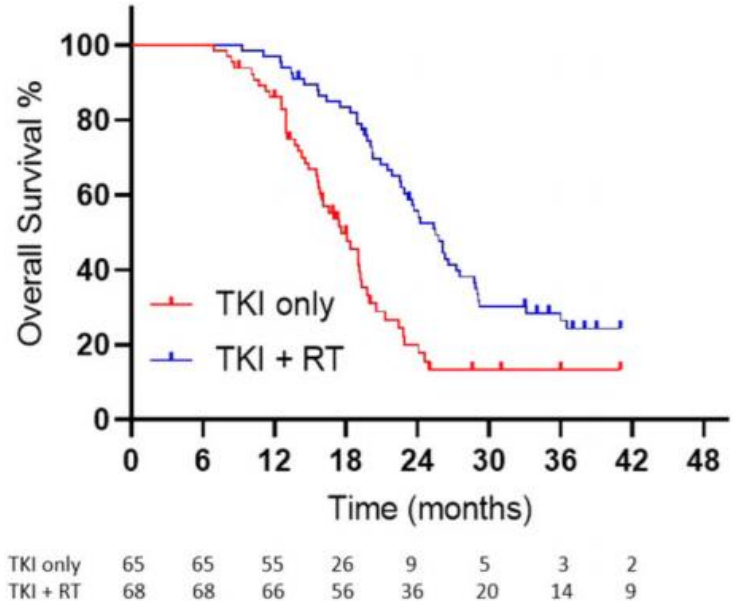
JNCI: Journal of the National Cancer Institute, 2023, 115(6), 742–748

Table 1. Clinicopathologic characteristics of the study population[a]

Parameter	TKI only (n = 65)	TKI + RT (n = 68)
Age, y		
Mean (SD)	63 (11)	67 (10)
Sex, No. (%)		
Male	26 (40.0)	25 (36.8)
Female	39 (60.0)	43 (63.2)
Zubrod performance status, No. (%)		
0	31 (47.7)	36 (52.9)
1	33 (50.8)	32 (47.1)
2	1 (1.5)	0 (0.0)
Clinical T classification, No. (%)		
1	9 (13.8)	5 (7.4)
2	16 (24.6)	17 (25.0)
3	22 (33.8)	20 (29.4)
4	17 (26.2)	23 (33.8)
Unknown	1 (1.5)	3 (4.4)
Clinical N classification, No. (%)		
0	8 (12.3)	8 (11.8)
1	23 (35.4)	19 (27.9)
2	24 (36.9)	27 (39.7)
3	10 (15.4)	13 (19.1)
Unknown	0 (0.0)	1 (1.5)
EGFR mutation, No. (%)		
Exon 19	47 (72.3)	45 (66.2)
Exon 21	18 (28.7)	23 (33.8)
Number of metastases, No. (%)		
1-2	38 (58.5)	32 (47.1)
3-4	23 (35.4)	30 (44.1)
5	4 (6.2)	6 (8.8)
TKI, No. (%)		
Gefitinib	38 (58.5)	32 (47.1)
Erlotinib	23 (35.4)	30 (44.1)
Icotinib	4 (6.2)	6 (8.8)



mPFS: 20.2 vs. 12.5 months
HR 0.22, (p<0.001)



mOS: 25.5 vs. 17.6 months
HR 0.44, (p<0.001)

JNCI: Journal of the National Cancer Institute, 2023, 115(6), 742–748

Table 2. Multivariable analyses of progression-free and overall survival

Variable[a]	Progression-free survival		Overall survival	
	HR (95% CI)	P[b]	HR (95% CI)	P[b]
Zubrod performance status (0 vs 1-2)	0.50 (0.22 to 0.75)	.02	0.01 (0.01 to 0.44)	.02
Clinical T classification (T3-4 vs.T1-2)	1.10 (0.99 to 1.22)	.09	2.06 (1.08 to 5.54)	.02
Clinical N classification (N2-3 vs N0-1)	—	—	1.56 (1.19 to 3.69)	.06
Number of metastases (3-5 vs 1-2)	1.96 (1.30 to 4.70)	.004	1.93 (1.21 to 3.07)	.004
EGFR mutation (exon 19 deletion vs exon 21 mutation)	0.94 (0.61 to 1.43)	.09	0.09 (0.02 to 0.38)	.001
Randomization arm (TKI only vs TKI + RT)	1.39 (1.07 to 1.95)	.005	2.11 (1.31 to 5.97)	.004

JNCI: Journal of the National Cancer Institute, 2023, 115(6), 742–748

Table 3. Toxicities possibly, probably, or definitely related to protocol treatment[a]

Toxicity	TKI only, No. (%)			TKI + RT, No. (%)		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Skin rash	47 (72.3)	5 (7.7)	4 (6.2)	46 (67.6)	8 (11.8)	2 (2.9)
Pruritus	20 (30.8)	7 (10.8)	1 (1.5)	22 (32.4)	5 (7.4)	0 (0.0)
Fatigue	47 (72.3)	0 (0.0)	1 (1.5)	46 (67.6)	0 (0.0)	0 (0.0)
Neutropenia	20 (30.8)	0 (0.0)	0 (0.0)	16 (23.5)	0 (0.0)	0 (0.0)
Anemia	18 (27.7)	0 (0.0)	0 (0.0)	22 (32.4)	0 (0.0)	0 (0.0)
Thrombocytopenia	3 (4.6)	0 (0.0)	0 (0.0)	3 (4.4)	0 (0.0)	0 (0.0)
Transaminitis	11 (16.9)	0 (0.0)	1 (1.5)	8 (11.8)	0 (0.0)	1 (1.5)
Diarrhea/nausea	43 (66.2)	0 (0.0)	0 (0.0)	38 (55.9)	0 (0.0)	0 (0.0)
Esophagitis	18 (27.7)	2 (3.1)	0 (0.0)	24 (35.3)	2 (2.9)	1 (1.5)
Pericarditis	0 (0.0)	1 (1.5)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)
Pleural effusion	0 (0.0)	0 (0.0)	2 (3.1)	2 (2.9)	0 (0.0)	0 (0.0)
Pneumonitis (symptomatic)	1 (1.5)	1 (1.5)	0 (0.0)	3 (4.4)	3 (4.4)	1 (1.5)
Pneumonitis (asymptomatic)	14 (21.5)	1 (1.5)	0 (0.0)	19 (27.9)	1 (1.5)	0 (0.0)

JNCI: Journal of the National Cancer Institute, 2023, 115(6), 742–748

elcc European Lung Cancer Congress 2023

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)

Analysis of Adverse Events (AEs)

Saumil Gandhi, MD PhD

Assistant Professor

The University of Texas MD Anderson Cancer Center

Organisers

ESMO IASLC

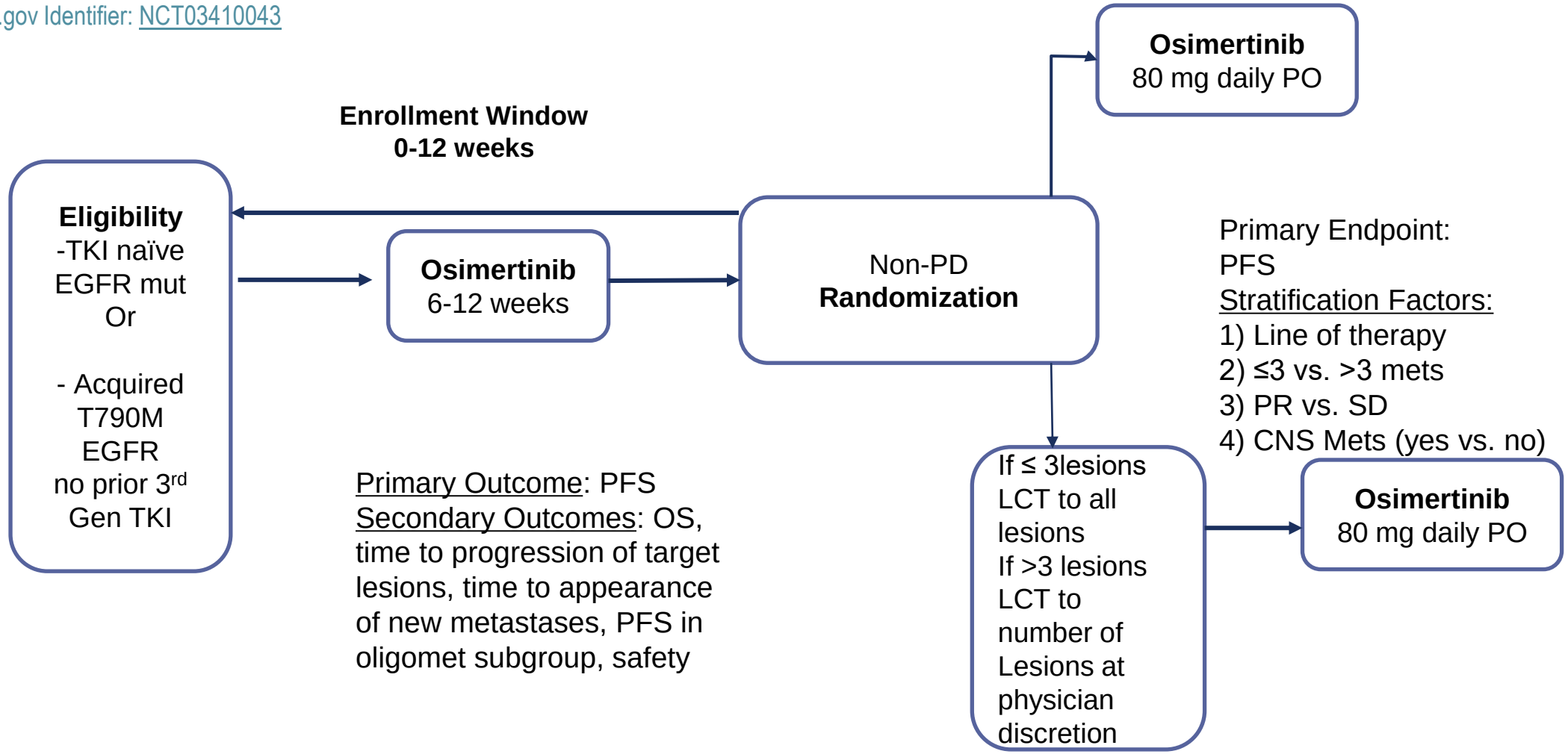
Partners

ESTRO ETOP·IBCSG PARTNERS

THE UNIVERSITY OF TEXAS MD Anderson Cancer Center

Multicenter Phase II Randomized Study of Osimertinib (OSI) With or Without LCT

ClinicalTrials.gov Identifier: NCT03410043



N = 120 randomized patients treated per assigned arm

Patient Characteristics

Characteristic	Osimertinib (N=63)	Osimertinib + LCT (N=59)
		Number of patients (%)
Age		
Median	62 yrs	64 yrs
Range	(30 - 81)	(39 - 88)
Sex		
Male	21 (33.3)	22 (37.2)
Female	42 (66.7)	37 (62.7)
Smoker		
Yes	13 (20.6)	15 (25.9)
No	50 (79.4)	44 (74.6)
EGFR Mutation		
L858R	18 (28.6)	22 (27.3)
Exon 19 del	43 (68.2)	35 (59.3)
T790M	2 (3.2)	2 (3.4)
Oligometastatic Disease		
Baseline	19 (30.2)	18 (30.5)
Randomization	26 (41.2)	24 (40.6)

Adverse Events of Any Cause

- Pts evaluated every 3 months until progression
- All possible, probable, and definite treatment related AEs per CTCAE v4.0 analyzed
- Median f/u 16 months (range: 2 - 49)
- No grade 4 or 5 AEs

LCT Modality	N(%)
Radiation	35 (59)
Surgery	17 (29)
Radiation and Surgery	7 (12)

Event	Osimertinib (N=63)		Osimertinib + LCT (N=59)	
	Grade 1-2	*Grade 3*	*Grade 1-2*	*Grade 3*
	Number of patients with event (percent)			
Any event	61(96.8)	10(15.9)	58(98.3)	12(28.9)
Acute kidney injury				1(1.7)
Alkaline phosphatase increased	4(6.3)		5(8.5)	
Anemia	8(12.7)		6(10.2)	1(1.7)
Anorexia	12(19.0)		10(16.9)	
Arterial injury				1(1.7)
Back Pain	10(15.9)		7(11.9)	
Blurred vision	5(7.9)		5(8.5)	
Constipation	9(14.3)		9(15.3)	1(1.7)
Cough	23(36.5)		17(28.8)	
Creatinine Increased	18(28.6)		16(27.1)	
Diarrhea	31(49.2)		27(45.8)	2(3.4)
Dizziness	6(9.5)		3(5.1)	
Dry eye	3(4.8)		1(1.7)	
Dry mouth	1(1.6)		2(3.4)	
Dry skin	22(34.9)		20(33.9)	
Dysgeusia	1(1.6)		3(5.1)	
Dysphagia	3(4.8)		7(11.9)	
Dyspnea	11(17.5)		18(30.5)	
Ejection fraction decreased	1(1.6)	1(1.6)	1(1.7)	
Empyema				2(3.4)
Epistaxis	3(3.2)			
Esophagitis	1(1.6)		4(6.8)	
Fatigue	34((54.0)		33(55.9)	1(1.7)

Adverse Events of Any Cause

- Pts evaluated every 3 months until progression
- All possible, probable, and definite treatment related AEs per CTCAE v4.0 analyzed
- Median f/u 16 months (range: 2 - 49)
- No grade 4 or 5 AEs

LCT Modality	N(%)
Radiation	35 (59)
Surgery	17 (29)
Radiation and Surgery	7 (12)

Event	Osimertinib (N=63)		Osimertinib + LCT (N=59)	
	Grade 1-2	*Grade 3*	*Grade 1-2*	*Grade 3*
	Number of patients with event (percent)			
Gait disturbance	2(3.2)		1(1.7)	
Headache	6(9.5)		4(6.8)	
Hyperkalemia	4(6.3)		1(1.7)	
Hypokalemia	1(1.6)			1(1.7)
Hyponatremia	11(17.5)	3(4.8)	5(8.5)	4(6.8)
Hypoxia		1(1.6)		
Insomnia	2(3.2)		3(5.1)	
Intraoperative hemorrhage				1(1.7)
Leukopenia	6(9.5)		6(10.2)	1(1.7)
Limb edema			4(6.8)	
Lymphopenia	1(1.6)		3(5.1)	
Musculoskeletal pain	14(22.2)		16(27.1)	
Nail loss			2(3.4)	
Nausea or vomiting	20(31.7)		10(16.9)	
Neutropenia	1(1.6)		3(5.1)	
Non-cardiac chest pain	4(6.3)		5(8.5)	1(1.7)
Oral mucositis	5(7.9)	1(1.6)	2(3.4)	
Paronychia	35(55.6)		34(57.6)	
Pleural effusion	3(4.8)		6(10.2)	1(1.7)
Pneumonitis	2(3.2)	2(3.2)	6(10.2)	1(1.7)
OT Prolongation	1(1.6)			1(1.7)
Respiratory failure		1(1.6)		
Restrictive cardiomyopathy		1(1.6)		
Retinal detachment		1(1.6)		
Skin disorders (rash, pruritis)	41(65.1)		38(64.4)	1(1.7)

Adverse Events of Any Cause

- Pts evaluated every 3 months until progression
- All possible, probable, and definite treatment related AEs per CTCAE v4.0 analyzed
- Median f/u 16 months (range: 2 - 49)
- No grade 4 or 5 AEs

Event	Osimertinib (N=63)		Osimertinib + LCT (N=59)	
	Grade 1-2	*Grade 3*	*Grade 1-2*	*Grade 3*
	Number of patients with event (percent)			
Thrombocytopenia	12(19.0)		8(13.6)	1(1.7)
Thromboembolic event				1(1.7)
Transaminitis	10(15.9)	3(4.8)	7(11.9)	
Weight loss	2(3.2)		5(8.5)	

LCT Modality	N(%)
Radiation	35 (59)
Surgery	17 (29)
Radiation and Surgery	7 (12)

Approach to LCT with Surgery

Osimertinib held 7 days prior to surgery (N = 24)

Type to Surgery	N(%)
Lobectomy	19 (79)
Lobectomy and wedge resection	1 (4.2)
Wedge resection	2 (8.3)
Segmentectomy	1 (4.2)
Adrenalectomy	1 (4.2)

Technique	N(%)
Thoracotomy	19 (79)
Laparoscopic	3 (13)
Unknown	2 (8)

Relevant treatment related AEs in surgery cohort

Event	Grade 1	Grade 2	Grade 3
Arterial injury			1 (4.2)
Empyema			2 (8.3)
Dyspnea	4 (16.7)	1 (4.1)	

Approach to LCT with Radiation

77% continued Osimertinib during radiation at treating physician discretion (N = 42)

	N(%)
Radiation Modality	
VMAT or IMRT	30 (71)
SBRT	15 (36)
3D Conformal or 2D Conformal	7 (17)
Site	
Lung	38 (90)
Bone	9 (21)
Brain	3 (7)
Other	4 (10)
Dose	
45 - 60 Gy in 15 fx	25 (60)
50 Gy in 4 - 5 fx	9 (21)
60 - 70 Gy in 9 - 10 fx	3 (7)
30 - 40 Gy in 10 fx	8 (19)
20 - 30 Gy in 3 - 5 fx	3 (7)
19 - 20 GY in 1 fx	3 (7)
50 Gy in 25 fx	1 (2)

Organ at Risk	Median	Range
Lung		
V20 Gy	17%	(3%- 31.6%)
Mean	8.2 Gy	(0.14 Gy - 18.4 Gy)
Esophagus		
Mean	9.2 Gy	(0.47 Gy - 36.7 Gy)
Heart		
Mean	6.0 Gy	(0.02 Gy - 24.9 Gy)

Relevant treatment related AE in radiation cohort

Event	Grade 1	Grade 2	Grade 3
Pneumonitis	1 (2.3)	5 (11.9)	1 (2.3)
Esophagitis	3 (7.1)	1 (2.3)	
Dyspnea	12 (28.5)	1 (2.3)	

G1-3 Pneumonitis

Lung V20 Gy		
≥ 25%	< 25%	
4 / 9	2 / 29	p < 0.007

IASLC 2023 World Conference on Lung Cancer
SEPTEMBER 9-12, 2023 | SINGAPORE

BRIGHTSTAR: Local Consolidative Therapy with Brigatinib in Tyrosine Kinase Inhibitor-Naïve ALK-Rearranged Metastatic NSCLC

Yasir Y Elamin[1], Saumil Gandhi, Maliazurina Saad, Sadiq Rehmani, Mara B Antonoff, Don L Gibbons, Xiuning Le, Marcelo V Negrao, Vincent Lam, Mehmet Altan, Janet Tu, Carl M Gay, Lauren Byers, Tina Cascone, George Blumenschein, Joe Chang, Ara Vaporciyan, Zhongxing Liao, Stephen Swisher, Jiani Yin, Keunchil Park, Pingkuan Zhang, Jia Wu, John V Heymach

[1]MD Anderson Cancer Center, USA

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

Patient Characteristics (n=34)

Patient characteristics (n=34)	N (%)
Median age, (range)	55 (33-73)
Gender	
Male	14 (41%)
Female	20 (59%)
Histology	
Adenocarcinoma	33 (97%)
Squamous	1 (3%)
EML4-ALK variants	
Variant 1	10 (29%)
Variant 2	2 (6%)
Variant 3a/b	18 (53%)
E6a:A19	1 (3%)
Unknown	3 (9%)
Number of metastases at baseline	
≤3	6 (18%)
>3	28 (82%)

Objective Response to Brigatinib

Response to brigatinib at 8 weeks	
Partial response	27 (79%)
Stable disease	7 (21%)

LCT details

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

Radiation and surgery details

Radiation	N*
SBRT	8
IMRT/VMAT	20
2D/3D conformal radiation	8
Proton beam therapy	1
Brigatinib held during radiation?	**(total n=29)**
Yes	19
No	10
Surgical Procedures**	**(total n=5)**
Pulmonary lobectomy	3
Sublobar pulmonary resection	1
Adrenalectomy	1

* Nine patients received two modalities of radiation
** Two patients had complete pathological response and 1 patient had complete pathological response at the primary tumor

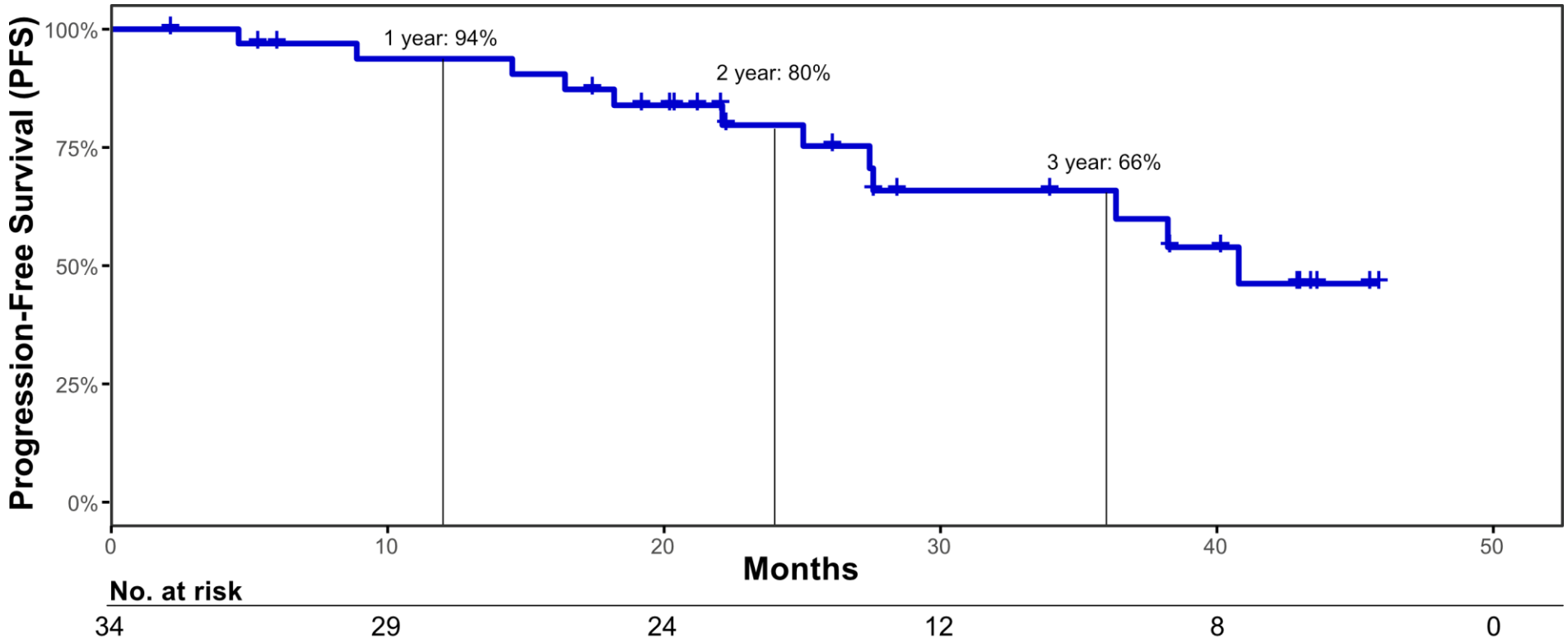
Safety of Brigatinib and LCT

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

Progression Free Survival



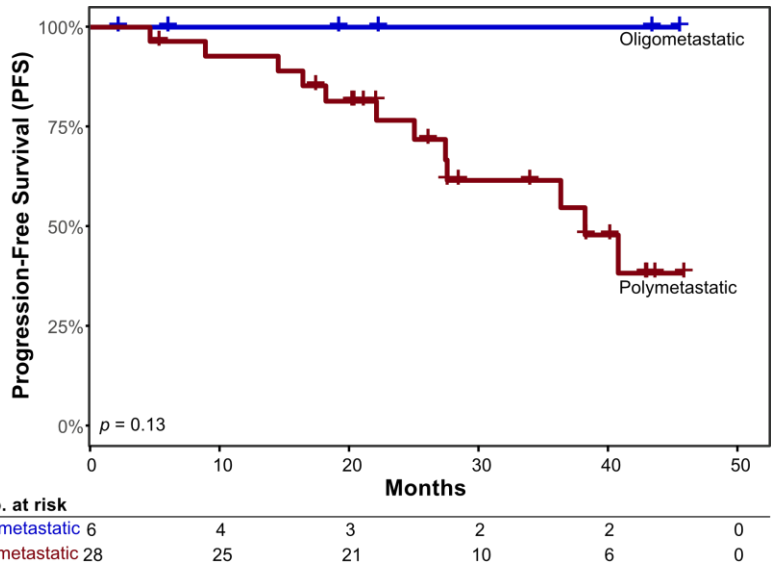
Progression Free Survival

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

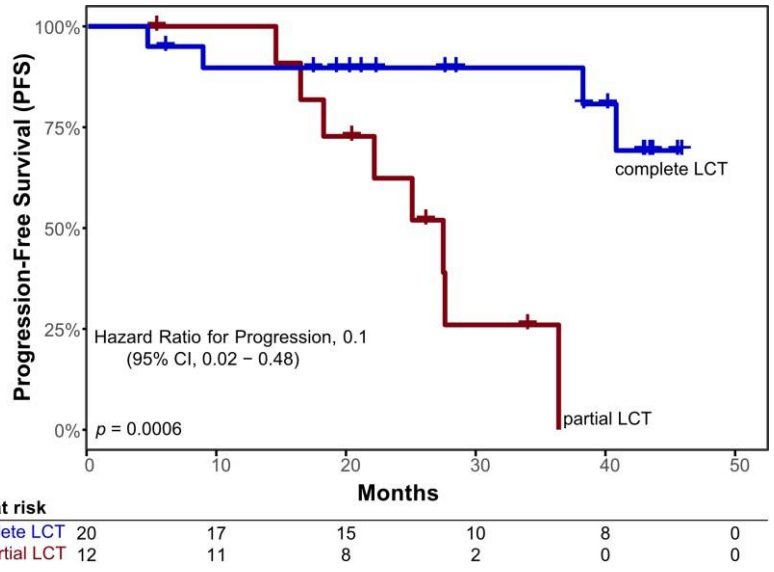
*Includes only patients who did not progress at 12-week on ALTA 1L. PFS calculated from randomization

Predictors of outcome

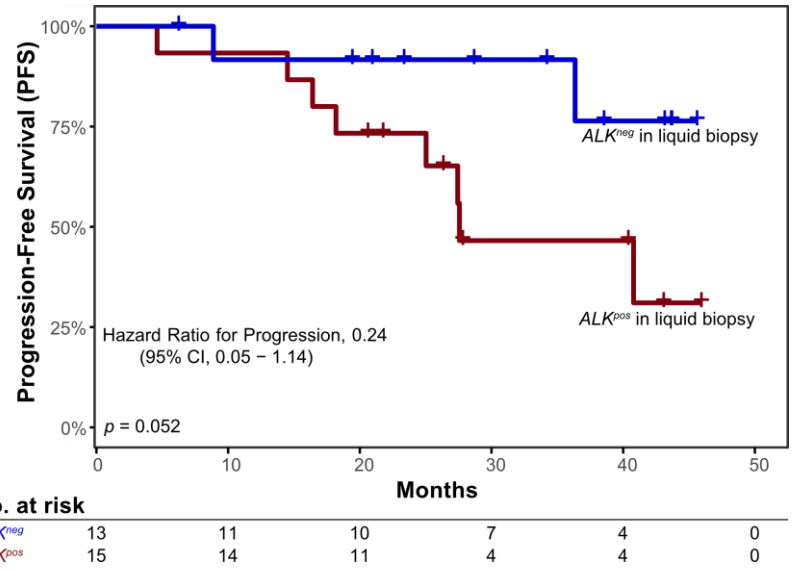
No of mets at baseline



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

Perioperative and oncologic outcomes of pulmonary resection for synchronous oligometastatic non–small cell lung cancer: Evidence for surgery in advanced disease

Patients with resected oligometastatic* NSCLC

Single-Center Database

(2000-2017)

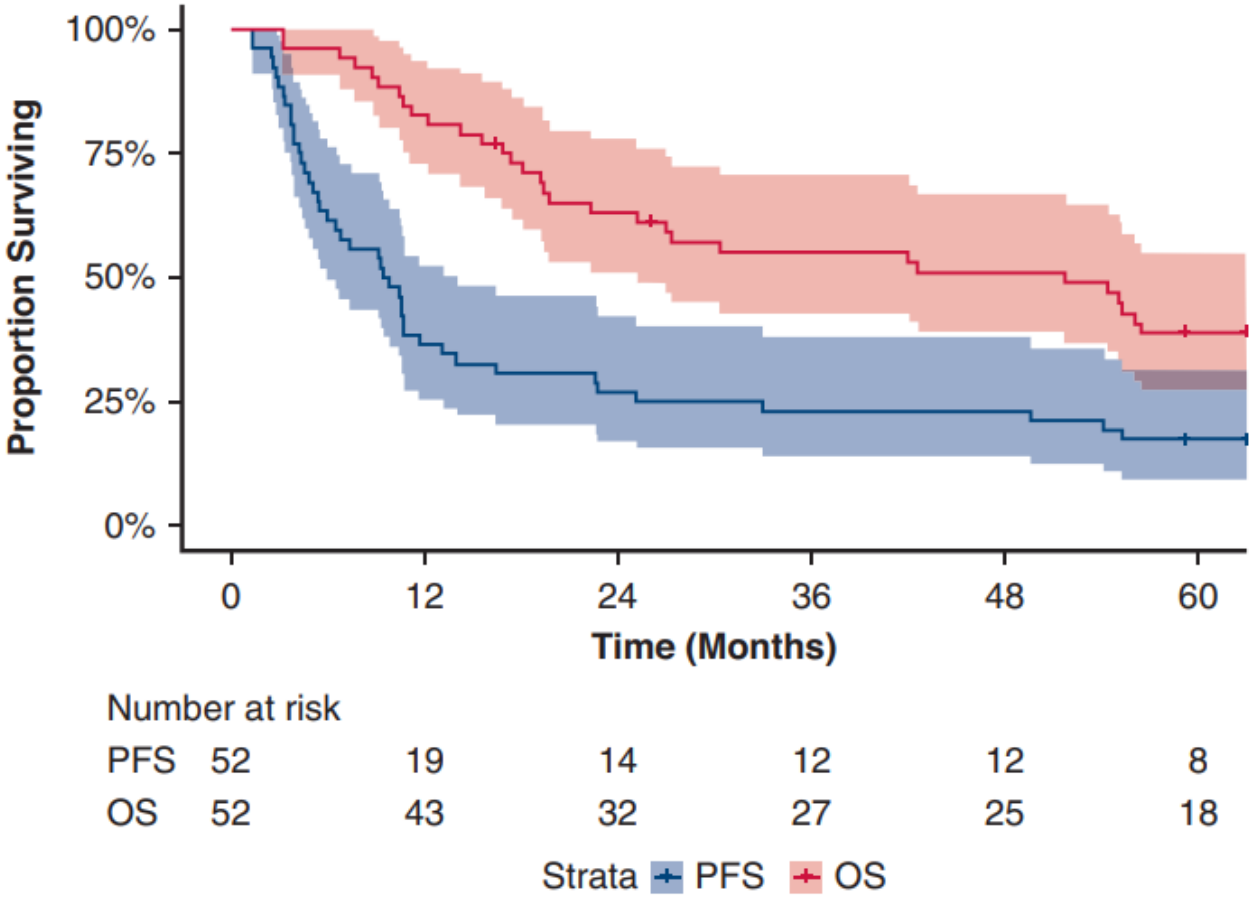
52 patients identified

*(≤ 3 synchronous metastases)

Characteristic	N (%)
Number of Metastatic Sites	
1	34 (65.4)
2	15 (28.9)
3	3 (5.8)
Location of Metastases	
Brain	27 (51.9)
Bone	9 (17.3)
Adrenal	5 (9.6)
Liver	4 (7.7)
Distant Node	3 (5.8)
Extent of Resection	
Sublobar	5 (9.6)
Lobectomy	43 (82.7)
Pneumonectomy	4 (7.7)
Surgical Approach	
Thoracotomy	43 (82.7)
Thoracoscopy	9 (17.3)

- Patients presenting to a single center (2000-2017) with sOMD (≤3 metastasis, intrathoracic node as a single site)
- Underwent resection of the primary tumor were retrospectively reviewed
- EGFRm (12 pts, 23.1%)

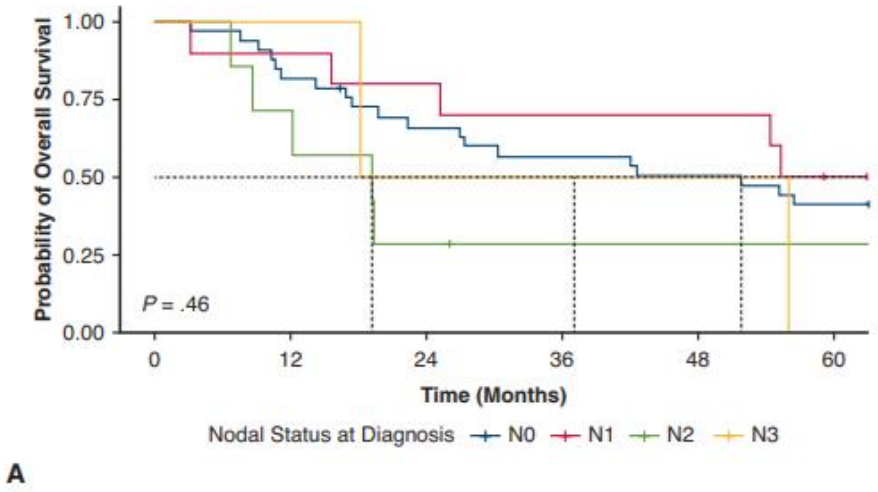
J Thorac Cardiovasc Surg. 2024 Jun;167(6):1929-1935

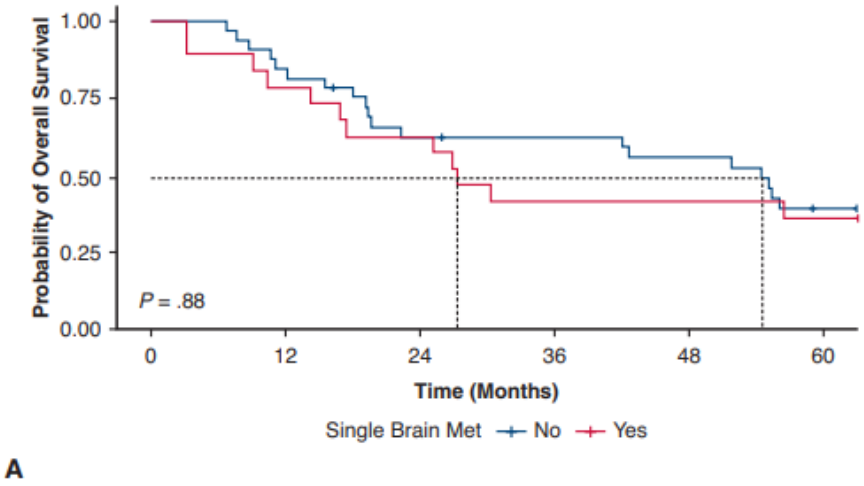


mPFS: 9.4 months (5.5-11.6)
mOS: 51.7 months (22.3-65.3)

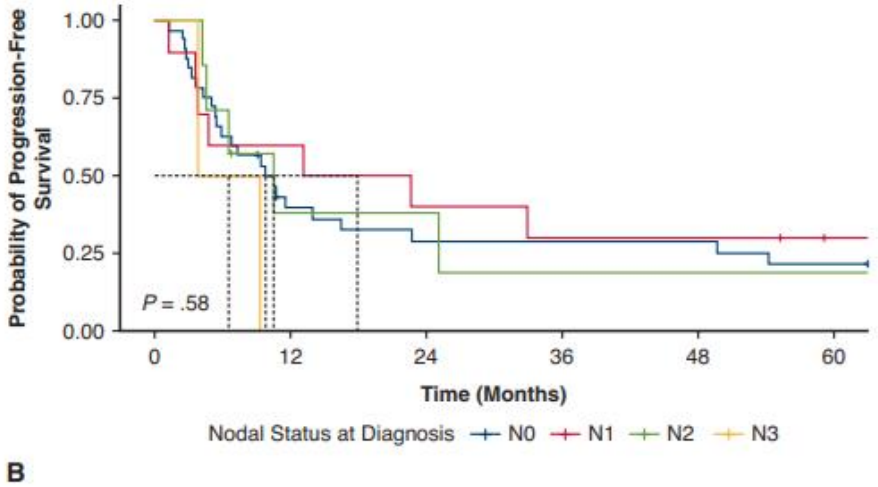
J Thorac Cardiovasc Surg. 2024 Jun;167(6):1929-1935

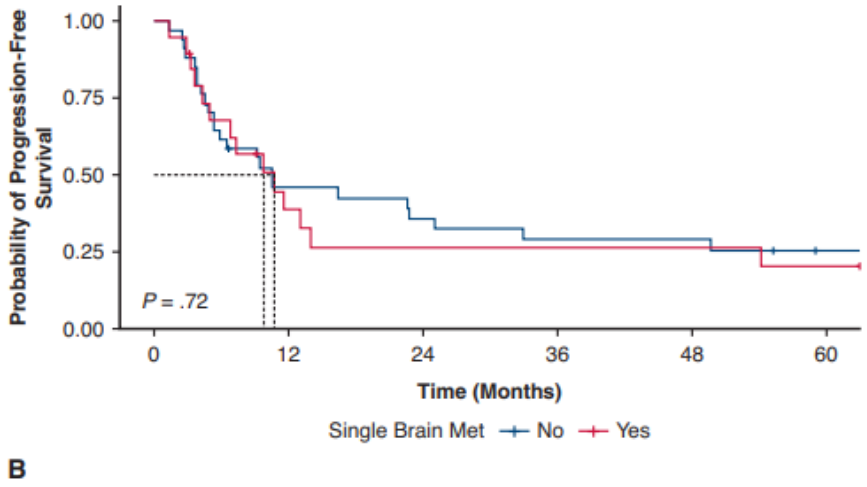
OS





PFS





Nodal involvement

Single brain metastasis

J Thorac Cardiovasc Surg. 2024 Jun;167(6):1929-1935

Secondary Outcomes

Most patients (n = 47, 90.4%) received comprehensive LCT to all sites of disease. There was no 30- or 90-day mortality. Ten patients (19.2%) developed major cardiovascular complications, and 8 patients (15.4%) developed major pulmonary complications. Operations were reported as more difficult than usual in 42.3% of cases (n = 22). Lymph nodes were reported to be adherent or hard in 28.9% or cases (n = 15). Despite the need for advanced resections, negative margins were achieved in 92.3% of cases (n = 48).

J Thorac Cardiovasc Surg. 2024 Jun;167(6):1929-1935

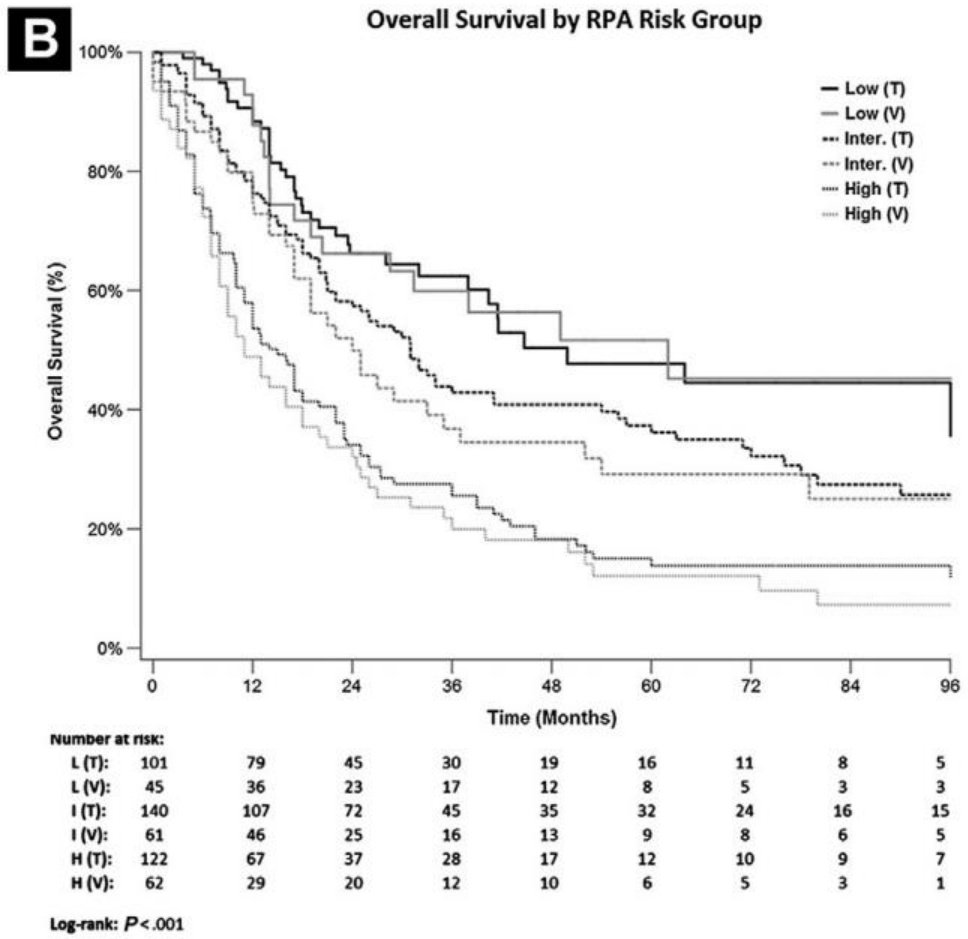
Contents

- Local consolidative therapy (LCT) & Oligometastatic disease (OMD)
- Clinical evidences of LCT
- LCT in oncogene-addicted OMD NSCLC
- Guidelines & Summary

An Individual Patient Data Metaanalysis of Outcomes and Prognostic Factors After Treatment of Oligometastatic Non–Small-Cell Lung Cancer

Allison B. Ashworth,[1] Suresh Senan,[2] David A. Palma,[1] Marc Riquet,[3] Yong Chan Ahn,[4] Umberto Ricardi,[5] Maria T. Congedo,[6] Daniel R. Gomez,[7] Gavin M. Wright,[8] Giulio Melloni,[9] Michael T. Milano,[10] Claudio V. Sole,[11] Tommaso M. De Pas,[12] Dennis L. Carter,[13] Andrew J. Warner,[1] George B. Rodrigues[1]

- Low-risk: mOMD, N0 ➔ 5 yr OS 47.8%
- Intermediate risk: sOMD ➔ 5 yr OS 36.2%
- High-risk: sOMD, N1/2 ➔ 5 yr OS 13.8%



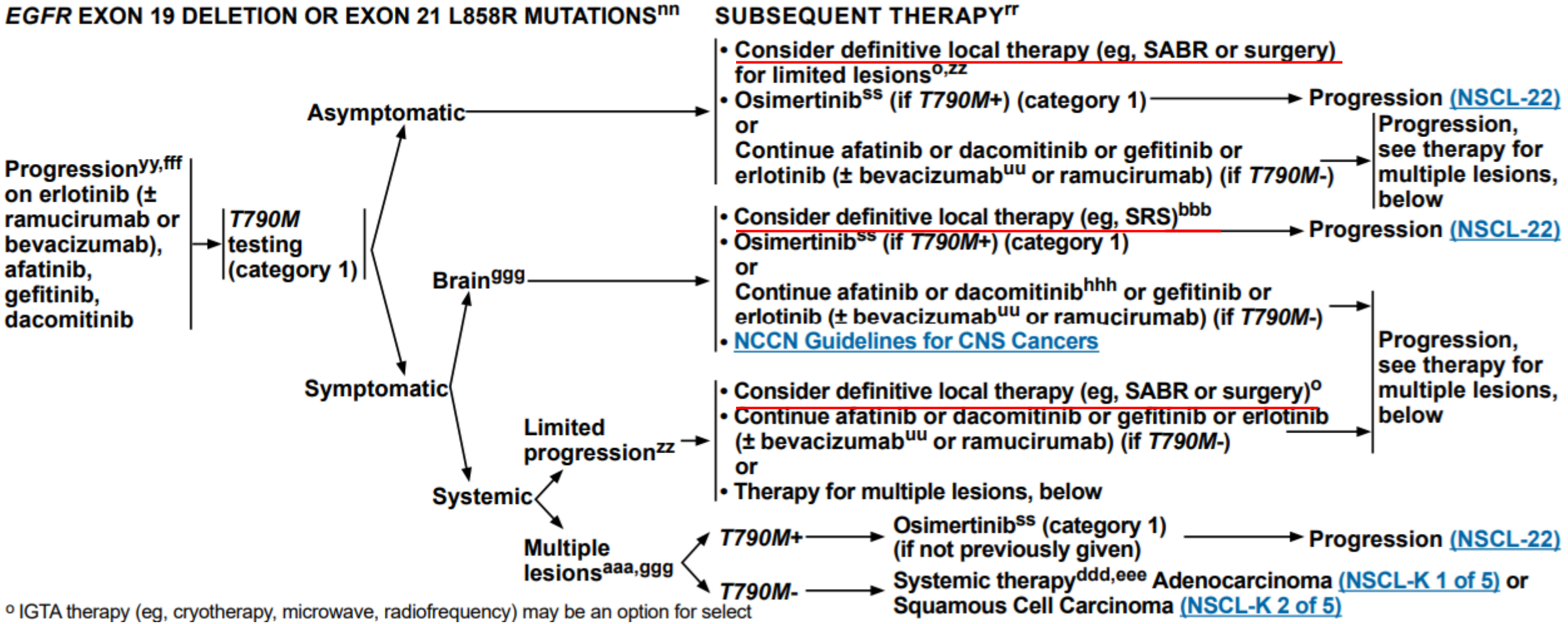
Clin Lung Cancer. 2014 Sep;15(5):346-55.

Patient selection for LAT

	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

J Clin Oncol. 2022 Feb 20;40(6):635-641

NCCN Guidelines



o IGTA therapy (eg, cryotherapy, microwave, radiofrequency) may be an option for select

Future studies..

- Optimal timing and sites
- Optimal method
- Toxicity and side effects
- Long term survival and QOL

Summary

- OMD: A maximum of 5 metastases and 3 organs
  - sOMD, mOMD (oligorecurrence), oligoprogression
- Clinical evidences
  - 3 phase II RCT: ↑ PFS, OS, tolerable safety profile
  - Ongoing phase III clinical trials
- LCT in oncogene-addicted OMD NSCLC
  - SINDAS trial: ↑ PFS, OS, tolerable safety profile
  - NORTHSTAR, BRIGHTSTAR
  - Surgery
- Patient selection
  - Good PS, Low tumor burden, Effective systemic therapy