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Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC):

A Randomized Phase II/III Trial

July 2022

Table 1 Outcomes From Completed Prospective for Patients With Oligometastatic and Oligoprogressive NSCLC

Study	Design	Local Treatment Arms	Patients	RT Dose	Treatment Site	Systemic Therapy	Primary Endpoint	Outcome	Toxicity (G3+)
De Ruysscher 2012	Prospective single arm, Phase II	Radiation or Surgery	44	Brain: 21 Gy/1; 24 Gy/3 pt undergoing resection received WBRT (30 Gy/10) Lung: 54 Gy/3 Other non-stereotactic regimens included (EQD2 > 60 Gy)	1-4 sites, extra/intracranial disease 97.5% had 1-2 lesions treated	92.3% received platinum-based CHT	OS at 2 and 3 years	mFU 27.7 m mPFS 12.1 m mOS 16.7 m 2-yr OS 23.3% 3-yr OS 17.5%	Acute Esophagitis 15% Cough 2.6%
Collen 2014	Prospective single arm, Phase II	SAbR	26	SAbR 50 Gy/10	1-5 metabolically active sites; extra/intracranial disease 46% > 1 lesion treated 46% > 1 organ involved	65.4% received platinum-based induction CHT	CMR rate	mFU 16.4 m mPFS 12.2 m mOS 23 m 1-yr PFS 45% 1-year OS 67% CMR 30% OMR 60%	Acute Cough 8% Late None
Iyengar 2014	Prospective single arm, phase II	SAbR	24	SAbR 19-20 Gy/1 27-33 Gy/3 35-40 Gy/5	< 7 sites, extracranial disease (< 4 in liver and lung each) 62.5% >3 lesions treated	100% concurrent erlotinib (50-150 mg /day)	6-m PFS	mFU 11.6 m mPFS 14.7 m mOS 20.4 m	Grade 3 24%[†] Grade 4 4%[‡] Grade 5 13%[*]
Iyengar 2018	Prospective, randomized, Phase II	SAbR+ maintenance CHT vs maintenance CHT alone	29 (closed early after interim analysis showed benefit	SAbR 18-24 Gy/1 24.6-33 Gy/3 30-37.5 Gy/5 Hypofractionated 45Gy/15	Primary disease plus up to 5 extracranial sites with no more than 3 sites in the liver or lung	Maintenance therapy: Docetaxel, bevacizumab, gemcitabine, pemetrexed, erolitinib	PFS	mFU 9.6 m mPFS 9.7 m vs 3.5 m SS favoring local therapy arm mOS not reached in local therapy arm vs 17 m in maintenance arm	Similar grade 3+ toxicity profiles between the two arms. 2 grade 3 AE and 1 grade 4 AE in maintenance arm; 4 grade 3 AE in local therapy arm[§]
Theelan 2018	Prospective randomized, Phase II	Pembrolizumab after SAbR to a single tumor site vs pembrolizumab alone	76	SAbR 24 Gy/3	Only extracranial lesions treated with SAbR >1 metastatic lesion with size < 5 cm	Pembrolizumab (200 mg/kg every 3 weeks)	ORR	mFU 23.6 m 12-week ORR 36% vs 18% NS favoring SAbR arm mPFS 6.6 m vs 1.9 m favoring SAbR arm mOS 15.9 m vs 7.9 m favoring SAbR arm	35 grade 3+ toxicities in the experimental arm and 37 grade 3+ in the control arm; no difference between the arms
Bauml 2019	Prospective single arm, Phase II	Pembrolizumab after SAbR, surgical resection, chemoradiation, or radiofrequency ablation	45	Unspecified radiation regimens	1-4 sites; Intracranial and extracranial lesions were treated; 30 patients were treated with SAbR 93% had 1-2 metastases	Median of 11 cycles of pembrolizumab (200 mg every 3 weeks)	PFS	mFU 25 m mPFS 19.1 m mOS 41.6 m	5 pneumonitis (one grade 4), 2 grade 3 colitis, and 2 adrenal insufficiency (one grade 3)
Palma 2019	Prospective, multicenter randomized, Phase II	'Standard' palliative treatment vs standard of care and SAbR to all sites of metastatic disease	18 patients with NSCLC	SAbR regimens permitted 30-60 Gy/3-5 depending on location SRS regimens permitted 16-24Gy/1	<6 sites of metastases (intracranial and extracranial) 75% had 1-2 metastases	Not specified however the two groups did not differ in receipt of systemic therapy	OS	mFU 26 m mPFS 12 vs 6 m in favor of SAbR arm mOS 41 vs 28 m in favor of SAbR arm	5% grade 5 rate in treatment arm vs 0% in the control arm
Gomez 2016, 2019	Prospective multicenter randomized, Phase II	Radiation, chemoradiation, or resection +/- maintenance treatment vs maintenance treatment alone	49 (closed early after interim analysis showed benefit)	Regimen per primary radiation oncologist—hypofractionated RT and concurrent CRT was allowed	≤3 metastatic lesions 35% of entire cohort had 2-3 nonregional metastases after initial systemic therapy	Could receive: platinum doublet CHT, TKI targeting EGFR mutation, crizotinib	PFS	mFU 38.8 m mPFS 14.2 m vs 4.4 m SS favoring local therapy arm mOS 42.2 m vs 17 m favoring local therapy arm	Grade 3 Esophagitis (n = 2) pneumothorax (n = 1) anemia (n = 1)

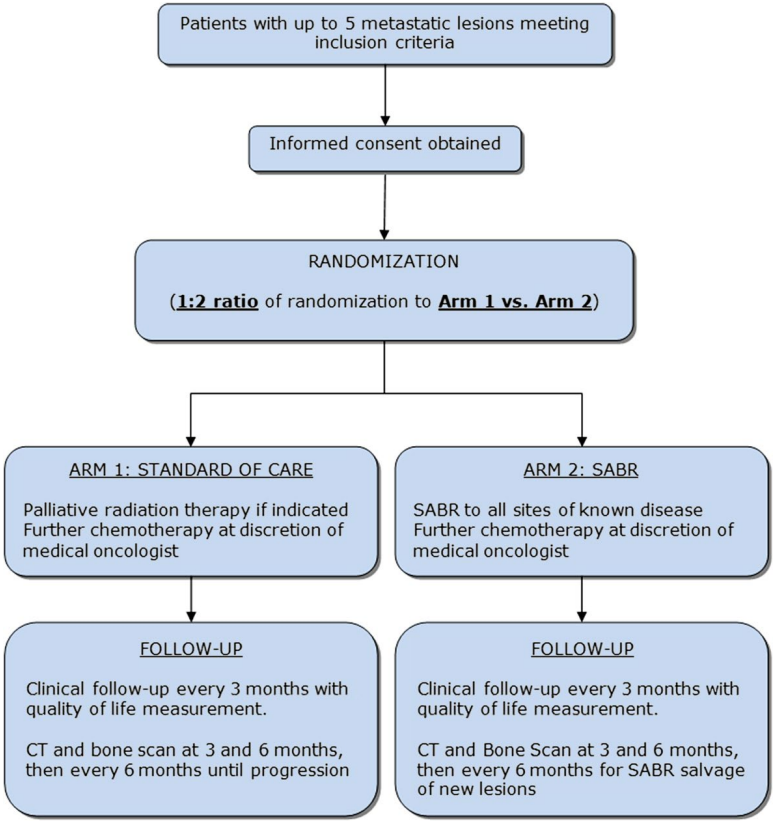
Review > Semin Radiat Oncol. 2021 Jul;31(3):235-241. doi: 10.1016/j.semradonc.2021.03.002.

Local Ablative Therapy in Oligometastatic NSCLC

Xingzhe Li [1], Daniel Gomez [1], Puneeth Iyengar [2]

1) No current randomized data showing OS benefit from **larger** studies with uniform NSCLC patient populations

SABR COMET – All cancer histologies



MDACC-Uof Col-London Ontario

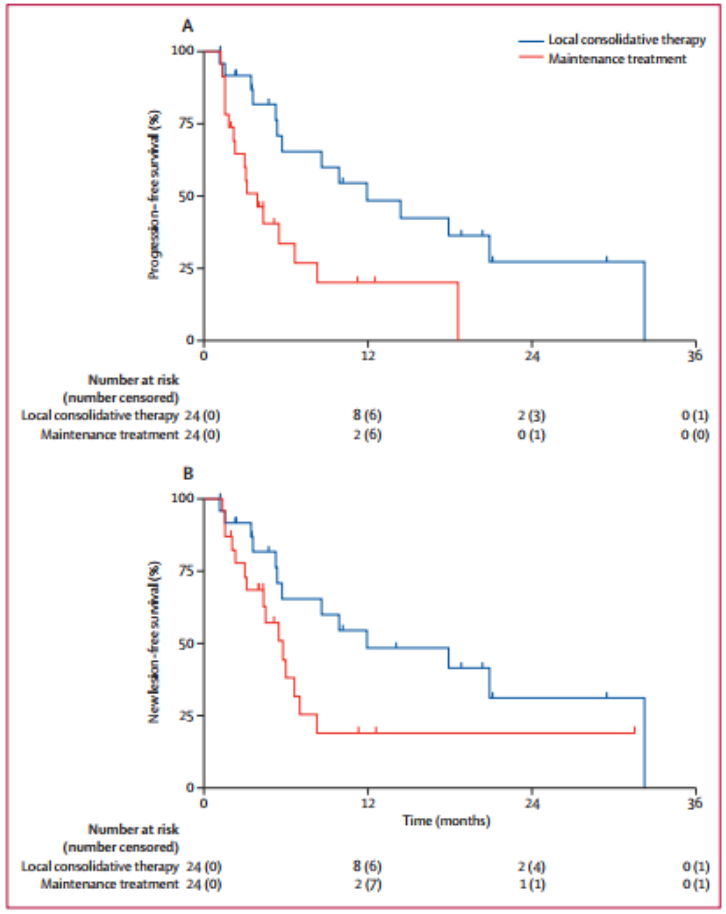


Figure 2: Progression-free survival (A) and time to appearance of disease at a new site (B)

Surgery and radiation allowed
Targetable mutation positive disease allowed
Observation in maintenance allowed
Chemoradiation allowed for local therapy
IO not standard at time these studies were conducted

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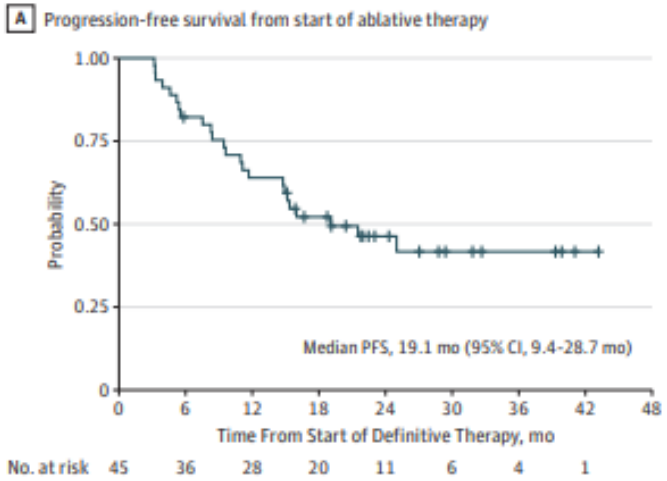
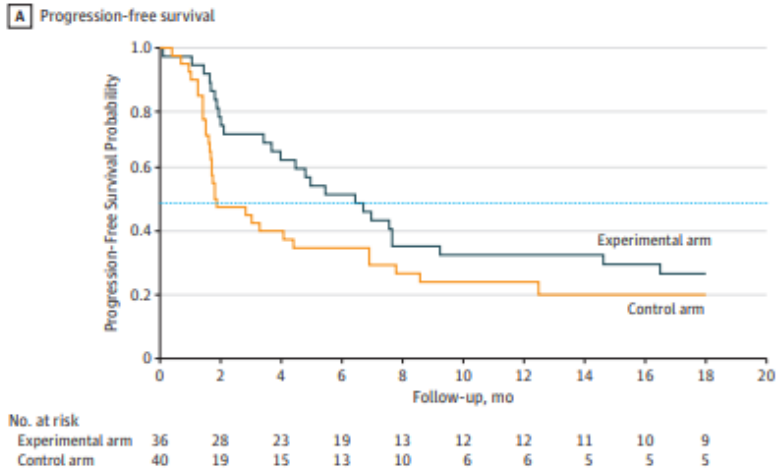
2) With better IO/systemic therapy outcomes, the benefits of local therapy may be enhanced or diluted

Radiation -/+ IO (Pacific) is different than IO -/+ Radiation?

1) IO after LCT single arm Phase II (Bauml et al, 2019)

2) IO -/+ Salvage Local Therapy RPh2 in 2nd line setting (Willemijn et al, 2019)





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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**

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The study is event-driven and plans to randomize up to **378** eligible patients with 2:1 ratio into the experimental and control arms. Guarding against ineligibility or lack-of-data rate of up to 5%, the targeted accrual of randomized patients for the entire phase II/III study is **400**.

The primary hypothesis of this study is that LCT and maintenance systematic therapy (Arm 2) will improve the progression-free survival (phase II) and overall survival (phase III), compared to the maintenance systematic therapy alone (Arm 1). We therefore project that, for the standard maintenance systemic therapy, the 6 month and 12 month rates of PFS are approximately 60% and 39%, and 12 month and 24 month rates of OS are 68% and 47%, respectively. For the phase II portion, we consider an improvement in 6 month and 12 month rates of PFS from 60% and 39% to approximately 75% and 57%, respectively, to warrant a phase III study. This improvement is approximately equivalent to a hazard reduction of 40% in PFS ($HR_{PFS} = 0.6$). For the entire study, we aim to demonstrate an improvement in 12 month and 24 month rates of OS from 68% and 47% to 77% and 61%. This improvement is approximately equivalent to a hazard reduction of 32% in OS ($HR_{OS} = 0.68$).

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NRG LU 002 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

SECONDARY OBJECTIVES

- Evaluate effect of adding LCT to systemic therapy in limited stage IV NSCLC on PROs and Quality of Life studies
- Collect biospecimens → evaluate correlation between clinical outcomes and circulating tumor DNA (ctDNA); after systemic therapy, after local therapy, at recurrence

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Eligibility Criteria

Metastatic NSCLC diagnosis – de novo or recurrent stage IV distribution.

Received 1st line/induction systemic therapy (4-5 cycles/courses) - stable disease or partial response

Permitted:

- Prior systemic therapy as part of concurrent treatment approach for previously diagnosed stage III NSCLC, as adjuvant therapy for previously resected NSCLC or other previous cancers
- Patients with brain metastases are eligible if these lesions previously have been "treated" and patient has no clinical or radiographic evidence of progression prior to enrollment

Must have measurable disease at enrollment and 0-3 extracranial metastatic disease sites that are technically amenable to LCT - Measurable disease can be primary and/or metastatic disease. Hypofractionated radiation can be used to treat primary/nodal disease.

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Radiation Doses

PTV Dosimetry Compliance for SBRT

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Fractions
PTVXY_2400	D95%[Gy]	24	16-27	1
PTVXY_3000	D95%[Gy]	30	24.5-33	3
PTVXY_3400	D95%[Gy]	34	28-37.5	5

PTV Dosimetry Compliance for Primary Site

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable	Fractions
PTV_4500	D95%[Gy]	45	42-48 (excluding 45)	15

45Gy in 15Fx permitted for mets if needed

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Systemic Therapy

Maintenance therapy → Systemic therapy protocol treatment ideally begun either:

- within 2 weeks of registration on the maintenance systemic therapy (Arm 1)
- within 2 weeks of the completion of LCT (Arm 2)
- tailored to patient/histology

Maintenance drugs:

- **Pemetrexed, Gemcitabine**
- **Pembrolizumab, Pembrolizumab/Pemetrexed, Ipi/Nivo, Atezo**

NOTE: Must refer to the package insert for complete details on safety and treatment information. Premedications should be given according to the package insert and institutional guidelines for each agent.

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Previous amendment:

1) FDA approved IO allowed as first line and in maintenance as single agent or in combination therapy. To date, that includes Pembrolizumab single agent, Pembro/Pemetrexed/ Platinum, and Pembro/Platinum/Paclitaxel in induction and Pembro or Pembro/Pemetrexed in maintenance.

2) Surgery allowed as option for consolidation of mets. One site of disease will still need to receive radiation. Drs. Donington and Swisher are Surgical Co-Chairs.

3) With modified inclusion criteria and stratification for immunotherapy, approximately 378 patients will need to be accrued in 2:1 randomization favoring local therapy arm.

4) **Patients can receive radiation for palliation and still be enrolled on study as long as there are areas to consolidate after induction systemic therapy.**

ACCRUAL

218 patients enrolled.

Trial reached enrollment for interim analysis of Ph2 portion of study.

For the phase II portion, we consider an improvement in 6 month and 12 month rates of PFS from 60% and 39% to approximately 75% and 57%, respectively, to warrant a phase III study. This improvement is approximately equivalent to a hazard reduction of 40% in PFS (HRPFS = 0.6).

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After 142 patients, we evaluated data:

1) 116 patients or 80% of patients had received IO-based systemic therapy.

2) 26 patients or 20% had received cytotoxic chemotherapy-only regimens.

This study has become an IO -/+ LCT trial due to changing SOC. Chemo still permitted.

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LUNG

NRG-LU002: Amendment 6; version date May 26, 2021 and Study Memorandum dated June 24, 2021. Also posted - Amendment 5; version date March 30, 2021.

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Modifications/Amendments

1) Include all allowable FDA IO regimens for induction / ”maintenance” – Atezo, Nivo, Ipi in maintenance. Weight-based dosing for Pembro now permitted.

2) Bev not permitted.

3) Times to restart systemic therapy – Give range for patients to get registered – After cycle/course 4 and before start of cycle/course 6. Bryan Faller NCORP study champion.

4) Loosen restrictions in eligibility regarding CrCl.

5) Previous IO permitted if used in stage I-III settings.

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Modifications to Facilitate Registered Pts –

1) Dosi normal tissue constraints for 45/15.

2) 45/15 for select mets.

3) Modified Version of irRC.

4) Increase time allowed to restart maintenance.

5) Follow up imaging after progression – SOC.

6) Reiterate ILD exclusion.

7) Reminder about need to have any residual disease – met and/or primary for consolidation.

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QUESTIONS?

- **Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted**
- **For questions concerning eligibility**, please contact the Biostatistics/Data Management Center - see contact list on protocol title page
- **For radiation therapy-related eligibility questions**, please contact RTQA - see contact list on protocol title page
- If there is any concern, please consult the Study Chair, Radiation Co-Chairs, Surgical Co-Chairs, or Med Physics Co-Chairs before or after treatment planning
- Please remember that SBRT doses are well below the ablative doses used to treat patients with curative intent. Furthermore, in previous experiences using these SBRT schemas, minimal toxicities and high rates of local control are observed. Therefore, it is expected that the SBRT will be well tolerated.

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