Ongoing clinical trials (phase II–IV) regarding the treatment of oligometastatic NSCLC

Name, NCT identifier (country)	Design	N	^{18}F-FDG PET	Brain imaging	Molecular status	Number of metastases	Treatment(s)	Endpoints	Notes
sOMD only									
CHESS, NCT03965468 [European (ETOP)]	Phase II, single-arm	47	Yes	NR	No EGFR/ALK/ROS1 alterations	≤3 (one of which must be extra-cerebral)	Durvalumab + carboplatin + paclitaxel + SBRT of all oligo-metastatic lesions (starting 1 week after C1D1; 10 fr) → restaging at 3 months: if no PD → definitive local treatment (surgical resection of primary tumor or RT 60–66 Gy to the primary tumor) → continues durvalumab (until PD or for a maximum of 1 year from start of therapy)	1^{ry}: 12-month PFS; 2^{ry}: OS; pattern of PD; response to induction tx; TANM; ORR; DoR; QoL; toxicity	
NCT04255836 (China)	Phase II, single-arm	35	NR	NR	No EGFR or ALK alteration	≤3 metastatic organs & ≤5 metastatic lesions[†]	CT (paclitaxel + carboplatin or pemetrexed + cisplatin) + durvalumab × 4 cycles → SBRT 50–60 Gy/≤10 f + durvalumab → durvalumab until PD	1^{ry}: PFS; 2^{ry}: OS, toxicity, treat failure patterns, ORR	
NCT03119519 (China)	Phase II, randomized	148	NR	NR	All comers	≤5	Standard platinum-based doublet CT or EGFR-TKI (gefitinib or erlotinib) → 3D-CRT or IMRT to primary thoracic foci or remediable oligometastatic focus	1^{ry}: PFS; 2^{ry}: local control, thoracic PFS, OS	
ImmunoSABR (25), NCT03705403 (European)	Phase II, randomized	126	Yes	Yes	All comers	≤5	With or without previous treatment, in the 1st, 2nd or 3rd line of treatment: SoC: wait and see or surgery and/or CT and/or standard (symptomatic) RT and/or SABR (OMD) *vs.* SoC [SABR to all lesions (OMD)] or radiotherapy (diffuse disease) + L19–IL2 (darleukin) up to 6 cycles [+ aPD(L)1 if SOC]	1^{ry}: PFS; 2^{ry}: OS, QoL, out of field radio-immune response, toxicity, biomarkers	Includes both oligometastatic (≤5 lesions) and poly-metastatic patients (6–10 lesions)
PROMISE-005, NCT03808337 (USA)	Phase II, randomized	142	NR	NR	No EGFR/ALK/ROS1 alterations; or with molecular alterations, with PD under 1st-line TKI	Primary & ≤5	SoC systemic therapy *vs.* SBRT to all sites of known metastatic disease (± concurrent SoC systemic therapy) – minimum 30 Gy/5 fr per site → SoC systemic therapy	1^{ry}: PFS; 2^{ry}: OS	Includes breast and NSCLC
OITROLC, NCT02076477 (China)	Phase III, randomized	420	NR	NR	Not specified	≤5	Upfront CT/RT (primary tumor + LN + bone + intracranial) → CT ×2 cycles *vs.* CT ×2 cycles → same CT, concurrent with RT[Δ]	1^{ry}: RR; 2^{ry}: PFS, QoL, toxicity	
SARON (26), NCT02417662 (UK)	Phase III, randomized	340	Yes	Yes	No actionable molecular aberration	≤5 in ≤3 organs (including ≥1 extra-cranial lesion)	2 cycles of CT/immunotherapy → no PD: systemic therapy alone *vs.* systemic therapy ×2 more cycles → radical RT (conventional [50–55 Gy/20 fr or 60–64 Gy/30–32 fr] or SABR [54 Gy/3 fr, 55 Gy/5 fr or 60 Gy/8 fr]) to the primary (±LN[ν]) + SABR (several schemes) to the metastatic sites → maintenance therapy allowed	1^{ry}: OS; 2^{ry}: PFS, toxicity, Local Tumor Control, QoL	
Oncogenic driver alterations only									
Sindas, NCT02893332 (China)	Phase III, randomized	200	NR	Yes	Only EGFR-mutated (except T790M)	Primary & ≤5	TKI (gefitinib or erlotinib) *vs.* TKI + consolidative SBRT (25 Gy/5 fr to 40 Gy/5 fr) to all sites of disease → TKI	1^{ry}: PFS 2^{ry}: OS, local control	Interim results presented (see *Table 1*)
NCT03916913 (China)	Phase II, single-arm	85	No*	No*	Only EGFR-mutated	≤3 at baseline	≥3 months of TKI → no PD → RT on all disease sites (primary + metastasis)	1^{ry}: PFS[¶] 2^{ry}: overall response, OS[¶], local control[¶], TANM[¶], toxicity, QoL	
rOMD only									
NCT04275687 (China)	Phase II, single-arm	35	NR	NR	Not specified	0	Patients with locoregional recurrence only: peripherally located recurrent tumors: SBRT (50–60 Gy/10 fr) only; centrally located recurrent tumors: adaptive hypofractionated RT: 30-40Gy in 6–10 fr → 4 weeks after → no PD → adaptive re-planning → 24–35 Gy in 4–7 fr (boost) + concurrent CT: weekly docetaxel + nedaplatin	1^{ry}: OS; 2^{ry}: local control, toxicity	
NCT04306926 (China)	Phase II, single-arm	59	NR	NR	No EGFR, ALK or ROS1 alterations	≤5	SBRT 3 days before TQB2450 (anti-PD-L1)	1^{ry}: PFS; 2^{ry}: OS, ORR, DCR	
CORE, NCT02759783 (UK)	Phase II/III, randomized	245	NR	NR	Not specified	≤3, all extra-cranial	SoC *vs.* SoC + SBRT	1^{ry}: PFS; 2^{ry}: toxicity, QoL, OS, local lesion control, FFWMD	Includes breast, prostate and NSCLC
SABR-COMET 10 (27), NCT03721341 (USA)	Phase III, randomized	159	NR	NR	Not specified	4–10, ≤5 cm of diameter; brain metastases: ≤3 cm or a total volume ≤30 cc	Controlled primary tumor (≥3 months since original tumor treated definitively, with no progression at primary site) → rOMD: SoC (palliative RT [8 Gy/1 fr, 20 Gy/5 fr or 30 Gy/10 fr], CT, immunotherapy or observation); SoC + SBRT (20 Gy/1 fr, 30 Gy/3 fr or 35 Gy/5 fr)	1^{ry}: OS; 2^{ry}: PFS, TANM, QoL, toxicity	Any tumor type
sOMD and rOMD									
NCT02975609 (China)	Phase II, randomized	100	No*	Yes	All comers	≤5 & ≤5 cm of diameter (each lesion)	4–6 cycles chemotherapy (platinum-based doublet CT) → no PD → randomized to: conventional fractionated RT to all metastatic sites + primary tumor (5 Fx/W, 3 Gy/Fx, Dt: PTV-G: 30 Gy/10 F/2 W for mets, Dt: 60 Gy/30 F for primary tumor and LN+) *vs.* SBRT (30 Gy/3–5 F) to all metastatic sites + primary tumor	1^{ry}: PFS; 2^{ry}: OS, toxicity	
OMEGA, NCT03827577 (Italy)	Phase III, randomized	195	Yes	Yes	All comers	≤3	Before any systemic therapy or after 3 months of treatment without PD: LAT (lung resection, if primary in place + LAT of all metastatic sites*) + standard systemic treatment *vs.* standard systemic treatment	1^{ry}: OS	
STEREO-OS, NCT03143322 (France)	Phase III, randomized	196	NaF-PET & FDG-PET	Yes	Not specified	≤3 bone metastases (only)	Systemic treatment + SBRT (9 Gy × 3 fr or 7 Gy × 5 fr) *vs.* systemic treatment only (palliative RT on bone metastases is allowed if necessary). Note: primary tumor should be accessible to curative-intent treatment (surgery, CT/RT, etc.) for patients with synchronous metastases	1^{ry}: PFS; 2^{ry}: PFS at 2 and 3 years; bone PFS, local control; cancer specific survival, OS, toxicity, QoL, pain score, cost utility	Includes breast, prostate and NSCLC
peOMD									
NCT02805530 (Mexico)	Phase II, single-arm	25	NR	Yes	All comers	≤5 at diagnosis	EGFR-TKI or CT ×3 months → if SD/PR: radical treatment of all metastatic sites and the primary tumor (surgery, RT, CT/RT, SABR or RFA)	1^{ry}: OS	No ICI
ROLE, NCT01796288 (China)	Phase II, randomized	200	Yes	NR	All comers (if with non-squamous tumors)	≤5	1st-line chemotherapy → PD or toxicity → 2nd line with erlotinib → after 3 months → no PD: RT to primary and metastases + concurrent erlotinib *vs.* erlotinib only	1^{ry}: PFS; 2^{ry}: OS	
NCT01725165 (USA)	Phase II, randomized	94	NR	NR	All comers	≤3[β] after induction systemic therapy	Stage IV: 1st line therapy (CT ×4 cycles or EGFR/ALK TKI ×3 m) → SD/PR: LCT: ablation of all residual local and metastatic sites of disease by surgery and/or RT → surveillance or maintenance treatment *vs.* maintenance treatment (cross-over allowed)	1^{ry}: PFS; 2^{ry}: OS, toxicity, time to PD of prior metastatic lesions, time to new lesions, QoL	
CRAGMOLC, NCT03489616 (China)	Phase II, randomized	45	Yes	NR	No actionable molecular aberration	2–5, after induction systemic therapy	1st line CT → no PD: single-agent CT (maintenance therapy) + local RT (dose >4 Gy/fr or BED >45 Gy) + SC injection of rhGM-CSF 24 hours after CT; repeat in the other metastatic lesion; single-agent CT (maintenance therapy) only	1^{ry}: PFS; 2^{ry}: OS, abscopal effect rate	
NCT02045446 (USA)	Phase II, randomized	29	Yes	NR	No EGFR or ALK alteration	≤6 extra-cranial (primary + 5); ≤3 in the liver & ≤3 in the lung	1st-line CT ×4–6 cycles → PR/SD with ≤6 lesions: maintenance CT *vs.* consolidative SBRT to all sites of disease → maintenance CT	1^{ry}: PFS; 2^{ry}: OS, local control, toxicity, duration of maintenance CT	No ICI
NRG LU002, NCT03137771 (USA)	Phase II/III, randomized	300	NR	NR	No actionable molecular aberration	≤3, extra-cranial, after induction systemic therapy	Synchronous or metachronous metastases → induction systemic therapy: maintenance therapy (single agent CT and/or pembrolizumab) *vs.* SBRT over 2–4 weeks ± IMRT or CT/3D-RT over 3–5 weeks to the 1^{ry} tumor → maintenance therapy; patients may also undergo surgery	1^{ry}: PFS, OS; 2^{ry}: time to in-field failure, toxicity, time to new lesions, duration of maintenance CT	
LONESTAR, NCT03391869 (USA)	Phase III, randomized	270	NR	NR	No EGFR or ALK alteration	NR	Nivolumab + ipilimumab ×12 weeks (with no evidence of PD) → LCT (surgery and/or RT) → nivolumab + ipilimumab until PD/unacceptable toxicity or up to 2 years *vs.* nivolumab + ipilimumab until PD/unacceptable toxicity or up to 2 years	1^{ry}: OS in the overall population + OS in oligometastatic group 2^{ry}: PFS, TANM, local control, toxicity, QoL	
Oncogenic driver alterations only									
NCT02314364 (USA)	Phase II, single-arm	30	NR	NR	Only EGFR-mutated or ALK/ROS1-altered	≤5, extra-cranial, after induction	Within 6 months of first-line TKI (with no evidence of PD): receive SBRT with protons or photons	1^{ry}: distant failures 2^{ry}: toxicity, PFS, OS, local control	
NCT03667820 (USA)	Phase II, single-arm	37	NR	NR	Only EGFR mutated (exon 19 or 21)	NR	8 weeks of osimertinib → SABR to the persistent sites of disease	1^{ry}: PFS; 2^{ry}: OS, DoR, ORR, time to next therapy, TTF, toxicity	
NCT03410043 (USA)	Phase II, randomized	143	NR	NR	Only EGFR-mutated	NR	Osimertinib 6–12 weeks → LCT (surgery and/or RT up to 40 sessions) with osimertinib *vs.* only osimertinib	1^{ry}: PFS; 2^{ry}: OS, TTP of target lesions, PFS in oligometastatic group, toxicity	
NCT03595644 (China)	Phase II, randomized	72	NR	NR	Only EGFR-mutated (exon 19 or 21)	<5	EGFR-TKI ×3 months → SD/PR/CR: EGFR-TKI treatment *vs.* SBRT (40–50 Gy/5 F)	1^{ry}: PFS; 2^{ry}: OS	
pOMD									
NCT04486287 (China)	Phase II, single-arm	44	NR	NR	No EGFR, ALK or ROS1 alterations	NR	Progressing on 1st-line palliative systemic therapy → stereotactic ablation brachytherapy → sintilimab (anti-PD-1) until PD	1^{ry}: ORR; 2^{ry}: PFS, OS, DCR, toxicity	
NCT03557411 (China)	Phase II, single-arm	42	NR	NR	No EGFR, ALK or ROS1 alterations	≤5	PD after ≥1 line of CT: SHR-1210 (anti-PD-1) + concurrent hypofractionated RT (to at least 1 lesion)	1^{ry}: significant toxicity, 6 m-PFS; 2^{ry}: toxicity, PFS, ORR, DCR, OS	
PROMISE-004, NCT03808662 (USA)	Phase II/III, randomized	160	NR	NR	All comers	≤5 progressing metastases in one single extra-cranial organ	SBRT to all oligoprogressive sites (9–10 Gy ×3 fr or 10 Gy ×5 fr given every other day; all lesions should receive BED ≥60 Gy) *vs.* standard-of-care	1^{ry}: PFS; 2^{ry}: OS	Includes breast and NSCLC
SUPPRESS-NSCLC, NCT04405401 (Canada)	Phase II, randomized	68	NR	NR	All comers	≤5[♦] extra-cranial with ≤5 cm and in ≤3 organs	Systemic therapy (immunotherapy or TKI) → oligoprogession in ≤5 lesions: definitive SABR to all oligoprogressive lesions + continuation of current systemic therapy *vs.* SoC (switching to next systemic therapy line, BSC or continuing on current systemic therapy)	1^{ry}: PFS, OS; 2^{ry}: QoL, toxicity, local control, time to next systemic therapy	
STOP, NCT02756793 (USA)	Phase II, randomized	54	NR	NR	All comers	≤5 (with no previous RT or RFA)	Systemic therapy ≥3 months, with CR/PR/SD →pOMD: SoC [continue with current systemic agent(s) or observation or switch to next-line treatment] *vs.* SABR to all sites of progressive disease with continuation of current systemic agents. Further oligo-progressive lesions may be treated with SABR if possible	1^{ry}: PFS; 2^{ry}: OS, QoL, toxicity, local control, total time on CT, duration of current systemic agent tx after SABR, pattern of PD after SABR	
Oncogenic driver alterations only									
HALT, NCT03256981 (UK)	Phase II/III, randomized	110	NR	NR	With an actionable mutation	≤3 extra-cranial sites of PD	TKI therapy → response → pOMD: SBRT + continue the same TKI therapy *vs.* continue the same TKI therapy	1^{ry}: PFS; 2^{ry}: Time to next line of systemic therapy or palliative care; OS, pattern of PD, toxicity, QoL, ctDNA analysis for resistant sub-clones, time to failure of next treatment line	

[ν], lymph nodes included in the N1–3 categories of the IASLC 2009 staging criteria are treated in the conventional RT volume and are not counted as metastases. *, non-surgical local ablative therapy may be carried out either by SABR or SBRT or RFA according to site of metastasis, local expertise and availability of resources. [¶], time between the first date of TKI administration and the event. [†], supraclavicular and mediastinal lymph nodes are not classified as distant metastasis; other lymph node metastasis group lymph node region will be classified as one metastatic lesion. [♦], progression at the primary tumor site should be counted within the total of 5 lesions. For patients with lymph node metastases, each node is counted as one site of metastasis; brain metastases are not counted in the maximum number of lesions and should be treated as per standard of care. [β], each lesion (including a satellite nodule) will individually be counted as one, and intrathoracic lymph node involvement (N1–N3) will collectively be counted as one; in addition, patients can receive treatment to CNS lesions or other symptomatic lesions requiring urgent local therapy prior to randomization, but these lesions will be counted towards the total number after chemotherapy, and patients will only be eligible if there are remaining sites amenable to local therapy after up-front systemic therapy. [Δ], hypofractionated RT: accumulated dose BED ≥80 Gy (central lung cancer) or BED ≥100 Gy (peripheral lung cancer); in primary tumors >3 cm: conventional fractionated radiotherapy, accumulated dose BED = 60–66 Gy/30–33 f; regional lymph nodes: conventional fractionated radiotherapy, accumulated dose BED = 60–66 Gy/30–33 f; brain metastases: whole brain radiation therapy, 36 Gy/12 f, intracranial metastases: 48 Gy/12 f; bone metastasis: 36 Gy/12 f. 3D-CRT, three-dimensional conformal radiotherapy; BCS, best supportive care; BED, biologically effective dose; CT, chemotherapy; CT/RT, chemo-radiotherapy; DCR, disease control rate; DoR, duration of response; ETOP, European Thoracic Oncology Platform; FFWMD, freedom from widespread metastatic disease; fr, radiotherapy fraction; IMRT, intensity modulated radiotherapy; LAT, local ablative therapy; LCT, local consolidation therapy; NR, not reported on ClinicalTrials.gov; ORR, objective response rate; PD, progressive disease; QoL, quality of life; RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; rhGM-CSF, recombinant human granulocyte macrophage stimulating factor; SoC, standard of care; TANM, time to appearance of new metastases; TKI, tyrosine kinase inhibitor; OMD, oligometastatic disease; pOMD, oligoprogression.