BIOLOGIA E TRATTAMENTO RADIANTE CURATIVO DELLA **MALATTIA OLIGOMETASTATICA**

VIRTUAL
26 MARZO 2021

Trattamento della malattia oligometastatica
e oligo-progressiva. Stato dell'arte e prospettive in termini di studi clinici

NSCLC

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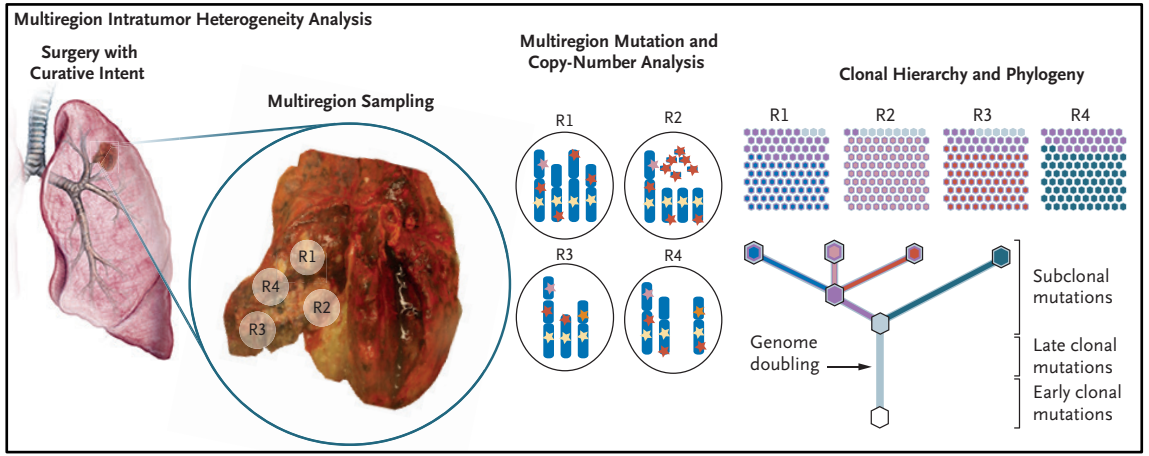
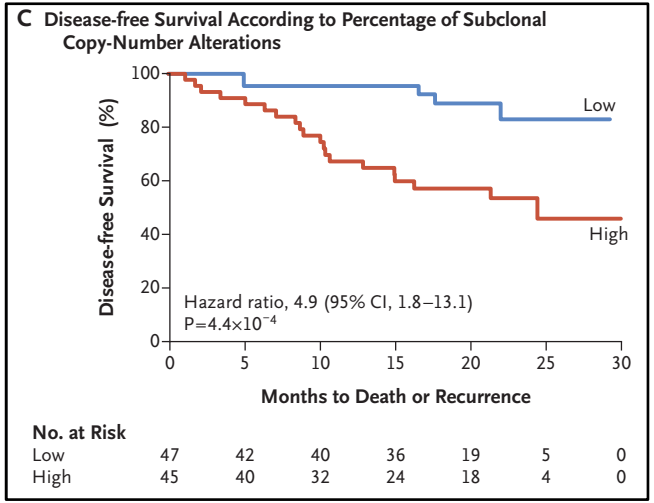
Disclosures

Advisory boards or speakers' fee

- *Astra Zeneca*
- *Accuray International*
- *-Roche*

Metastases is an evolutionary process in NSCLC

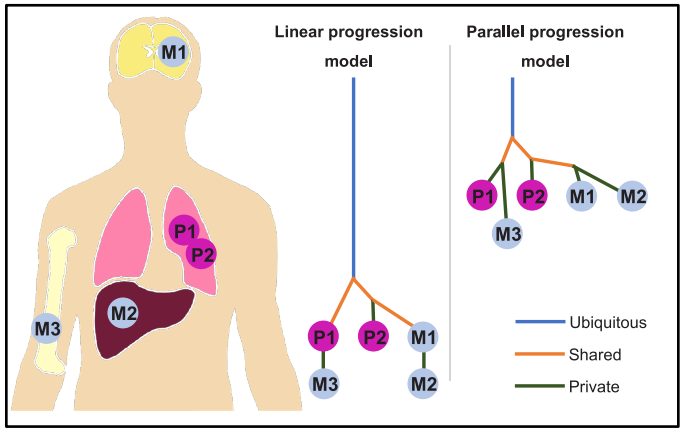


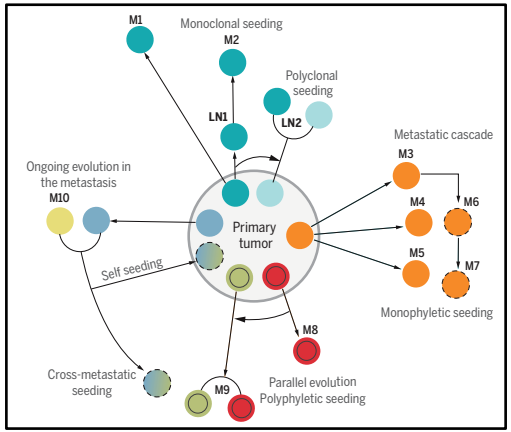


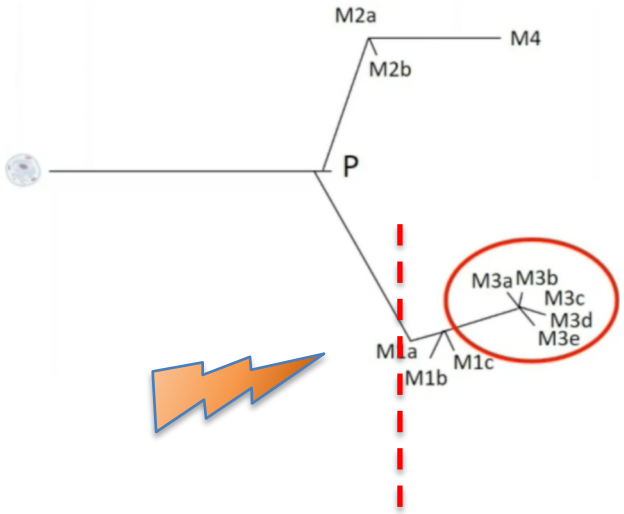
OSPEDALE POLICLINICO SAN MARTINO
Sistema Sanitario Regione Liguria

Jamal- Hanjani N Engl J Med 2017

Metastases is an evolutionary process





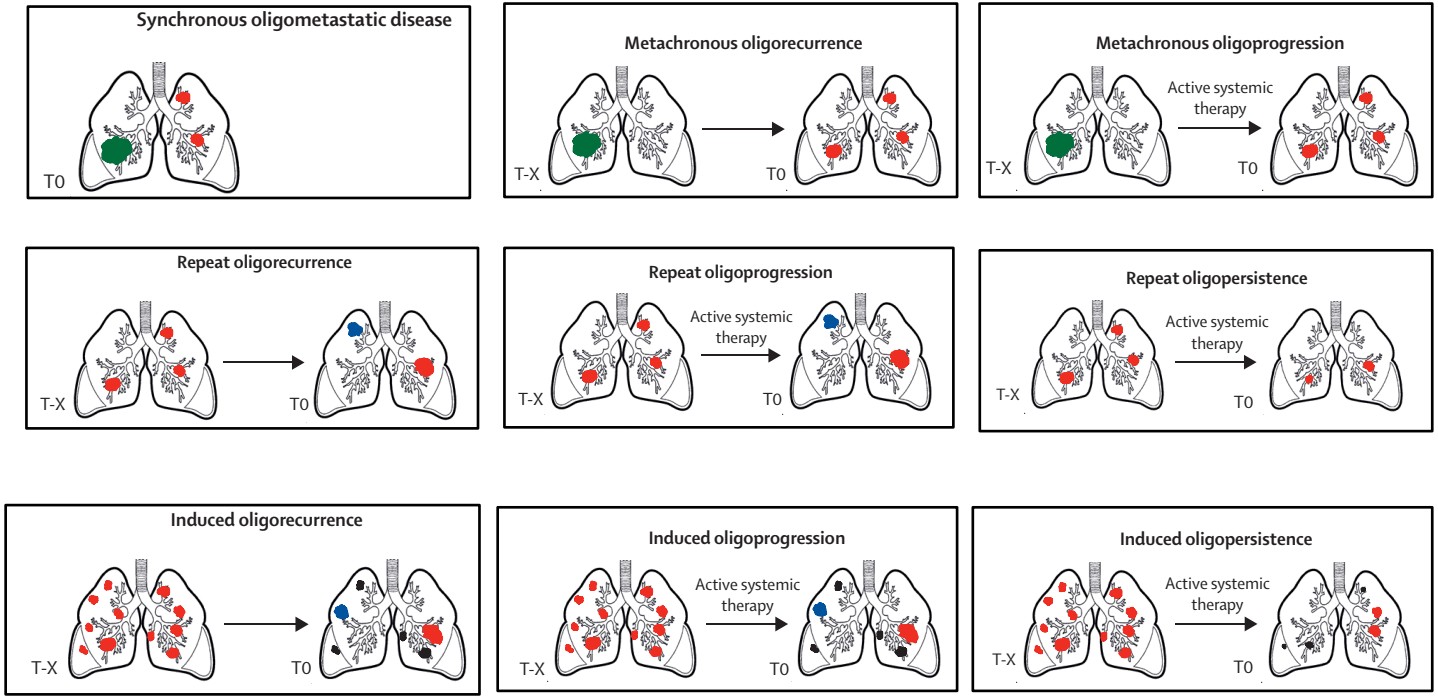


The direct metastases therapy principle

Jang- Gun Radiat Oncol J 2019
Tuarjlic Science 2017
Correa Cancer J 2016

Indeed we can define the oligometastatic disease (OMD)

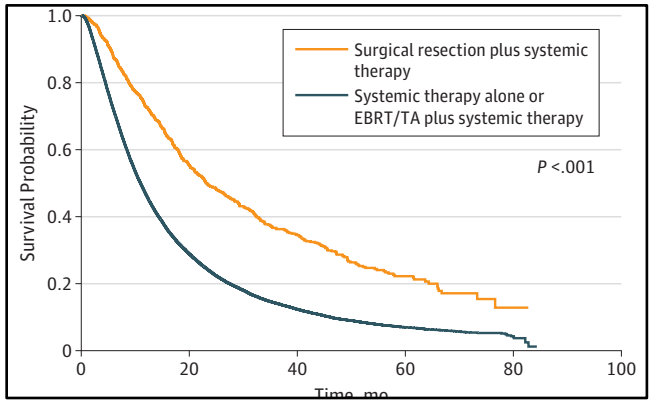
- **De- novo OMD**
- **Repeat OMD**
- **Induced OMD**



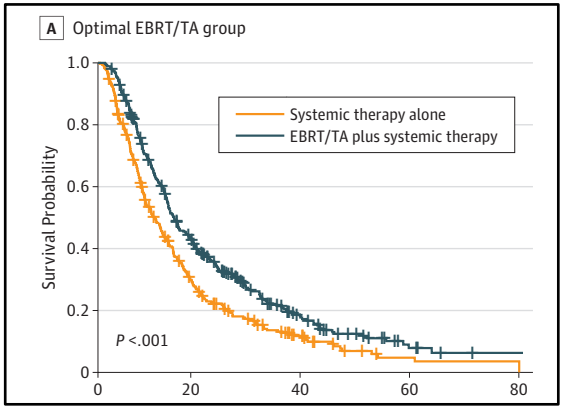
Guckemberger Lancet Oncol 2020

Registry data suggest the efficacy of local treatment in *NSCLC* OMD

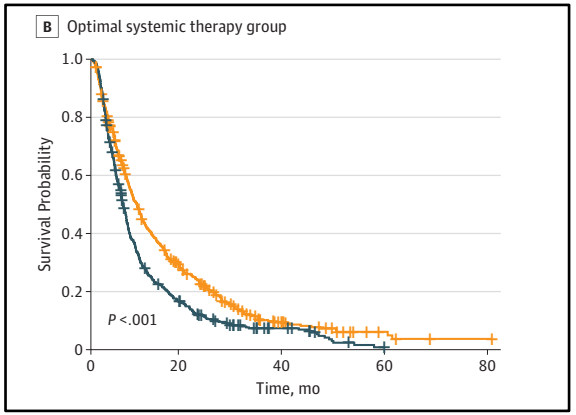
Surgery



External Beam RT; Thermal ablation



Systemic therapy in selected patients

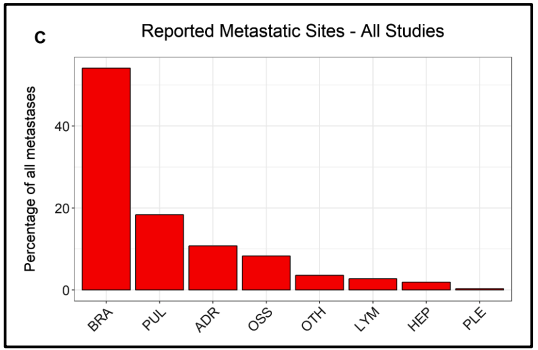


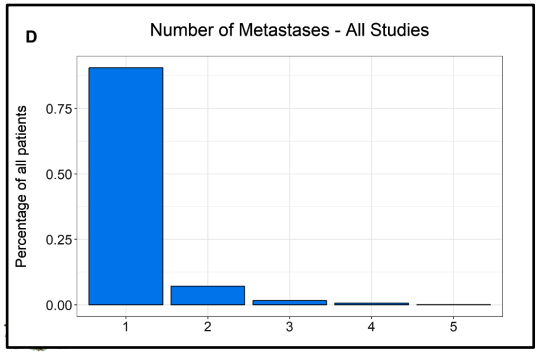
Local treatment + systemic therapy vs systemic therapy alone in stage IV NSCLC from NCD

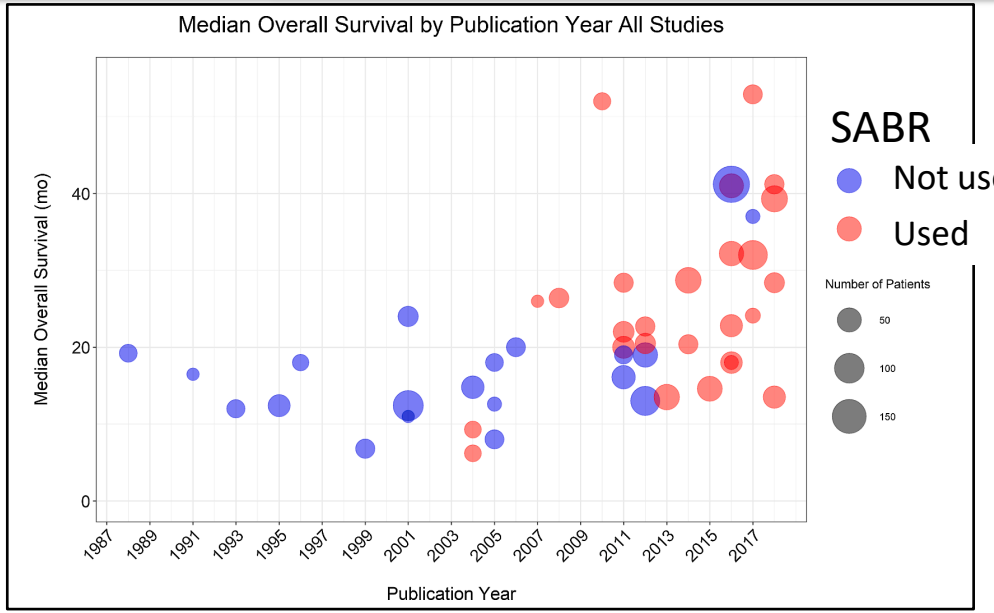
- 34887 pts
- up to 1 distant metastases to bone, brain , liver and lung
- small T and N1 and oligometastases are in favor of EBRT/TA
- median EQD2 (10) 46.9 Gy (IQR 39-70)
- **Local treatment to the primary tumor**

Uiligh J JAMA open 2019

Systematic review suggesting the efficacy of SABR in *NSCLC* OMD







- There is a shift in treatment modality for metastases directed treatment and OS benefit

Schanne, Cancer Treat Rev 2019

Delineating the best modality of local treatment in *NSCLC heterogeneous* scenario

Primary NSCLC

Locoregional stage	Early	Stage III N2	Locally advanced
Comorbidities	Low	Intermediate	Severe
Patient preference	Invasive	Undecided	Non-invasive

Optimal modality

OMD NSCLC

Location of OMD	Same lung	Contralateral lung	Extrathoraxcic
Systemtic Tx	Interrupted	Continuous	
Prior thoracic Tx	Radiotherapy	Surgery	

with the courtesy of M. Guckenberger

Phase II-III RCTs suggest the efficacy of local treatment in OMD

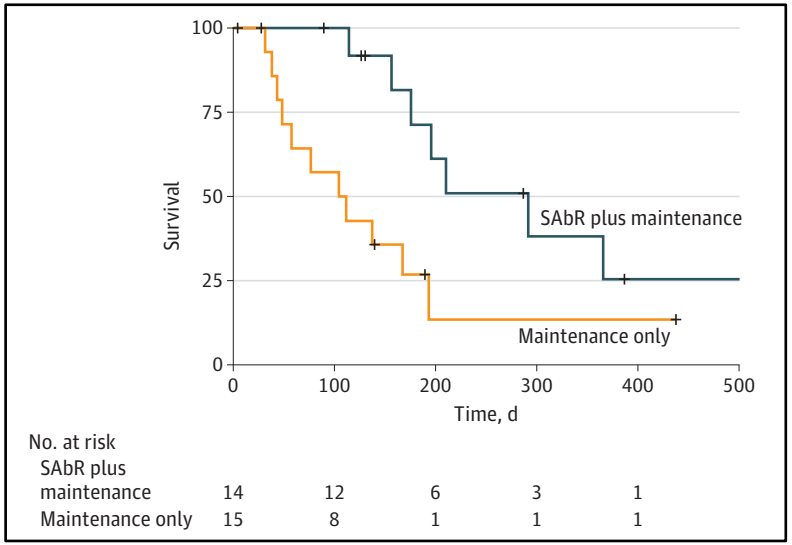
Study	# patients	Tumor origin	HR PFS	HR OS	Treatment
Iyengar Jama Oncol 2018	N= 29	NSCLC	**0.30**	-	SABR + HypoFx
Gomez JCO 2019	N= 49	NSCLC	**0.30**	0.41	SABR + Surgery + CRT
Palma JCO 2020	N= 18*	NSCLC*	**0.48***?	0.47*?	SABR
Wang ASCO 2020	N= 133	NSCLC	**0.62***	.068*	SABR

Total 229 patients

Study	RT dose	# metastases	HR PFS	RT site	Prior therapy
Iyengar Jama Oncol 2018	45 Gy / 15 fx 20-24 Gy / 1 fx 33 Gy /3 fx 30-37.5 /5 fx	< = 5	**0.30**	Primary and metastases	After 4-6 Platinum based CT
Gomez JCO 2019	60-66 Gy / 30-33 fx 45-60 Gy / 15 fx 30-70 Gy /10 fx 50 Gy /4 fx 18– 20 / 1 fx	< = 3	**0.30**	Primary and metastases	After 4 Platinum based CT After target x EGFR After target x ALK
Palma JCO 2020	60 Gy / 8 fx 35 Gy / 5 fx 54 Gy /3 fx 18 – 24 Gy /1 fx	<= 5 Max 3 x organ	**0.48**	All known disease Primary controlled	at diagnosis of OMD
Wang ASCO 2020	25– 40 Gy / 5 fx	<= 5 Max 2 x organ	**0.62**	All disease site & primary controlled	Concomitant with TKI (only EGR m)

RCTs suggest the efficacy of local treatment in *NSCLC* OMD

- early trial closure (limited number of patients)
- single institution
- 40% pretreated with WBRT
- 64% pretreated with Carbo + Pemetrexed or Carbo + Paclitaxel
- 65% maintenance therapy with Pemetrexed
- 7 patients treated on the primary
- Local failure was detected in 0/14 vs 6/15 in for SABR

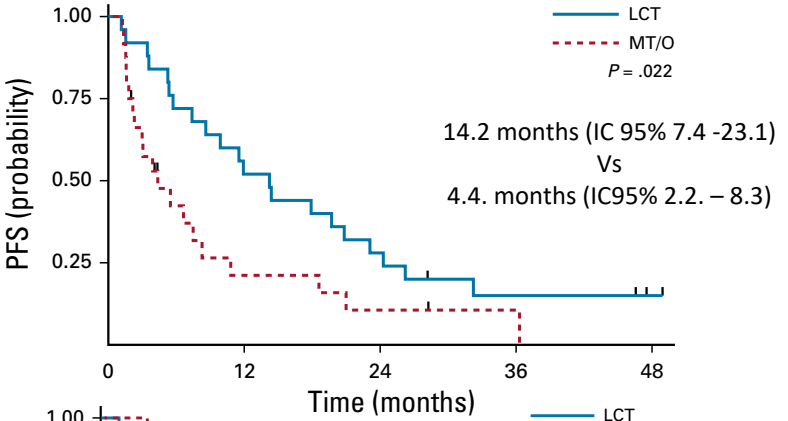


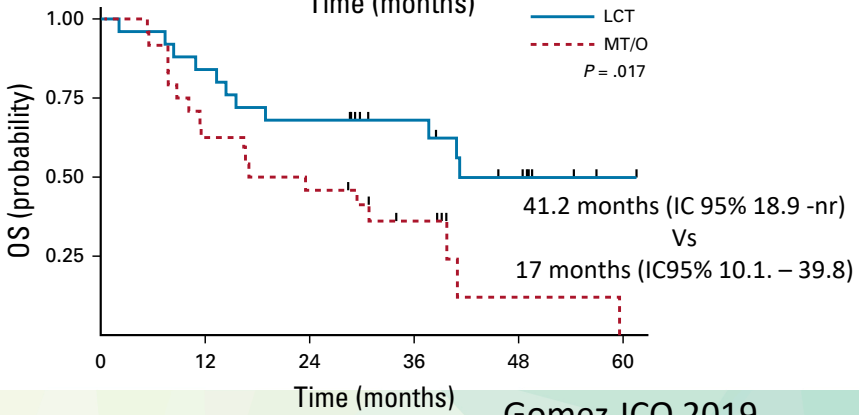
 # M+ sites prior chemotherapy <= 2 vs >2 1 Yr PFS 100% vs 38%

Iyengar JAMA Oncology 2018

RCTs suggest the efficacy of local treatment in *NSCLC* OMD

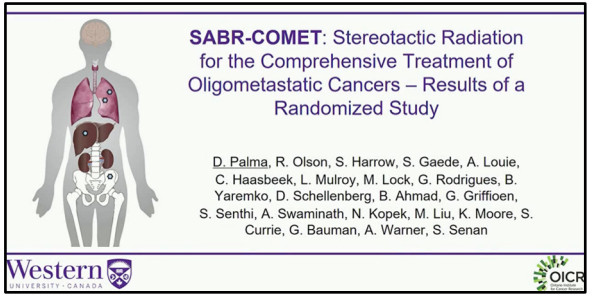
- early trial closure (limited number of patients)
- multicentric
- 30% presented CNS metastases
- 80% of patients were EGFR/ALK WT
- 38% of all relapsed patients progressed as OMD
- Local treatment to all the site of disease
- Aggressive consolidation therapy leads to PFS gain
- # of metastatic site < 2 in 68% of patients

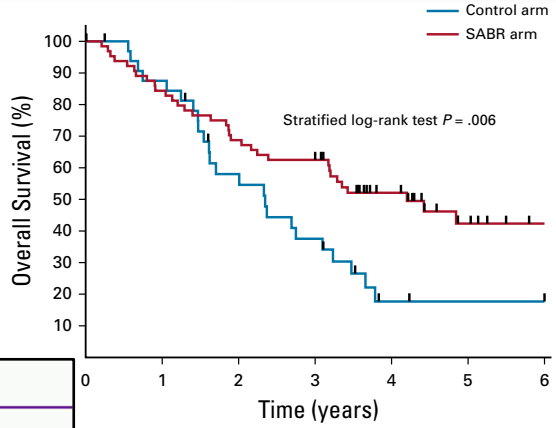


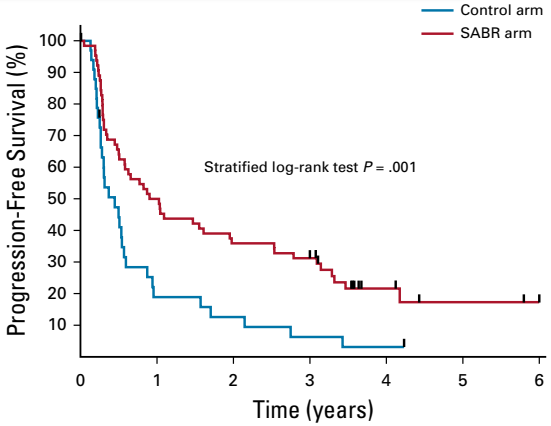


Gomez JCO 2019

RCTs suggest the efficacy of local treatment in *NSCLC* OMD







Sensitivity Analyses (not pre-specified)

1) Excluded all prostate patients to see if HR for OS and PFS remain <1
   - OS HR = 0.83
   - PFS HR = 0.61

2) Multivariable analyses for OS and PFS (to control for histology):

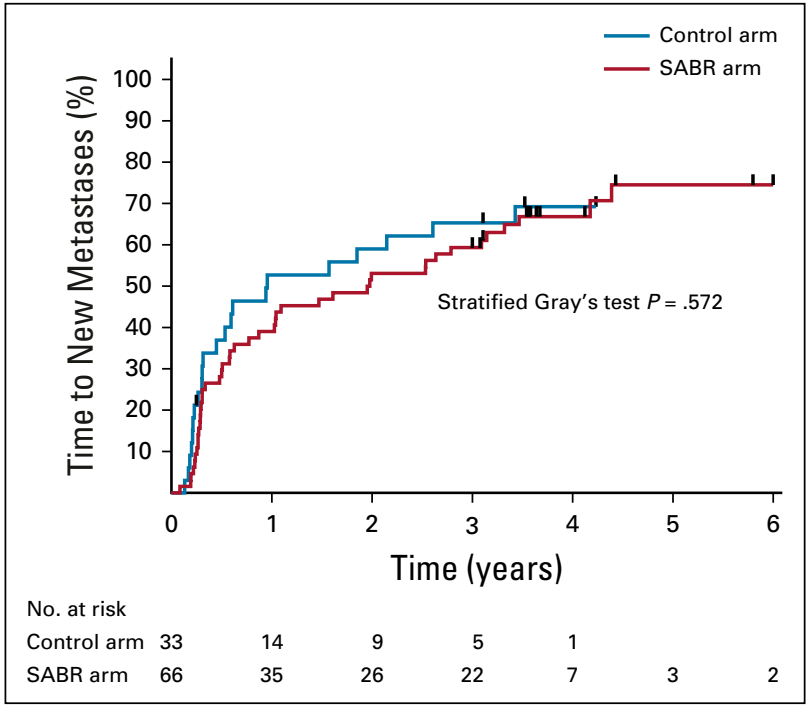
OS		
Factor	HR	P-value
Lung Primary (vs. other)	4.05	<0.001
SABR Arm (vs control)	0.60	0.12

PFS		
Factor	HR	P-value
Prostate Primary (vs. other)	0.14	<0.001
SABR Arm (vs control)	0.58	0.02

- Only 18 NSCLC patients
- Only 6 NSCLC patients in the control arm
- No information about systemic therapies
- No information about driver mutations
- Absolute benefit in OS at 5 yrs of 24.6% (for all tumors)

Palma JCO 2020

RCTs suggest the efficacy of local treatment in *NSCLC* OMD



- time to new metastases is the same between the 2 arms
- the new metastases after SABR were seeded before the treatment
- This principle enforce the potential of new SABR at oligoprogression

The long-term survival goal in *NSCLC*

- Systemic control (CT; CT + IT; TKI)
- Brain control (TKI; IT; PCI)
- Locoregional control (CT-RT; S; CT-RT-IT; CT-S
- *Local control (RT; SABR; S; RA; SABR+IT)*
- Treatment related events (Acute and late toxicity)
- Comorbidities

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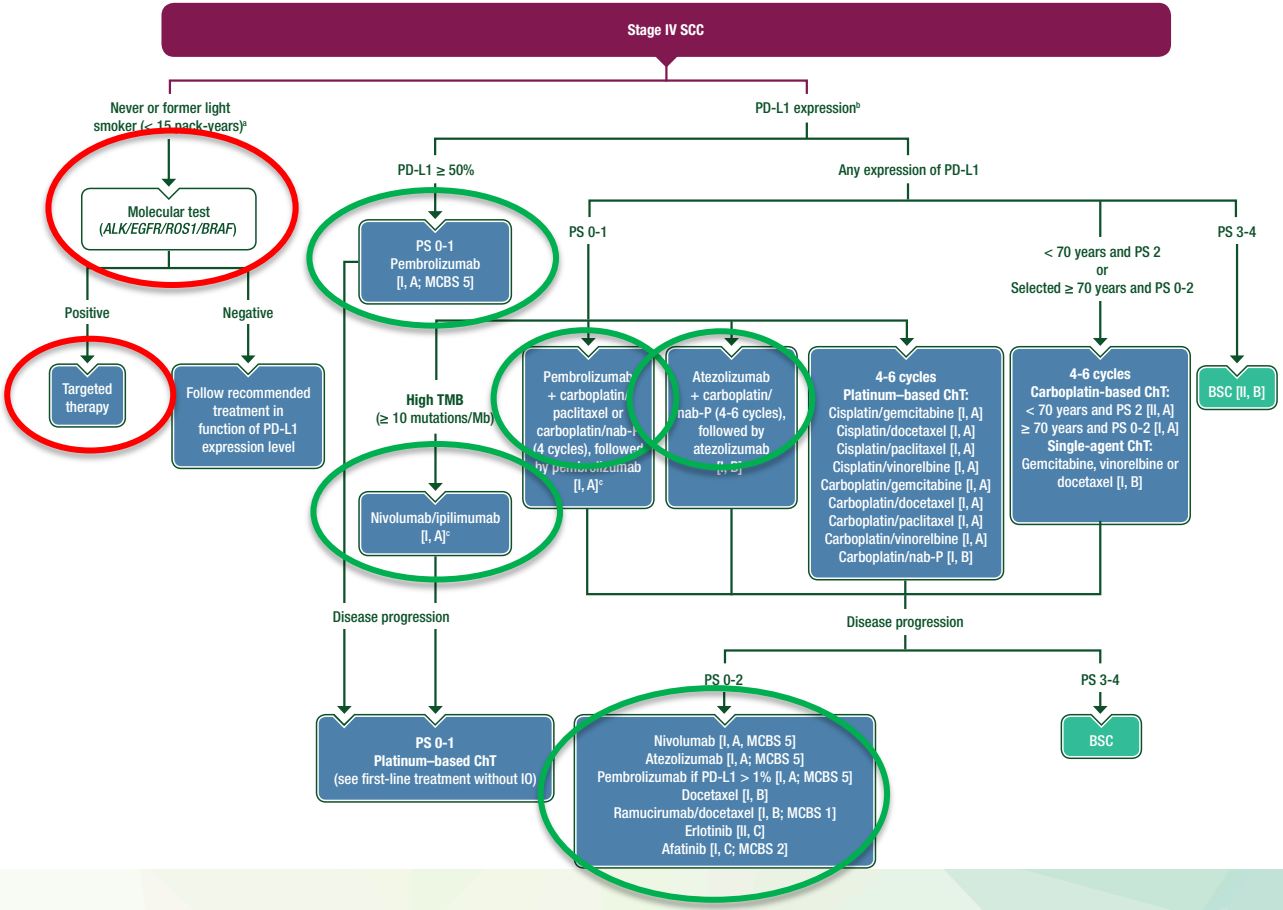
The scenario in stage IV NSCLC

Target therapy

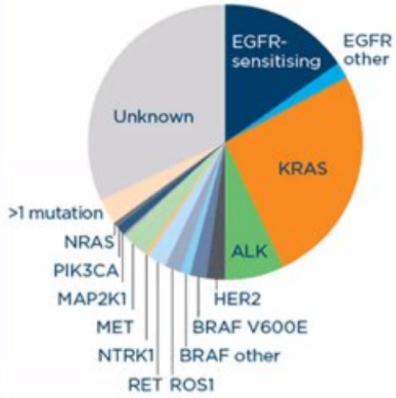
Immuno therapy



Tyrosine Kinase Inhibitors

Mutations in NSCLC

DRIVER MUTATIONS IN LUNG ADENOCARCINOMA



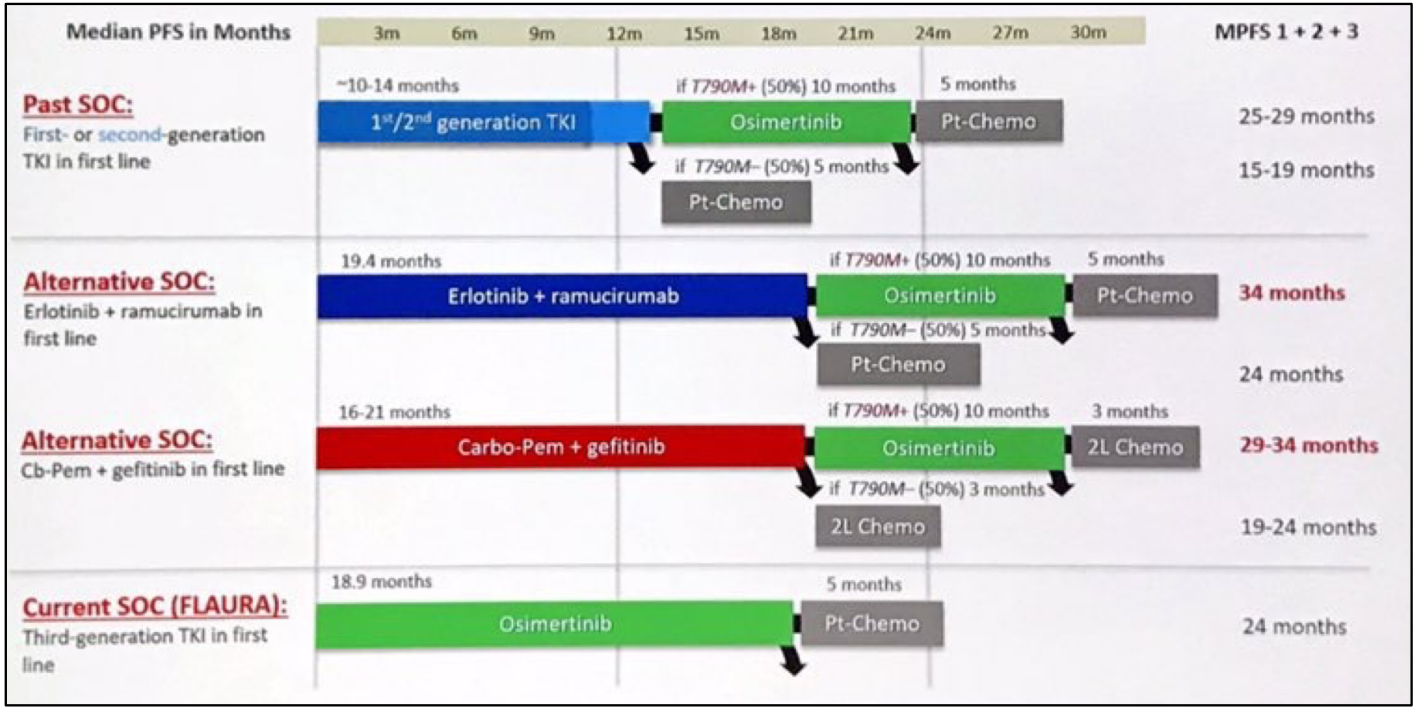
Driver mutations in lung adenocarcinoma	
EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%

***EGFR* sensitizing** Gefitinib; Erlotinib; Afatinib; Osimertinib; Dacomitinib
ALK Crizotinib; Alectinib; Ceritinib; Lorlatinib; Brigatinib
ROS1 Crizotinib; Cabozantinib; Ceritinib; Lorlatinib; Entrectinib; Ropotrectinib, DS-6051b
BRAF Vemurafenib, Dabrafenib; Dabrafenib + Trametinib
NTRK1 Entrectinib; Larotrectinib; loxo-195; DS-6051b; repotrectinib
HER2 Trastuzumab emtansine; Afatinib; Neratinib-temsirolimus; Dacomitinib; Poziotinib; XMT-1522; TAK-788; DS-8201a
RET Selpercatinib; Cabozantinib; Apatinib; Vandetanib; Ponatinib; Lenvatinib; BLU-667
MET Crizotinib; Cabozantinib; Capmatinib; Savolitinib; Tepotinib; Merestinib; Glesatinib

City of Hope.

Adapted from LUNGevity

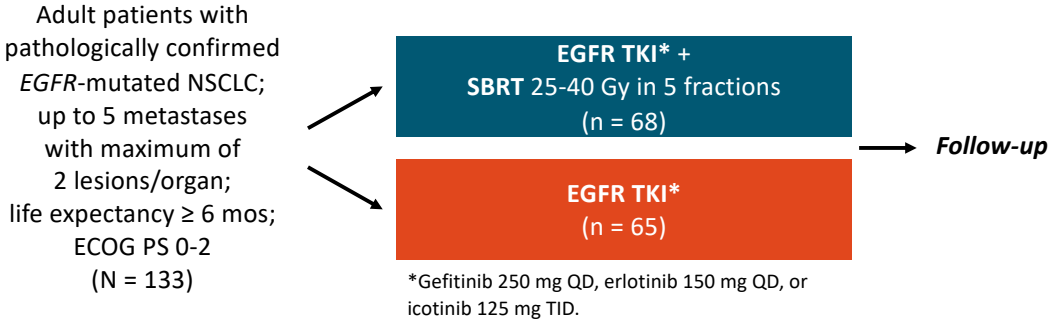
Tyrosine Kinase Inhibitors



RCTs suggest the efficacy of local treatment in *NSCLC* OMD

SINDAS Interim Analysis: Study Design

- Multicenter, open-label, randomized phase III trial in China (January 2016 - June 2019)



- Primary endpoint: PFS
- Secondary endpoint: OS
- Other endpoint: safety

Wang. ASCO 2020. Abstr 9508.

Slide credit: clinicaloptions.com

RCTs suggest the efficacy of local treatment in *NSCLC* OMD

SINDAS Interim Analysis: PFS and OS

Median Outcome, Mos	EGFR TKI + SBRT (n = 68)	EGFR TKI Only (n = 65)	HR
PFS (primary endpoint)	20.2	12.5	0.618 (95% CI: 0.394-0.969; log-rank *P* < .001)
OS (secondary endpoint)	25.5	17.4	0.682 (95% CI: 0.456-1.001; log-rank *P* < .001)

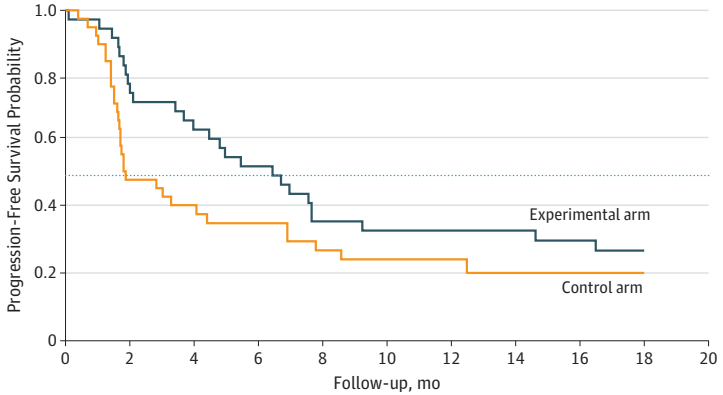
- After median follow-up of 19.6 mos, EGFR TKI + SBRT significantly prolonged PFS and OS vs EGFR TKI only

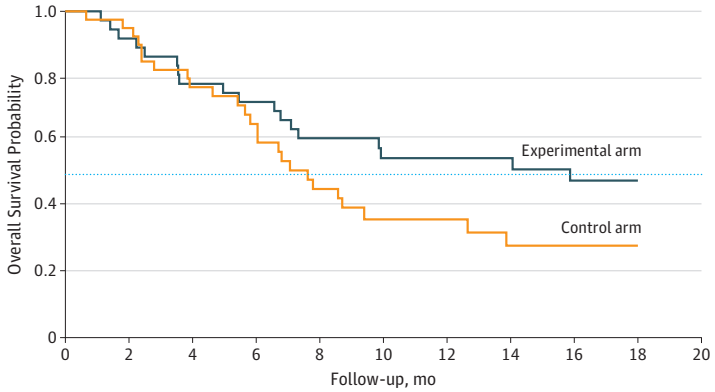
Wang ASCO 2020

What for immunotherapy and *NSCLC* OMD?

- RCT for SABR + immunotherapy and OMD in NSCLC ?
- Is there any “abscopal” improvement in disease response with SABR and OMD?
- Is there any synergic effect for local control between SABR and IT in OMD?

PEMBRO alone vs PEMBRO-RT randomized PHASE II





- ***8 Gy x 3 fx***
- Median PFS for SABR was 6.6 months (IC95% 4– 14.6) vs 1.9 (IC95% 1.7-6)
- Median OS for SABR was 15.9 months (IC95% 7.1 – nr) vs 7.6 (IC95% 6 – 13.9)
- Is this the “abscopal” effect
- A significant PFS and OS benefit (HR 0.49 and HR 0.49) in PDL-1 negative subgroup

Theelen JAMA Oncol 2019

The long-term survival goal in *NSCLC*

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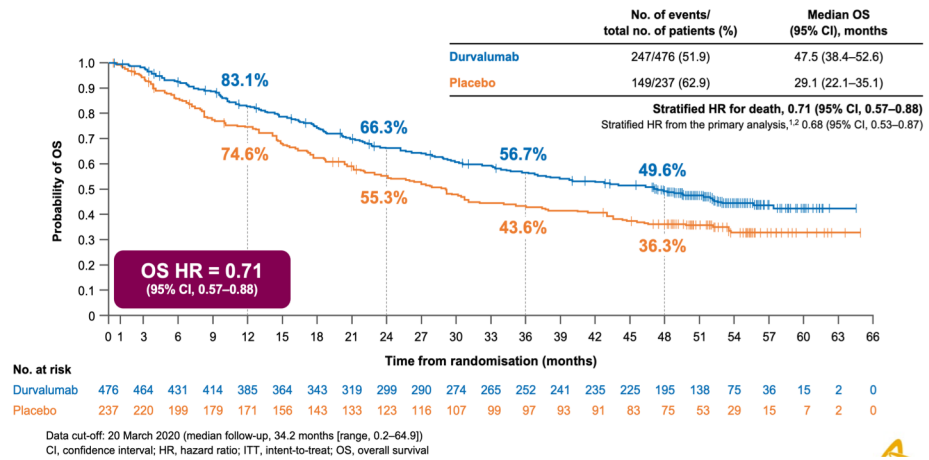
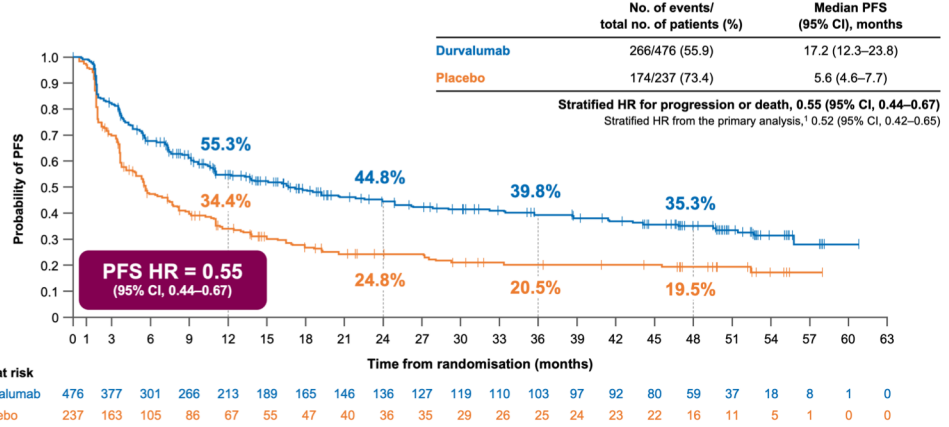
The revolution of IT in stage III *NSCLC*



Data cut-off: 20 March 2020 (median follow-up, 34.2 months [range, 0.2–64.9])
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival



PACIFIC

Faivre-Finn C et al, ESMO 2020

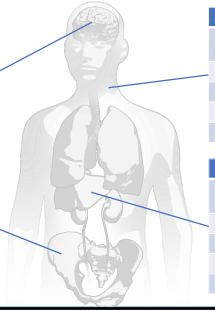
More OMD after CT-RT + IT?

New Extrathoracic Lesions at First Progression per Site (BICR)*

- The patterns of extrathoracic lesion numbers per organ were similar regardless of treatment

BRAIN	No. of patients (%)	
No. of new brain lesions	Durvalumab (n=26)	Placebo (n=26)
1	12 (46.2)	9 (34.6)
2	8 (30.8)	9 (34.6)
3–5	6 (23.1)	5 (19.2)
>5	0	3 (11.5)

BONE	No. of patients (%)	
No. of new bone lesions	Durvalumab (n=6)	Placebo (n=3)
1	6 (100)	2 (66.7)
2	0	0
3–5	0	1 (33.3)
>5	0	0



LYMPH NODES	No. of patients (%)	
No. of new lymph node lesions	Durvalumab (n=3)	Placebo (n=3)
1	1 (33.3)	1 (33.3)
2	1 (33.3)	1 (33.3)
3–5	0	1 (33.3)
>5	1 (33.3)	0

LIVER	No. of patients (%)	
No. of new liver lesions	Durvalumab (n=6)	Placebo (n=5)
1	0	3 (60.0)
2	0	2 (40.0)
3–5	2 (33.3)	0
>5	4 (66.7)	0

*With a data cutoff of March 22, 2018, median duration of follow-up was 21.2 months (range 0.2–43.1)

Patient	Brain	Thorax	Abdominal	Osseous	Local-Regional Failure?	Distant Metastasis?	Ablative Candidate*
1	N	Y	N	N	Marginal	N	Y
2	Y	Y	N	Y	In-Field	Y	N
3	N	Y	N	N	Marginal	Y	Y
4	N	Y	N	N	Out-of-Field	Y	N
5	N	Y	N	N	Marginal	Y	Y
6	N	Y	Y	N	In-Field	Y	N
7	N	Y	N	Y	In-Field	Y	N
8	N	Y	N	N	In-Field	Y	N
9	Y	Y	Y	N	In-Field	Y	N
10	N	Y	N	N	Marginal	Y	Y
11	Y	N	N	N	N	Y	Y
12	N	Y	N	N	N	Y	Y
13	N	N	Y	N	N	Y	Y
14	N	Y	Y	N	N	Y	N
15	N	Y	Y	N	N	Y	Y
16	Y	N	N	N	N	Y	Y
17	N	Y	N	N	N	Y	N
18	N	Y	N	N	N	Y	N

* Candidacy for Ablative Therapy: ≤5 discrete sites of disease, no progression of treated primary tumor, no pleural effusion.

➢ more than 50% of PD are candidate to focal ablation

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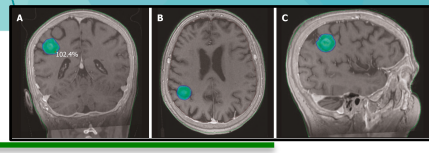
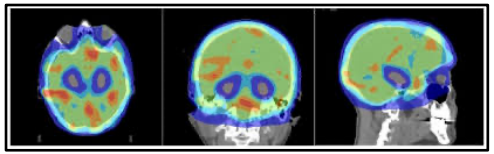


SRS in limited # brain metastases

Long-Term Survival in Patients With Synchronous, Solitary Brain Metastasis From Non–Small-Cell Lung Cancer Treated With Radiosurgery *(Flannery IJROBP 2007)*

In metastatic NSCLC, approximately 30% of patients will have brain metastases at first diagnosis



PCI in high risk brain metastases NSCLC

PRoT- BM randomize Phase II trial *(Arrieta et al IGRBOP 2021)*

- Patients harboring EGFR mutations, ALK rearrangements or elevated CEA
- Standard of care plus PCI 25 Gy / 10 Fx vs standard of care
- The 24 months CBM was 7% vs 38% in favor of PCI (HR 0.12)

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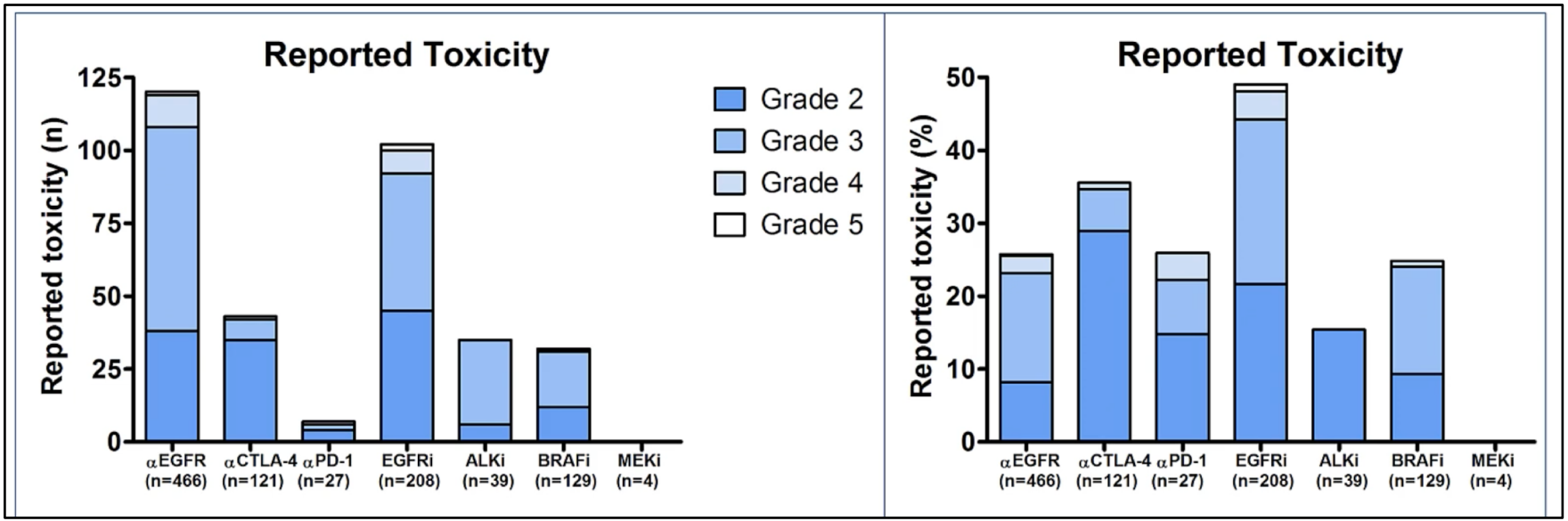
- Systemic control (CT; CT + IT; TKI)
- Brain control (TKI; IT; PCI)
- Locoregional control (CT-RT; S; CT-RT-IT; CT-S)
- *Local control (RT; SABR; S; RA; SABR+IT)*
- **Treatment related events (Acute and late toxicity)**
- Comorbidities

SABR for oligometastases



Kroze Cancer treatment Rew 2017

Toxicity from RCTs

Study	# patients	Tumor origin	HR PFS	HR OS	Toxicity
Iyengar Jama Oncol 2018	N= 29	NSCLC	**0.30**	-	Similar in the 2 arms
Gomez JCO 2019	N= 49	NSCLC	**0.30**	0.41	No grade 4 and equal in the groups
Palma JCO 2020	N= 18*	NSCLC*	**0.48***?	0.47*?	3 pts G5- long term OK
Wang ASCO 2020	N= 133	NSCLC	**0.62***	.068*	Slightly worse in SABR but no significative

Kroze Cancer treatment Rew 2017

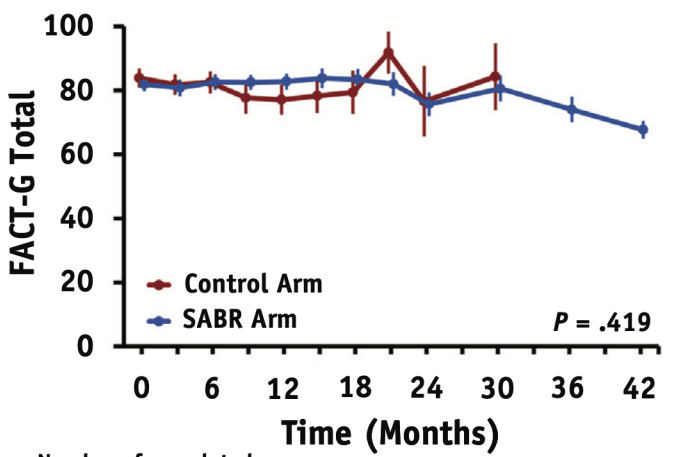
Original Study

The NIPRO Study: An Observational, Retrospective, Multicenter Study on the Safety of the Radiotherapy and Immunotherapy Combination for Advanced-Stage NSCLC

Marco Perna,[1] Vieri Scotti,[1] Patrizia Ciammella,[2] Paolo Borghetti,[3] Elisa D'angelo,[4] Niccolò Giaj Levra,[5] Alessandra Fozza,[6] Matteo Mariotti,[1] Viola Salvestrini,[1] Federica Bertolini,[7] Stefano Vagge,[8] Maria Taraborrelli,[9] Lorenzo Falcinelli,[10] Alessandra Taddeo,[3] Roberto Rossi,[2] Gianluca Costantino,[3] Luca Frassinelli,[4] Andrea Riccardo Filippi,[11] Carlo Greco,[12] Davide Franceschini,[13] Domenico Genovesi,[9] Frank Lohr,[4] Stefano Maria Magrini,[3] Filippo Alongi,[14,15] Lorenzo Livi,[1] Alessio Bruni[4]

The Quality of Life

Quality of Life Outcomes After Stereotactic Ablative Radiation Therapy (SABR) Versus Standard of Care Treatments in the Oligometastatic Setting: A Secondary Analysis of the SABR-COMET Randomized Trial



Number of completed surveys

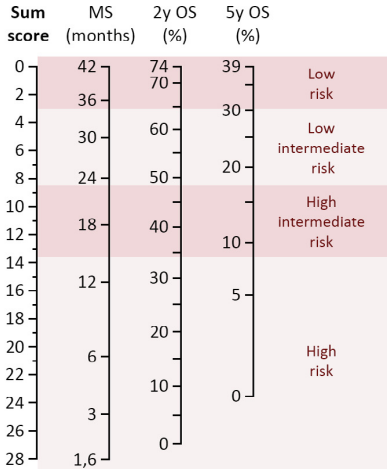
control	31	23	14	10	4	3		
SABR	60	47	48	32	23	12	13	6

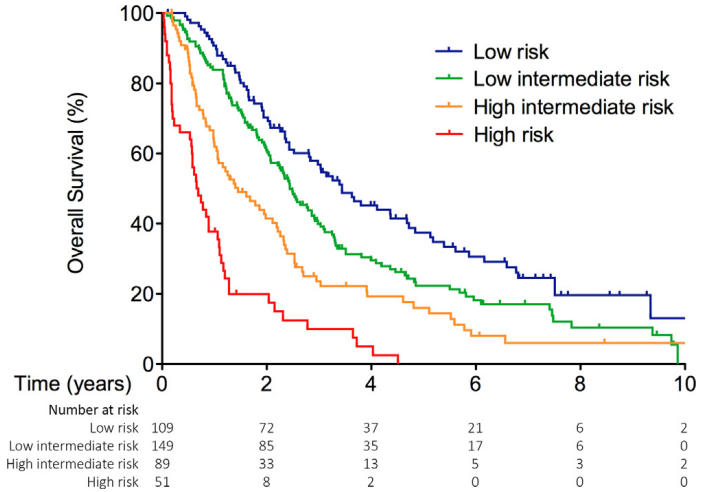
Olson R IJROBP 2019

Predictive and Prognostic models for SABR and NSCLC

Nomogram

Risk factor presence	Points
Male sex	4
Timing: synchronous disease	2
Brain metastasis present	7
Non-adenocarcinoma	7
KPS < 80 (ECOG > 1)	8
Sum score:	... →





The METABANK

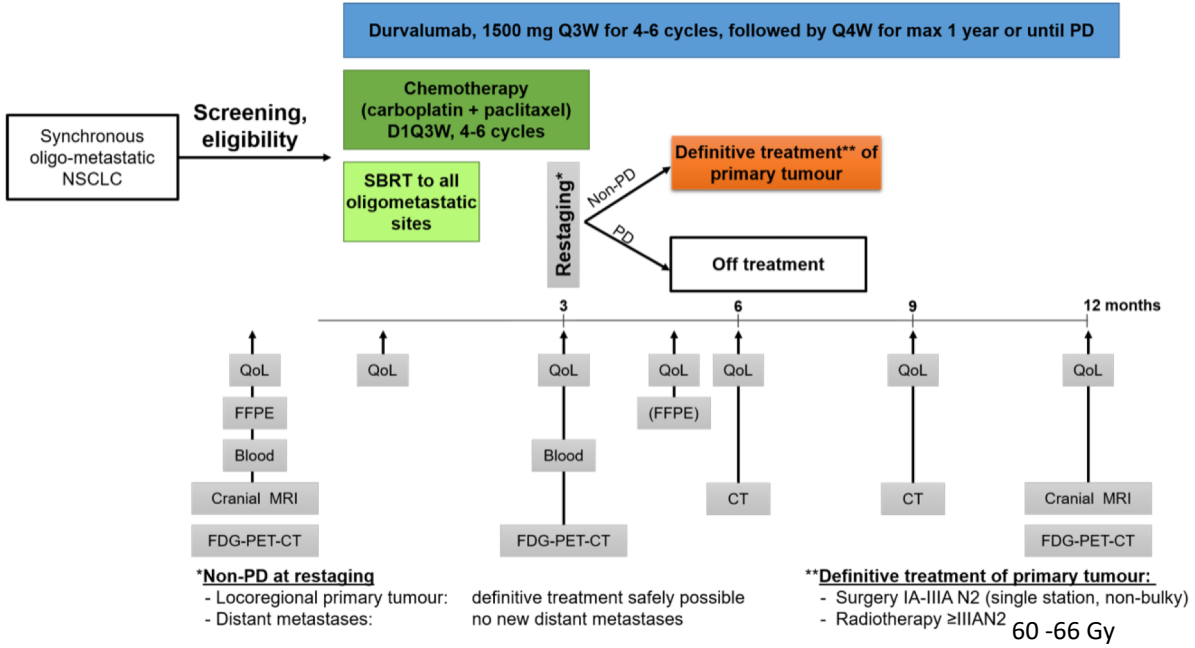
- none effective biomarkers for SABR

Van Den Begin, Radiother Oncol 2019

Upcoming clinical research in NSCLC

NSCLC	NCT02417662	NCT0313771	NCT03391869	NCT02759783	NCT03721341*	NCT03862911	NCT03410043	NCT03965468
Estimated completion	August 2022	April 2022	December 2022	October 2024	January 2029	May 2029	January 2023	December 2021
Number of patients	340	378	270	245	159	297	143	47
Study type	Phase III	Phase II/III	Phase III	Phase II/III	Phase III	Phase III	Phase II	Phase II
Number of metastases	1-3	1-3	> 1	1-3	4-10	1-3	> 1	1-3 + primary

Upcoming clinical research



CHESS

Immunotherapy, Chemotherapy, Radiotherapy and Surgery for Synchronous Oligo-metastatic NSCLC

- multicenter single arm phase II
- Primary endpoint PFS
- Secondary endpoint: pattern of disease progression, DPFS, ORR, response to induction, duration of response, toxicity and QoL
- SAAK & SLCG (P.I. Guckenberger)

Upcoming clinical research

NRG LU 002

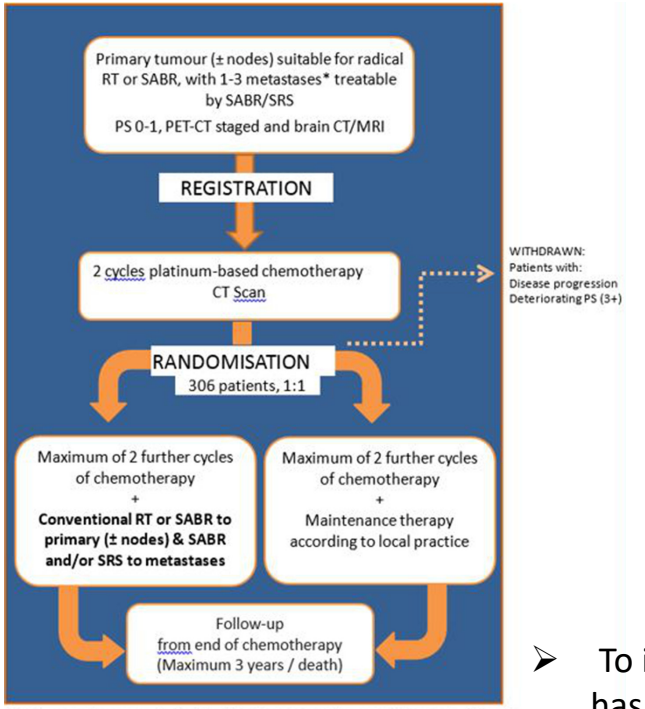
Patients with metastatic NSCLC having completed 4 cycles or courses of first-line/induction systemic therapy Restaging studies reveal no evidence of progression and limited (≤ 3 discrete sites) metastatic disease, all of which must be amenable to SBRT +/- Surgery	STRATIFY	Histology: Squamous vs. Non-squamous Systemic Therapy: Immunotherapy vs Cytotoxic Chemotherapy	RANDOMIZE	Arm 1: Maintenance systemic therapy alone Arm 2: SBRT or SBRT and Surgery to all sites of metastases (≤ 3 discrete sites) plus 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.

NRG ONCOLOGY™

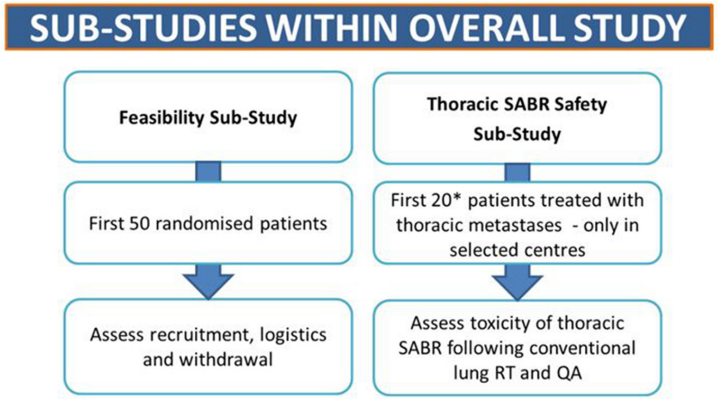
Maintenance Systemic Therapy Versus Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy For Limited Metastatic Non-Small Cell Lung Cancer (NSCLC):
A Randomized Phase II/III Trial

- Phase 2/3 multi-center: maintenance chemotherapy or SBRT + maintenance chemotherapy
- Primary histology: all NSCLC
- Primary outcome measure: PFS
- P.I.: Yengar P.

Upcoming clinical research



*The **SARON trial:** a multicentre, randomised controlled phase III trial comparing the addition of stereotactic ablative radiotherapy and radical radiotherapy with standard chemotherapy alone for oligometastatic non-small cell lung cancer*



- To investigate the impact the addition RT using SABR/ SRS or conventional RT has on OS in oligometastatic NSCLC that are treated with first-line standard systemic therapy.

Upcoming clinical research

SABR-COMET-10

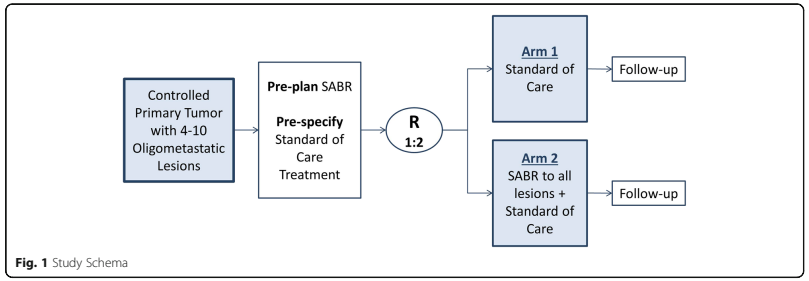
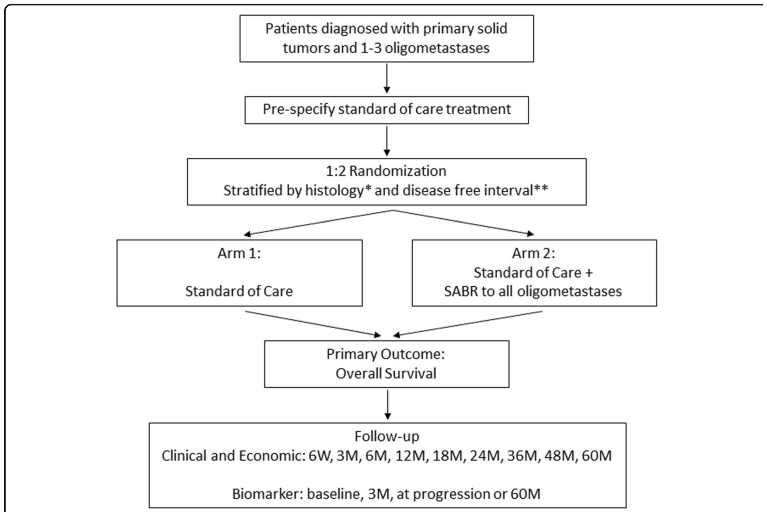


Fig. 1 Study Schema

SABR-COMET-3



Upcoming clinical research when time for RCTs results is too far

ESTRO 2020

Piet Ost
Ghent University

OligoCare

a pragmatic Observational basket study

Baseline Characteristics

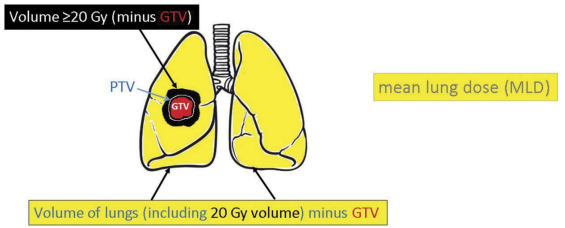
	BASELINE population (N=147) N (%)
Type of primary disease	
NSCLC	21 (14.3)
Breast cancer	22 (15.0)
Colorectal cancer	39 (26.5)
Prostate cancer	65 (44.2)
Number of OMD sites	
1	129 (88)
>1	18 (12)
RT treatment	
Machine type LINAC	153 (89)
Image guidance CBCT	150 (88)
Treatment planning VMAT	150 (88)

ESTRO 2020 Baseline Characteristics

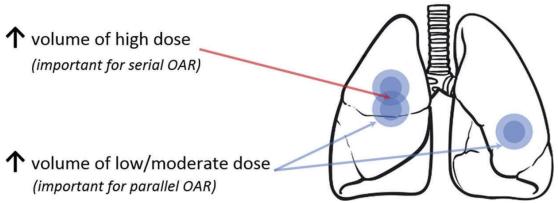
OMD site	Total (N=220) N (%)
Adrenal gland	2 (0.9)
Bone marrow	9 (4.1)
Brain	10 (4.5)
Kidney	2 (0.9)
Liver	33 (15.0)
Lung	56 (25.5)
Non-regional LN	35 (15.9)
Non-vertebral bones	36 (16.4)
Pancreas	1 (0.5)
Pleura	1 (0.5)
Spine	18 (8.2)
Other	17 (7.7)

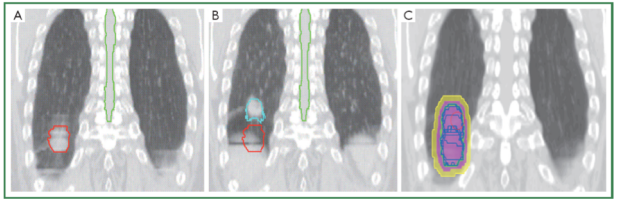
- the use of registries is useful to detect a treatment efficacy in routine clinical practice

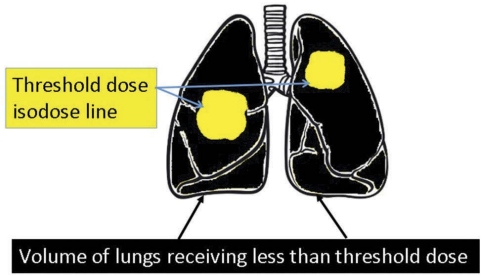
New technical issues for multiple targets

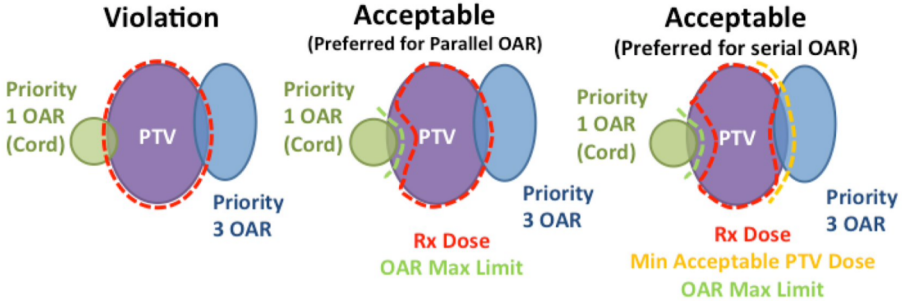


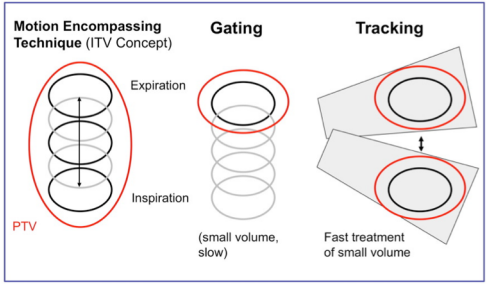
mean lung dose (MLD)





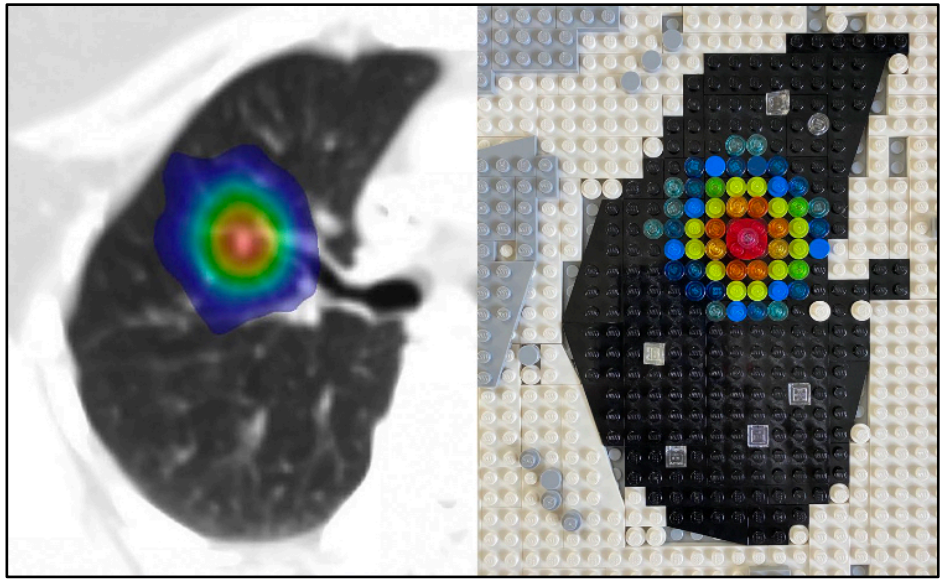






Conclusions

- There is EBM on local treatments impact for OMD in NSCLC
- The majority of the “local treatment” and the most suitable strategy is SABR
- High local control in NSCLC OMD
- Safe combination with systemic therapies
- Waiting for phase III to increase # of patients
- More information are needed for precise patients selection and fractionation schedules
- What is the optimal timing to integrate SABR in the oncogenic driven era?
- How big will the impact of NSCLC OMD be in the radiotherapy departments?



Thanks

The importance of imaging to assess the OMD in NSCLC

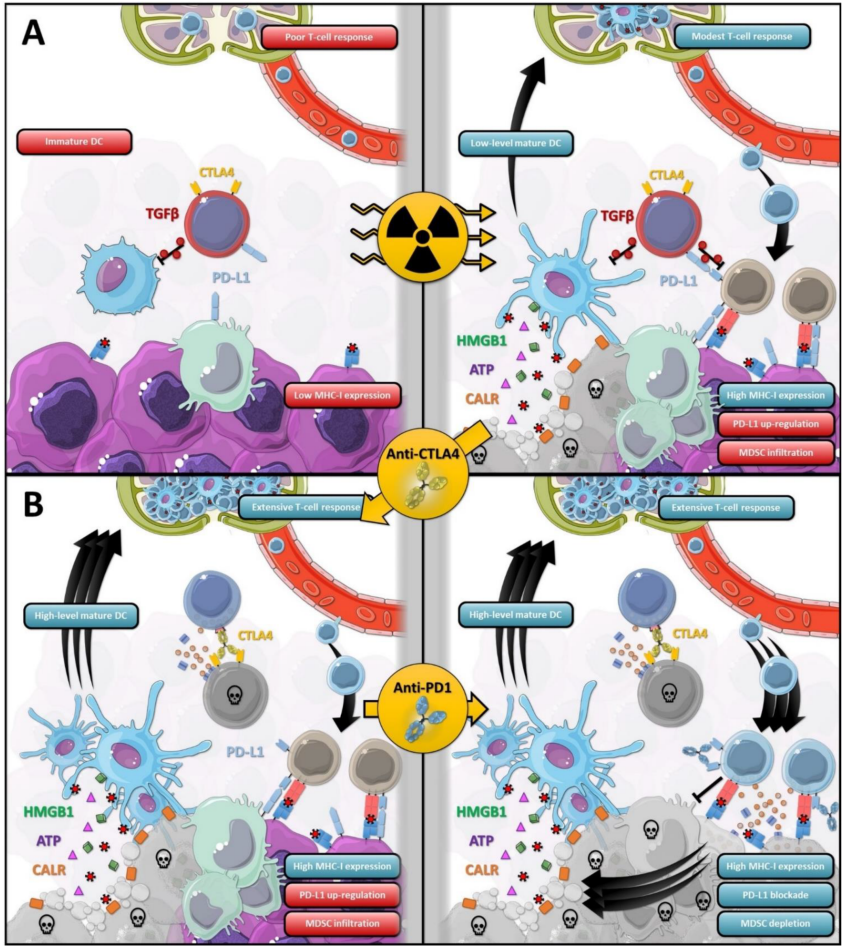

A
Poor T-cell response
Immature DC
CTLA4
TGFβ
PD-L1
Low MHC-I expression
Modest T-cell response
Low-level mature DC
CTLA4
TGFβ
PD-L1
HMGB1
ATP
CALR
High MHC-I expression
PD-L1 up-regulation
MDSC infiltration
Anti-CTLA4
B
Extensive T-cell response
High-level mature DC
CTLA4
PD-L1
HMGB1
ATP
CALR
High MHC-I expression
PD-L1 up-regulation
MDSC infiltration
Anti-PD1
Extensive T-cell response
High-level mature DC
CTLA4
HMGB1
ATP
CALR
High MHC-I expression
PD-L1 blockade
MDSC depletion

TABLE 2 | Selected ongoing trials of SBRT treatment in oligometastatic NSCLC.

Title	Patients	Study design	Estimated completion
Stereotactic Ablative Radiotherapy for Oligometastatic Non-small Cell Lung Cancer (SARON). A Randomized Phase III Trial. (53) Institution: University College London ClinicalTrials.gov identifier: NCT02417662	340	Phase 3 multi-center: chemotherapy alone (standard platinum based doublet chemotherapy or chemotherapy + radical radiotherapy (conventional RT and SABR) Primary histology: all NSCLC *1–3 oligometastatic lesions* Primary outcome measure: OS	August 2022
Maintenance Systemic Therapy vs. Local Consolidative Therapy (LCT) Plus Maintenance Systemic Therapy for Limited Metastatic Non-small Cell Lung Cancer (NSCLC): A Randomized Phase II/III Trial (NRG LU-002) Institution: NRG Oncology ClinicalTrials.gov identifier: NCT03137771	300	Phase 2/3 multi-center: maintenance chemotherapy or SBRT + maintenance chemotherapy Primary histology: all NSCLC *1–3 oligometastatic lesions* Primary outcome measure: PFS	April 2022
Randomized Phase III Trial of Local Consolidation Therapy (LCT) After Nivolumab and Ipilimumab for Immunotherapy-Naive Patients With Metastatic Non-small Cell Lung Cancer (LONESTAR) -Strategic Alliance: BMS Institution: M.D. Anderson Cancer Center ClinicalTrials.gov identifier: NCT03391869	270	Phase 3 multi-center: systemic treatment only with nivolumab and ipilimumab or induction nivolumab and ipilimumab followed by local consolidative therapy with surgery and/or radiotherapy Primary histology: all NSCLC *>1 oligometastatic lesions* Primary outcome: OS	December 2022
A Randomized Trial of Conventional Care vs. Radioablation (Stereotactic Body Radiotherapy) for Extracranial Oligometastases (CORE) Institution: Royal Marsden NHS Foundation Trust ClinicalTrials.gov identifier: NCT02759783	245	Phase 2/3 multi-center: standard of care or standard of care + SBRT Primary histology: breast, prostate, or NSCLC *1–3 oligometastatic lesions* Primary outcome measure: PFS	October 2024
A Randomized Phase III Trial of Stereotactic Ablative Radiotherapy for the Comprehensive Treatment of 4–10 Oligometastatic Tumors (SABR-COMET 10) Institution: Lawson Health Research Institute ClinicalTrials.gov identifier: NCT03721341	159	Phase 3 multi-center: stereotactic ablative radiotherapy, plus standard of care treatment: chemotherapy, immunotherapy, hormones, or observation given at the discretion of the treating oncologist Various histology including NSCLC *4 to 10 oligometastatic lesions* Primary outcome: OS	January 2029
Randomized Phase II Trial of Local Consolidation Therapy (LCT) After Osimertinib for Patients With EGFR Mutant Metastatic Non-small Cell Lung Cancer (NSCLC) (NORTHSTAR) Institution: M.D. Anderson Cancer Center ClinicalTrials.gov identifier: NCT03410043	143	Phase 2 multi-center: osimertinib followed by local consolidative therapy with surgery and/or radiotherapy or maintenance osimertinib alone Primary histology: NSCLC *>1 oligometastatic lesion* Primary outcome: PFS	January 2023
A Multicentre Single Arm Phase II Trial Assessing the Efficacy of Immunotherapy, Chemotherapy and Stereotactic Radiotherapy to Metastases Followed by Definitive Surgery or Radiotherapy to the Primary Tumor, in Patients With Synchronous Oligo-metastatic NSCLC Institution: European Thoracic Oncology Platform ClinicalTrials.gov identifier: NCT03965468	47	Phase 2 multi-center: durvalumab, carboplatin/paclitaxel chemotherapy, followed by SBRT to all oligometastases. Restaging at 3 months Definitive local treatment with surgical resection of primary tumor or RT 60–66 Gy to the primary tumor if no disease progression. *1–3 oligometastatic lesions* Primary outcome: PFS	December 2021

RT, radiotherapy; SBRT, stereotactic body radiation therapy; SABR, stereotactic ablative radiotherapy; OS, overall survival; PFS, progression free survival.