Klinik für RadioOnkologie, UniversitätsSpital Zürich, Universität Zürich

OMD Symposium Hamburg 2018

Oligometastatic disease in NSCLC

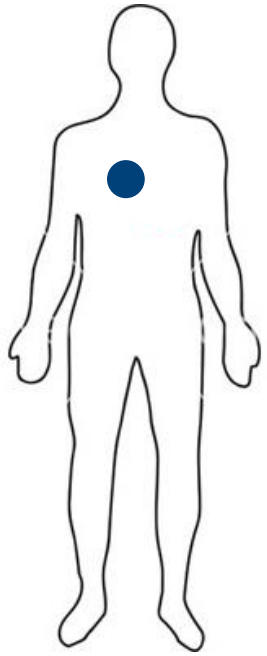
Matthias Guckenberger

UniversitätsSpital Zürich
Universität Zürich[UZH]

Oligometastatic Disease (OMD)

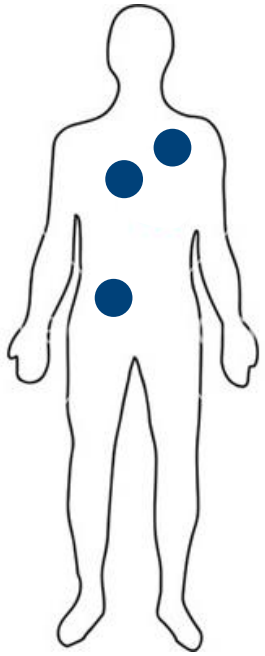
Hellman & Weichselbaum JCO 1995

Localized



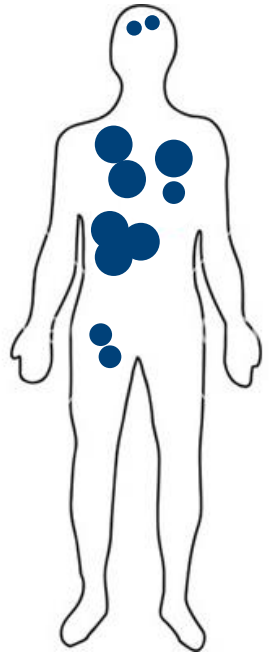
Cure with local treatment

Oligometastatic



Cure with local treatment possible

Systemic



Local Tx for symptom control

Oligo-metastatic NSCLC

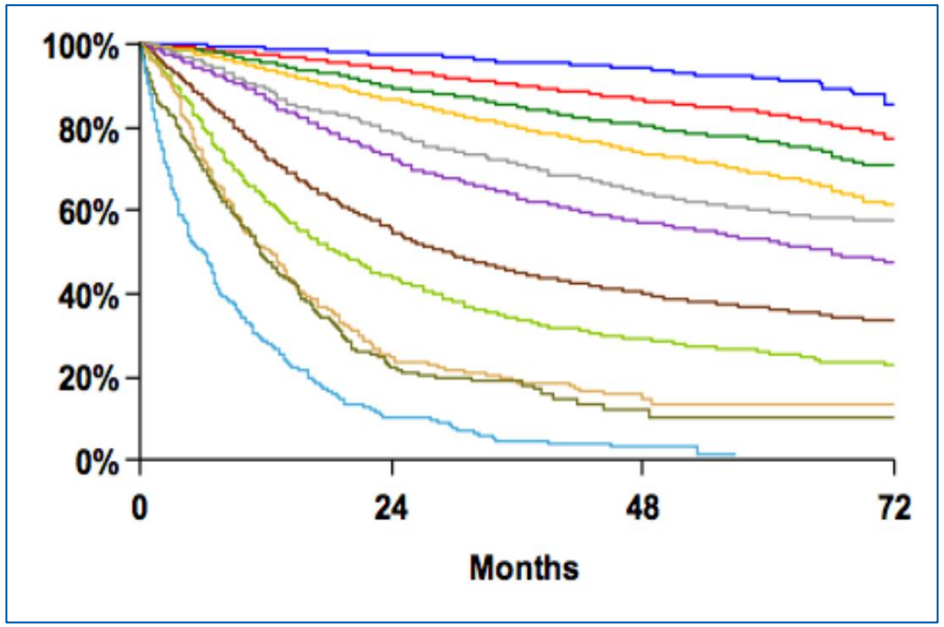
Incidence of Oligometastases @ first diagnosis of stage IV NSCLC

	Oligo-metastases
Rusthoven 2009	**53 %**
Yano 2013	**55 %**
Torok 2013	**52 %**
Parikh 2014	**26 %**

➢Frequent in the literature – not as frequent in my experience

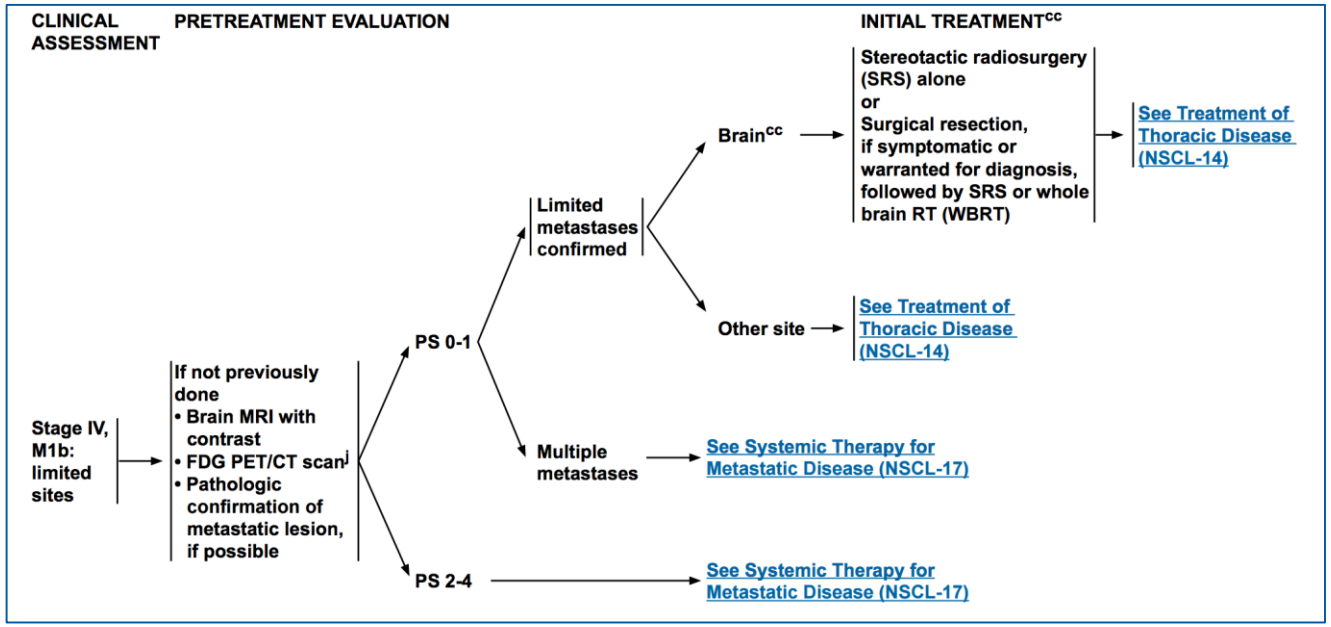
Recognition of oligometastases – guideline level

Distinct stage



Goldstraw JTO 2015

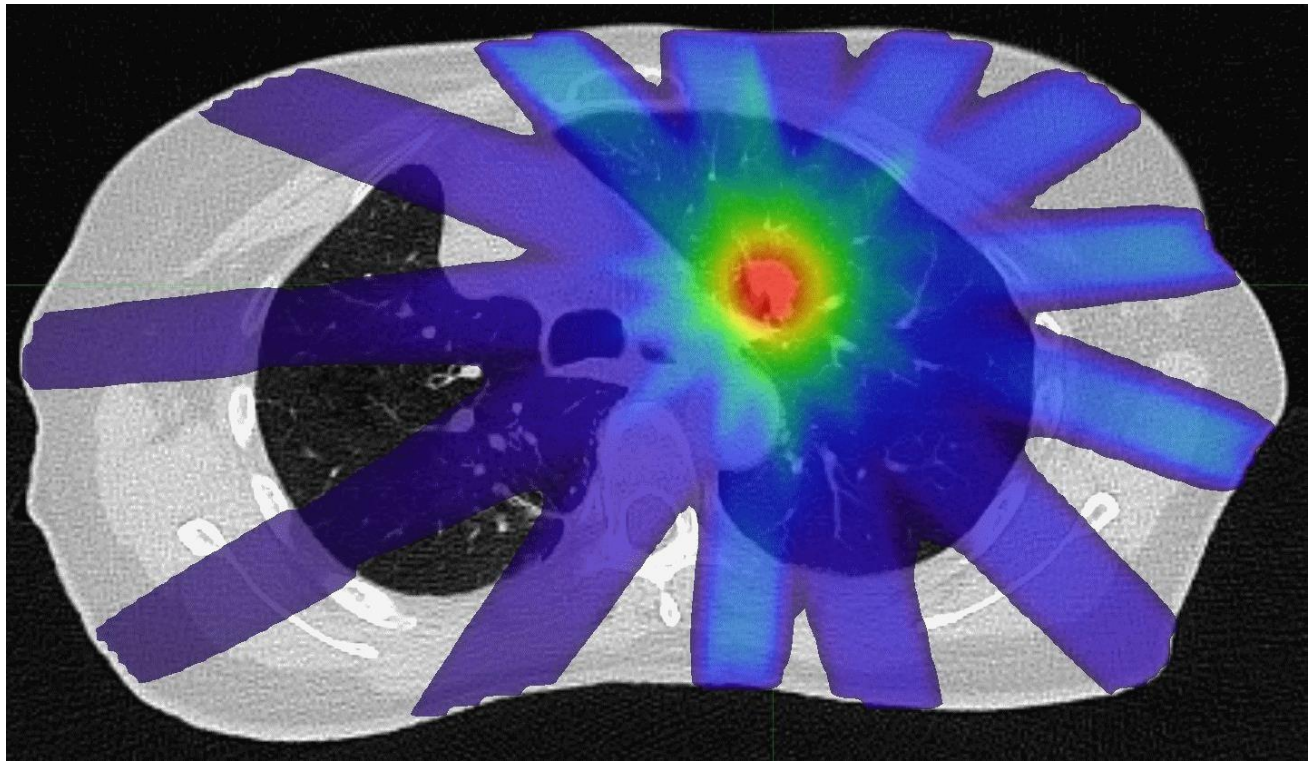
Therapeutic consequences

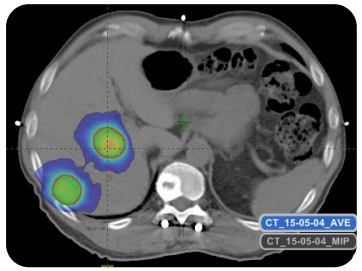


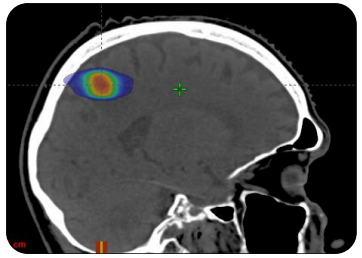
NCCN v3.2017

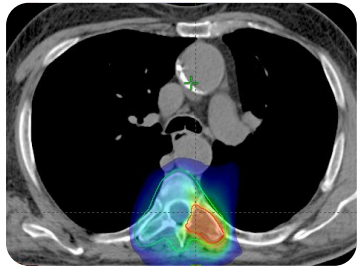
- Separate stage M1b: single extra-thoracic lesion
- Radical treatment recommended incurrent guidelines

Stereotactic Radiotherapy









- Non-invasive
- Outpatient procedure
- 1-5 treatment sessions

➢ Low toxicity profile

➢ Local control > 80-90%

➢ Well suited for the needs in an oligometastatic situation

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Local efficacy of SBRT in the metastatic situation

Retrospective DB of SBRT for pulmonary oligometastases from Germany, Austria and Switzerland

	Lesions	Local control @ 2a
Breast	33	97%
NSCLC	**148**	**83%**
CRC	133	86%
RCC	56	91%
Sarcoma	20	70%
Esophagus	15	93%
Melanoma	15	87%
Others	105	89%
Overall	**525**	**87%**

Guckenberger Radiother Oncol 2015

➢ Excellent local metastatis control even in so-called radioresistant histologies

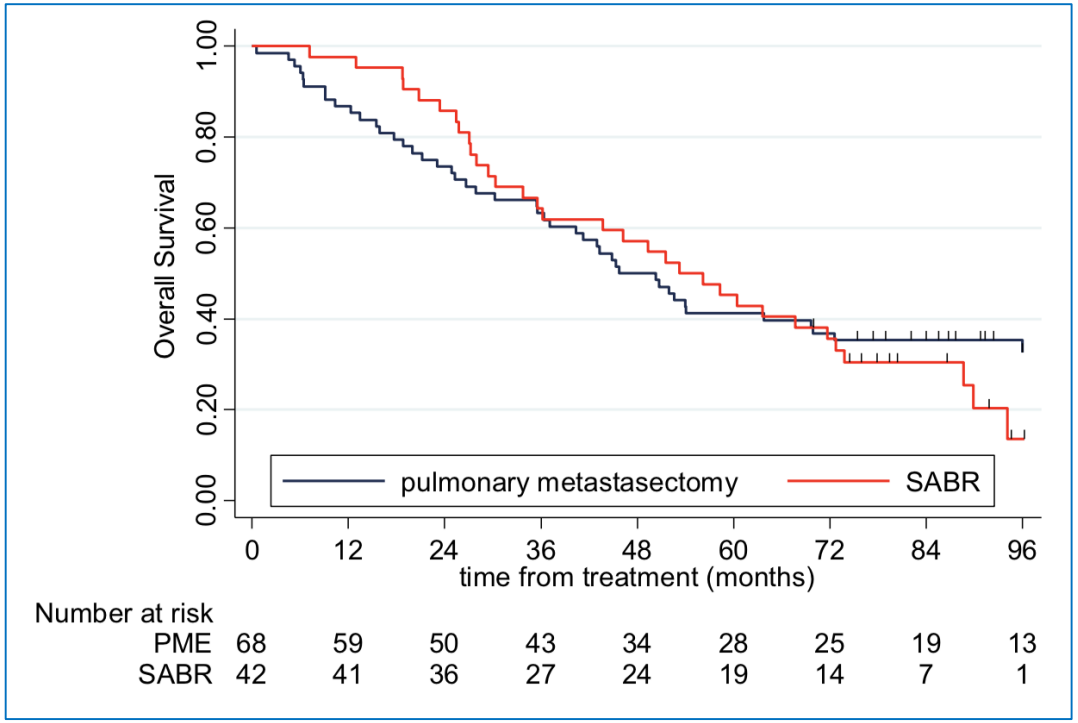
Toxicity profile of SBRT in Tx of oligometastases

	Study	Patients	Lesions	Toxicity grade ≥ 3
Salama Cancer 2012	Phase I	61	113	**9%**
Rusterhoven JCO 2009	Phase I / II	38	63	**8%**
Milano IJROBP 2012	Phase II	121	154	**0.8%**
Nuyttens IJROBP 2015	Phase II	30	57	**16%**
Guckenberger IJROBP 2009	Retrospective	84	118	**1%**
Trakul IJROBP 2012	Retrospective	X	38	**4.8%**
Dhakal IJROBP 2012	Retrospective	14	74	**0%**
Takeda Radiother Oncol 2011	Retrospective	34	44	**2.2%**

➢ Favourable toxicity profile

SBRT compared to surgical metastasectomy

Single-center retrospective comparison, propensity-score matching
„The first choice of treatment was surgery; SBRT was recommended in cases of adverse clinical factors.“



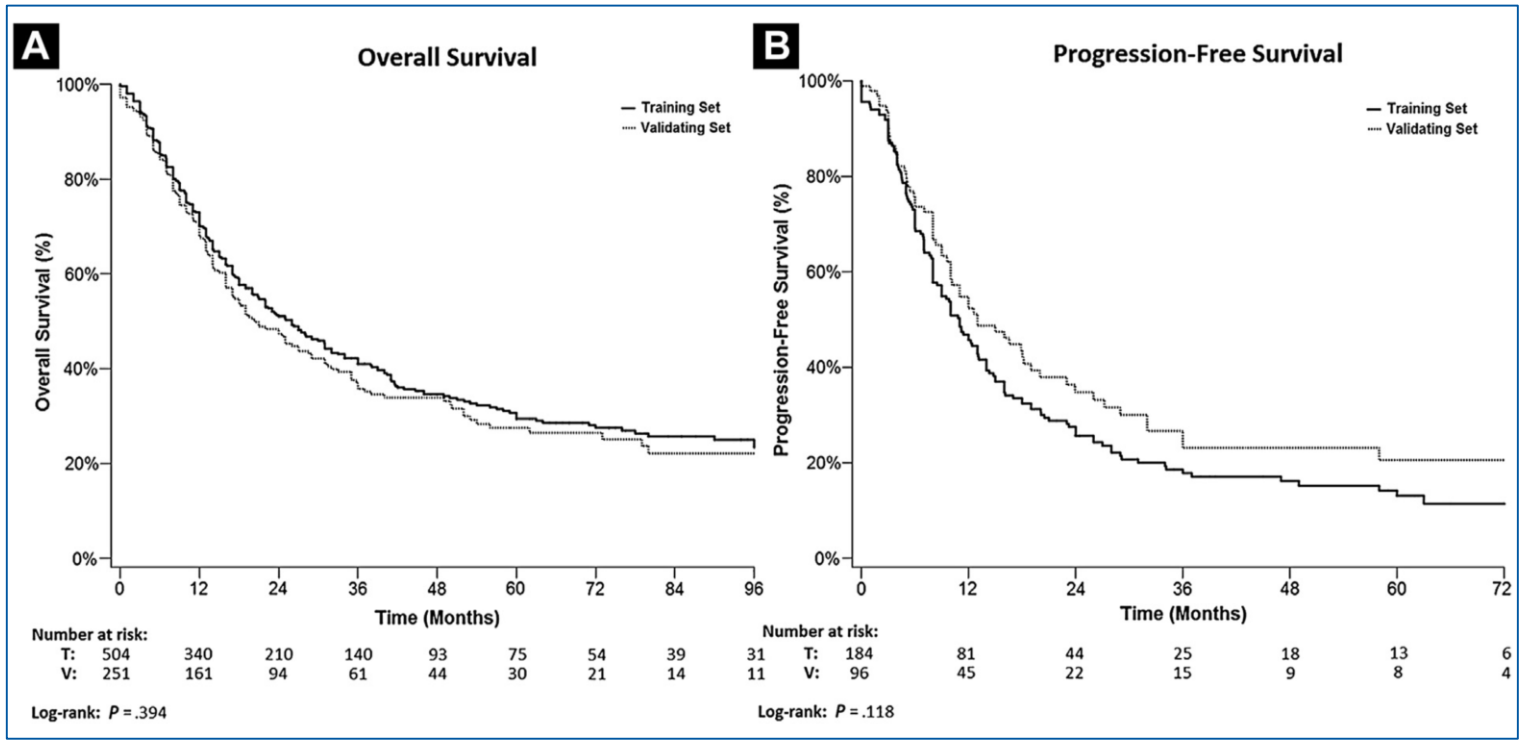
@ 5a	SBRT	Metastasectomy
Freedom from failure of local strategy	40%	40%
Progression-free survival	18%	20%
Freedom from local progression	83%	81%

Lodeweges JTO 2017

➢ Very similar outcome despite study design favoring surgical metastasectomy

Retrospective evidence for MDT in OMD

Individual patient meta-analysis: n=757

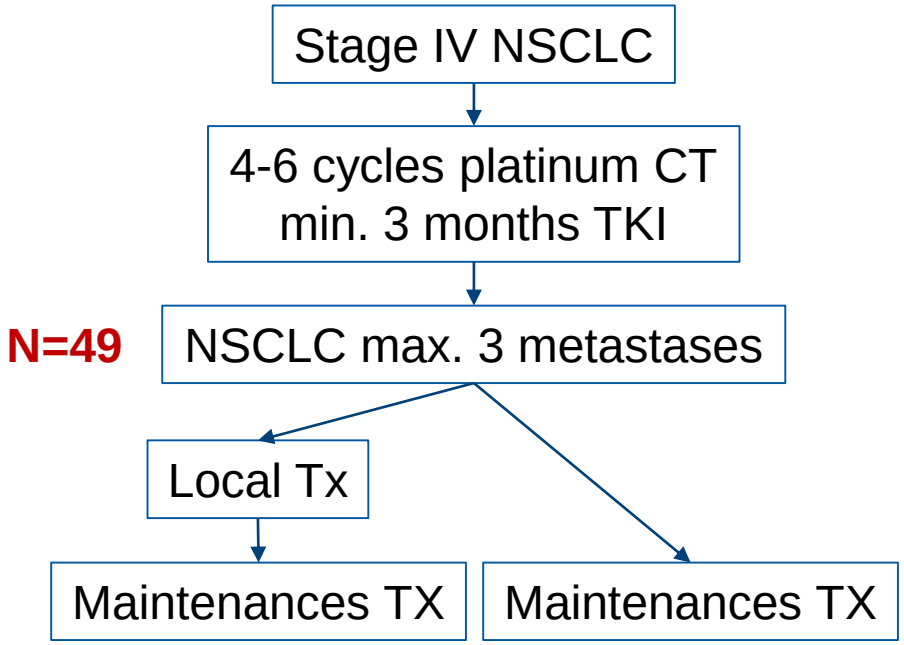


Ashworth Clin Lung Cancer 2014

- Factors predictive of OS: synchronous versus metachronous metastases, N-stage, adenocarcinoma histology

Prospective evidence for MDT in OMD I

Gomez Lancet Oncol 2016



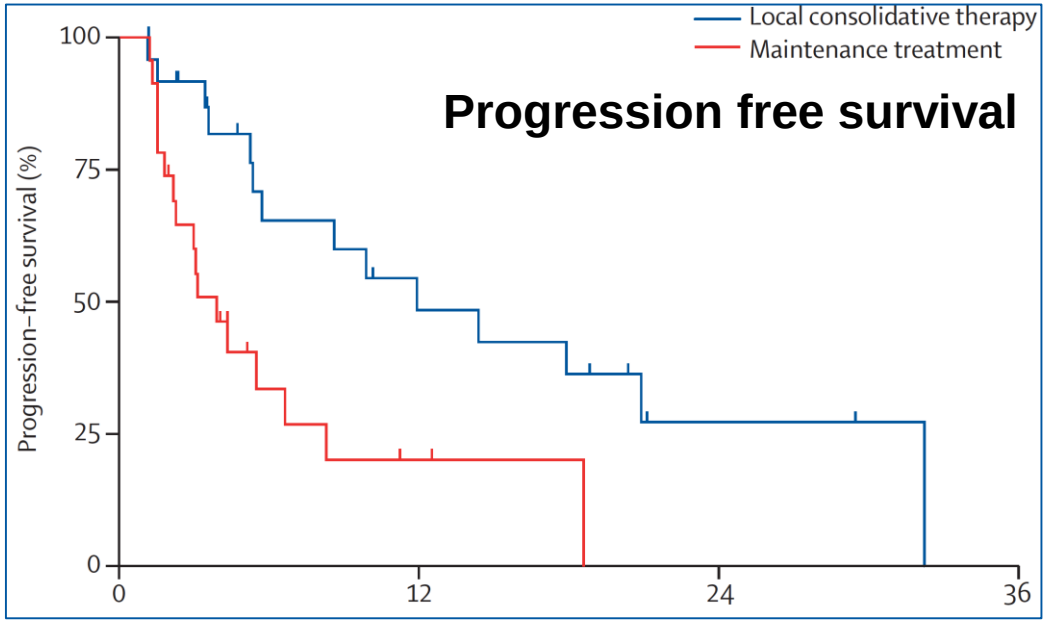
Gomez Lancet Oncol 2016

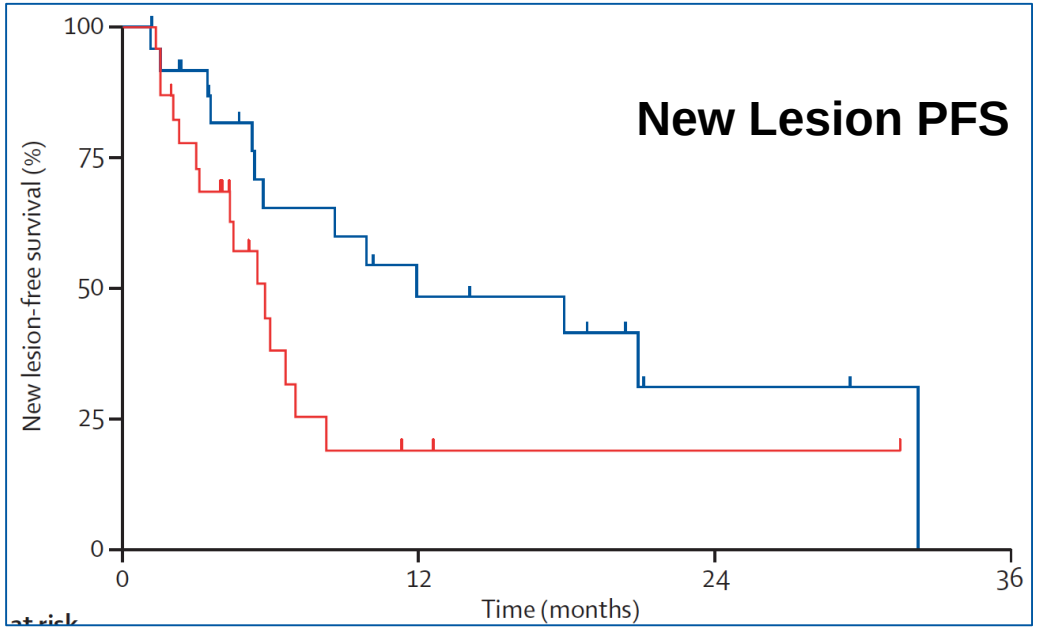
Treatment modality	
SBRT	48%
RCT	8%
SBRT & RCT	12%
Surgery & RT	24%
Surgery only	4%

➢ Toxicity with mostly radical SBRT: 20% grade III toxicity, no grade IV or grade V

Prospective evidence for MDT in OMD I

Gomez Lancet Oncol 2016





	Local +/- systemic	Systemic only
Median PFS	11.9 months	3.9 months
Median new lesion PFS	11.9 months	5.7 months

➢ LOCAL Tx delayed systemic progression of oligometastatic NSCLC

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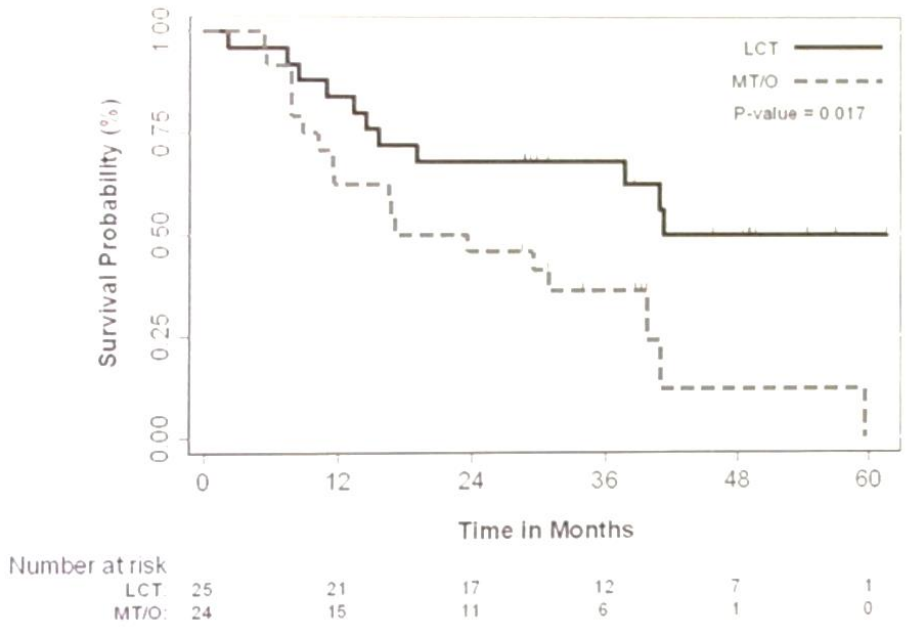
Prospective evidence for MDT in OMD I

Overall Survival



Median 17.0 months MT/O [HR=0.40, 95% CI 10.1–39.8, *P*=0.017] vs. 41.2 months LCT [95% CI 18.9–not reached]

ASTRO 2018

➢Significant OS benefit with HR = 0.40

Prospective evidence for MDT in OMD II

Iyengar JAMA Oncol 2017

NSCLC stage IV, no driver mutation

4-6 cycles platinum CT

N=29 SD or PR, max 5 metastases

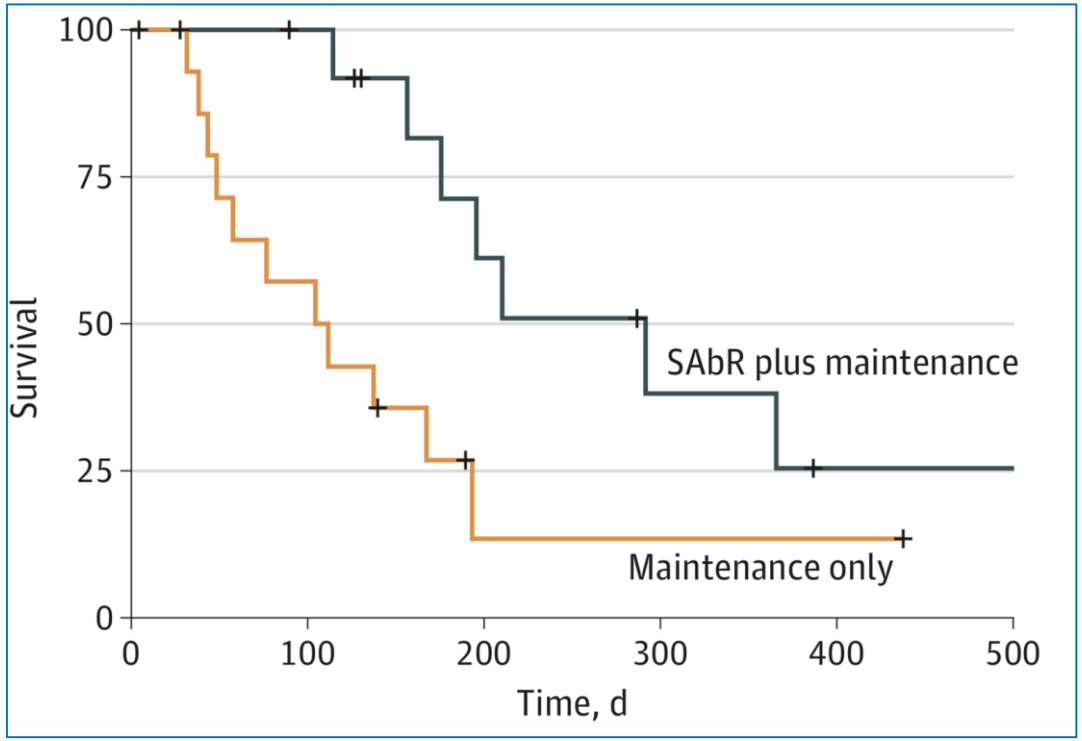
SBRT

Maintenances TX

Maintenances TX

Iyengar JAMA Oncol 2017

Progression free survival



➢ SBRT improved PFS w/o added toxicity and w/o delay of systemic Tx

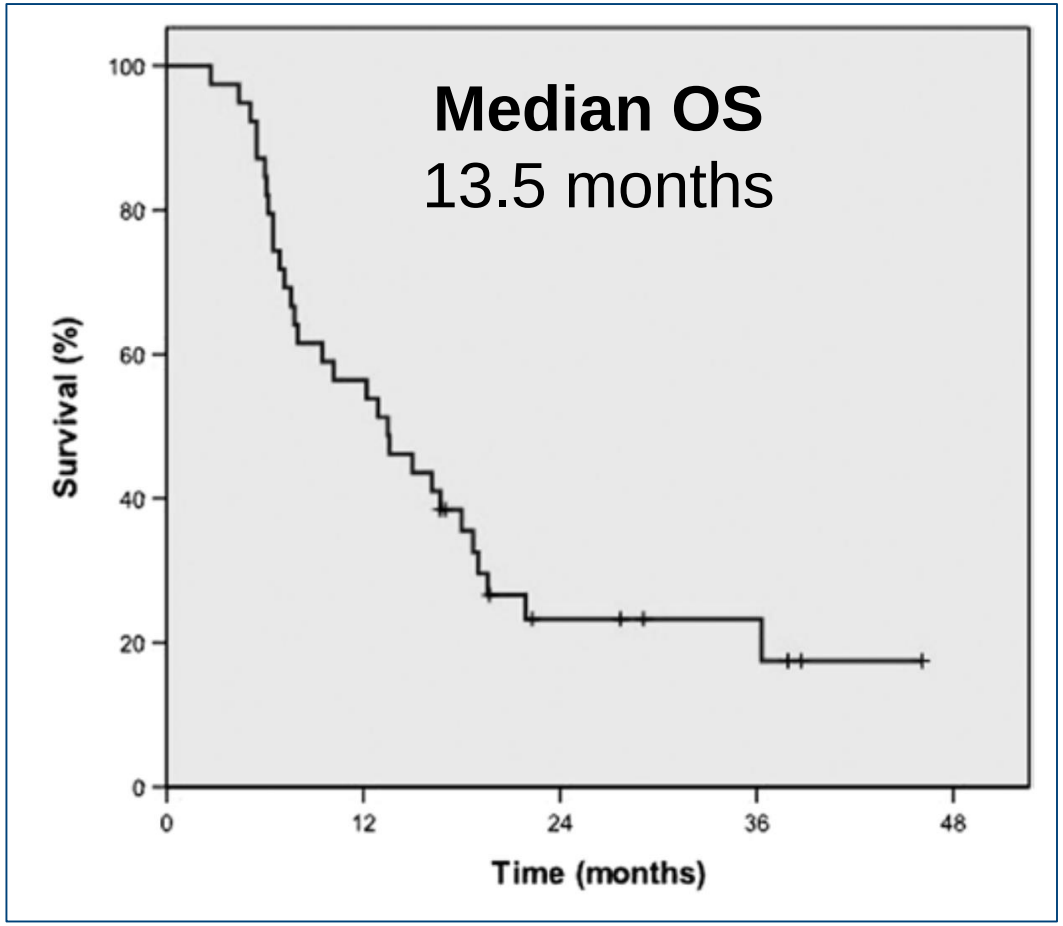
Prospective evidence for MDT in OMD III

Prospective phase II trial

N=39

Single metastatic lesion	87%
Local stage III disease	74%
Treatment:	
Surgery	0%
Radiotherapy	100%

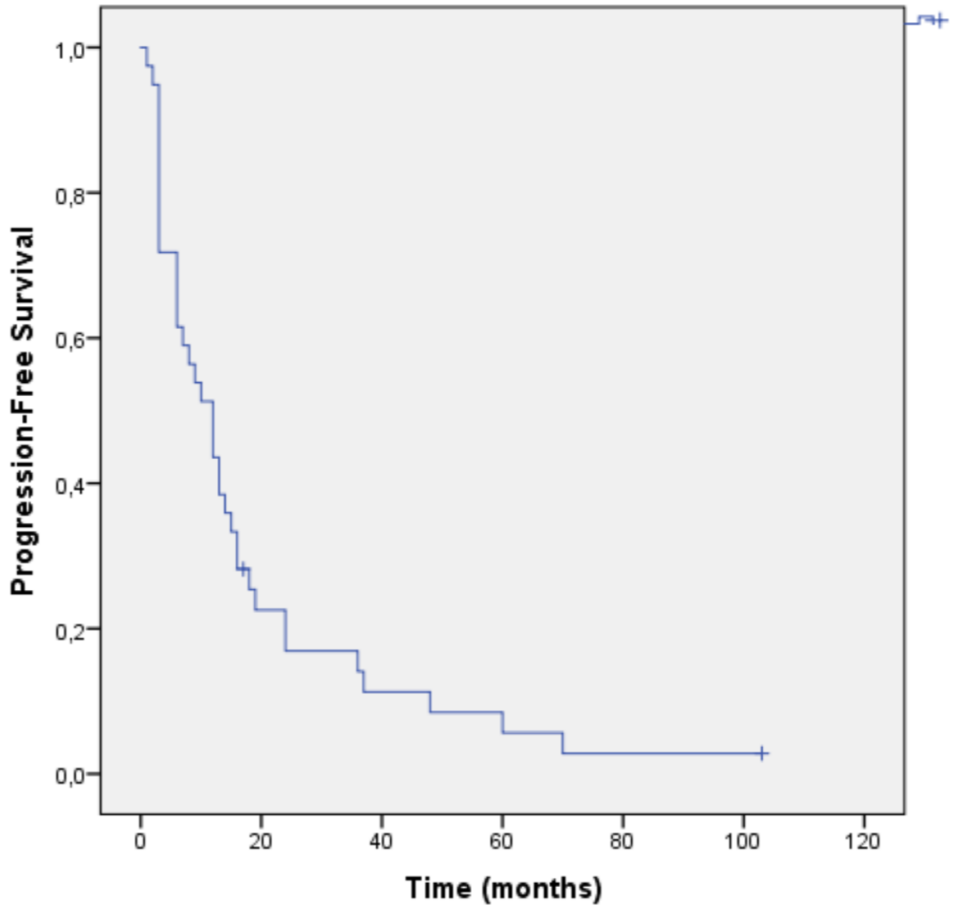
De Ruysscher JTO 2012



➢Survival very similar to stage III w/o metastatic disease

Prospective evidence for MDT in OMD III

minimal follow-up
exceeding 7 years



De Ruysscher JTO 2018

➢Only 3 / 39 patients free of disease after 5 years

Systemic diease progression

	Proportion of patients developing systemic progression after MDT
De Ruysscher JTO 2012	94%
Gomez Lancet Oncol 2016	*64 %*
Iyengar JAMA Oncol 2017	*47 %*

- OMD patients die of systemic diease progression
- Ideally synergistic effects of local and systemic Tx

Radiotherapy combined with immunotherapy

PACIFIC

Irresectable stage III NSCLC

RCT +/- Durvalumab

Metastases	- 36%
Brain metastases	- 50%

Antonia N Engl J Med, 2017

PEMBRO-RT

Advanced NSCLC (≥2nd line)

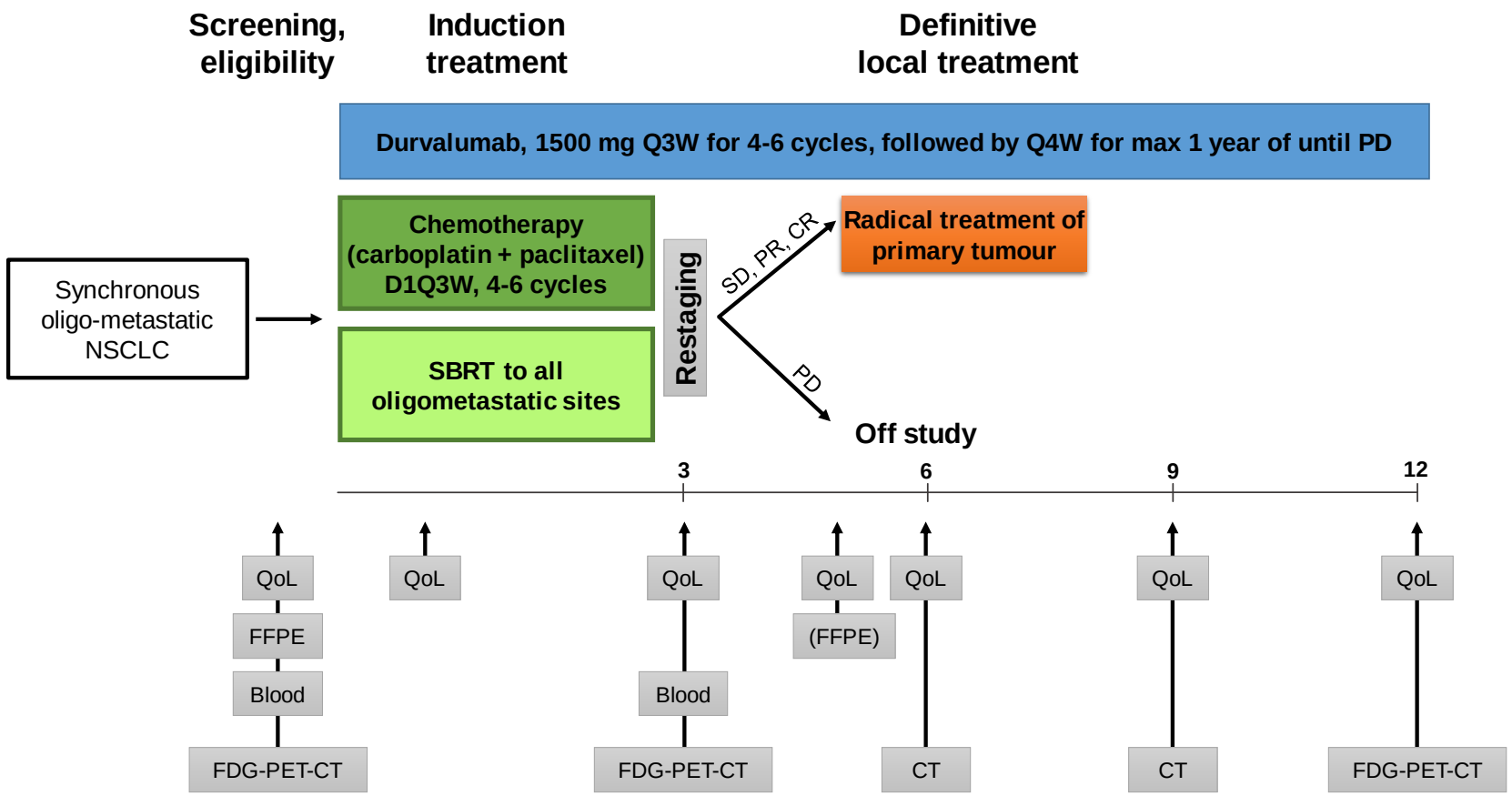
Pembrolizumab +/- SBRT

ORR	x 2.2
Median PFD	x 3.5

Theelen ASCO 2018

➢Immune-checkpoint inhibition & RT – ideal partners for OMD

ETOP CHESS study



Study design:

- Single arm multicentre phase II
- ETOP sponsored

Primary endpoint:

- PFS at 12 months

Secondary endpoints:

- OS
- Pattern of disease progression
- Response to induction therapy
- Quality of Life
- Toxicity

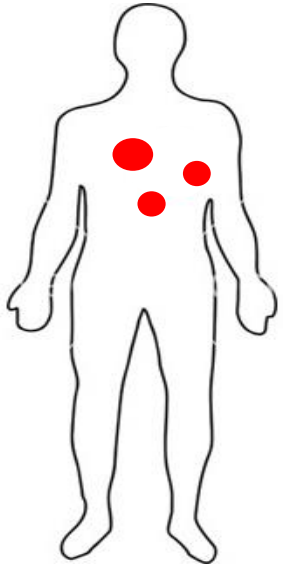
➢„Induction“ of IO, CT and SBRT to improve systemic disease control

Oligoprogressive NSCLC

Oligometastasis

- Limited number of metastases

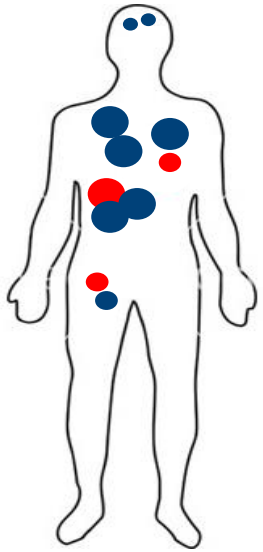
➢ Treatment of **all** lesions



Oligoprogression

- Multiple metastases
- Limited number of progressive metastases during systemic treatment

➢ Treatment **all progressive** lesions

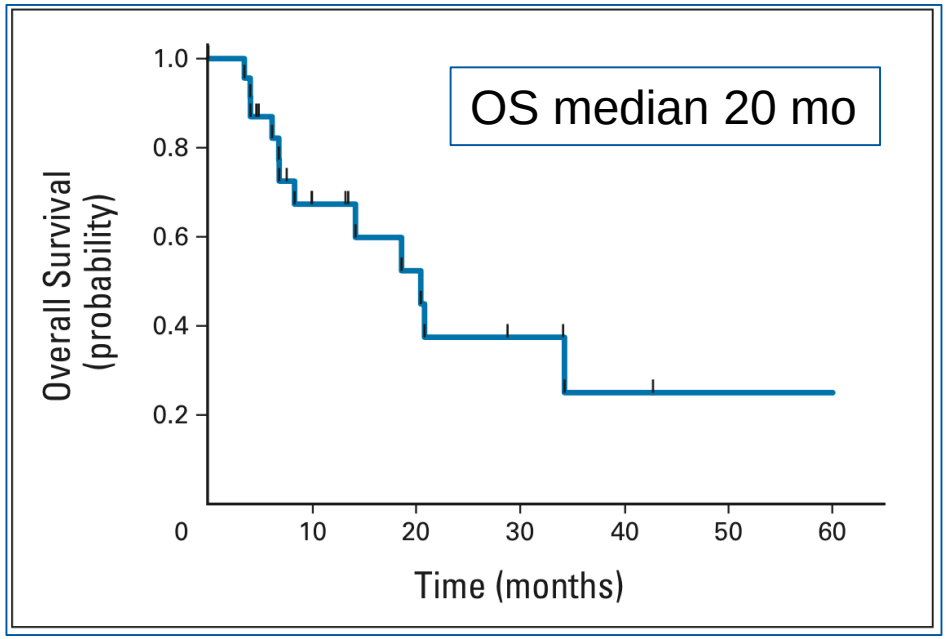


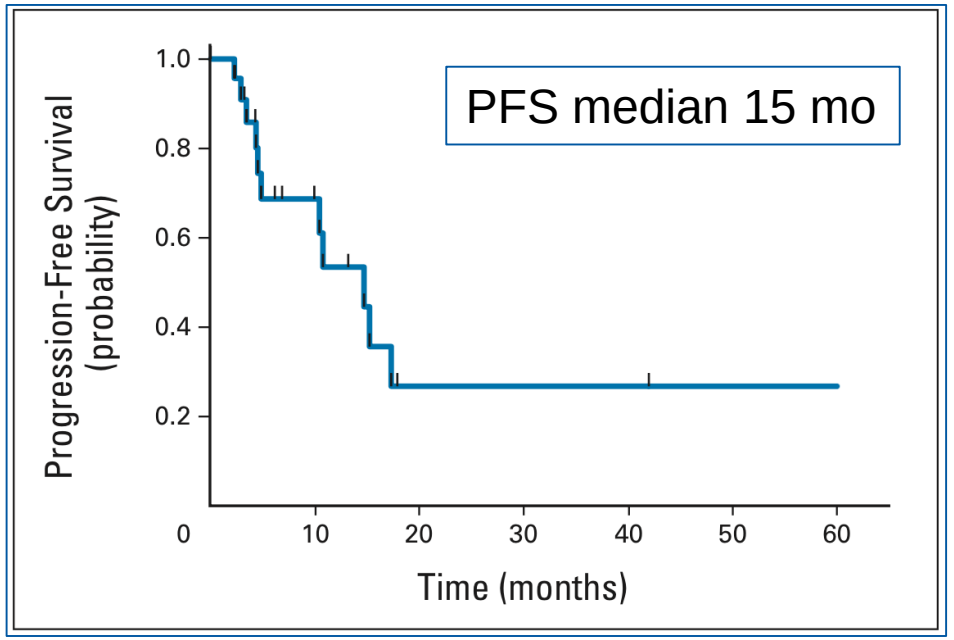
SBRT for oligoprogressive NSCLC

Metastatic platin-resistant NSCLC, maximum 5 sites based on FDG-PET

- SBRT to all progressive sites
- Switch to concurrent Erlotinib

Iyenger JCO 2014





- Very promising results considering very poor prognosis of platin-resistant NSCLC

Value of repeat histopathology

EGFR & KRAS status

Meta-analysis of EGFR and KRAS between primary & metastases (*Wang Con Oncol 2015*)

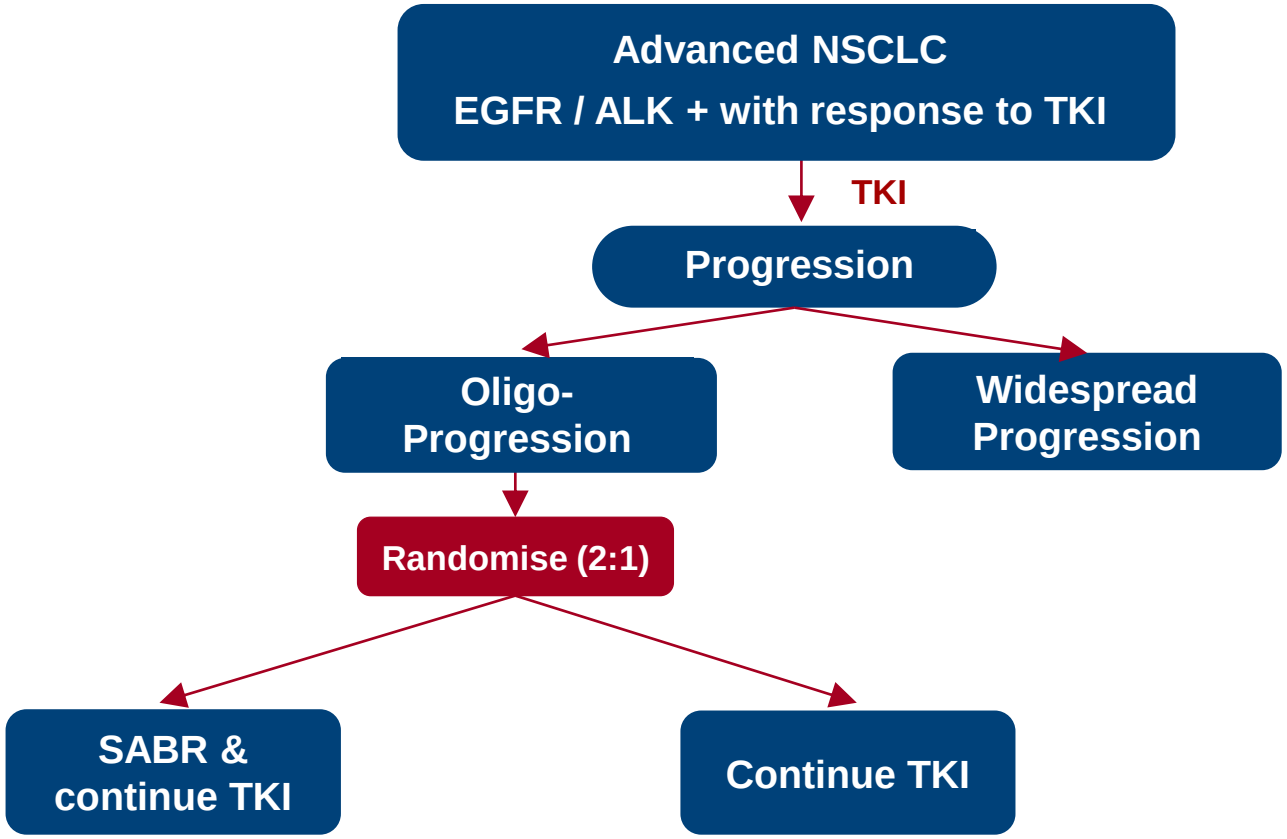
- „routine analysis of EGFR or KRAS gene status both in primary and metastatic tumours is not recommended“

PD-L1 status

- KEYNOTE-010 trial: benefit of Pembro irrespective of whether archival or new tumor samples (Herbst Lancet 2016)
- FIR study: high agreement of PD-L1 expression between paired archival and fresh tumor samples (Chaft JTO 2015)
- KEYNOTE-001, -010, -024: PD-L1 expression similar across prior lines of therapy (Aggarwal Ann Aoncol 2016)

➢Limited evidence that multiple samples or rebiopsy improve outcome

SBRT for oligoprogressive NSCLC – HALT Study



➢ SBRT only to avoid the risk of disease flare: 23% in *Chaft Cancer Res 2011*

Summary & Conclusion

- Oligometastatic NSCLC: well recognized but poorly defined
- SBRT – a highly effective and well tolerated local Tx option
- Highly promising data of local treatment improving PFS and OS
- However, majority of patients suffers from systemic disease recurrent
- Need for optimal systemic Tx combined with optimal local Tx

Thank you very much !

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