

Combined treatment of Brain metastases: Radiosurgery and Targeted therapy

Stephanie Kroeze, MD PhD

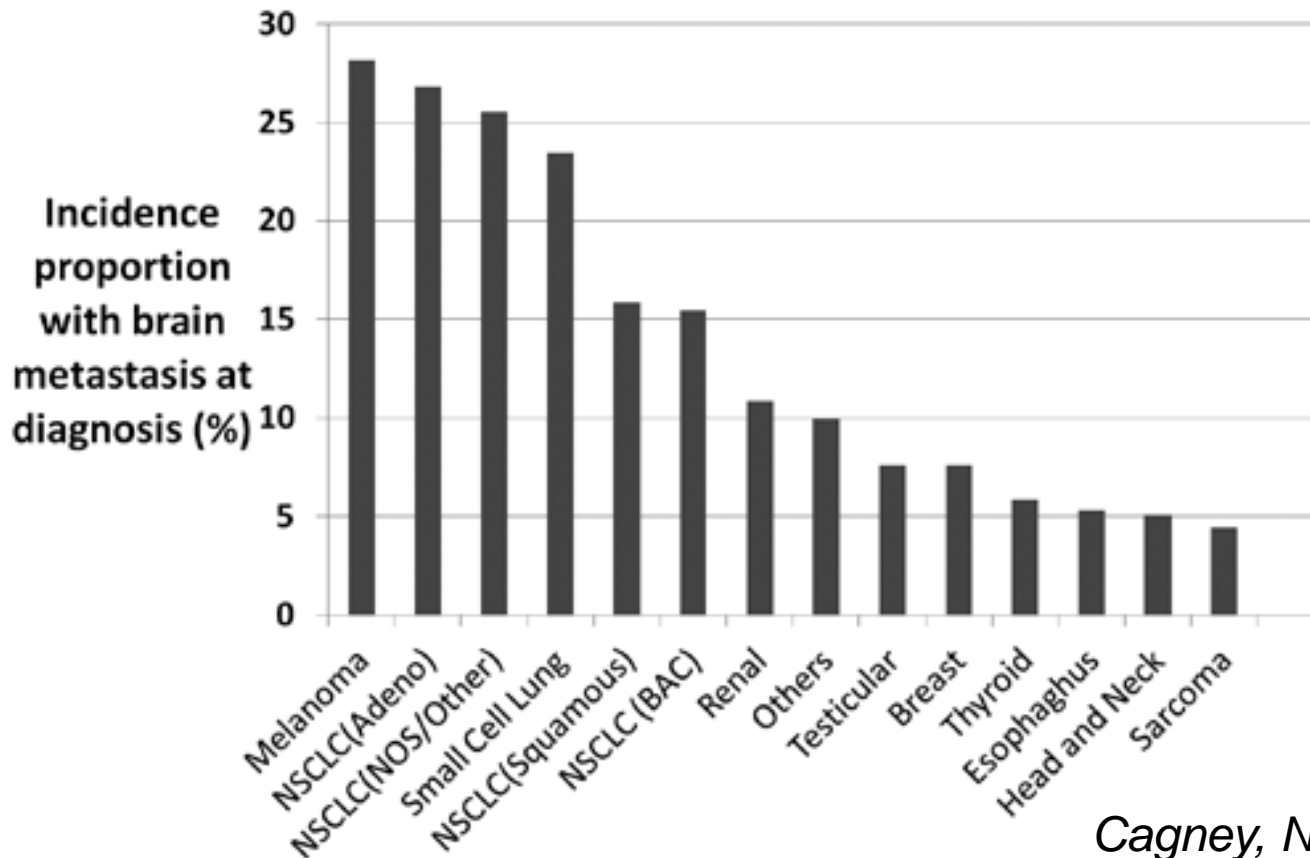


UniversityHospital
Zurich



- **Introduction brain metastases**
- Targeted therapy as monotherapy
- Efficacy of SRS combined with Targeted therapy
- Timing of combined SRT & Targeted therapy
- Safety of combined SRT & Targeted therapy

Brain metastases



Cagney, Neuro Oncol 2017

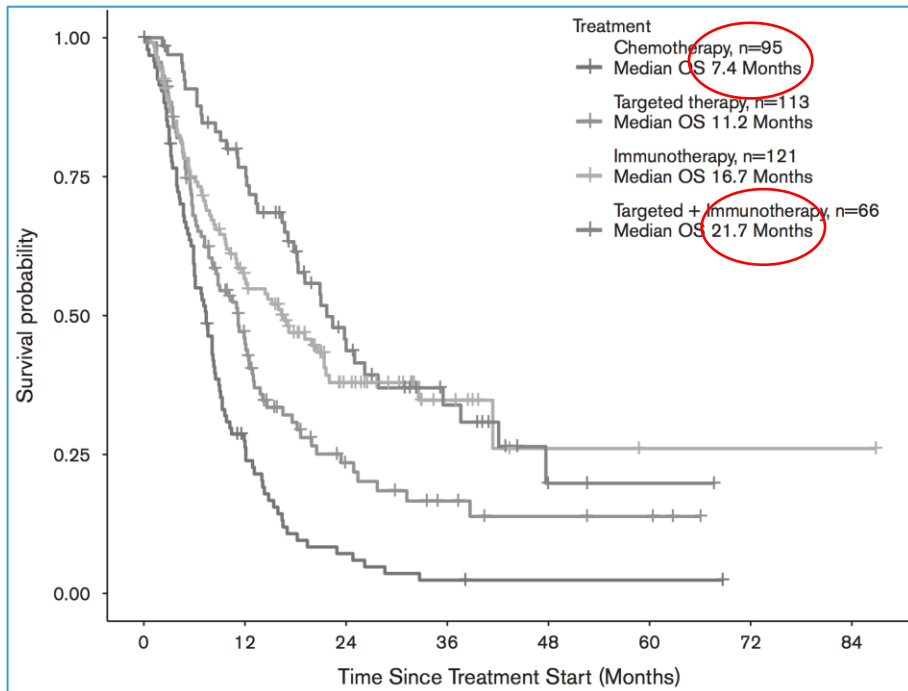
- **>10%** of cancer patients present with brain metastases at first diagnosis.
- In melanoma and NSCLC: **>25%**

- A further 30% will develop metachronous brain metastases.
- 50% have multiple brain metastases
- Important cause of morbidity and mortality, and influences quality of life
- Historically median survival of ~6 months

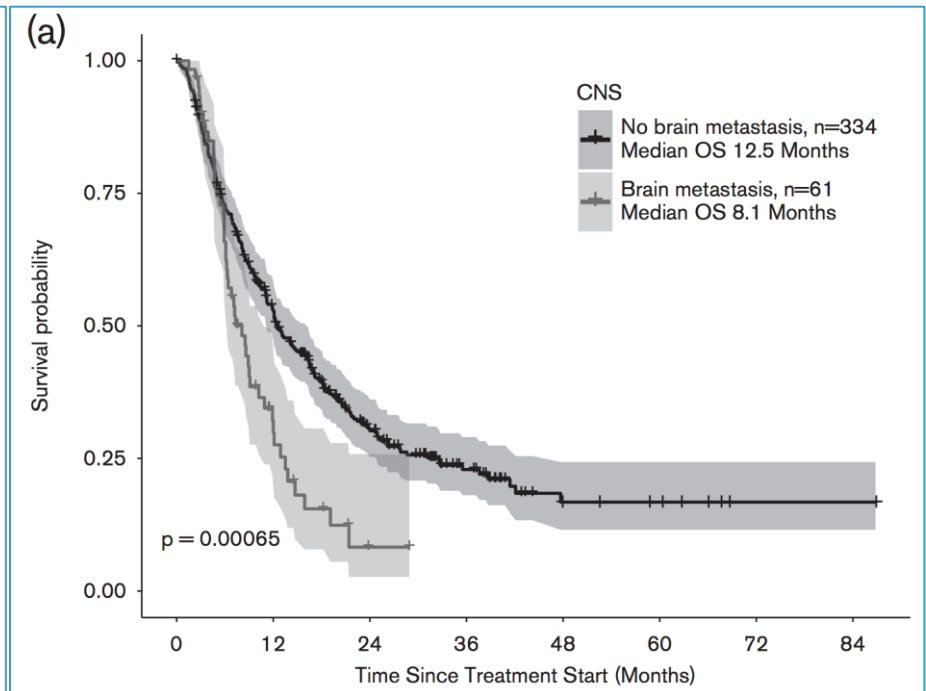
- Frequent clinical challenge
- Historically limited prognosis

- Introduction brain metastases
- **Targeted therapy as monotherapy**
- Efficacy of SRS combined with Targeted therapy
- Timing of combined SRT & Targeted therapy
- Safety of combined SRT & Targeted therapy

TT monotherapy for melanoma



Factor 3 better OS



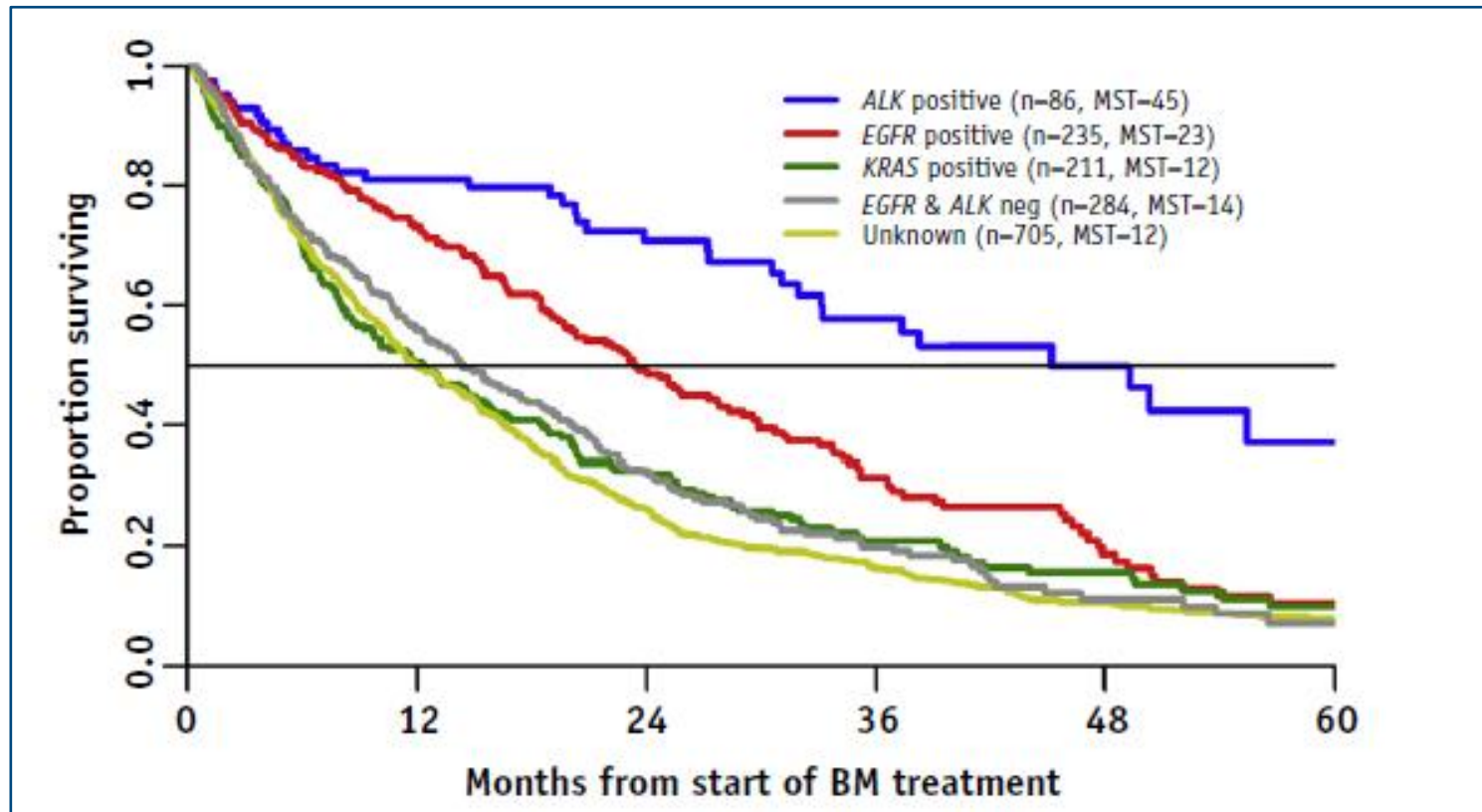
Factor 1.5 better OS

Mangana Melanoma Research 2017

- Frequently excluded in clinical trials
- Monotherapy suboptimal benefit in survival

TT monotherapy for NSCLC: TKIs

N=1521, retrospective multicenter trial, Gefitinib/Erlotinib/Crizotinib

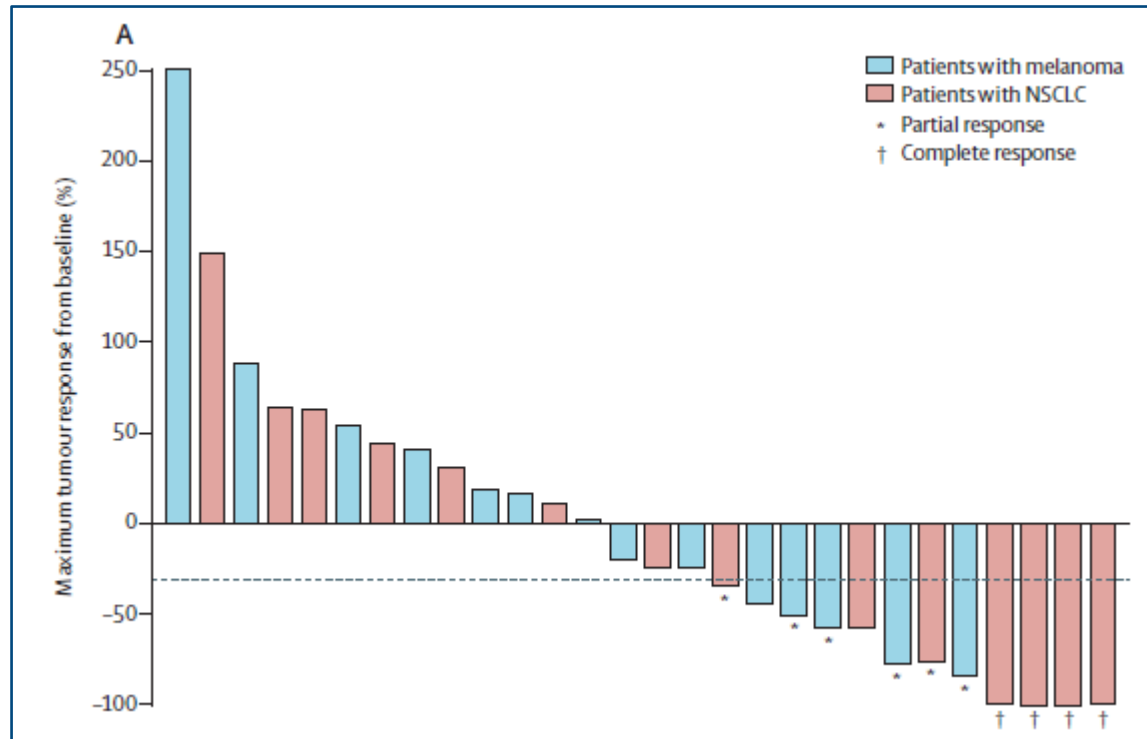


Sperduto, Int J radiat Oncol Biol Phys 2016

➤ OS only improved for ALK and EGFR-pos.
NSCLC

TT monotherapy for NSCLC: Immunotherapy

N=52, Melanoma/NSCLC, Phase II trial, treated with Pembrolizumab



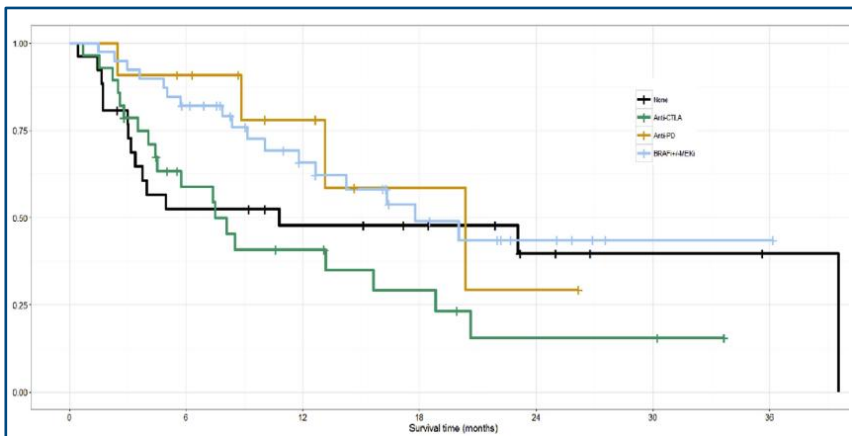
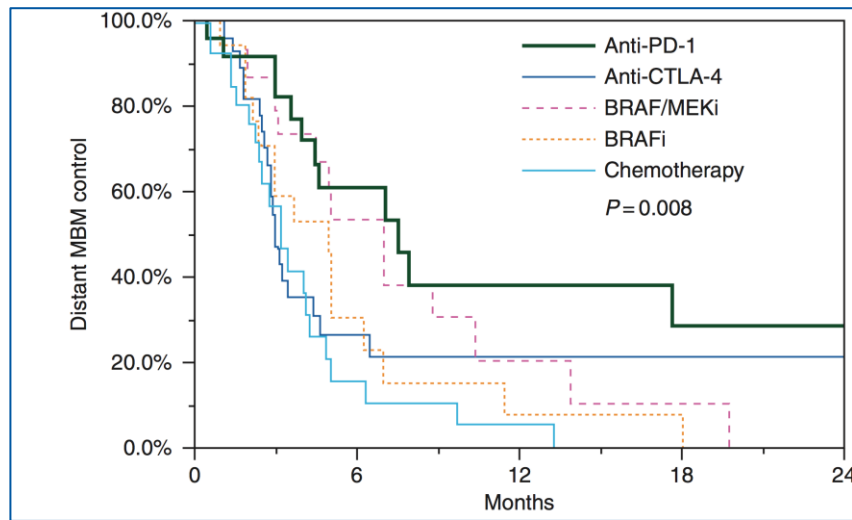
Goldberg, Lancet Oncol 2016

➤ Intracranial response in 22% melanoma patients and 33% NSCLC patients



- Introduction brain metastases
- Targeted therapy as monotherapy
- **Efficacy of SRS combined with Targeted therapy**
- Timing of combined SRT & Targeted therapy
- Safety of combined SRT & Targeted therapy

Efficacy: SRS & TT for Melanoma



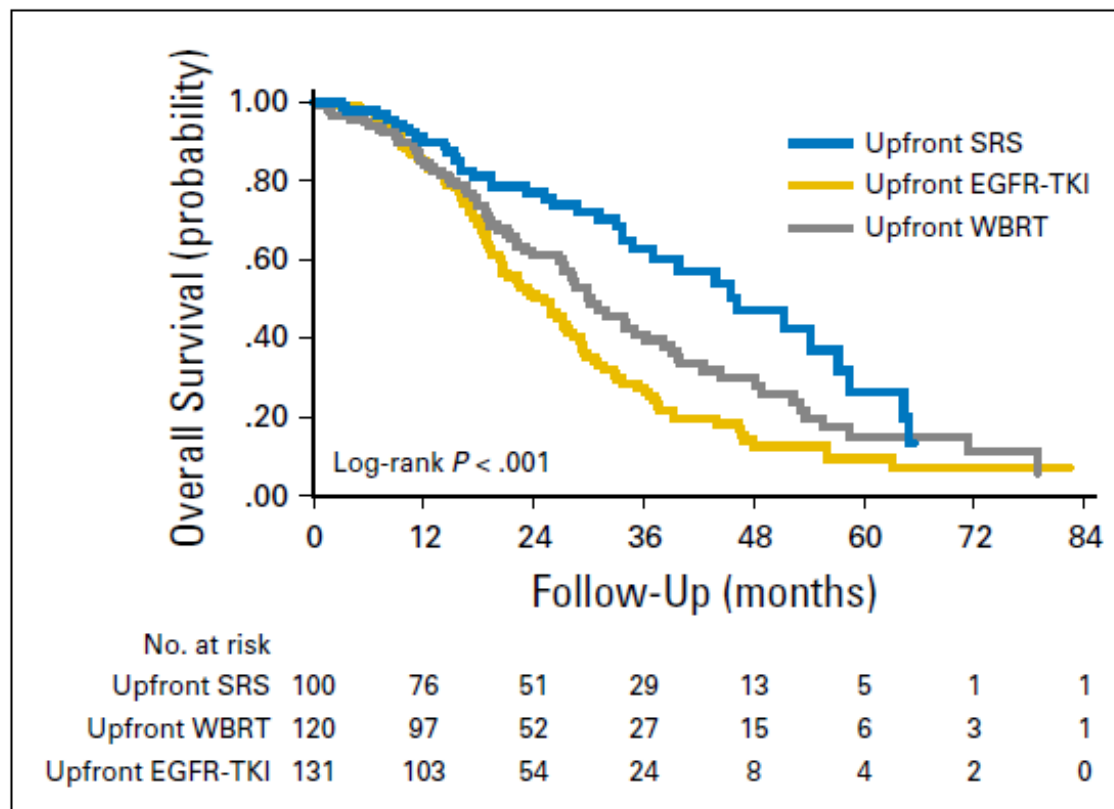
| | DBC | |
|--------------|---------------------------|------------|
| | Ahmed | Choong |
| Anti-PD1 | 38% (1y) | 13m |
| Anti CTLA-4 | 21% (1y) | 8m |
| BRAF/MEKi | 20% (1y) | 13m |
| BRAF | 8% (1y) | - |
| Chemotherapy | 5% (1y) | - |

Ahmed Annals of Oncol 2016
Choong, Eur J Cancer 2017

➤ **SRS & α -PD-1: promising distant brain control and OS**

Efficacy SRS & TT for NSCLC

N=351, retrospective multicenter trial, Erlotinib&SRS



| | OS | DBC |
|-------------------------------|------------|------------|
| SRS-> EGFR-TKI | 46m | 23m |
| WBRT-> EGFR-TKI | 30m | 24m |
| EGFR-TKI- > SRS | 25m | 17m |

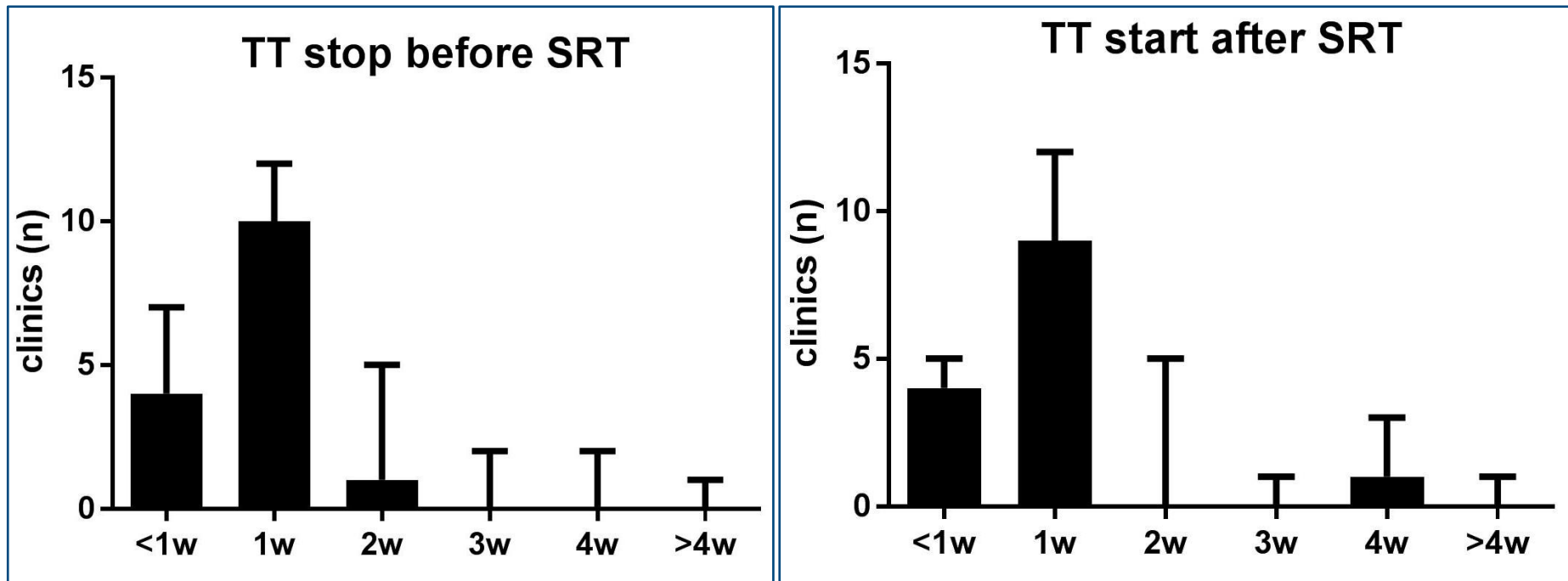
Magnuson JCO 2017

- SRS & EGFR-TKI resulted in longest OS
- Deferral of SRS is associated with inferior OS

- Introduction brain metastases
- Targeted therapy as monotherapy
- Efficacy of SRS combined with Targeted therapy
- **Timing of combined SRT & Targeted therapy**
- Safety of combined SRT & Targeted therapy

Timing SRS&TT

Survey among 19 radiation oncology clinics in German-Speaking countries

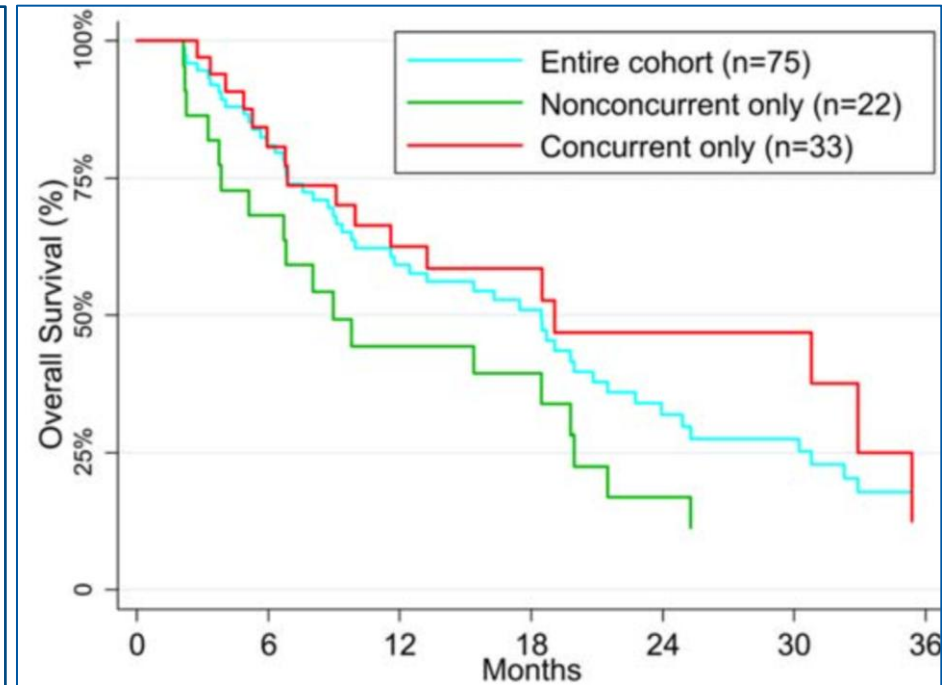
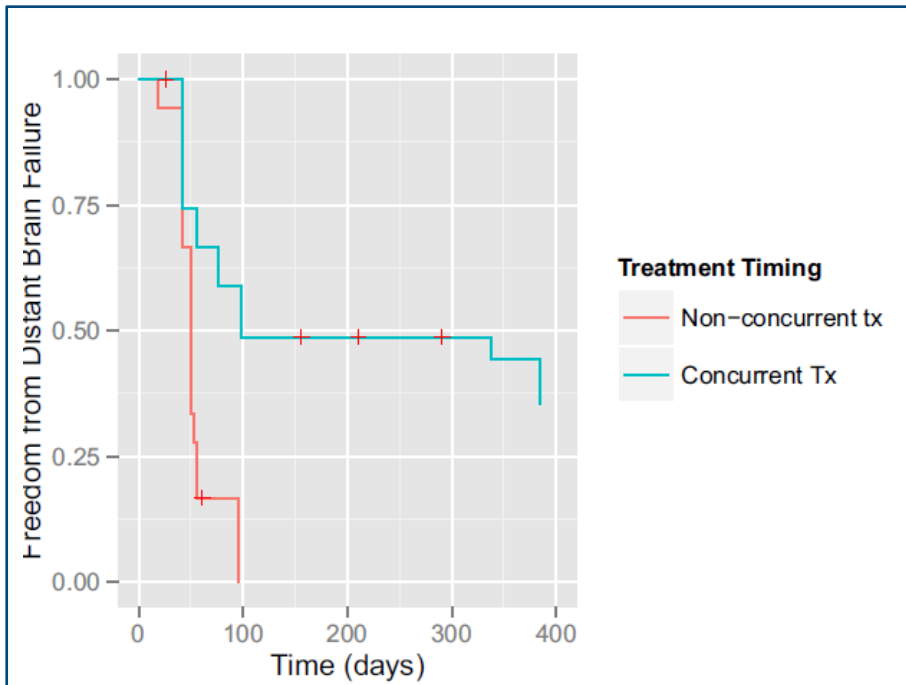


Kroeze, unpublished

- Currently, most radiation oncologists pause TT 1 week before&after SRS

Timing SRS&TT

Melanoma patients, treated with α -CTLA-4/PD-1



**BM Volume reduction 5m:
52% vs 15%**

**BM Volume reduction 6m:
95% vs 66%**

Yusuf World Neurosurg 2017

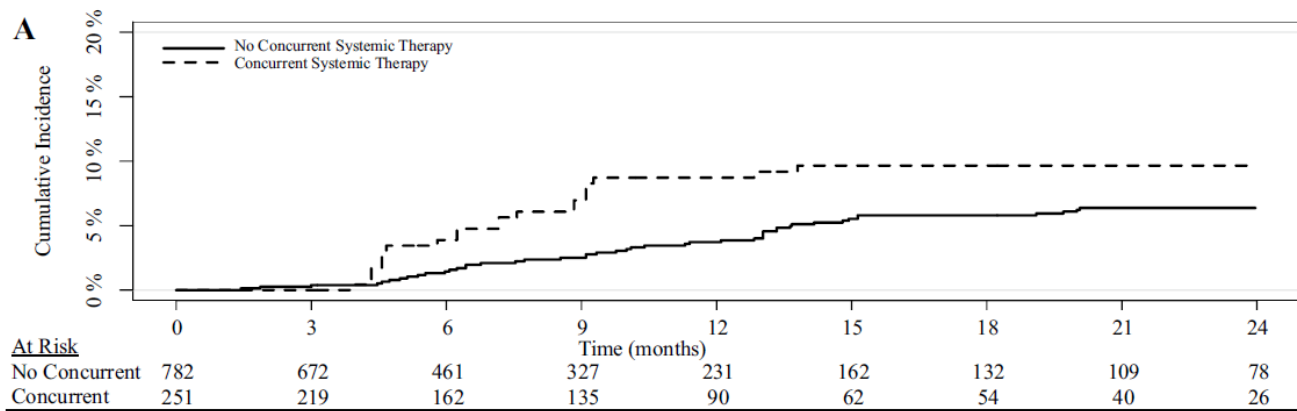
Qian Cancer 2016

- Synergistic effects of SRS & TT especially in concurrent treatment (+/- 4 weeks)

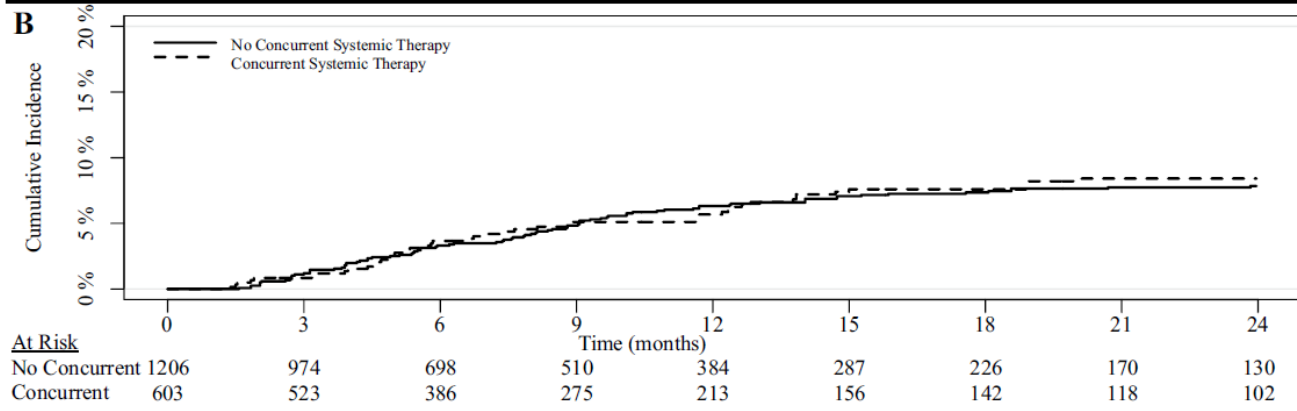
- Introduction brain metastases
- Targeted therapy as monotherapy
- Efficacy of SRS combined with Targeted therapy
- Timing of combined SRT & Targeted therapy
- **Safety of combined SRT & Targeted therapy**

N=445 patients with mostly NSCLC, treated with VEGFR-TKIs/ α -HER2/ α VEGR

**WBRT
+SRS
&TT**



**SRS
&TT**

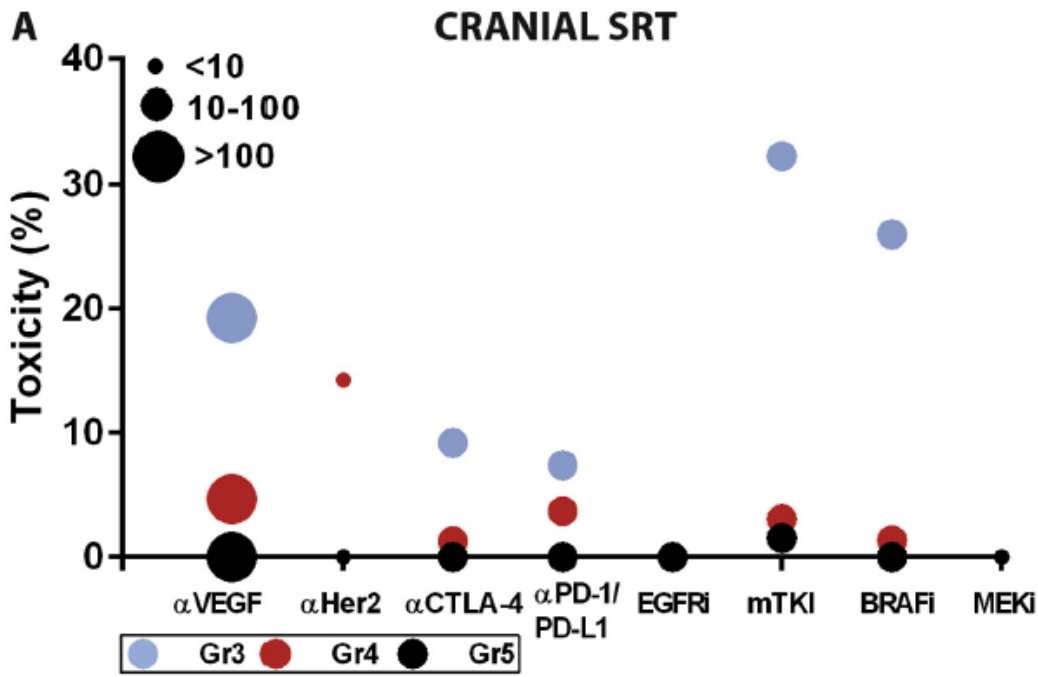


Kim, J Neurooncol 2017

➤ **Less toxicity (radionecrosis) with SRS&TT**

Safety SRS & TT

N=644 patients with BM of various histology, treated with TKIs/Immunotherapy



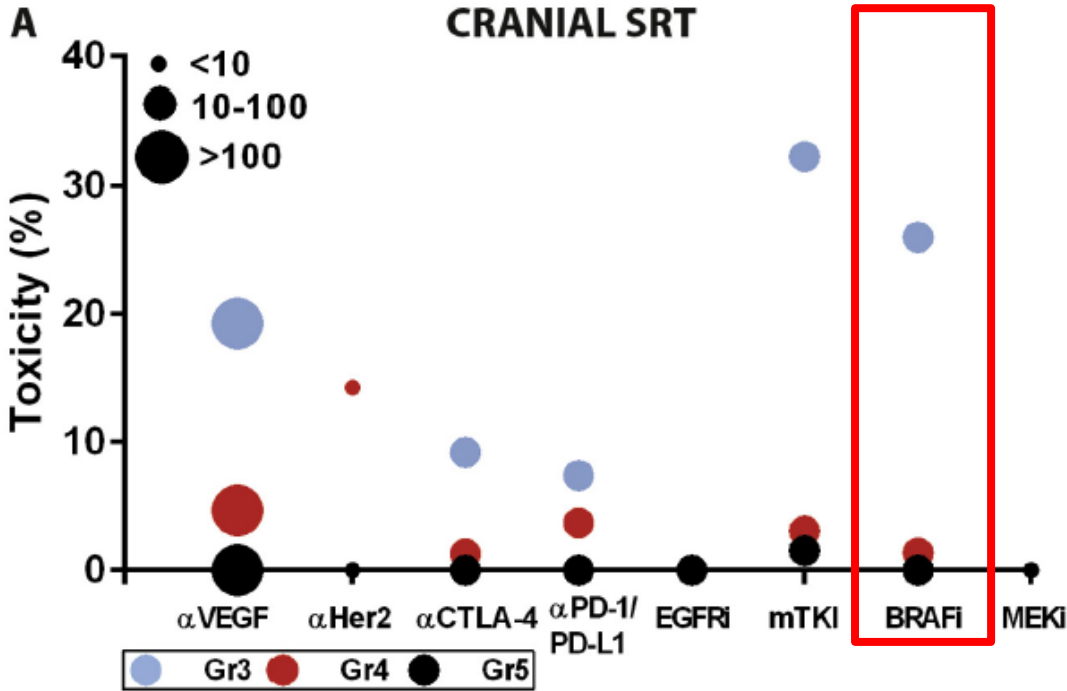
| Infield Toxicity | | |
|------------------|------|------|
| Gr 3 | Gr 4 | Gr 5 |
| 5.4% | 0.6% | 0% |

Kroeze Cancer Treat Rev 2017

- Combined SRS and TT well tolerated
- Additional risk of toxicity of SRS is low

Safety SRS & TT

N=75 patients with MBM, treated with Vemurafenib/Dabrafenib



| Severe toxicity | |
|--------------------------|-----|
| Intratumoral Haemorrhage | 15% |
| Cerebral edema | 9% |
| Headache | 3% |

Kroeze Cancer Treat Rev 2017

➤ Combination with BRAFi possible risk of cerebral haemorrhage&edema

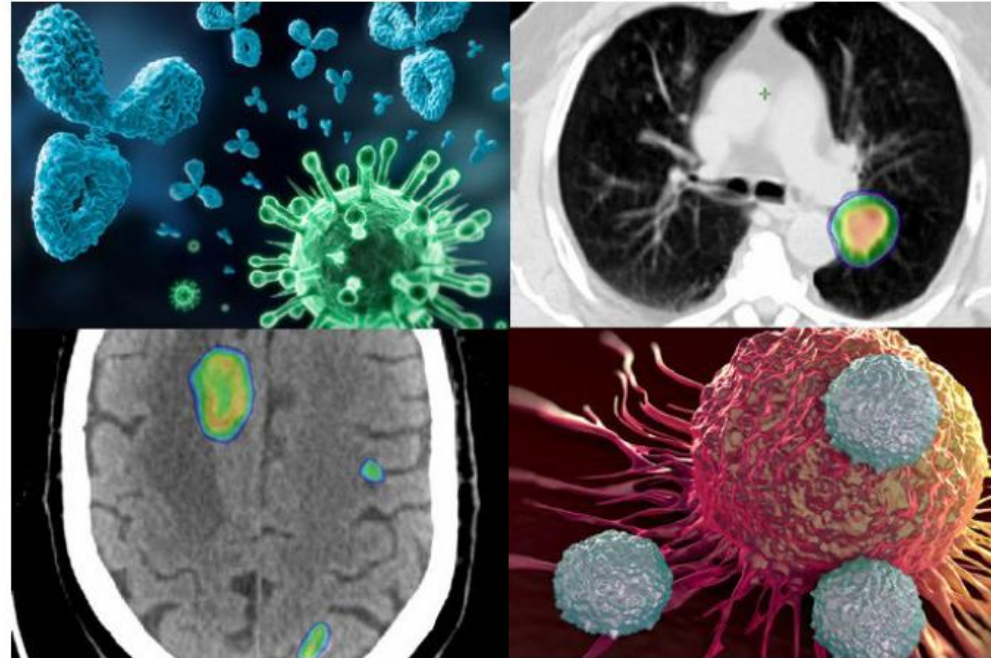
SUMMARY

- BM are frequently present and affect morbidity and mortality in metastasized patients
- TT not perfect as monotherapy for BM treatment
- Evidence for increased DBC and OS after combined treatment of SRS&TT
- SRS combined with TT appears to be safe
- Further studies to evaluate efficacy and toxicity are needed.

Thank you for your attention

.TOaSTT.

TOXICITY AND EFFICACY OF COMBINED STEREOTACTIC RADIOOTHERAPY AND SYSTEMIC TARGETED OR IMMUNE THERAPY



Contact:

- Matthias.Guckenberger@usz.ch
- Corinna.Fritz@usz.ch
- Stephanie.Kroeze@usz.ch