

Klinische Trials Neuro-oncologie

Targeted therapy en immunotherapie.



Maastricht UMC+



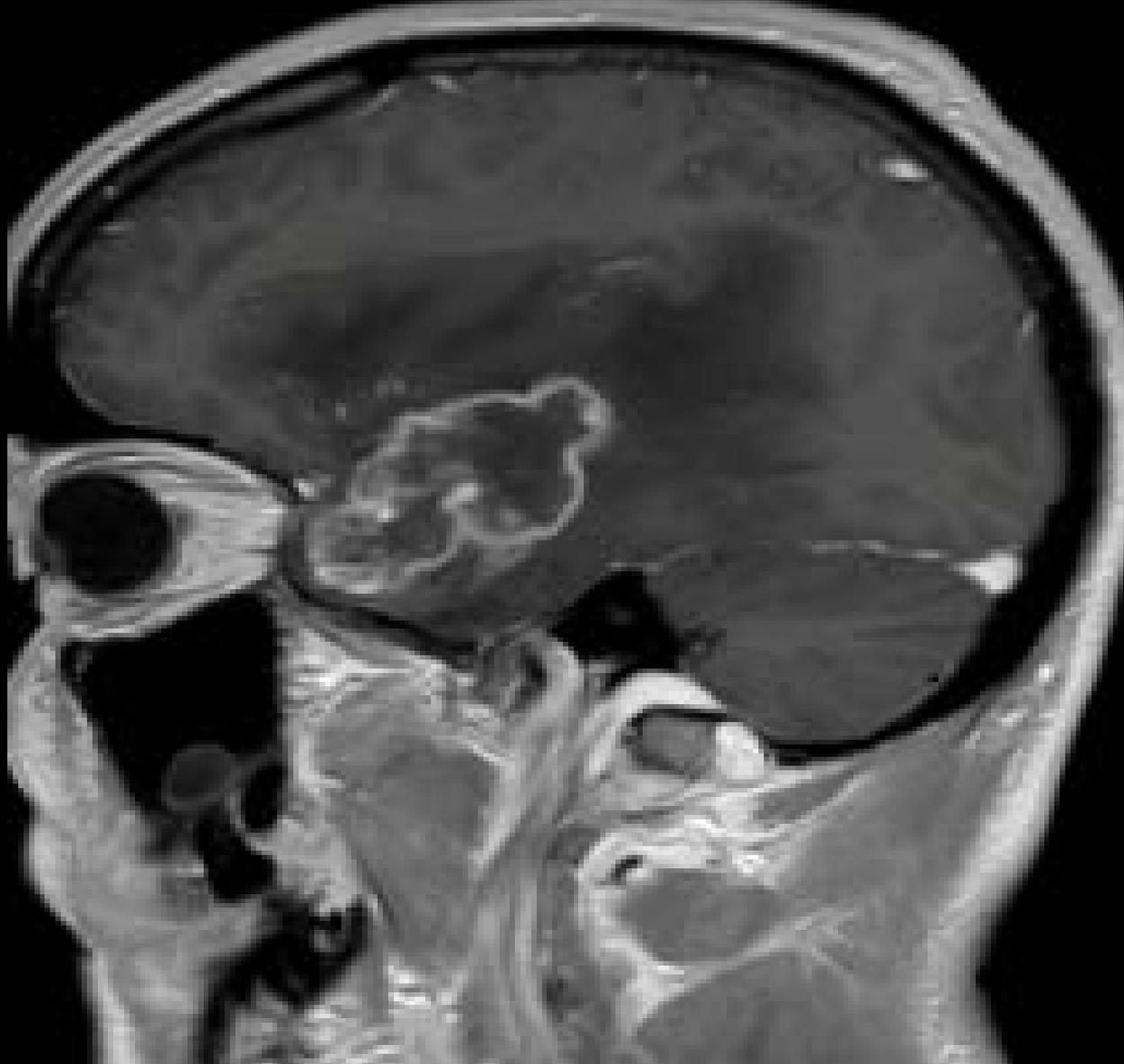
A. Hoeben, MD PhD

Internist-Oncoloog

Disclosure belangen spreker

(Potentiële) Belangenverstrengeling	Geen
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Glioblastoma



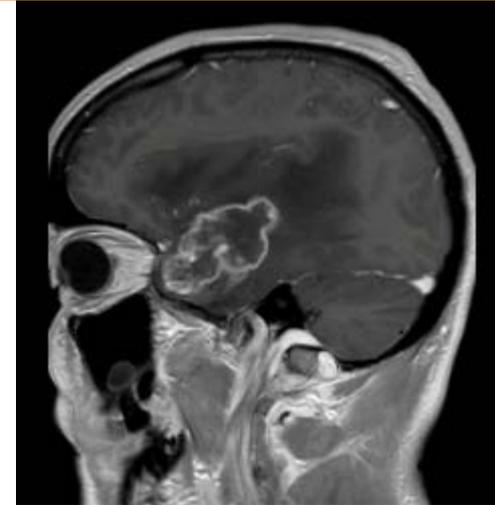
MRI T1W Gado

Content – GLIOBLASTOMA

- 1. Introduction: Standard of Care.**
- 2. Clinical Trials.**
- 3. Patient Tailored Treatments: Prognostic and Predictive Markers:
Non-Invasive Glioblastoma Testing.**
- 4. Translational en Preclinical Glioblastoma Research.**
- 5. Conclusion.**

Glioblastoma (IV): Facts.

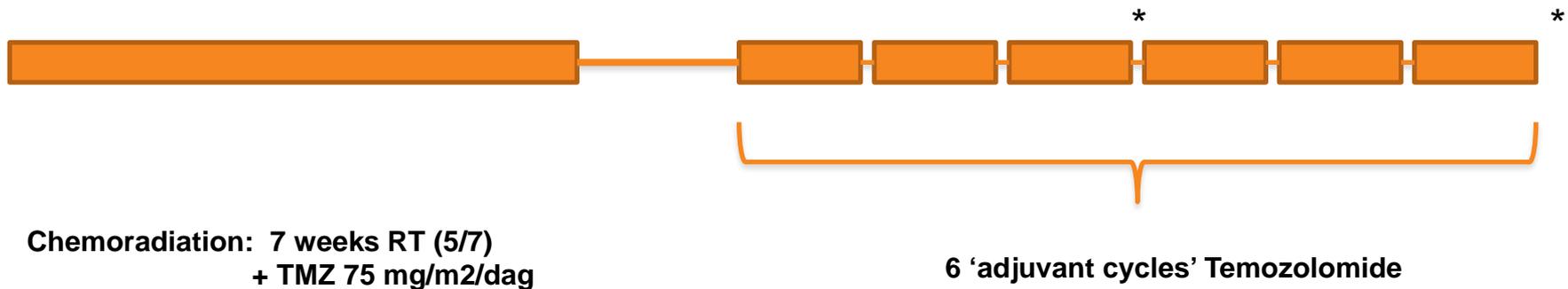
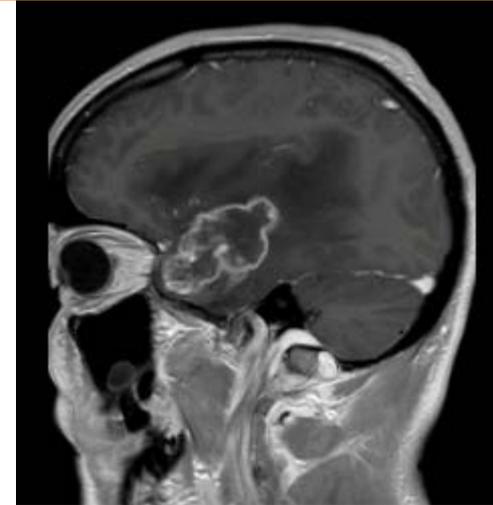
1. RARE: NL: 400-500 /year.
2. **INCURABLE**
3. DIFFERENT PROGNOSTIC SUBSETS
4. HETEROGENEOUS TUMOR

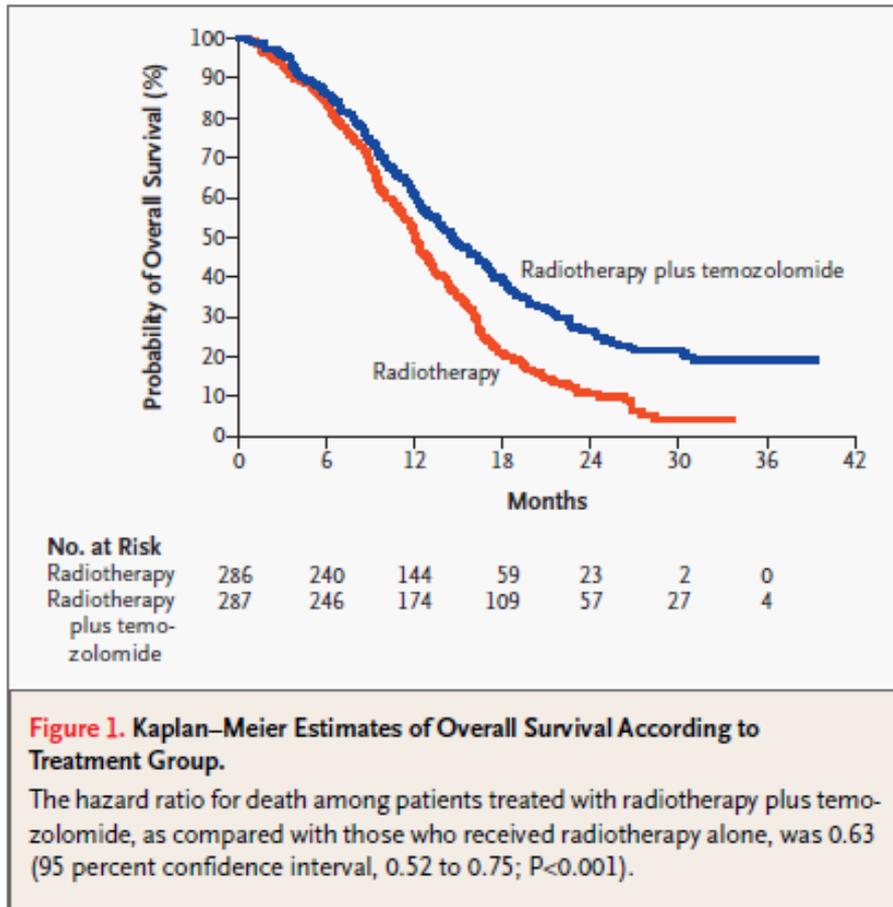


'de novo' Glioblastoma: Standard of Care

Multimodale therapie: STUPP treatment schedule.

- Debulking (survival advantage over biopsy)
- Stupp schema: RT + Temozolomide (vs RT)



**Table 3. Overall and Progression-free Survival According to Treatment Group.***

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

Median Overall Survival (mOS): 14,6 months RT+TMZ vs 12,1 months RT

Glioblastoma Recurrence

- No treatment options with survival benefit

'de novo'
Glioblastoma

Increase OS significantly
(tumor tailored)

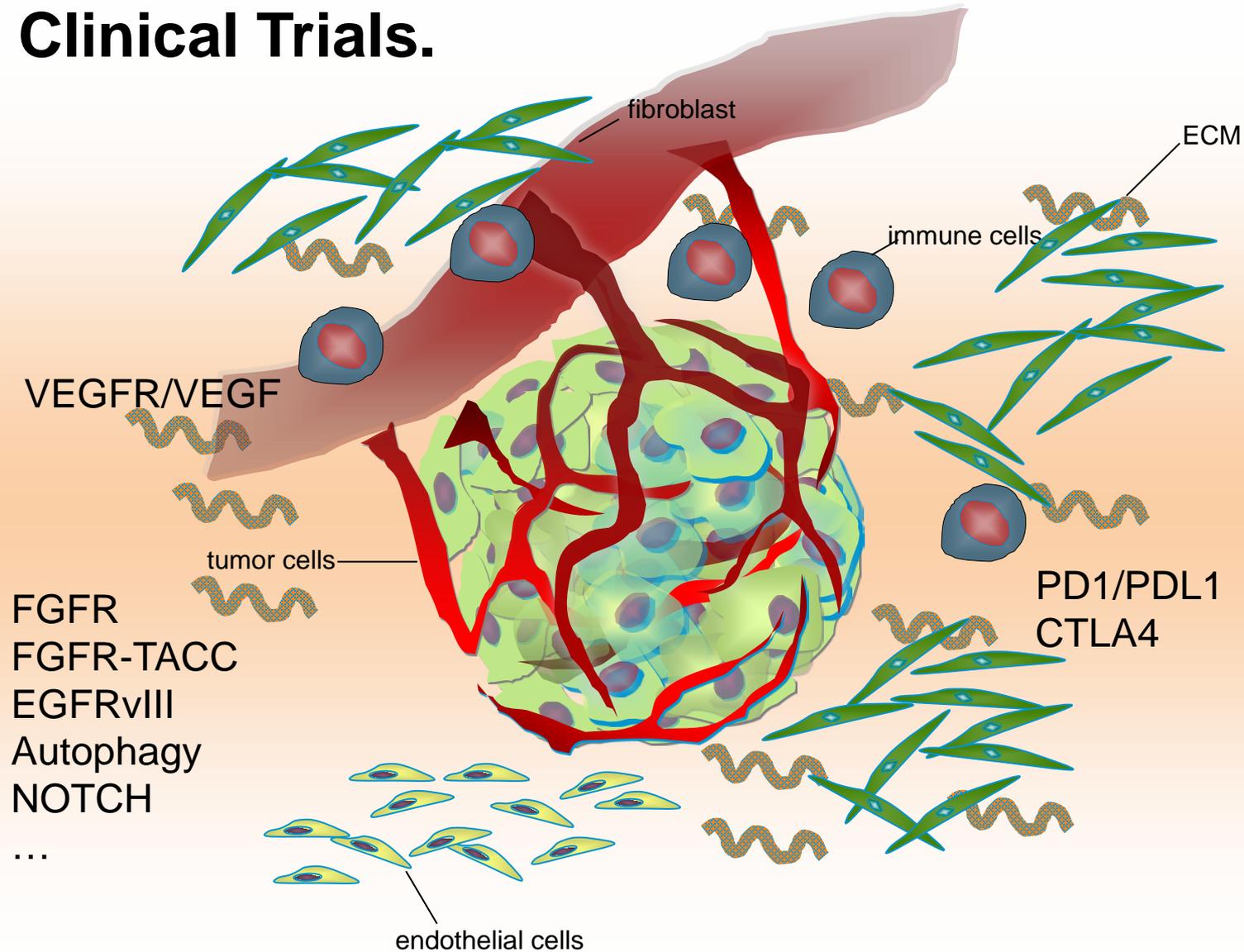
CURATION in subset GM

Recurrent
Glioblastoma

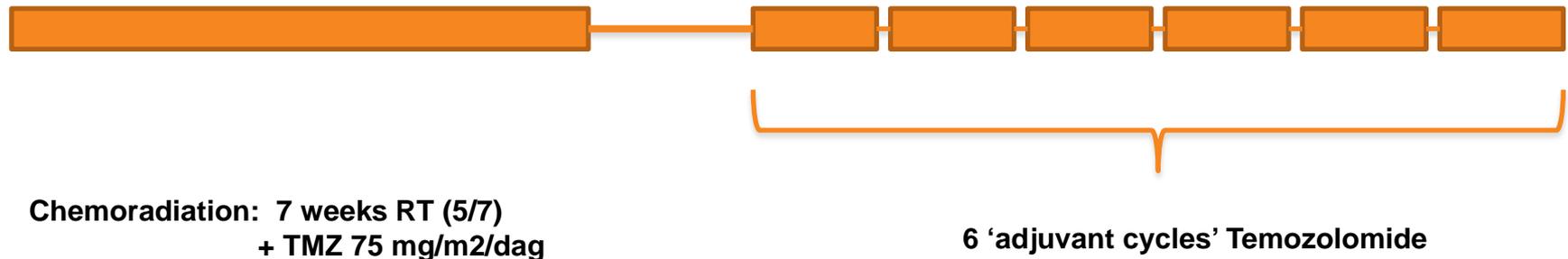
• Identify resistance to
therapy (tumor tailored)

• Increase OS significantly

2. Clinical Trials.

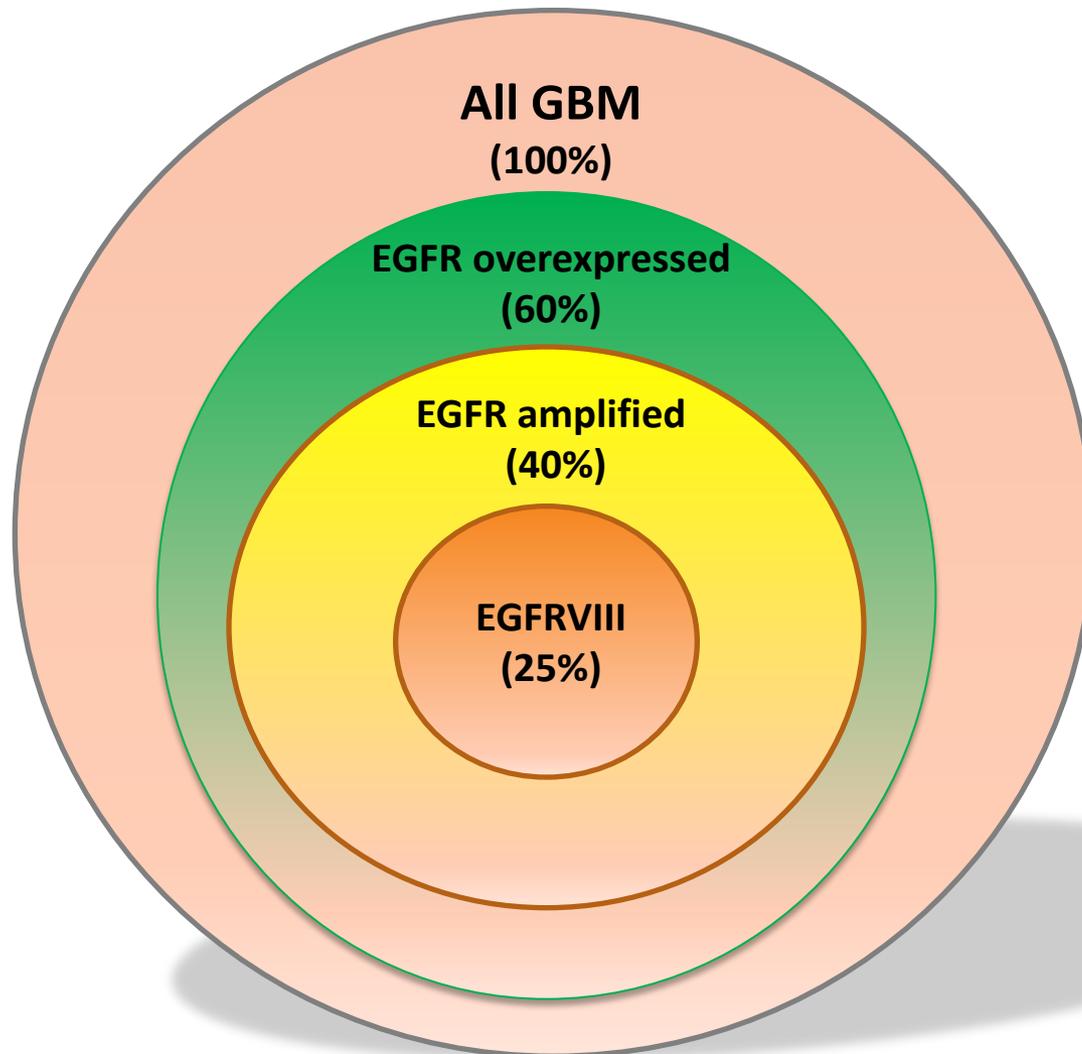


2.1 De Novo GM: 'Add-On STUPP'



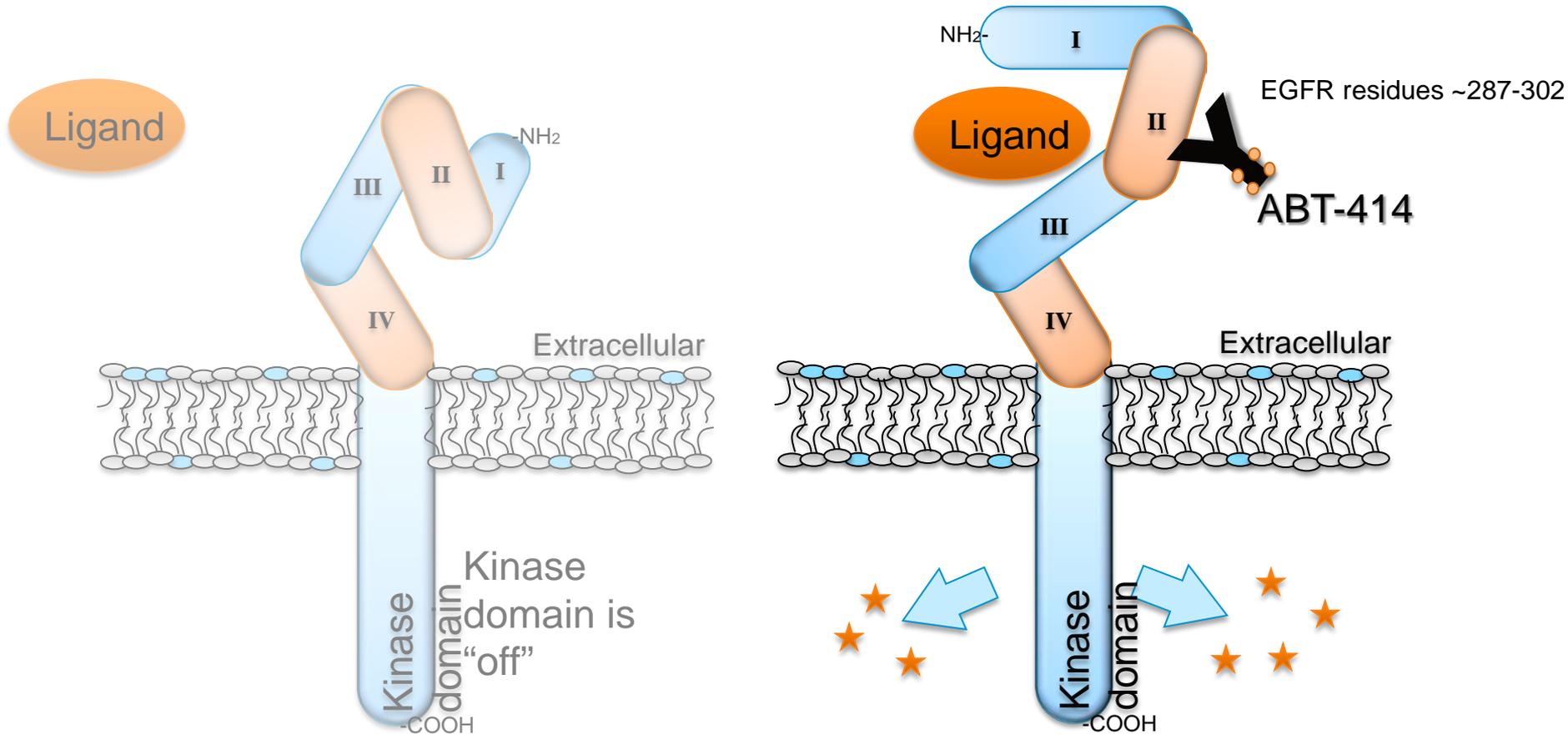
- a) ABT-414: Phase 2b/3 trial.
- b) Chloroquine: Phase 1 trial.
- c) Checkmate 498/548: Nivolumab: Phase 3 trial.
- d) Vaccination: ICT-107: Phase 2 trial.

a) ABT-414 studie: Immunotoxin.

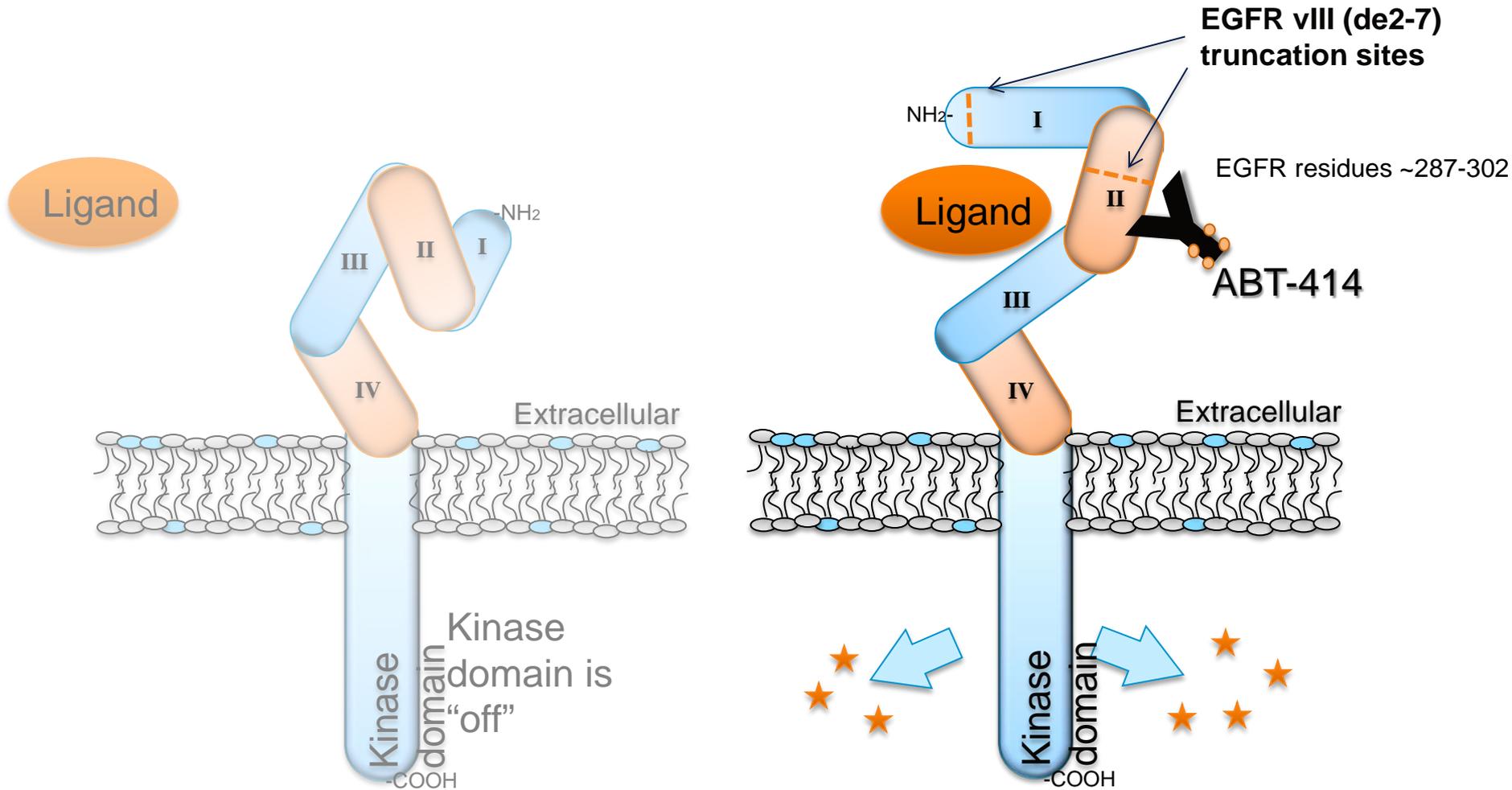


'de novo' GM harboring *EGFR* amplification

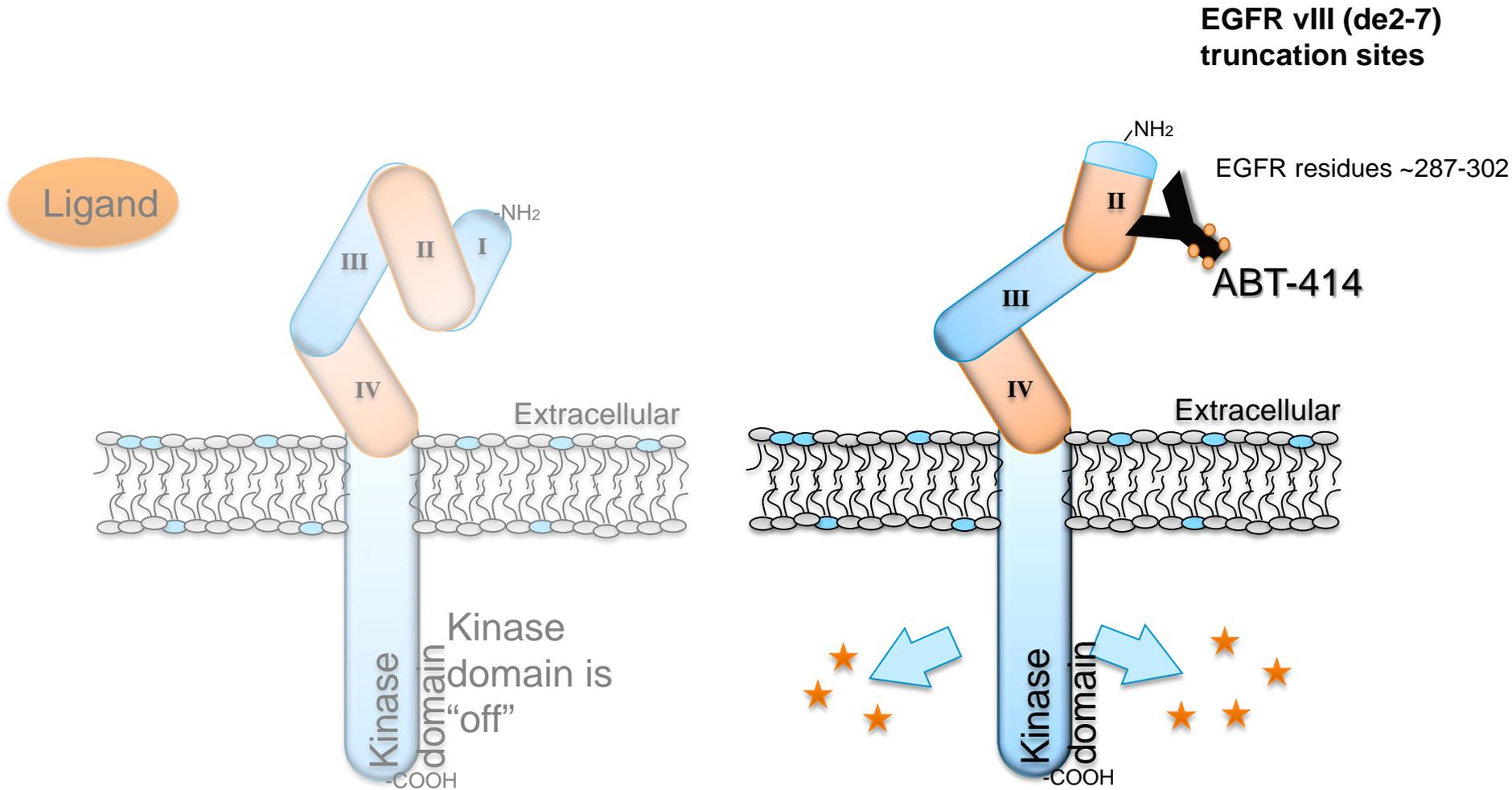
ABT-414: antibody-drug conjugate targets activated EGFR

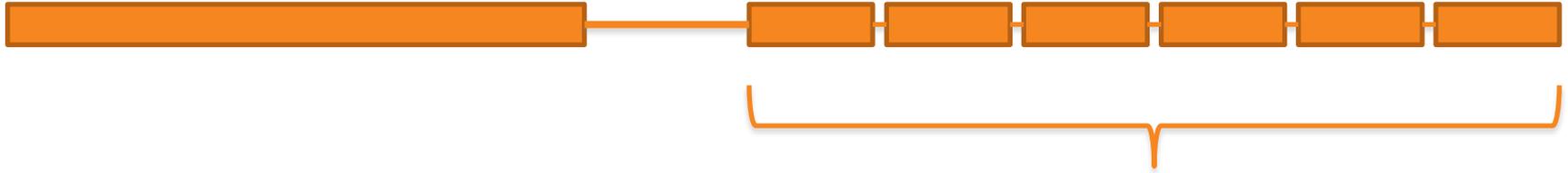


ABT-414 binds to both wild-type and EGFRvIII receptors



ABT-414 binds to both wild-type and EGFRvIII receptors

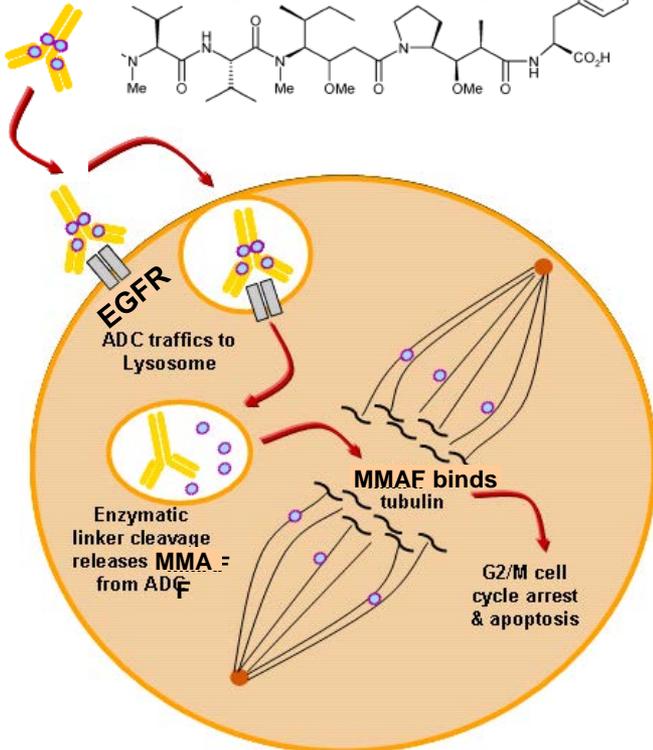




Chemoradiation: 7 weeks RT (5/7)
+ TMZ 75 mg/m²/dag

6 'adjuvant cycles' Temozolomide

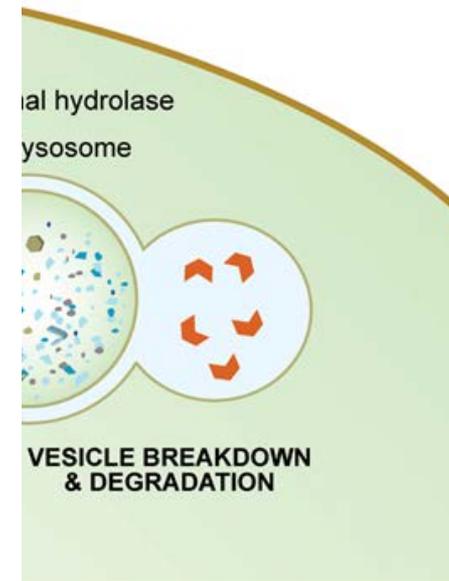
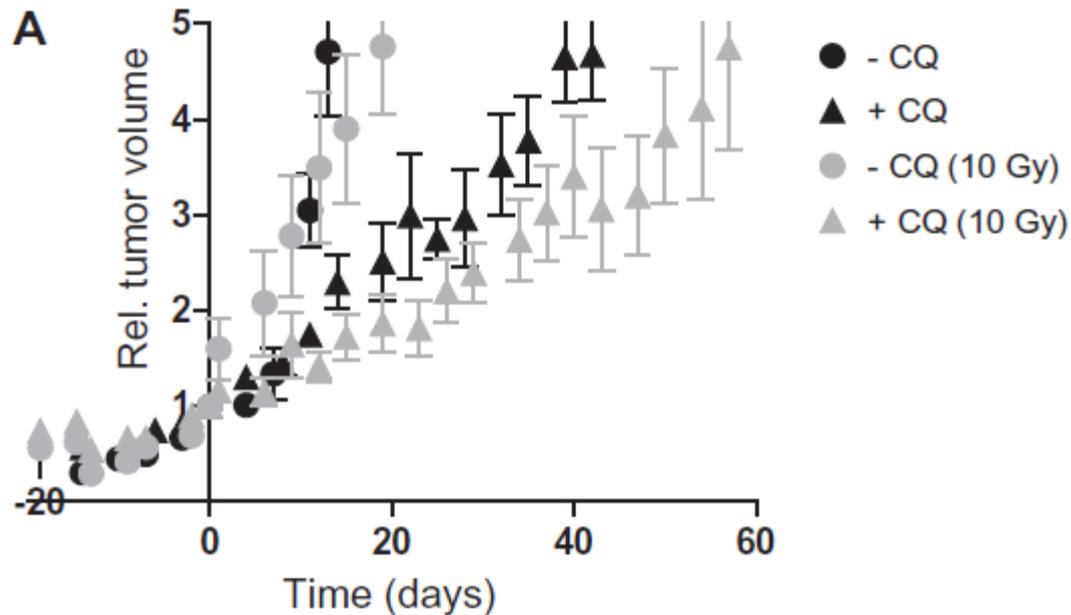
Monomethylauristatin F (MMAF)



Primary endpoints:

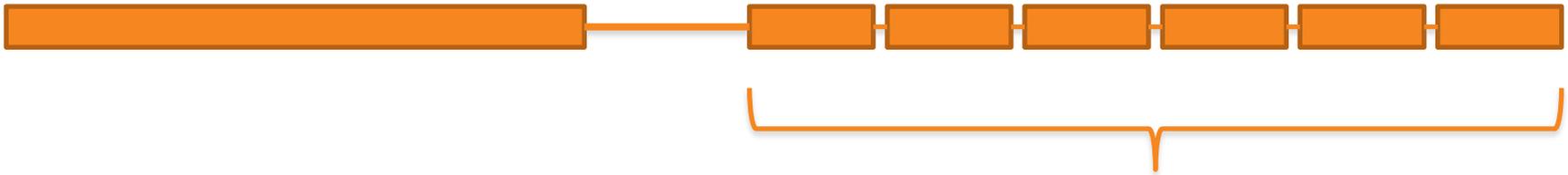
- Phase 2b: PFS
- Phase 3: OS

b) Chloroquine: autophagy inhibitor.



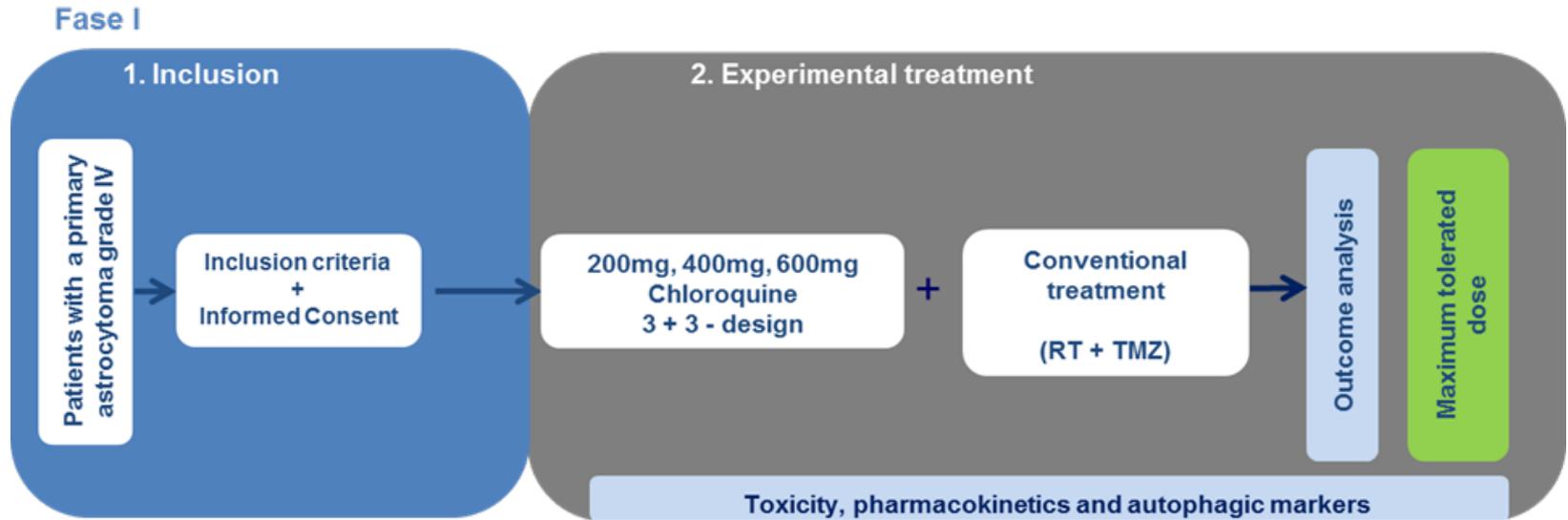
Jutten et al. Radiat Oncol., 2013, 108, 479-483

b) Chloroquine: autophagy inhibitor.

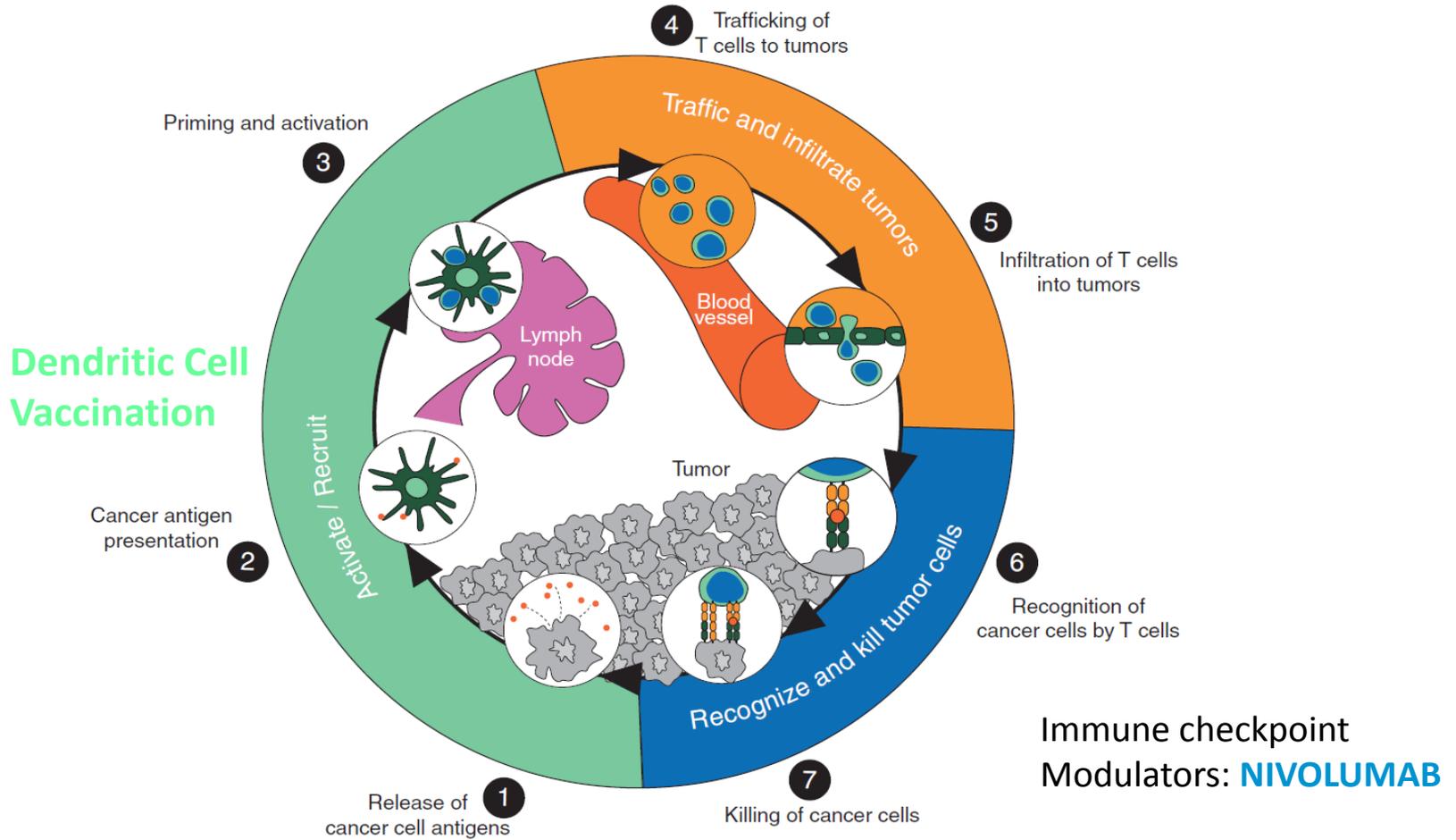


Chemoradiation: 7 weeks RT (5/7)
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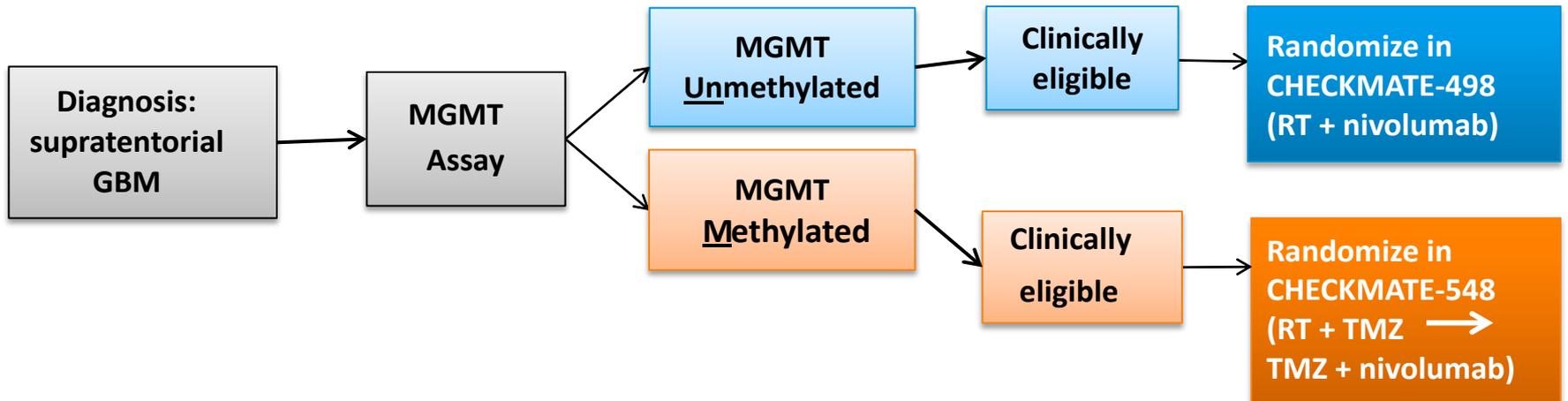
6 'adjuvant cycles' Temozolomide



c) Modulation Immune System.

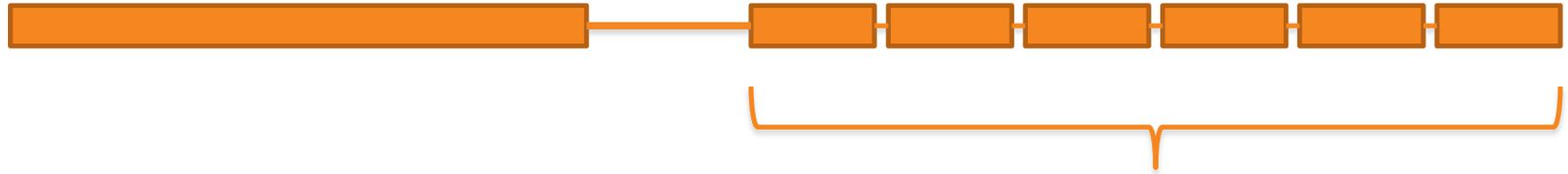


Immune checkpoint modulation: Checkmate 498/548: NIVOLUMAB



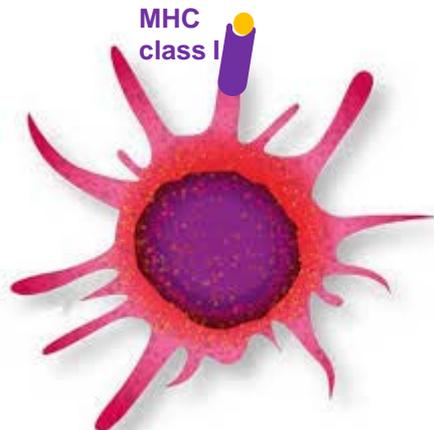
Time from surgery to start RT ≤ 42 days

Vaccinatie: ICT-107



Chemoradiation: 7 weeks RT (5/7)
+ TMZ 75 mg/m²/dag

6 'adjuvant cycles' Temozolomide



6 Antigen epitopes

- MAGE-1
- AIM-2
- Gp100
- IL-13Rα2
- Her2/neu
- TRO-2



DENDRITIC CELL VACCIN



Mature, peptide loaded dendritic cell

2.2 Recurrent GM

DRUP: Drug Rediscovery Protocol

Fresh frozen tumor biopsy

HARTWIG MEDICAL FOUNDATION:
Center for personalized Treatment's Core Sequencing Facility

DRUP Tumor Board
Oncogen; target available compound?

yes

INCLUSION

no

Standard of Care/other trial

DRUP: Drugs.

Already available:

Pembrolizumab, Nivolumab: anti-PD1

Regorafenib: multi TKI (VEGFR, KIT, BRAF, RET, PDGFR, FGFR)

Vismodegib: Hedgehog

Vemurafenib + Combimetinib: BRAF + MEK

Trastuzumab + Pertuzumab: HER2

Panitumumab/Erlotinib: EGFR

Olaparib: BRCA

3. Patient/Tumor Tailored Treatments.

Glioblastoma: Standard of Care

PROGNOSTIC MARKERS

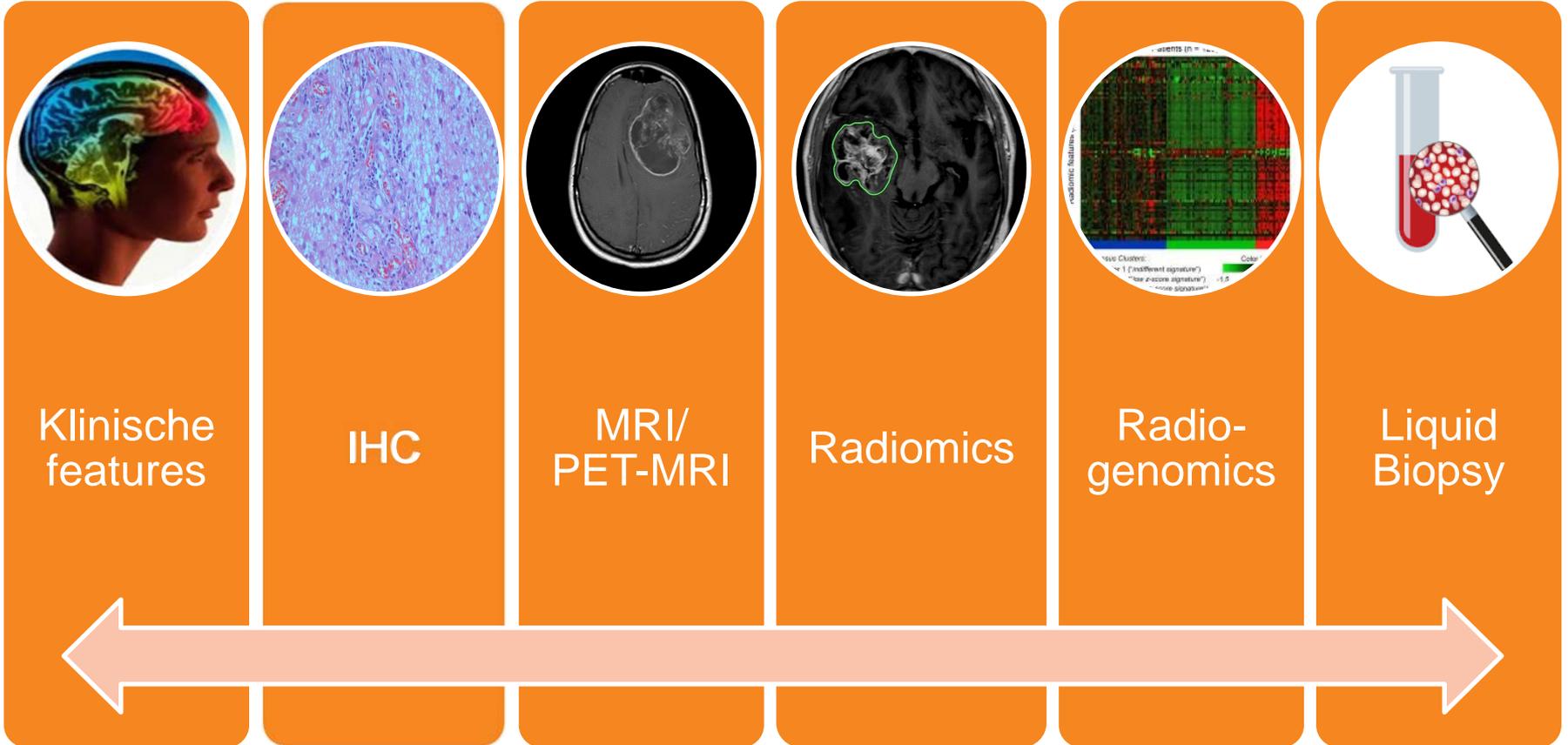
- IDH1

**NO TREATMENT CONSEQUENCE
(NON-ELDERLY)**

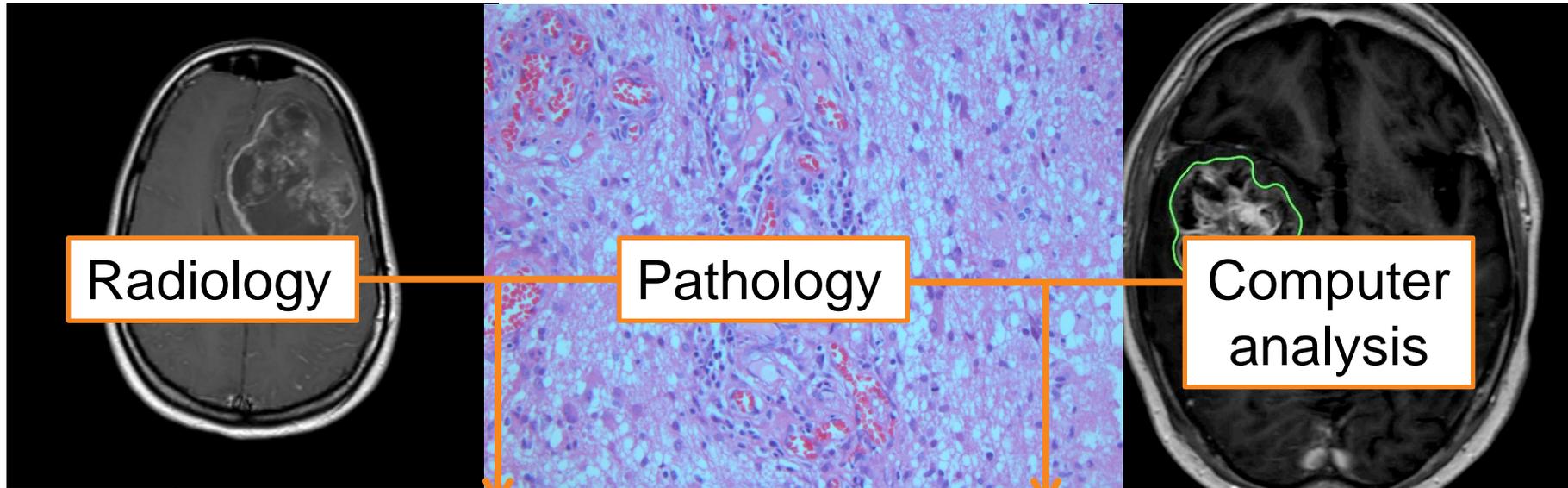
PREDICTIVE MARKERS

- MGMT promoter methylation

Platform of independent prognostic/predictive markers



Patient/Tumor Tailored Treatment



Radiology

Pathology

Computer analysis

edema
- Multifoc
- ..

Radiogenomics

(GSC)
molecul

Radiomics

Shapes

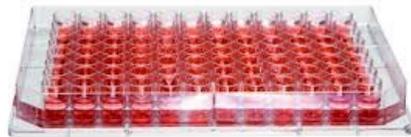
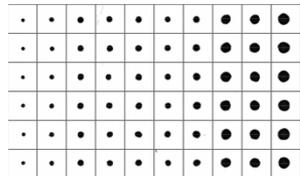
Liquid Biopsy
Biomarker profiles?

NON-INVASIVE GLIOBLASTOMA TESTING

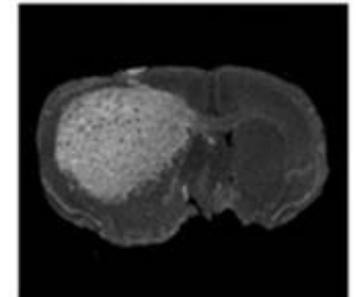
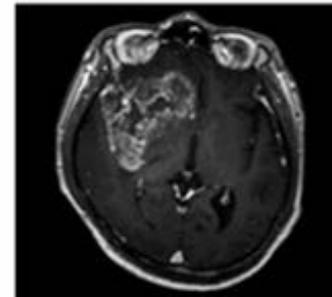
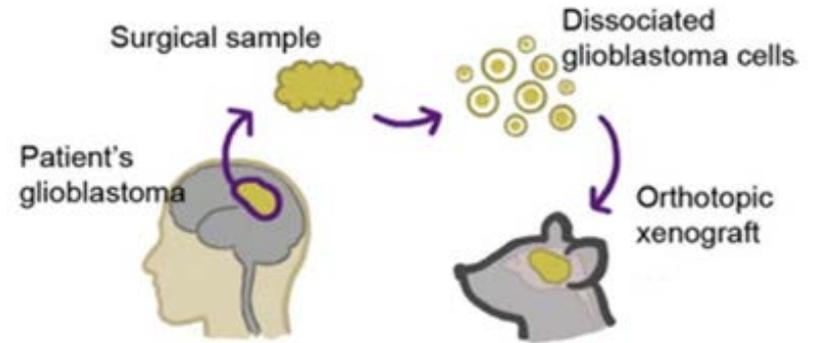
4. Translational and Preclinical Research.

IGLO: IMPROVING GLIOMA OUTCOME

in vitro platform



in vivo platform



Prof. Dr. Vooijs – MAASTRO lab
 Prof. Dr. Verhaegen – MAASTRO lab

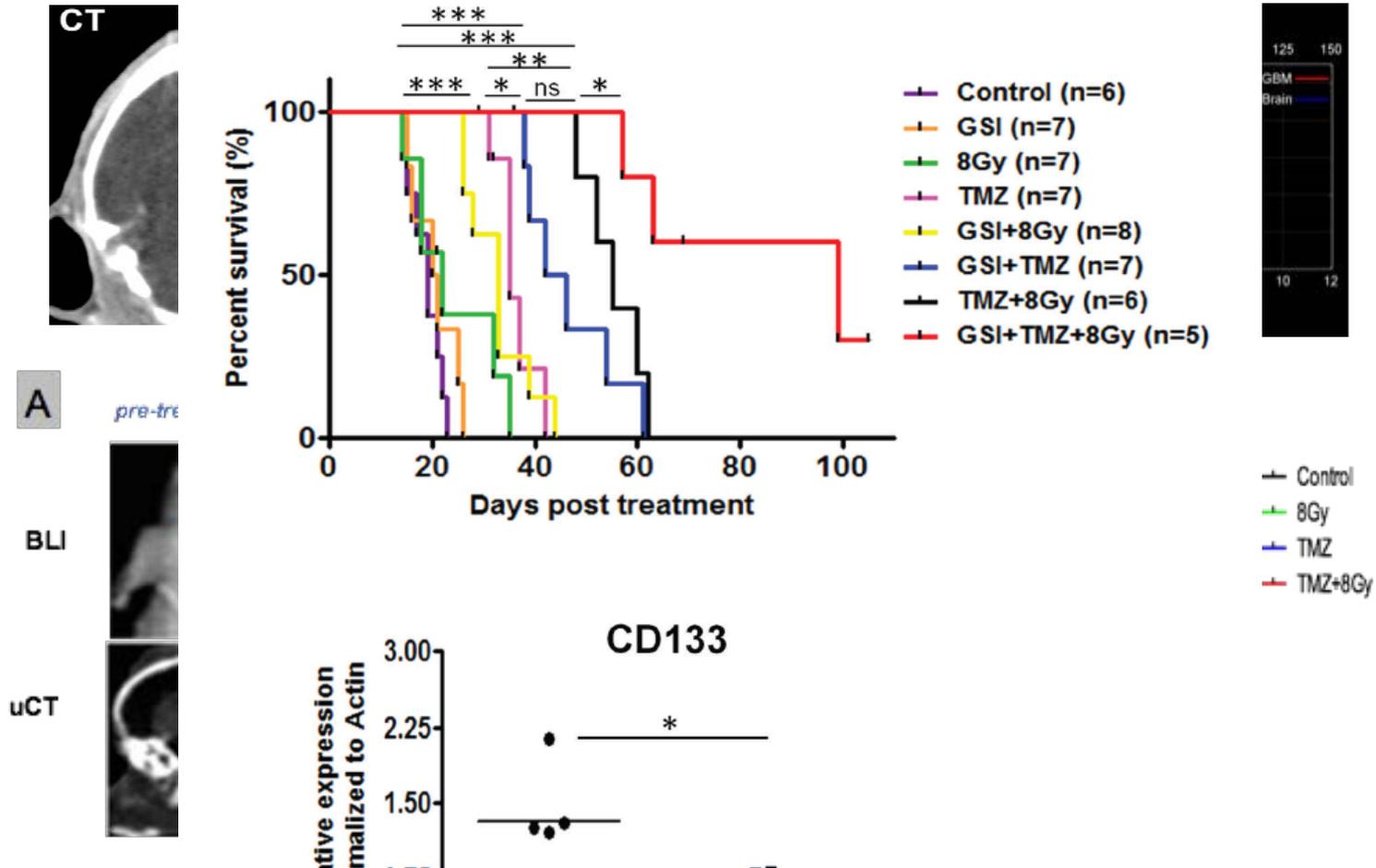
Maastricht UMC+



School for Oncology and Developmental Biology



Orthotopic Glioblastoma Model



- Preclinical rationale for new treatments.
- Identify essential druggable targets for TMZ resistance.

CONCLUSION: Development Clinical Trials Glioblastoma.

