CXCL12 inhibition in MGMT unmethylated glioblastoma – Results of an early proof-of-concept assessment in the multicentric phase I/II GLORIA trial (NCT04121455)

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Disclosures

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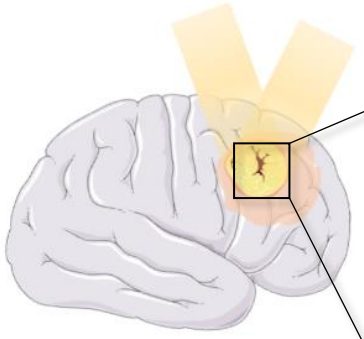
Background and rationale



Radiotherapy

↓

Hypoxia

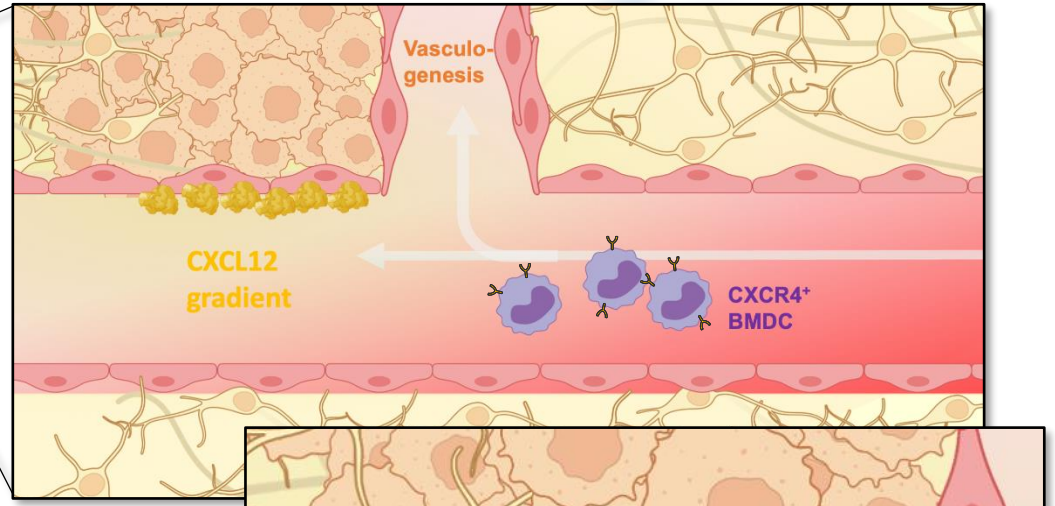
CXCL12 ↑

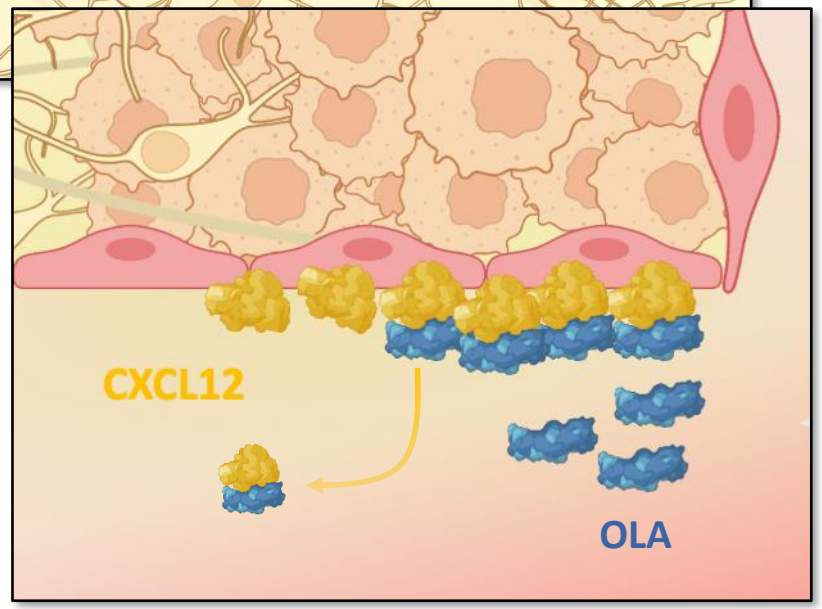
↓

Vasculogenesis | Immunosup-pressive TME

↓

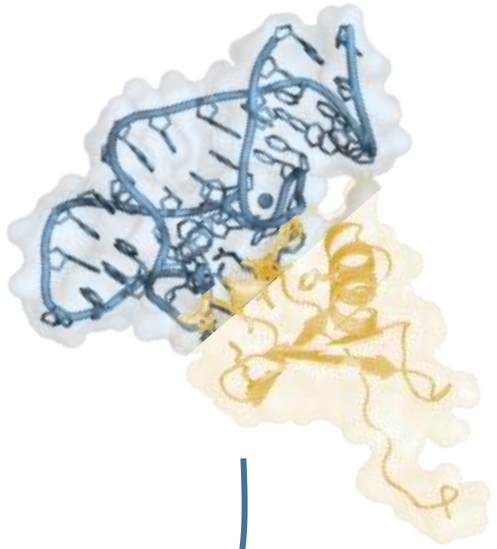
Tumor recurrence





Olaptesed pegol (OLA, NOX-A12)

RNA Spiegelmer (L-stereoisomer)



binds & neutralizes CXCL12

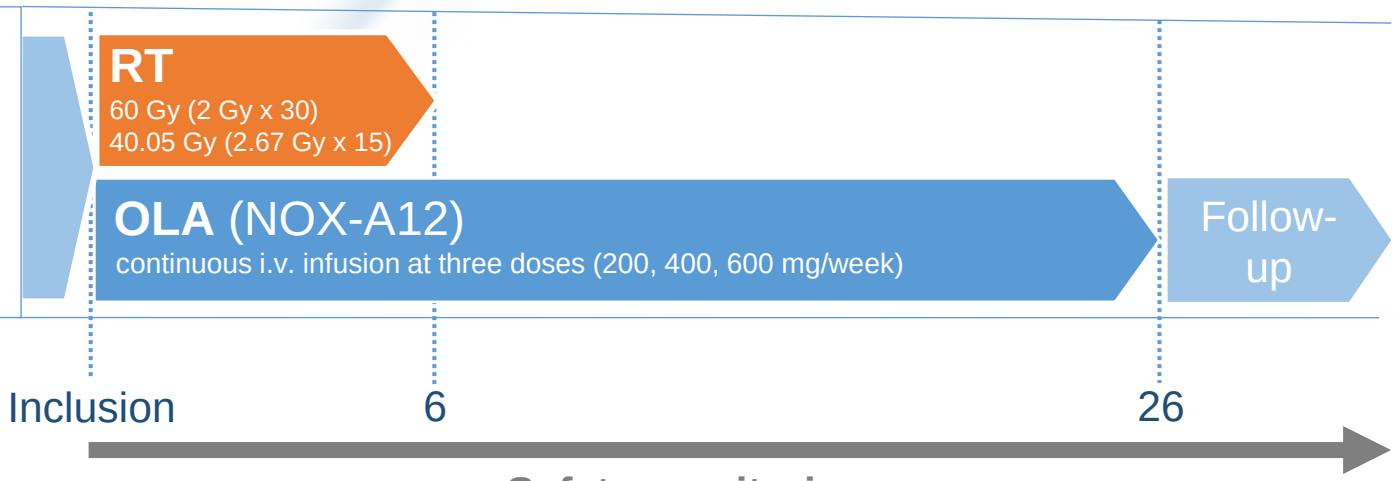
Ceradini, **Nat Med** 2004
Greenfield, **J Clin Invest.** 2010
Kioi, **J Clin Invest.** 2010
Liu, **Neuro Oncol.** 2014

CXCR4, C-X-C Motif Chemokine Receptor 4 (receptor for CXCL12)
BMDC, bone marrow derived cells
TME, tumor microenvironment

GLORIA Phase I/II Trial

Key inclusion criteria:

- Newly-diagnosed supratentorial glioblastoma WHO IV
- unmethylated MGMT promoter
- Incomplete resection/biopsy only
- ECOG ≤ 2



Safety monitoring
Advanced MRI (perfusion/diffusion)
CODEX® (multiplexed immunofluorescence imaging)

Primary Endpoint: Safety as per # of patients with treatment-related adverse events

Secondary Endpoints: OLA/NOX-A12 plasma levels, tumor vascularization/perfusion (advanced MRI), PFS-6, mPFS, OS, QoL, NANO

CONSORT of GLORIA and controls

GLORIA

11 screened

2 excluded

9 enrolled

3 cohort 1	RT + **200 mg**/week OLA
3 cohort 2	RT + **400 mg**/week OLA
3 cohort 3	RT + **600 mg**/week OLA

9 advanced MRI

1 CODEX*

Matched Imaging Control Cohort**

25 screened

12 no advanced MRI

13 advanced MRI

7 CODEX*

21 no paired samples

28 screened

CODEX Control Cohort

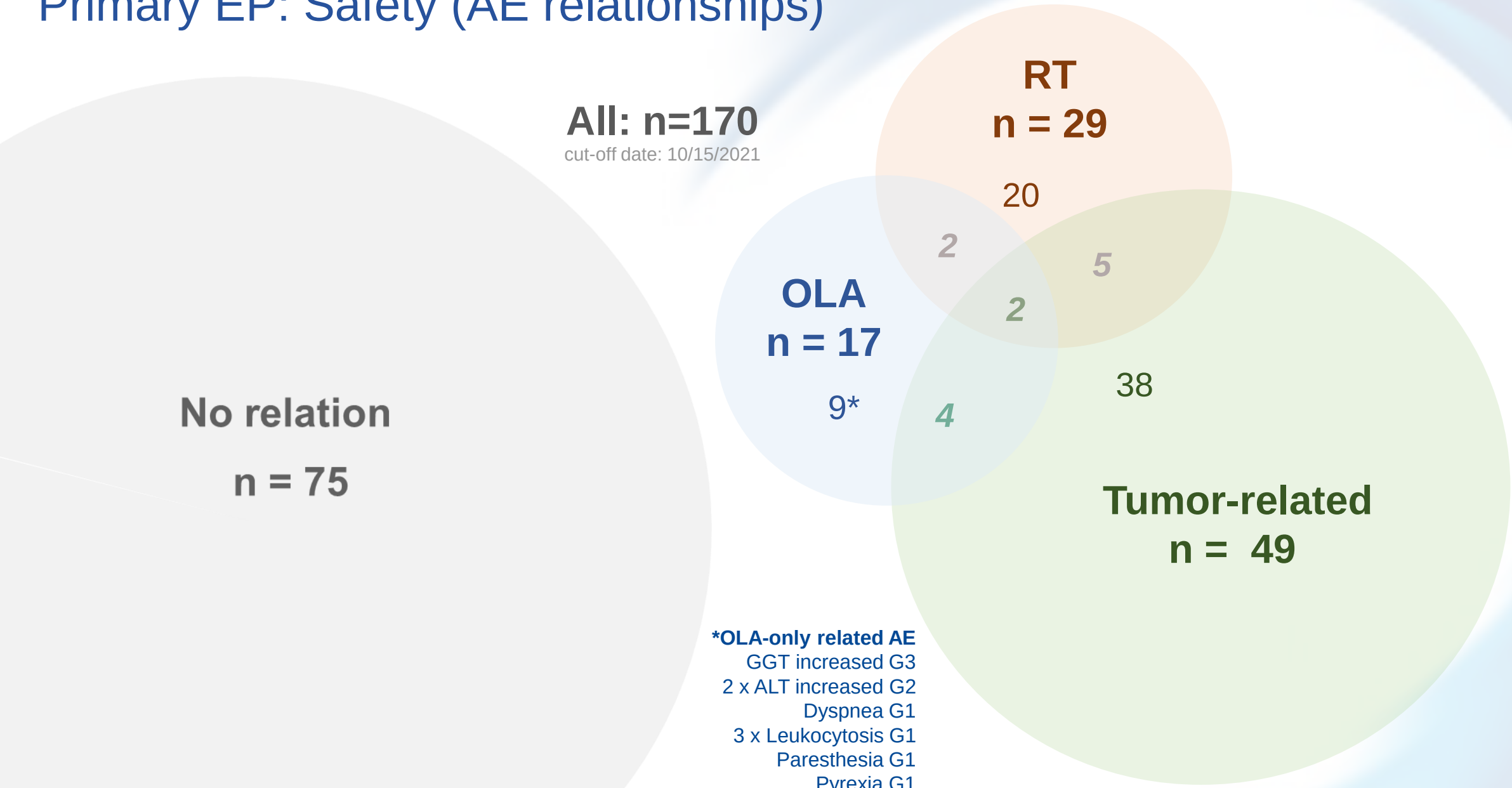
* Only performed for paired samples from 1st and 2nd surgery.

** Matched per MGMT promoter methylation status and extent of resection. Patients in the control cohort needed to have at least 3 consecutive scans.

Primary EP: Safety (AE relationships)

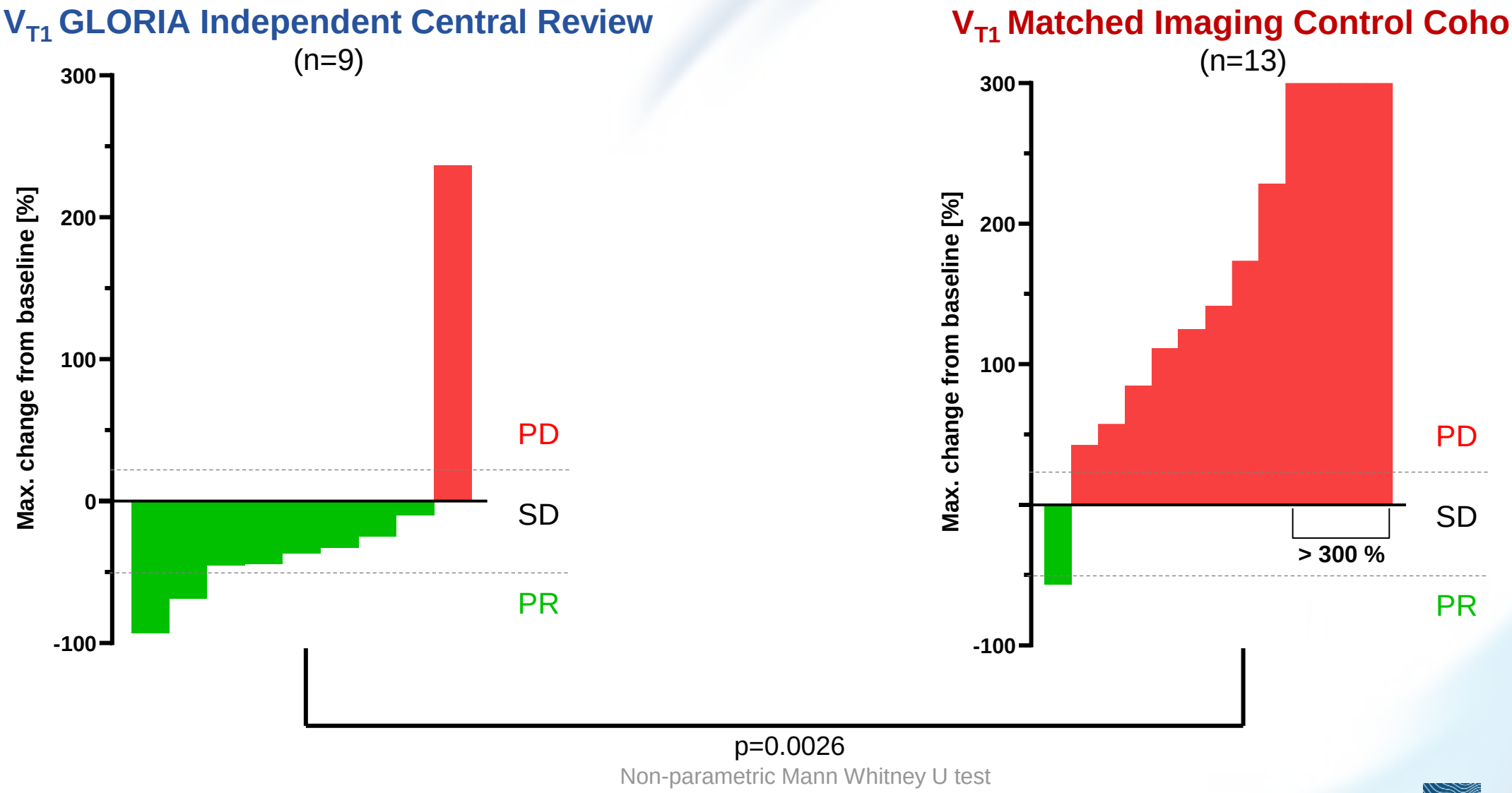
All: n=170

cut-off date: 10/15/2021



***OLA-only related AE**
GGT increased G3
2 x ALT increased G2
Dyspnea G1
3 x Leukocytosis G1
Paresthesia G1
Pyrexia G1

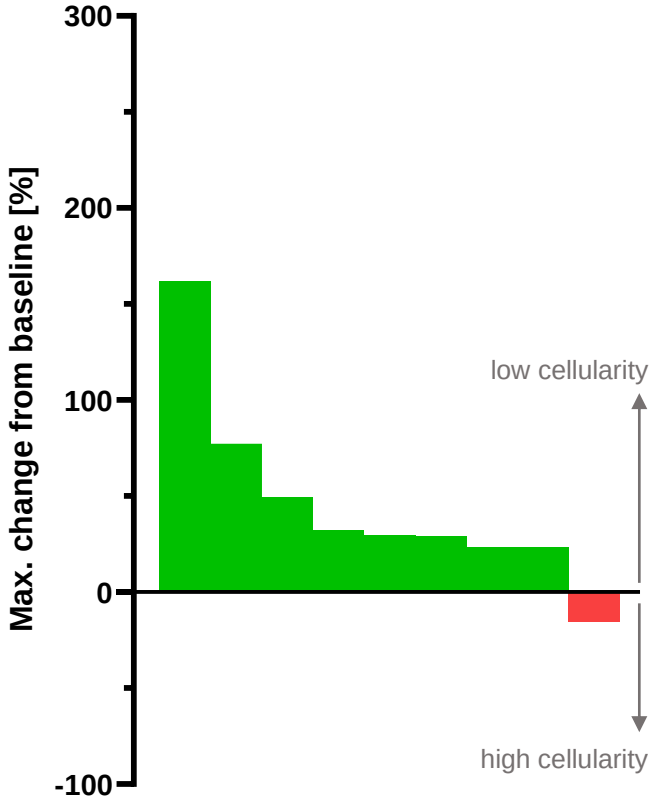
Best response under OLA (volume of T1 enhancing lesions)



Best response in cellularity and tumor perfusion under OLA

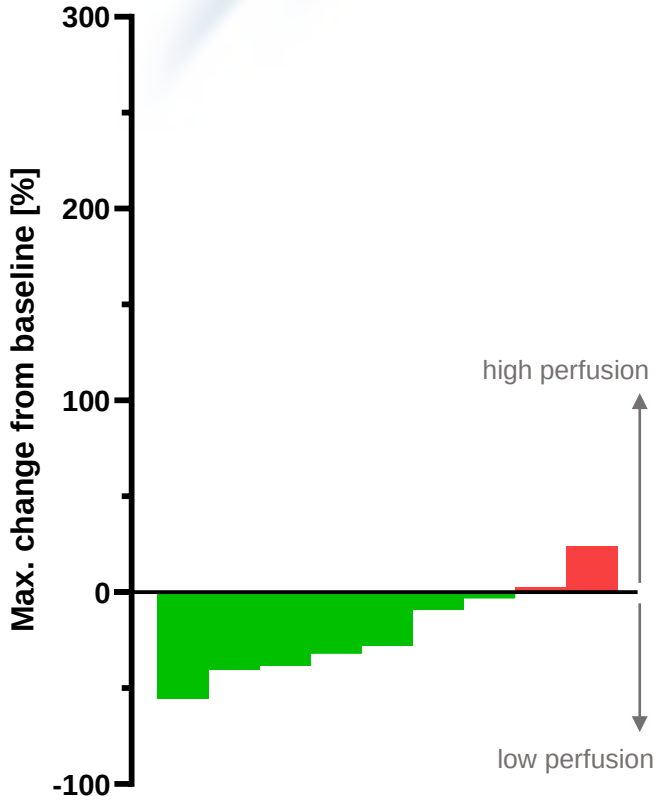
ADC mean

(Independent Central Review, n=9)



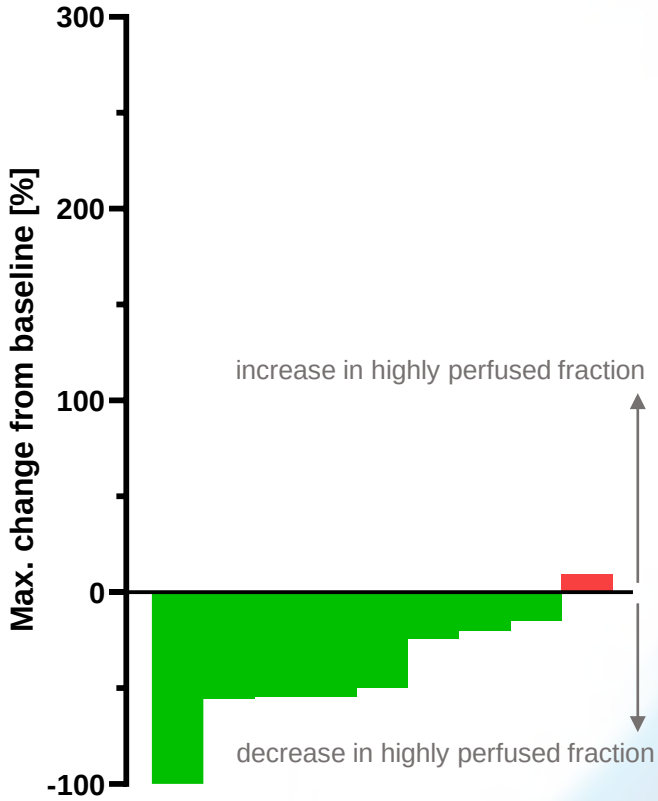
rCBV mean

(Independent Central Review, n=9)



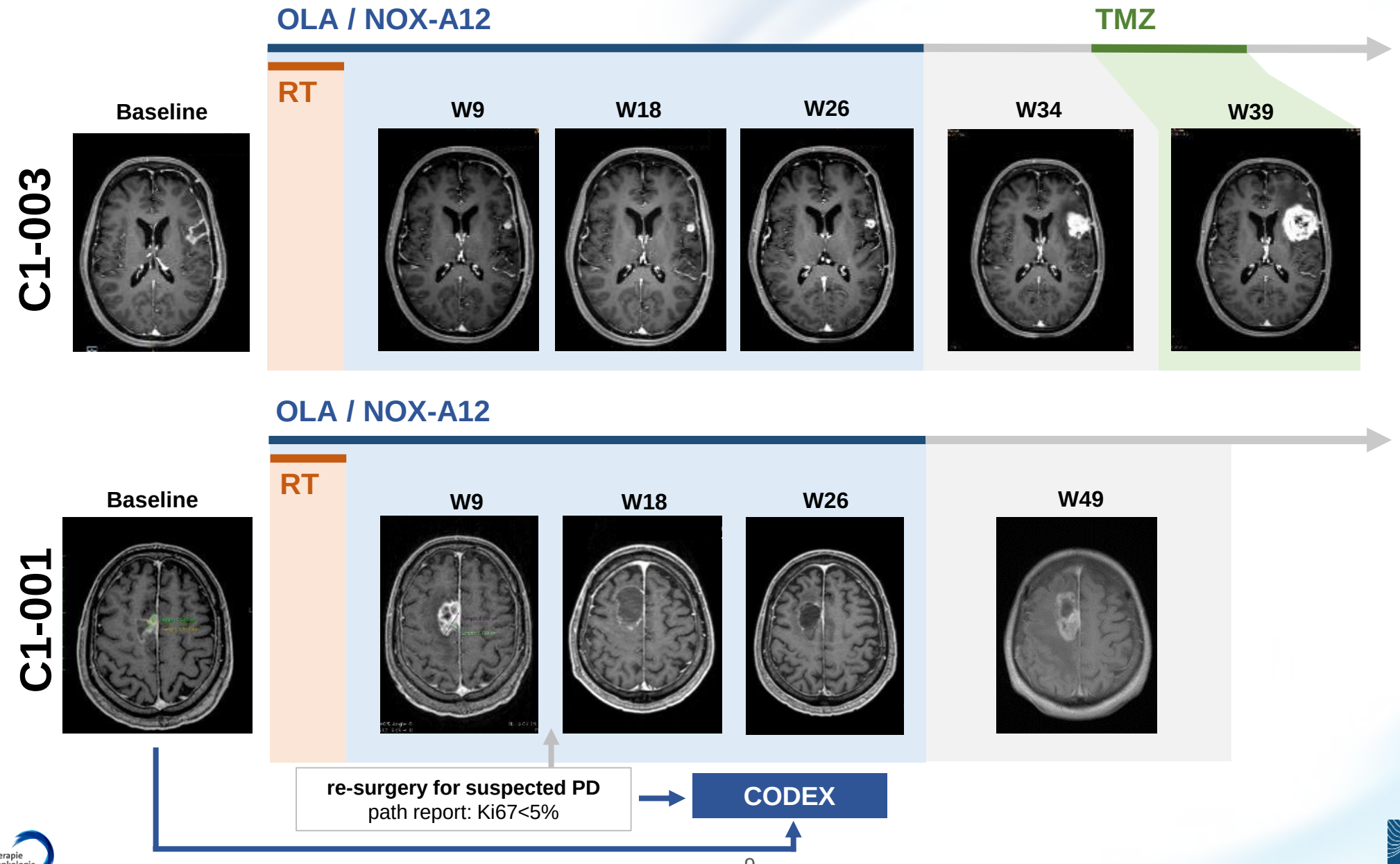
FTB^{high}

(Independent Central Review, n=9)



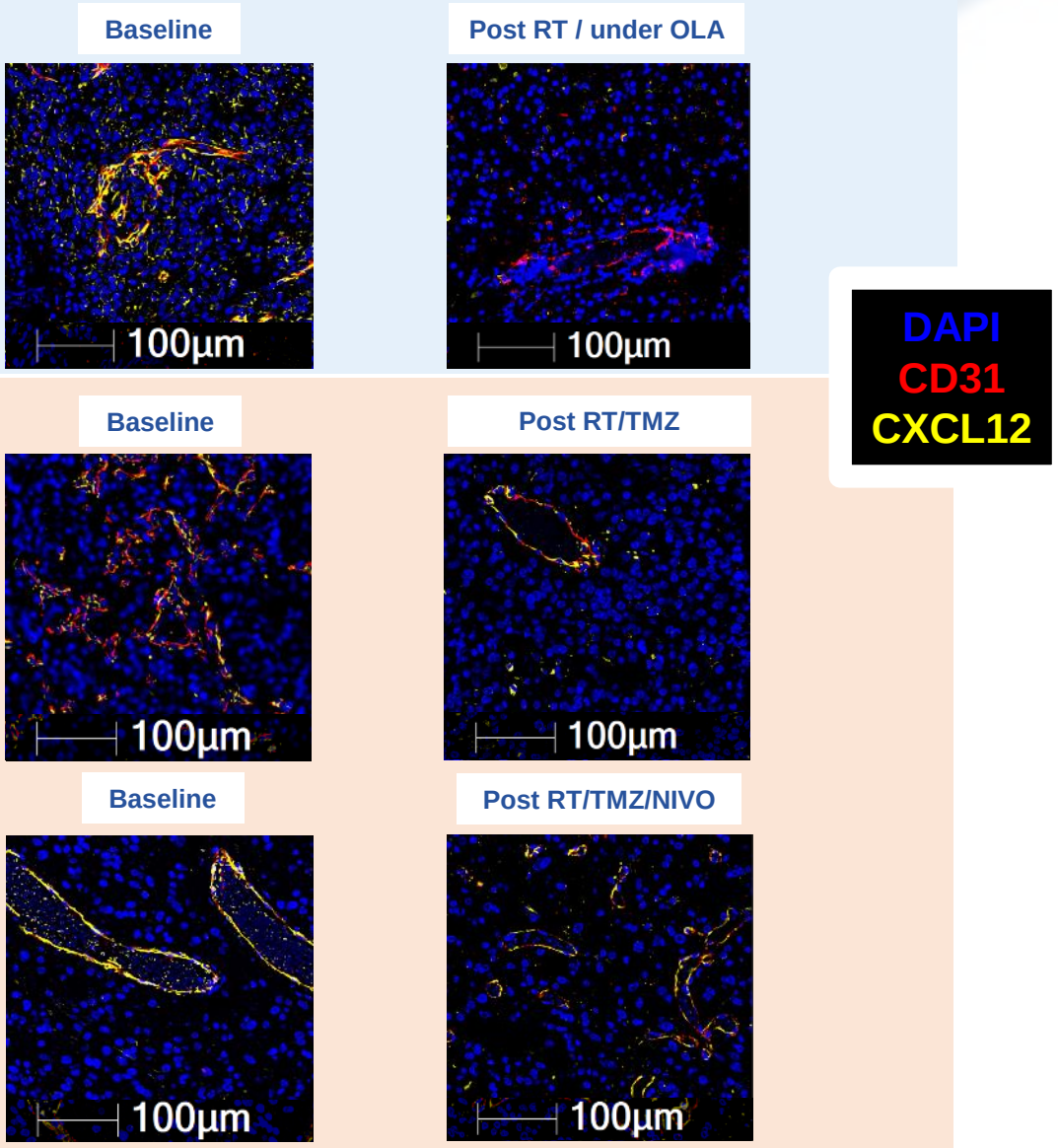
ADC, apparent diffusion coefficient (derived parameter from DWI sequences)
rCBV, standardized relative cerebral blood volume (derived parameter from DSC sequences)
FTB^{high} , fractional tumor burden with rCBV > 1.75

Exemplary response to RT/OLA

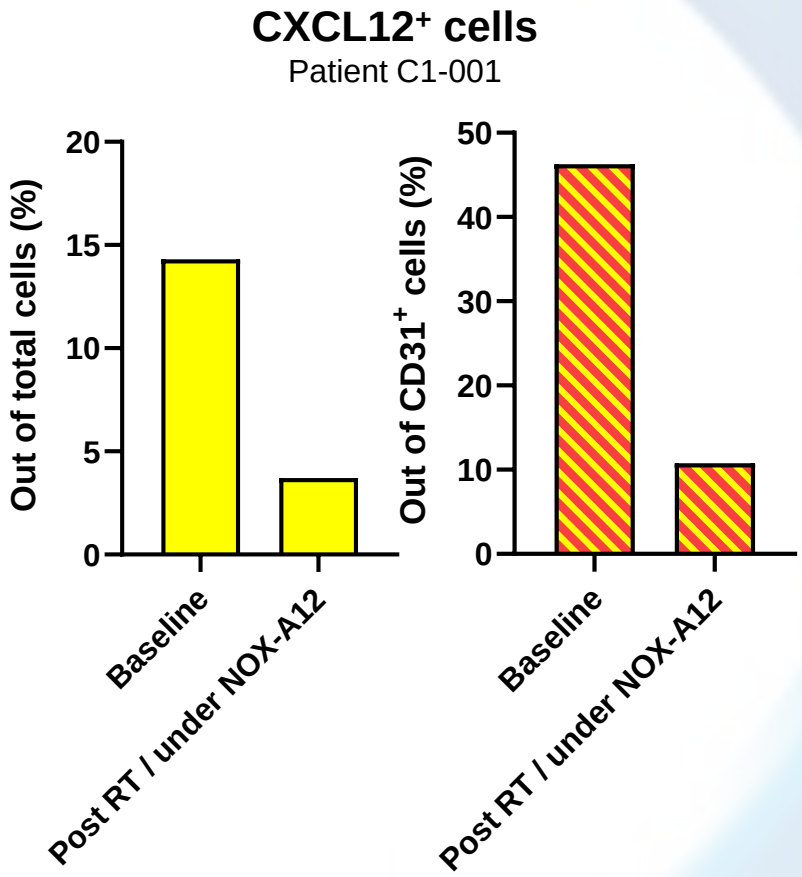


CODEX: RT/OLA reduces CXCL12 levels in the tumor endothelium

GLORIA
C1-001

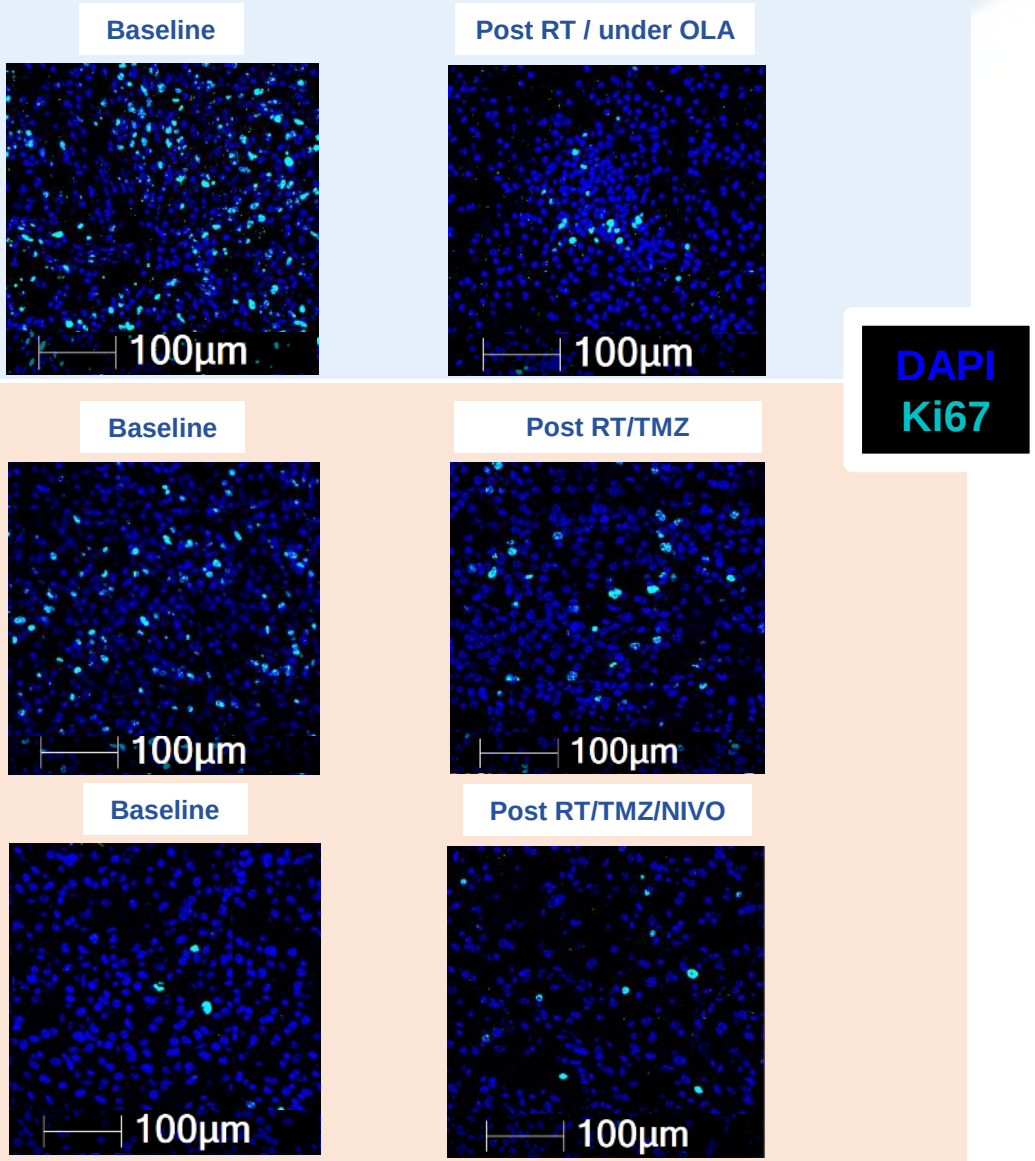


Images show areas of pathologist-confirmed tumor tissue



CODEX: RT/OLA reduces tumor cell proliferation

GLORIA
C1-001



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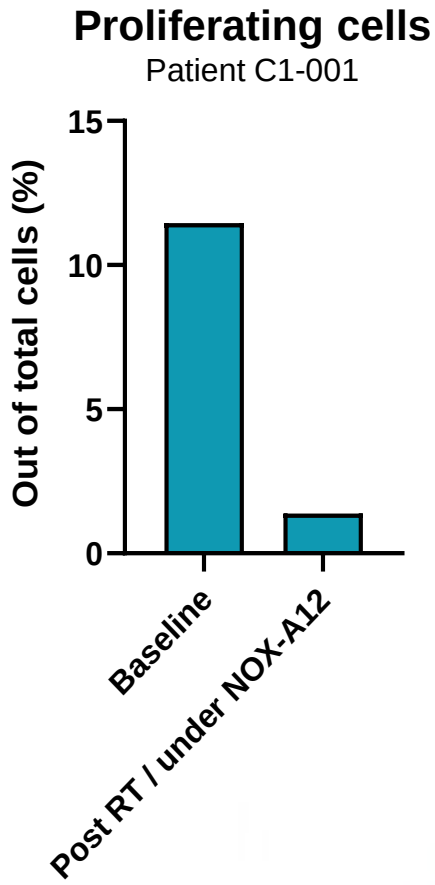
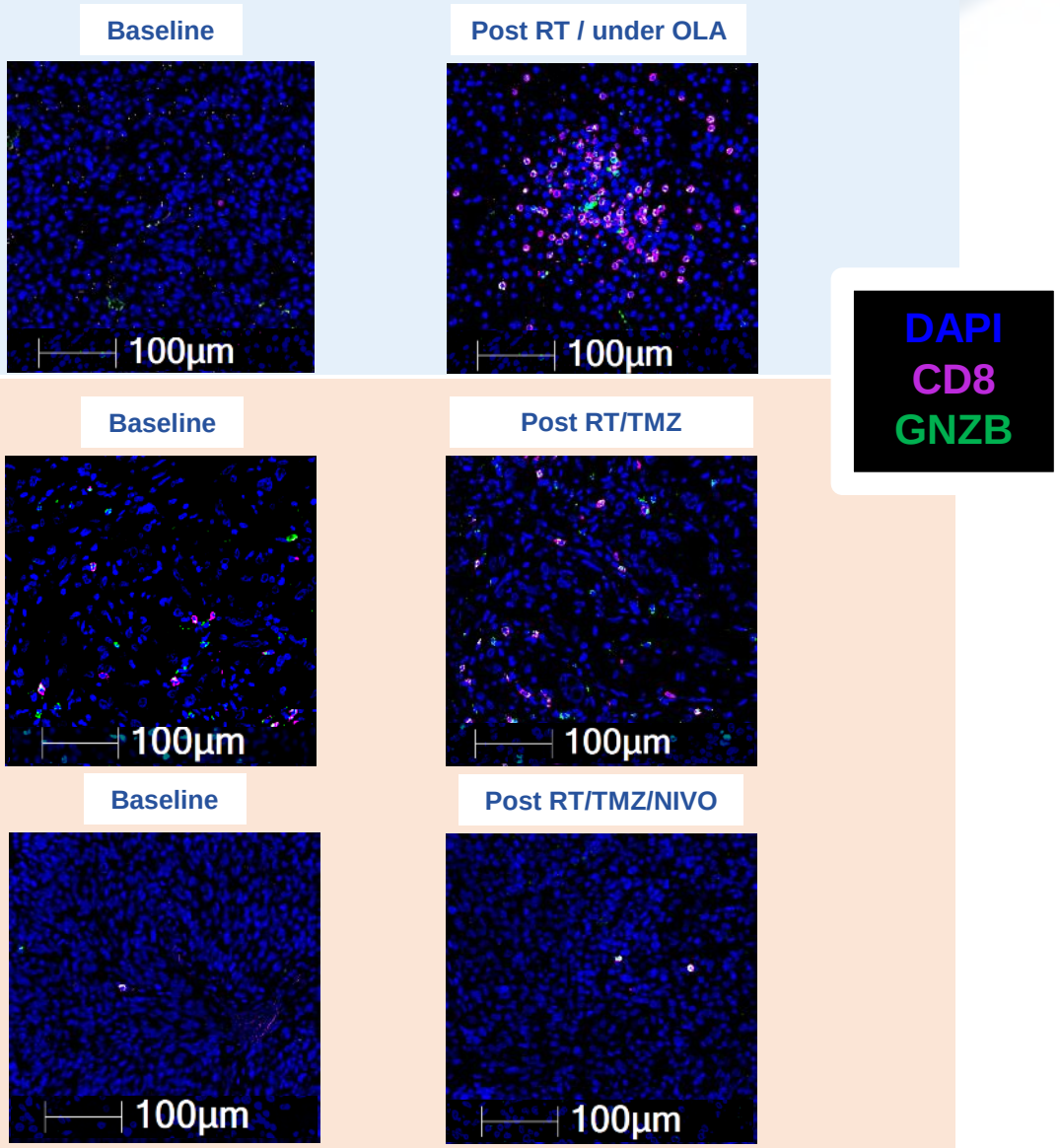


CODEX: Cytotoxic T cell infiltration and activation

GLORIA
C1-001



References

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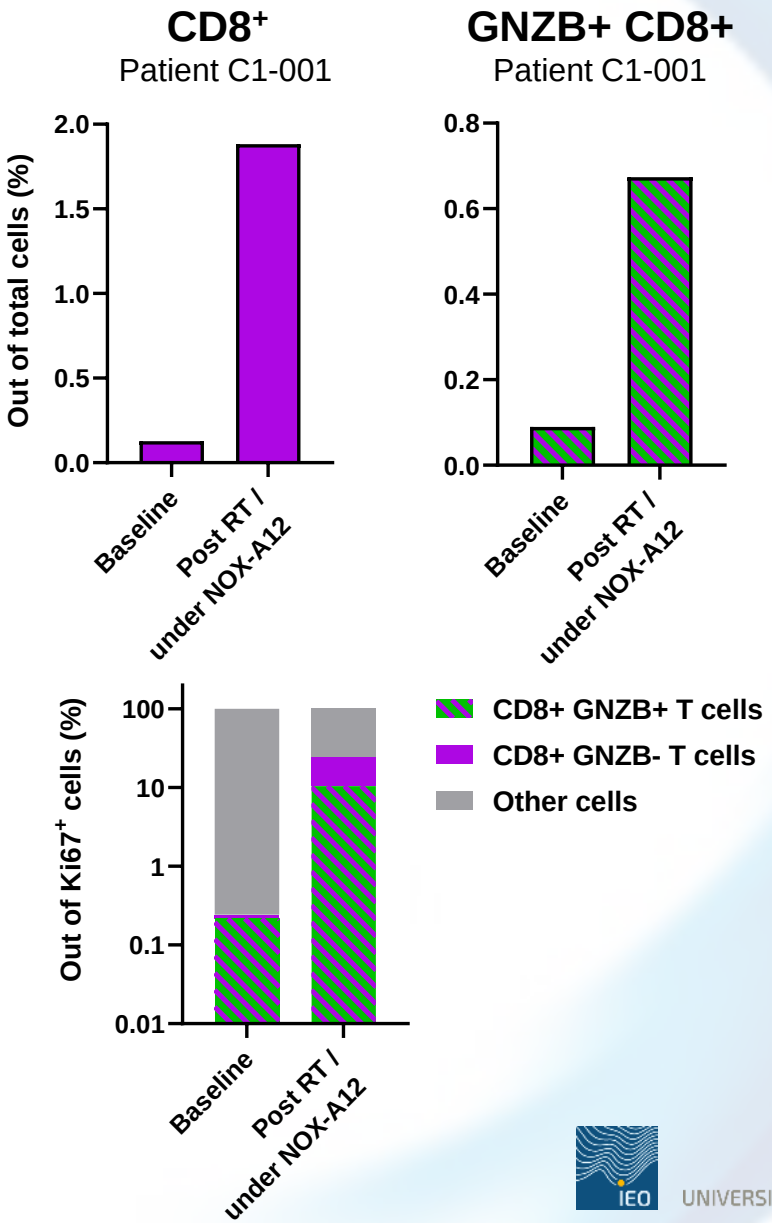
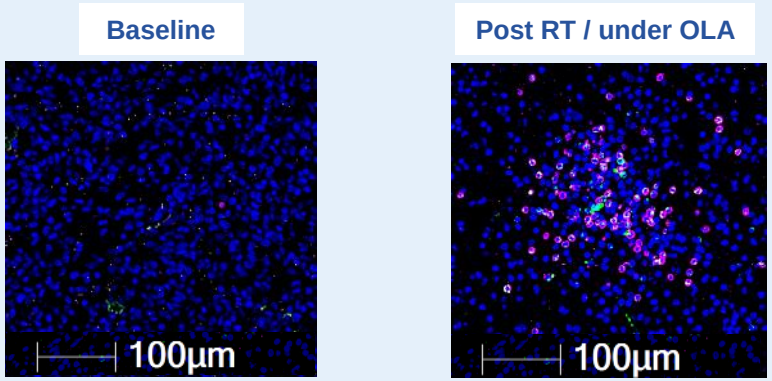
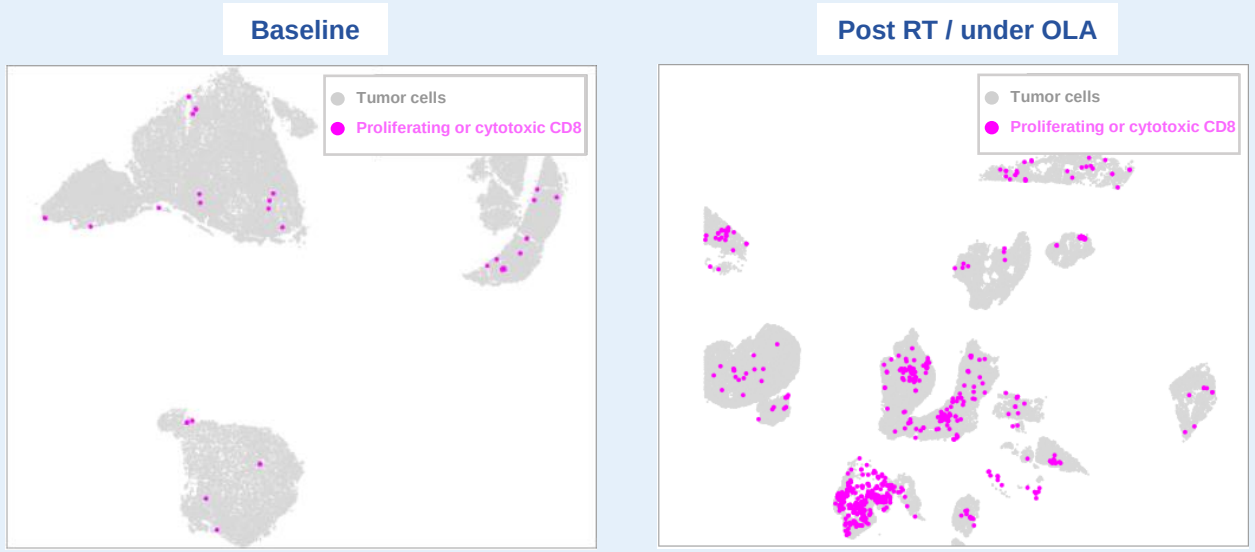


CODEX: Cytotoxic T cell infiltration and activation

GLORIA
C1-001



Whole slide spatial Analysis



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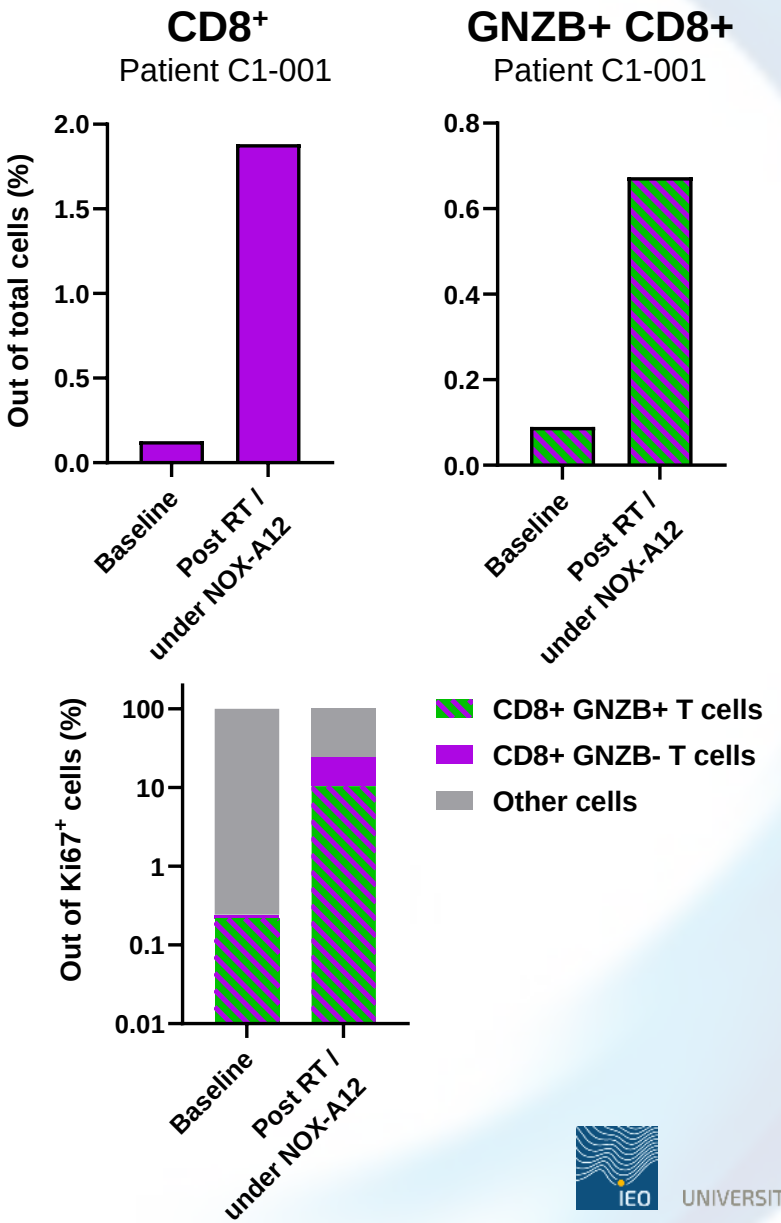

Conclusions – GLORIA Study

- **Combined RT + OLA (NOX-A12) treatment is feasible and safe**

- **Initial promising efficacy signals**
  - 8 out of 9 patients showed a response as per volume of T1-contrast (2 x PR)
  - reduced cellularity in 8 out of 9 patients
  - reduced perfusion 7 out of 9 patients

- **Tissue analysis** (re-surgery under OLA) **confirms mode(s) of action**:
  - CD31/CXCL12 co-localization is abrogated
  - Strong reduction in tumor cell proliferation
  - CD8+ T cell count increases by 15-fold
  - *De-novo* clusters of proliferating and cytotoxic CD8+ T cells

- **Follow-up ongoing**, **expansion cohorts planned**

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