KOL WEBINAR WITH DR. FRANK GIORDANO

NOX-A12 & RADIOTHERAPY COMBINATION: A DIFFERENTIATED AND PROMISING NEW APPROACH TO TREATING BRAIN CANCER

November 23, 2021 | 8:00 AM EST / 2:00 PM CET

WEBINAR PRESENTERS

MODERATOR

Guillaume van Renterghem
Managing Director
LifeSci Advisors

PRESENTERS

Dr. Frank Giordano
Chair & Director
Radiation Oncology Dept.
University Hospital Bonn

Lead investigator of NOX-A12 GLORIA Phase 1/2 study

Aram Mangasarian
CEO
NOXXON Pharma

Forward Looking Statements

The information and opinions contained in this presentation and any other information discussed at this presentation are provided as at the date of this presentation and are therefore of a preliminary nature, have not been independently verified and may be subject to updating, revision, amendment or change without notice and in some cases has not been audited or reviewed by the Company's auditors. This presentation is selective in nature and does not purport to contain all information that may be required to evaluate the Company and/or its securities. Neither the Company nor any other person is under any obligation to update or keep current the information contained in this presentation or to correct any inaccuracies in any such information which may become apparent or to provide you with any additional information. No reliance may or should be placed for any purpose whatsoever on the information contained in this presentation, or any other information discussed verbally, or on its completeness, accuracy or fairness. None of the Company, its investment banking representatives, or any of their respective directors, officers, employees, direct or indirect shareholders, agents, affiliates, advisors or any other person accept any responsibility whatsoever for the contents of this presentation, and no representation or warranty, express or implied, is made by any such person in relation to the contents of this presentation.

Certain information in this presentation is based on management estimates. Such estimates have been made in good faith and represent the current beliefs of applicable members of management. Those management members believe that such estimates are founded on reasonable grounds. However, by their nature, estimates may not be correct or complete. Accordingly, no representation or warranty (express or implied) is given that such estimates are correct or complete. Where this presentation quotes any information or statistics from any external source, it should not be interpreted that the Company has adopted or endorsed such information or statistics as being accurate. This presentation contains forward looking statements. These statements reflect the Company's current knowledge and its expectations and projections about future events and may be identified by the context of such statements or words such as "anticipate," "believe", "estimate", "expect", "intend", "plan", "project", "target", "may", "will", "would", "could", "might" or "should" or similar terminology. By their nature, forward looking statements are subject to a number of risks and uncertainties, many of which are beyond the Company's control that could cause the Company's actual results and performance to differ materially from any expected future results or performance expressed or implied by any forward looking statements. The Company undertakes no obligation to publicly release the results of any revisions to any forward looking statements in this presentation that may occur due to any change in its expectations or to reflect events or circumstances after the date of this presentation.

Aram Mangasarian
CEO
NOXXON Pharma

Introductory remarks on NOXXON Pharma

ABOUT NOXXON: Strong Value Proposition Through Differentiated Pipeline Targeting the TME

Clinical stage biotech company

Listed in 2016, Euronext Growth Paris

HQ in Berlin, Germany

Expert in Tumor Microenvironment

Mission to improve cancer treatment outcomes, when tumor microenvironment significantly limits survival

NOX-A12's highly differentiated dual mechanism of action

Focus on 2 large orphan cancer indications

~$6.5bn Addressable Market

In brain cancer (1st line GBM) and pancreatic cancer indications

Technology leverageable to numerous other solid tumors:
- Combination with Radiotherapy
- Combination with Immunotherapy

Robust commercial protection

Thanks to orphan drug status and patent families covering NOX-A12 & NOX-E36

Upcoming Catalysts

Q1 2022
Brain cancer
Phase 1/2 read-out

H1 2024
Pancreatic cancer
Phase 2 read-out

Treating Seed and Soil:
Targeting CXCL12 in the Glioblastoma Tumor Microenvironment

Frank A. Giordano, MD

Professor of Radiation Oncology
Director and Chair, Department of Radiation Oncology
University Hospital Bonn

Lead investigator of NOX-A12 GLORIA Phase 1/2 study

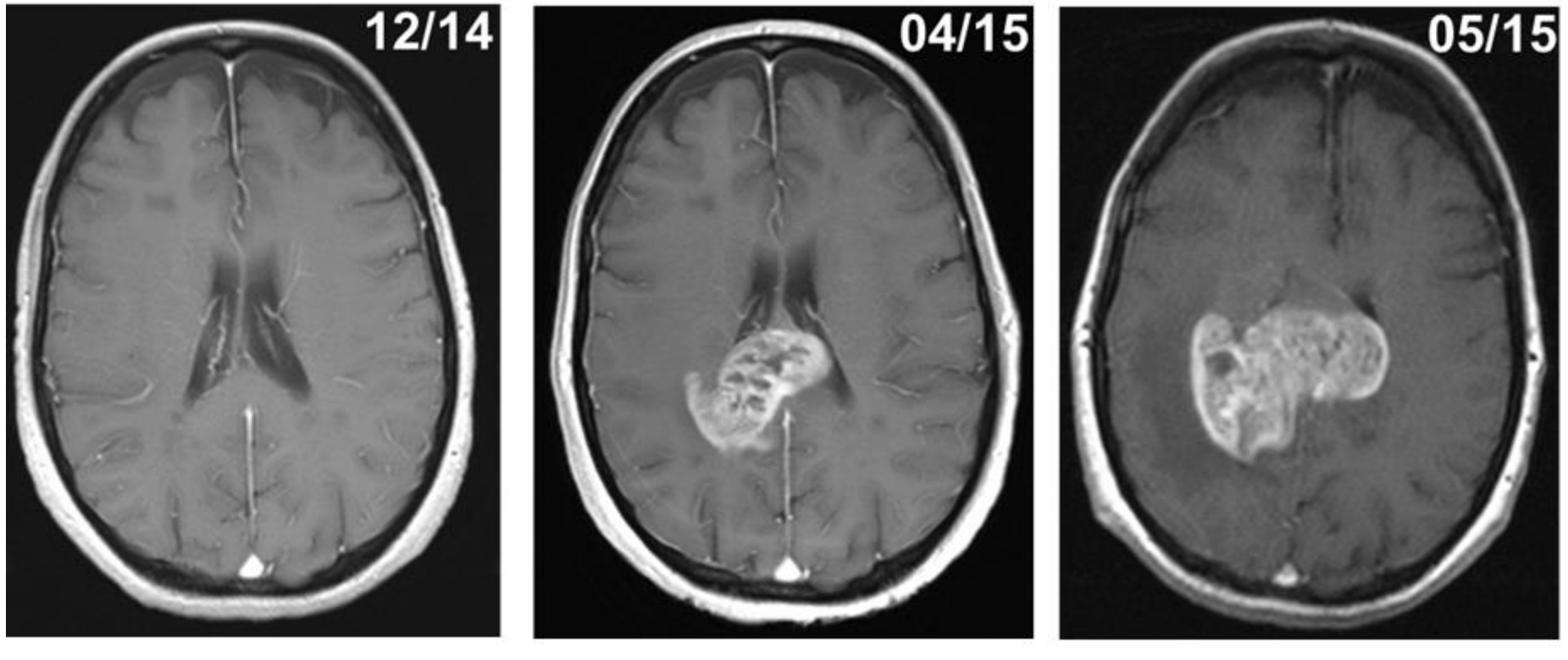
ukb Klinik für Strahlentherapie und Radioonkologie

IEO UNIVERSITÄT BONN

Brain tumor incidences (primary brain tumors)

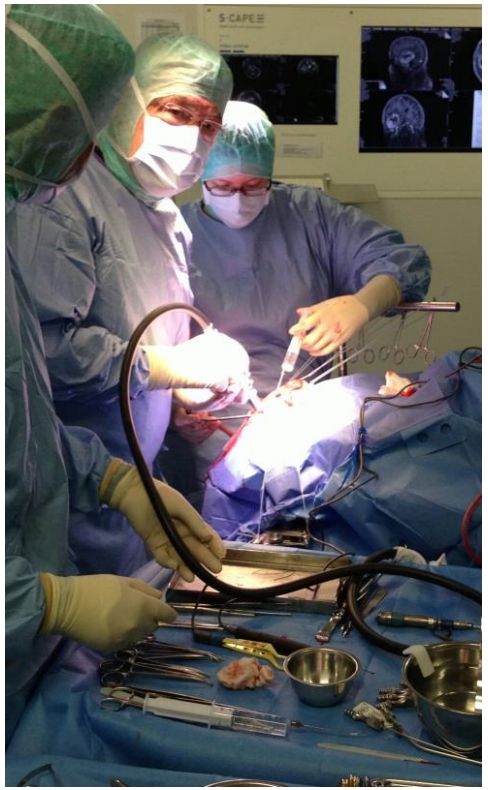
A case to remember

- 45 y/o female patient with a history of MS
- underwent MRT q3mo (for MS), last scan was before Xmas 2014
- came to ER in April 2014: progressive vertigo, nausea and muscle weaknesses

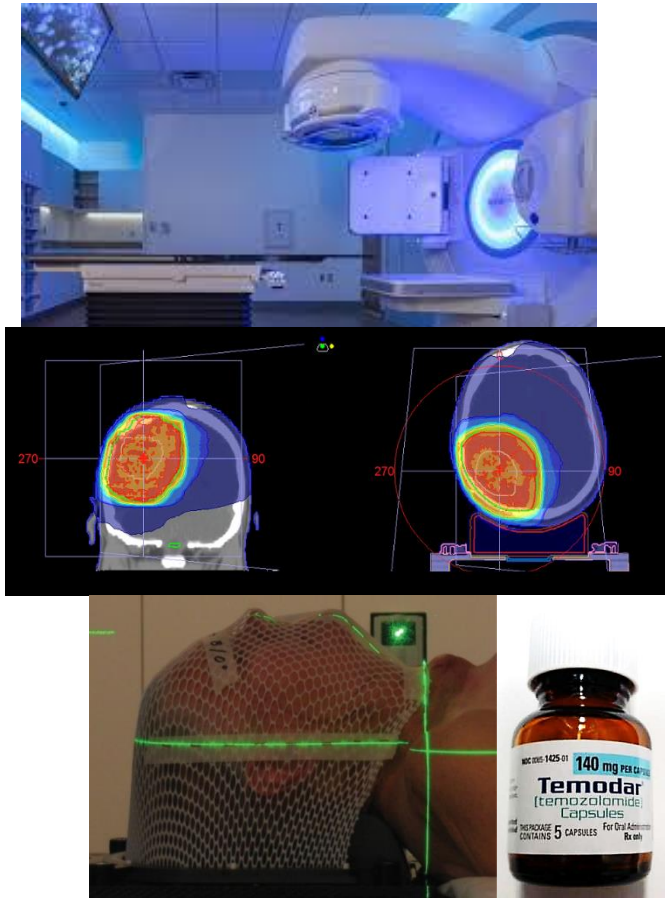


Standard of care for GBM: components

Surgery or Biopsy

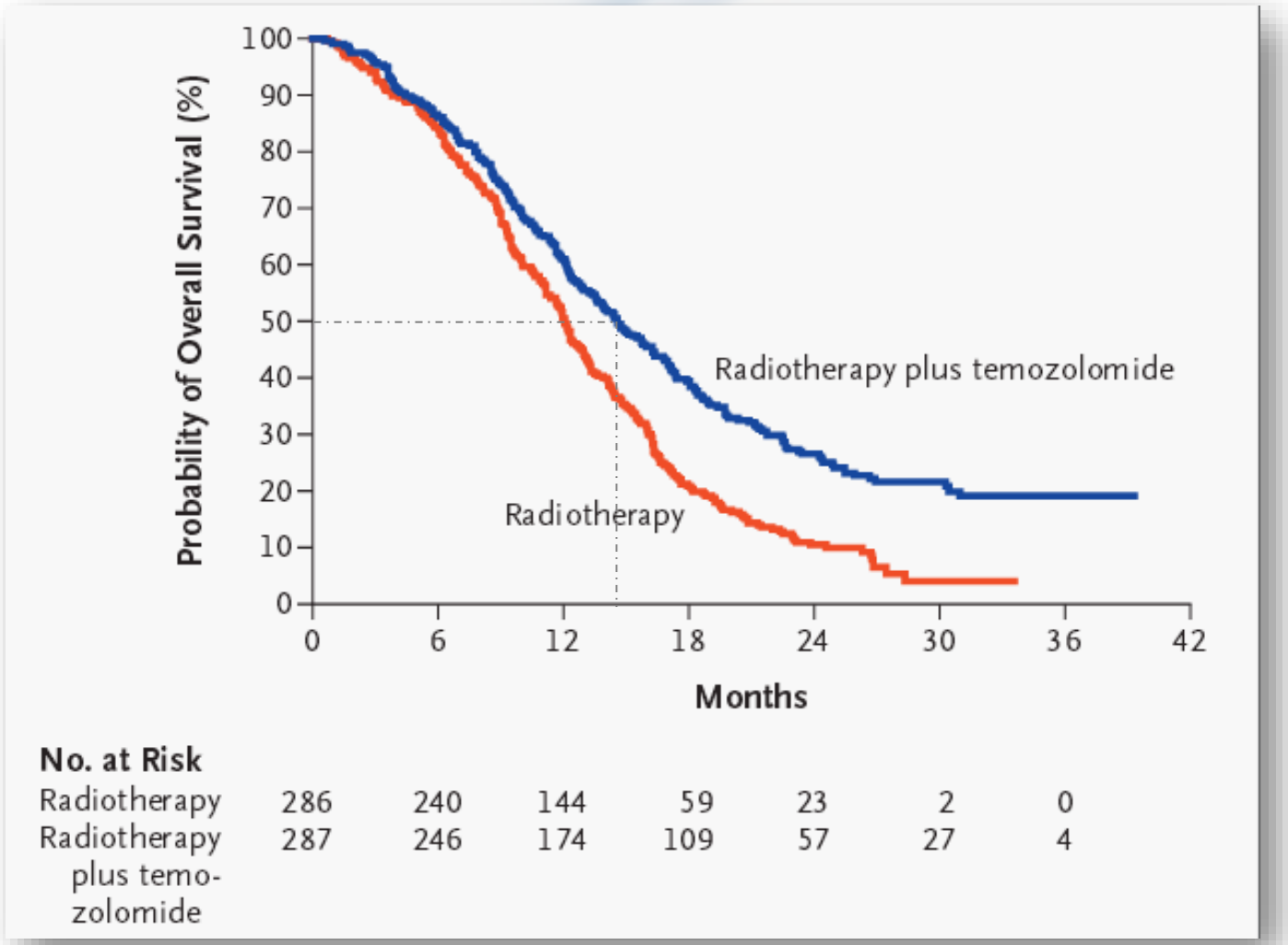


Radiotherapy
+ Chemotherapy



Maintenance
Chemotherapy

Standard of care for GBM: outcome



Stupp et al., 2005

Role of MGMT expression in GBM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

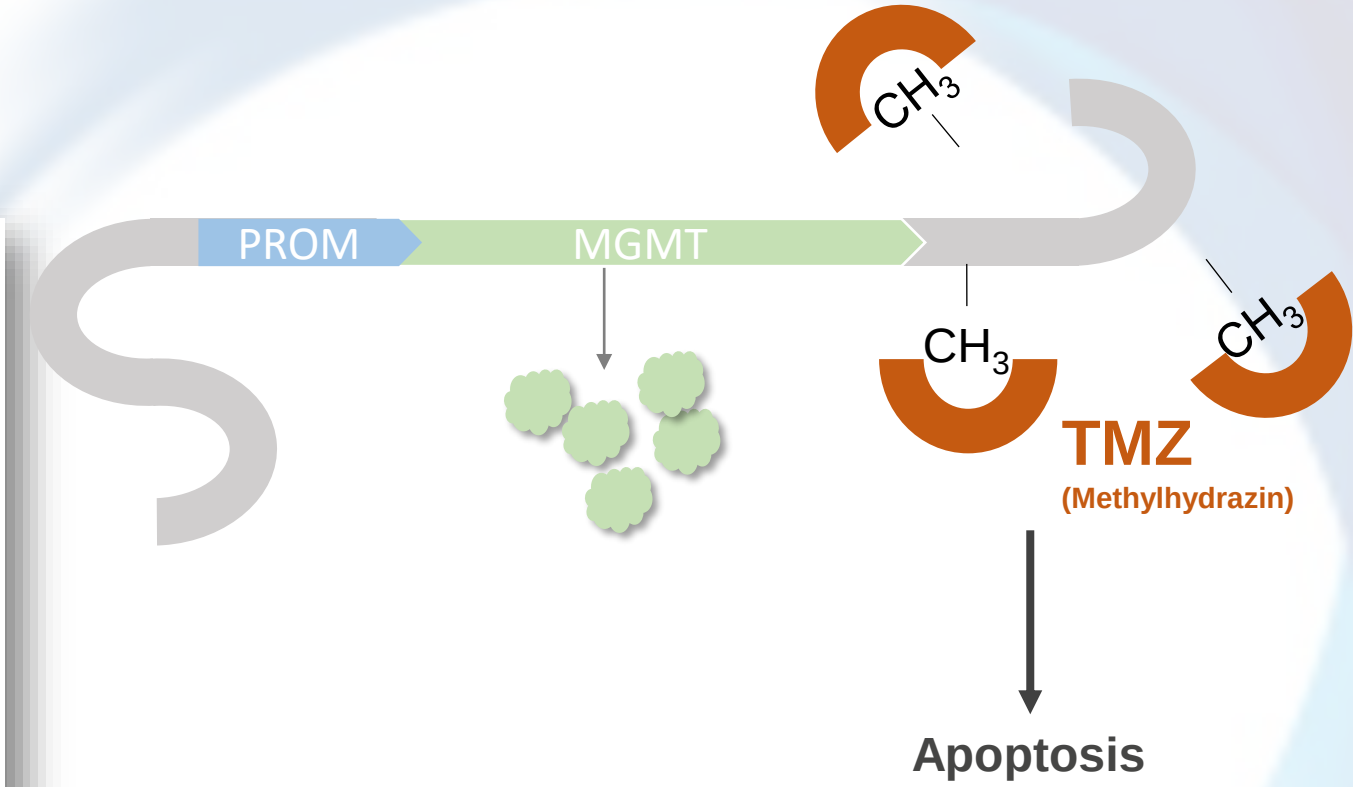
Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.

ABSTRACT

BACKGROUND

Epigenetic silencing of the *MGMT* (O^6-methylguanine–DNA methyltransferase) DNA-repair gene by promoter methylation compromises DNA repair and has been associated with longer survival in patients with glioblastoma who receive alkylating agents.

From the Laboratory of Tumor Biology and Genetics, Department of Neurosurgery (M.E.H., A.-C.D., M.-F.H., N.T.), the Departments of Radiotherapy (R.O.M.) and Neuropathology (R.C.J.), and the Multidis-



Role of MGMT expression in GBM

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma

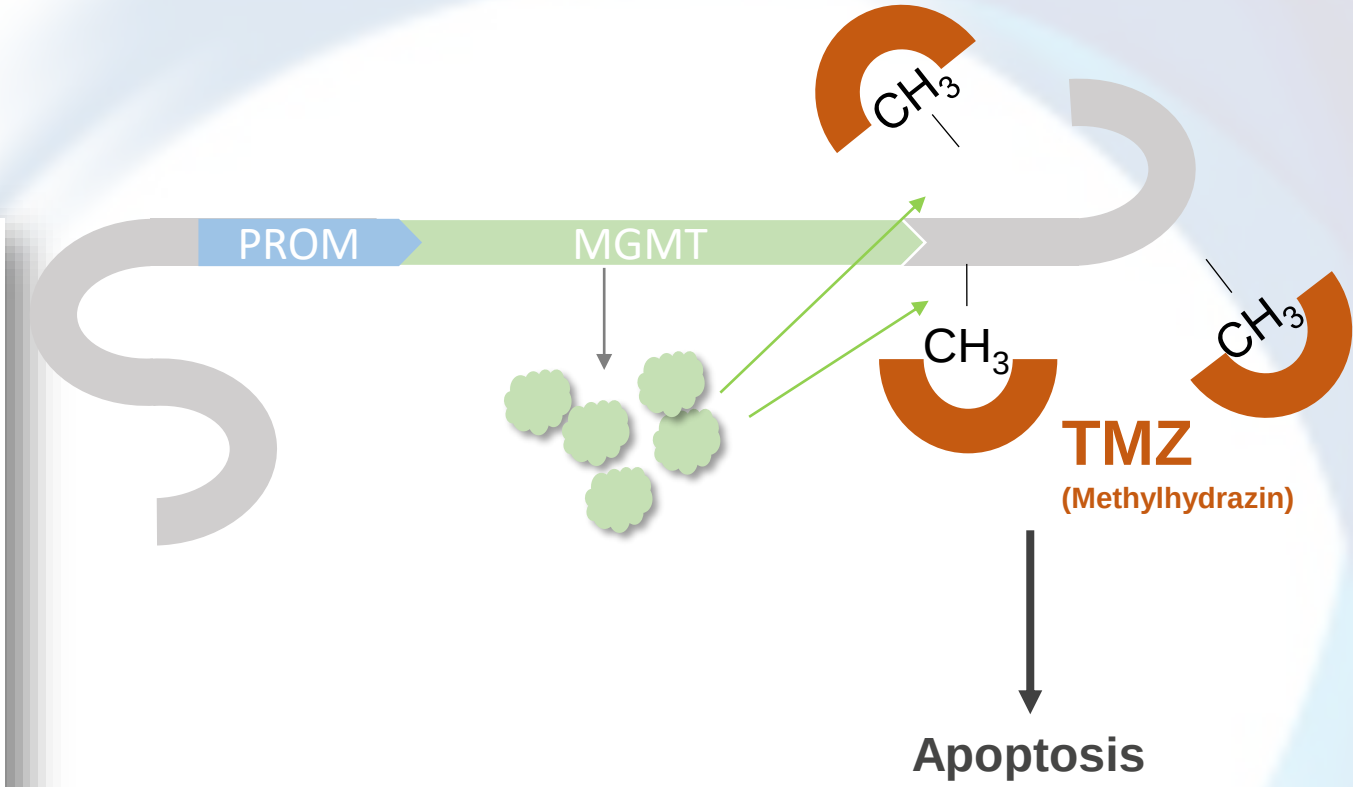
Monika E. Hegi, Ph.D., Annie-Claire Diserens, M.Sc., Thierry Gorlia, M.Sc., Marie-France Hamou, Nicolas de Tribolet, M.D., Michael Weller, M.D., Johan M. Kros, M.D., Johannes A. Hainfellner, M.D., Warren Mason, M.D., Luigi Mariani, M.D., Jacoline E.C. Bromberg, M.D., Peter Hau, M.D., René O. Mirimanoff, M.D., J. Gregory Cairncross, M.D., Robert C. Janzer, M.D., and Roger Stupp, M.D.

ABSTRACT

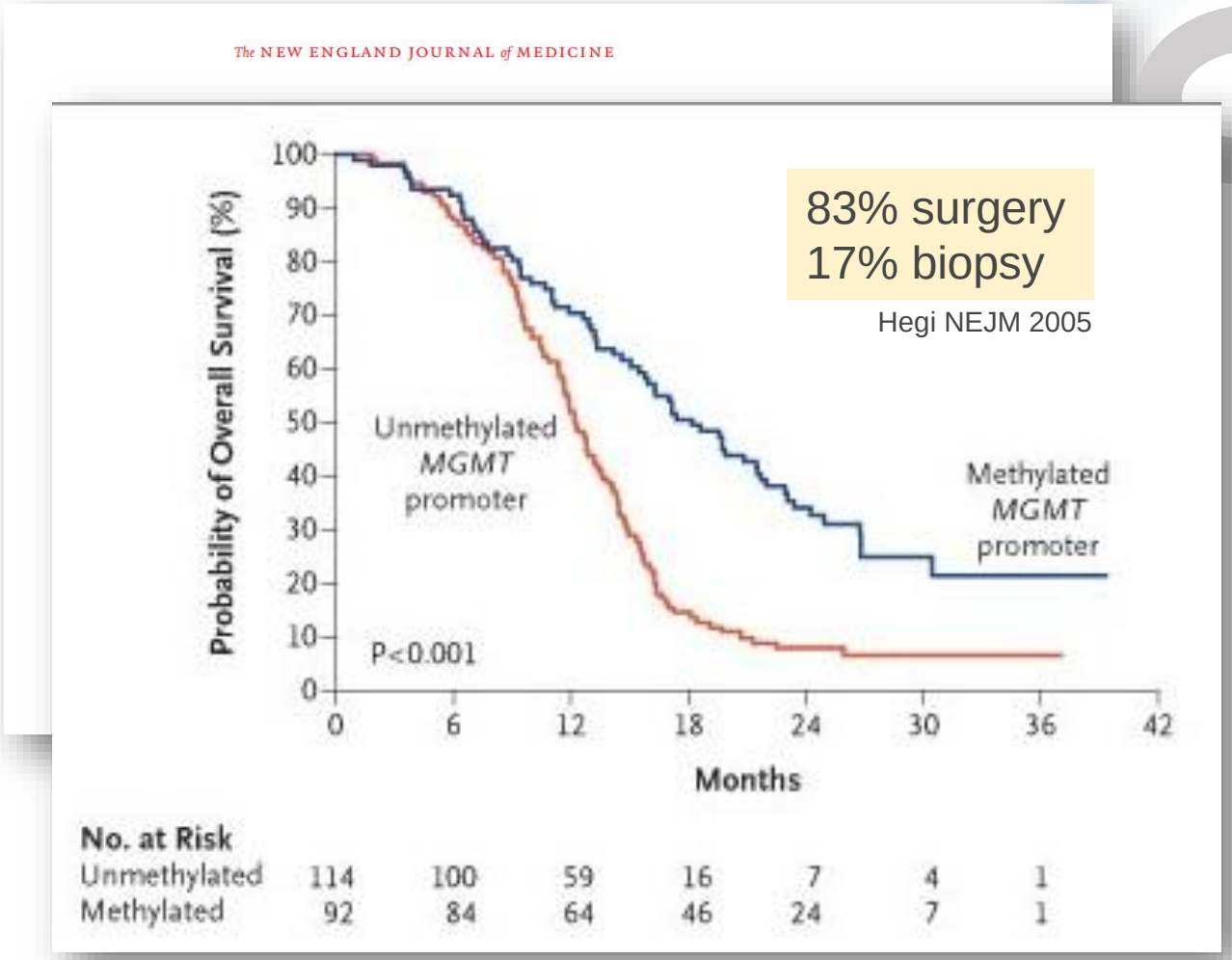
BACKGROUND

Epigenetic silencing of the *MGMT* (O^6-methylguanine–DNA methyltransferase) DNA-repair gene by promoter methylation compromises DNA repair and has been associated with longer survival in patients with glioblastoma who receive alkylating agents.

From the Laboratory of Tumor Biology and Genetics, Department of Neurosurgery (M.E.H., A.-C.D., M.-F.H., N.T.), the Departments of Radiotherapy (R.O.M.) and Neuropathology (R.C.J.), and the Multidis-

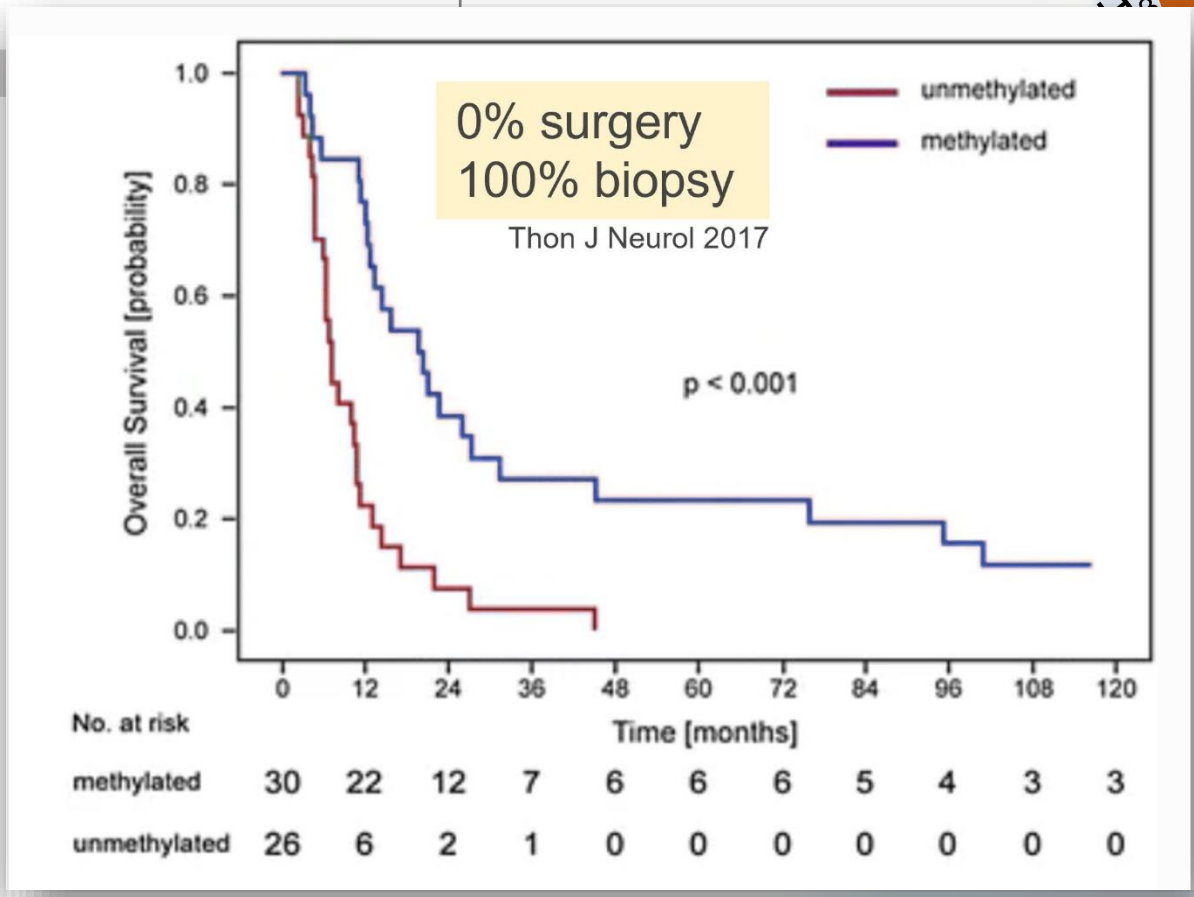


Role of MGMT expression in GBM



83% surgery
17% biopsy

Hegi NEJM 2005

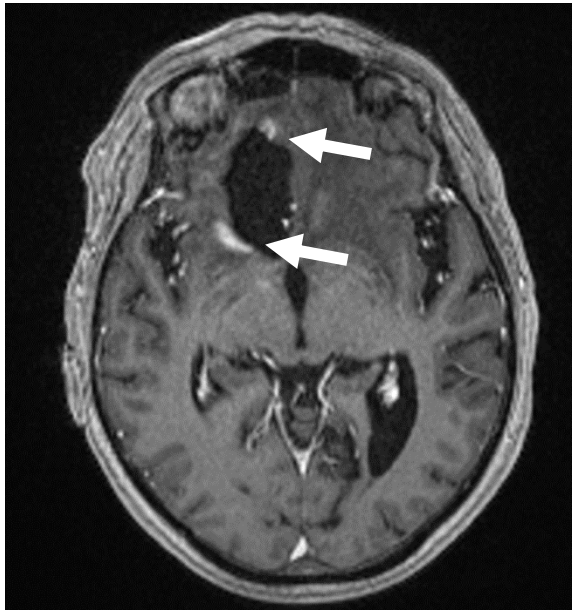


0% surgery
100% biopsy

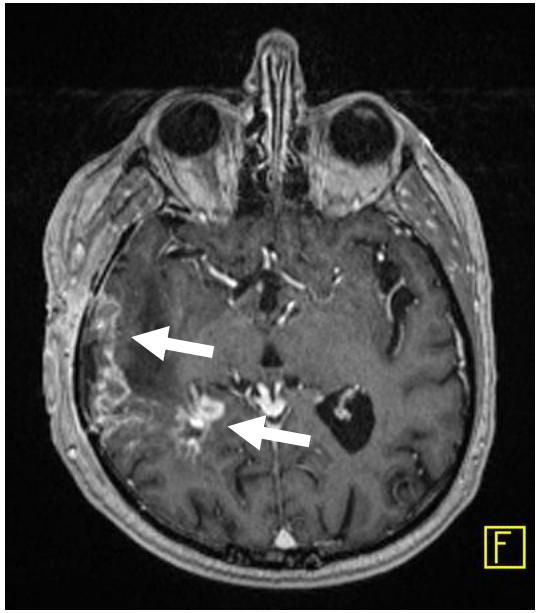
Thon J Neurol 2017

GBM recurrence patterns

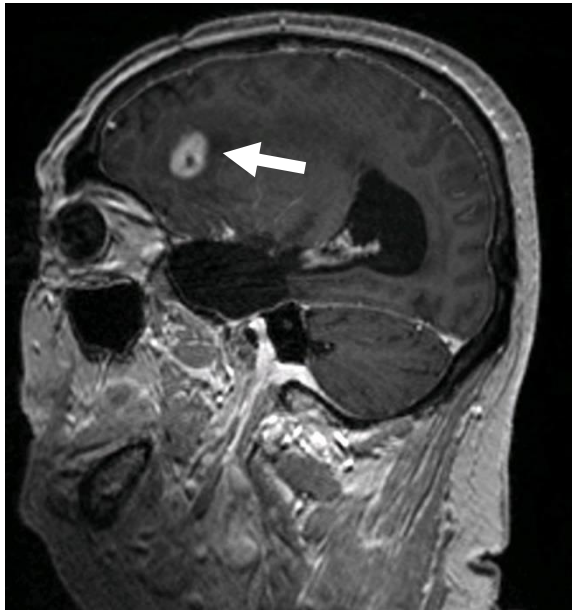
local 97-99%



combined ~1-3%

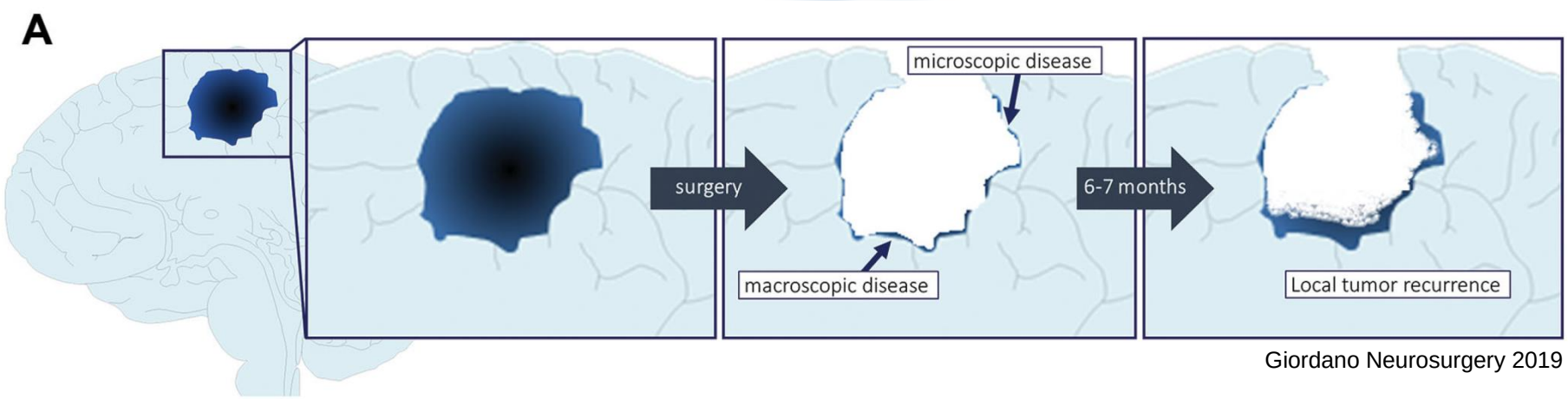


distant <1%



Choucair et al, 1986
Wallner et al, 1989
Gaspar et al, 1992
Petrecca et al, 2013

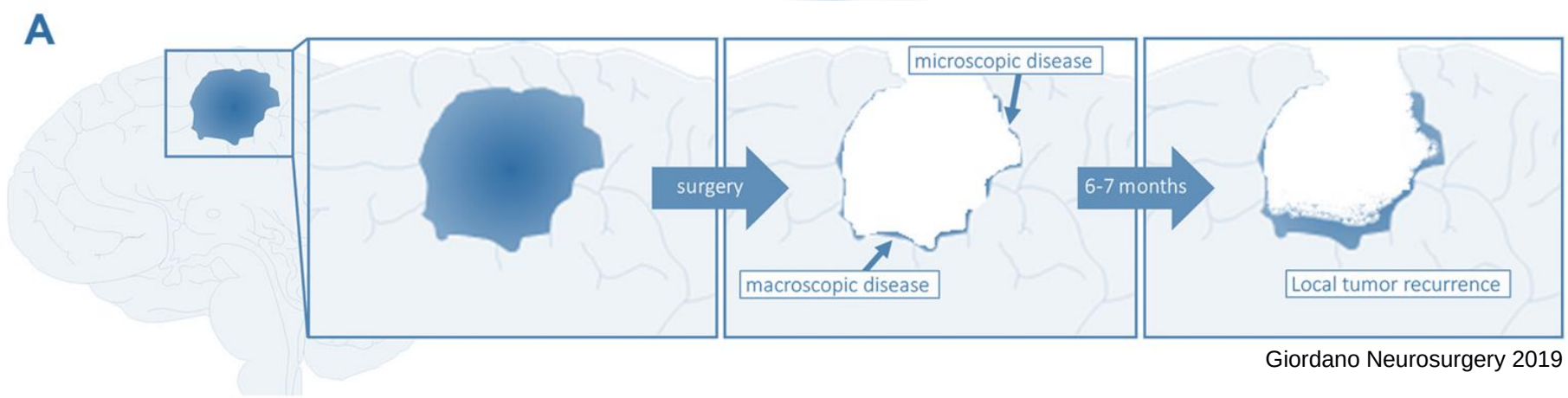
Reasons for rapid local recurrence



Giordano Neurosurgery 2019

- residual tumor cells remain even after “perfect” (or supramaximal) surgery
- GB stem cells show a high degree of radio- and chemoresistance
- highly effective revascularization after radiotherapy

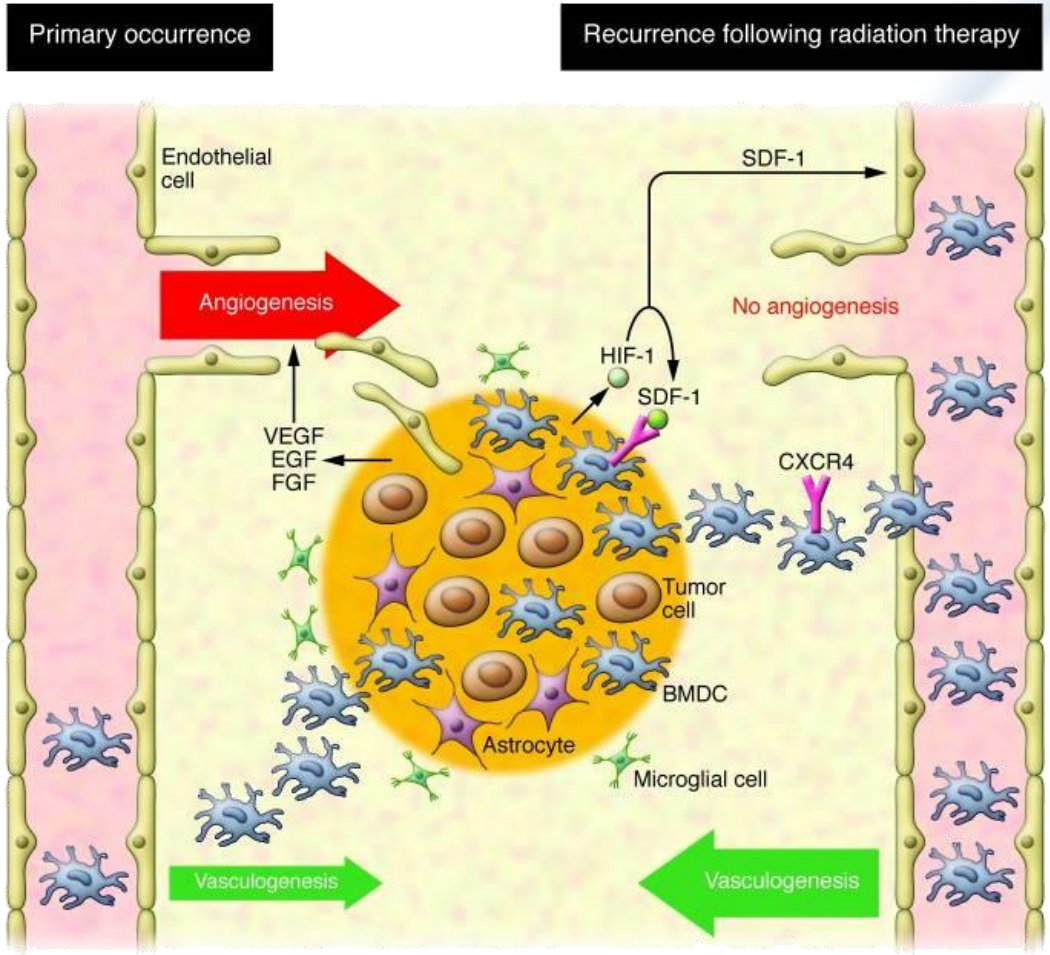
Reasons for rapid local recurrence



Giordano Neurosurgery 2019

- residual tumor cells remain even after “perfect” (or supramaximal) surgery
- GB stem cells show a high degree of radio- and chemoresistance
- **highly effective revascularization after radiotherapy**

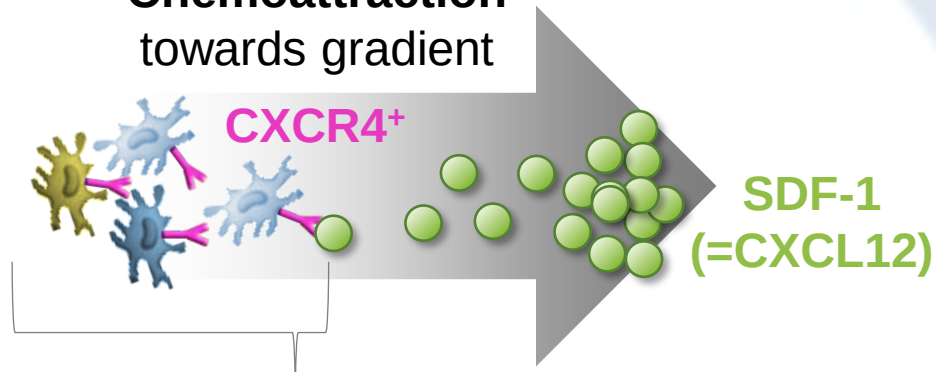
Mechanism of revascularization after RT



Greenfield J Clin Invest 2010

BMDC, Bone Marrow-Derived Cell
CXCR4, C-X-C Chemokine Receptor Type 4
EGF, Epidermal Growth Factor
FGF, Fibroblast Growth Factor
HIF-1, Hypoxia-inducible factor 1
SDF-1, Stem cell Derived Factor 1 (= CXCL12)
VEGF, Vascular Endothelial Growth Factor

Chemoattraction
towards gradient



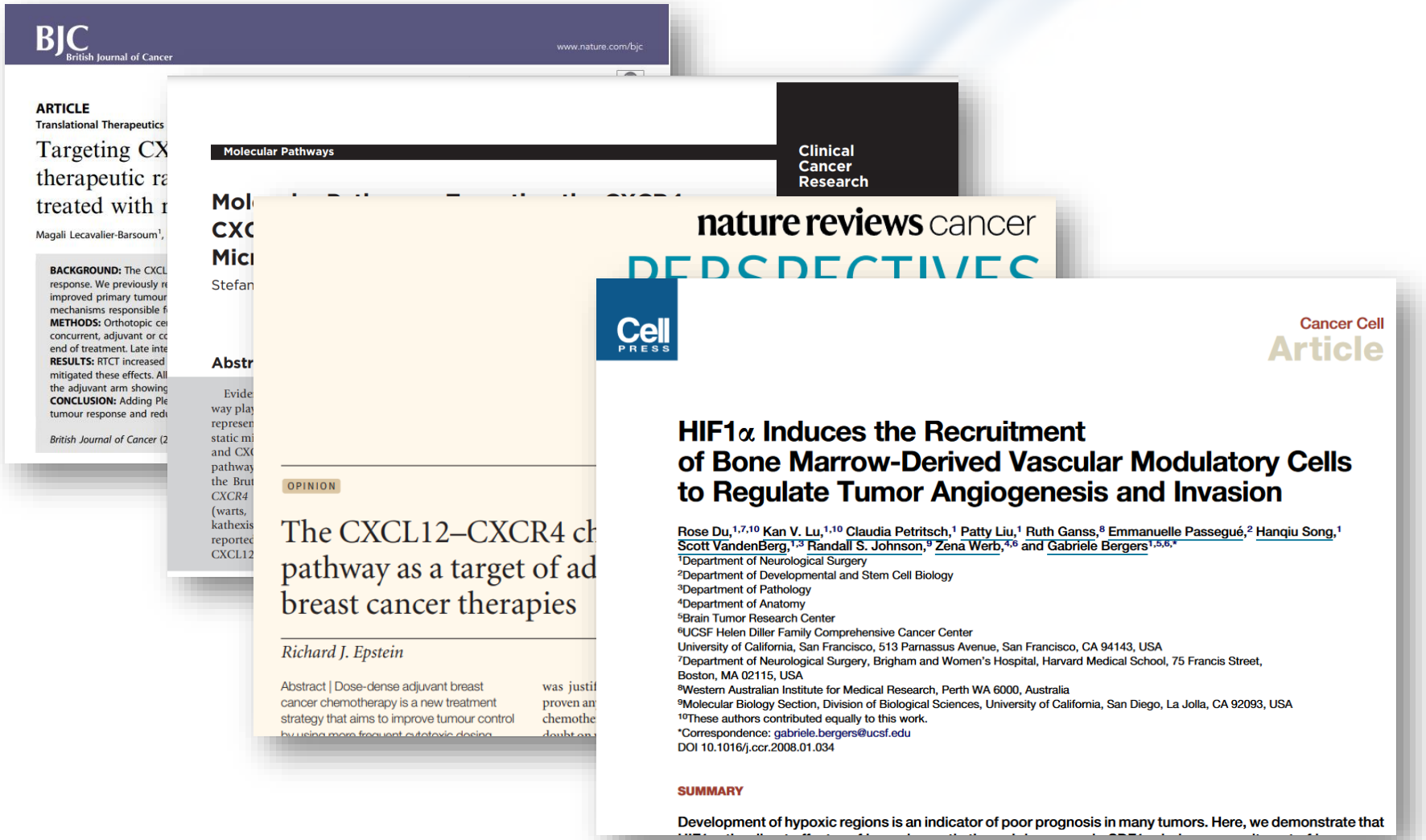
CXCR4+ myeloid cells

MP/TAM (microglia is CXCR4 negative)
monocytes (would not persist in intact brain)
CD11b+CD14+CD33+ myeloid-derived suppressor cells

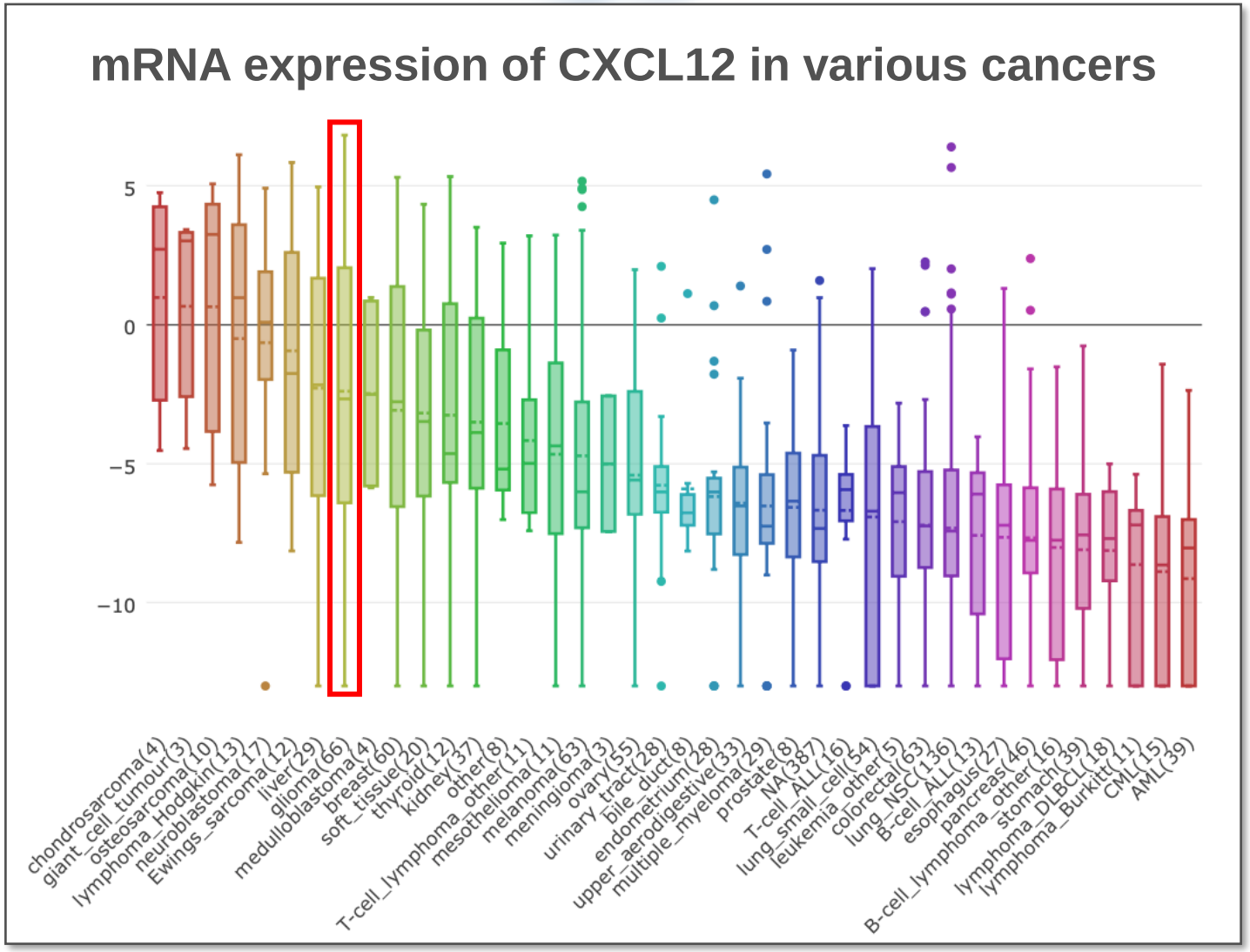
Vasculogenesis

Immunosuppression

Mechanism of revascularization after RT

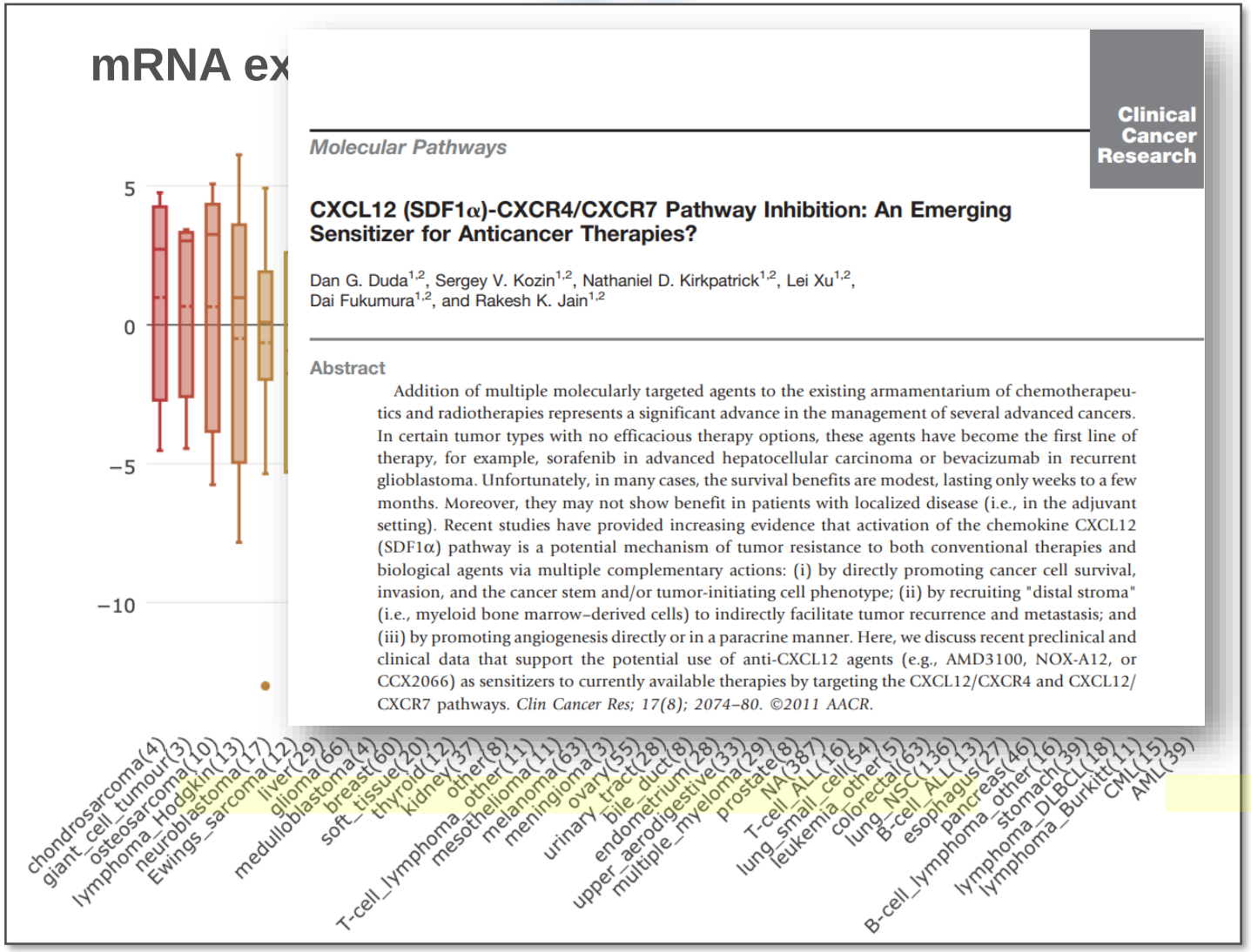


Targeting CXCL12 in other cancers



Broad Institute Cancer Cell Line Encyclopedia

Targeting CXCL12 in other cancers



Molecular Pathways

Clinical Cancer Research

CXCL12 (SDF1α)-CXCR4/CXCR7 Pathway Inhibition: An Emerging Sensitizer for Anticancer Therapies?

Dan G. Duda[1,2], Sergey V. Kozin[1,2], Nathaniel D. Kirkpatrick[1,2], Lei Xu[1,2], Dai Fukumura[1,2], and Rakesh K. Jain[1,2]

Abstract

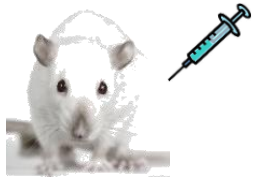
Addition of multiple molecularly targeted agents to the existing armamentarium of chemotherapeutics and radiotherapies represents a significant advance in the management of several advanced cancers. In certain tumor types with no efficacious therapy options, these agents have become the first line of therapy, for example, sorafenib in advanced hepatocellular carcinoma or bevacizumab in recurrent glioblastoma. Unfortunately, in many cases, the survival benefits are modest, lasting only weeks to a few months. Moreover, they may not show benefit in patients with localized disease (i.e., in the adjuvant setting). Recent studies have provided increasing evidence that activation of the chemokine CXCL12 (SDF1α) pathway is a potential mechanism of tumor resistance to both conventional therapies and biological agents via multiple complementary actions: (i) by directly promoting cancer cell survival, invasion, and the cancer stem and/or tumor-initiating cell phenotype; (ii) by recruiting "distal stroma" (i.e., myeloid bone marrow–derived cells) to indirectly facilitate tumor recurrence and metastasis; and (iii) by promoting angiogenesis directly or in a paracrine manner. Here, we discuss recent preclinical and clinical data that support the potential use of anti-CXCL12 agents (e.g., AMD3100, NOX-A12, or CCX2066) as sensitizers to currently available therapies by targeting the CXCL12/CXCR4 and CXCL12/CXCR7 pathways. *Clin Cancer Res; 17(8); 2074–80. ©2011 AACR.*

Broad Institute Cancer Cell Line Encyclopedia

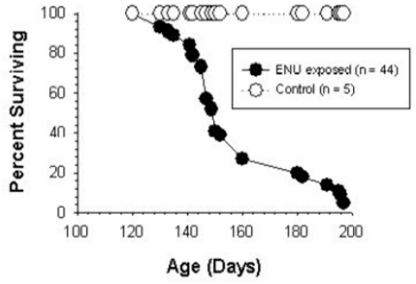
Strong pre-clinical evidence for radiotherapy + NOX-A12

Autochthonous brain tumor model in rats

- Spontaneous tumor development in immuno-competent host
- Diversity of tumor cell types with therapeutic resistance comparable to human situation
- Refractory to standard therapies

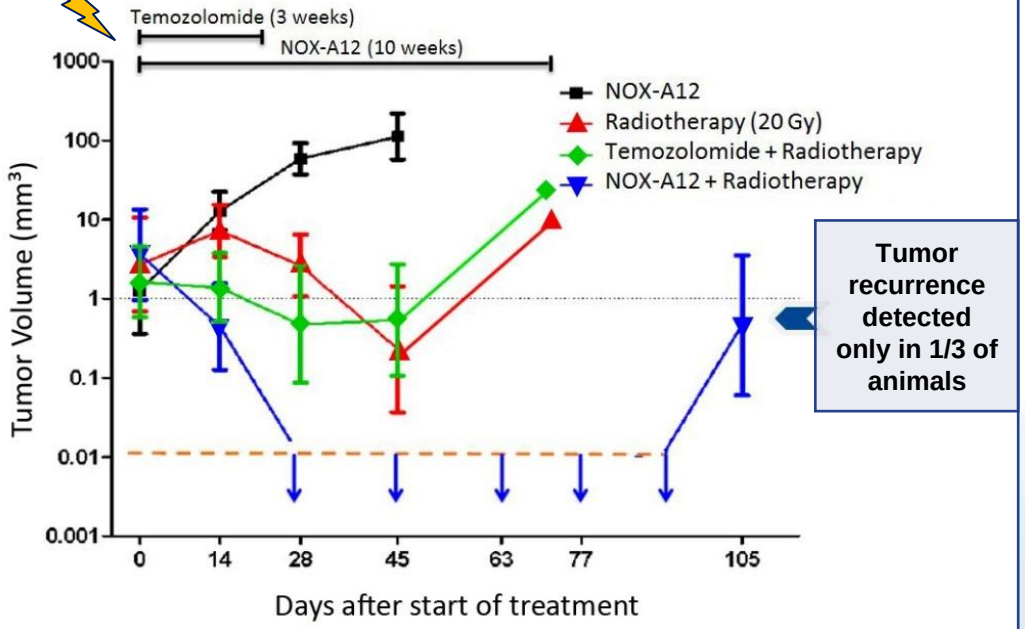


Pregnant rats:
ENU (carcinogen)
on gestational age
day 17 - 18



EFFECTS OF TREATMENTS

Radiotherapy
at day 0

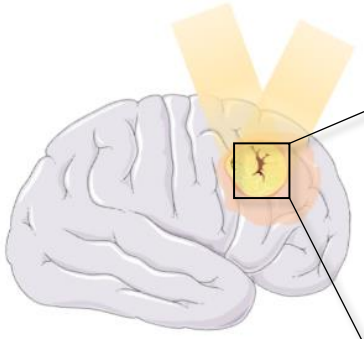


Tumor recurrence detected only in 1/3 of animals

Radiotherapy + NOX-A12 resulted in 100% complete response (66% durable) in a rodent brain cancer model

Liu Neuro-Oncology 2014

Background and rationale



Radiotherapy

↓

Hypoxia

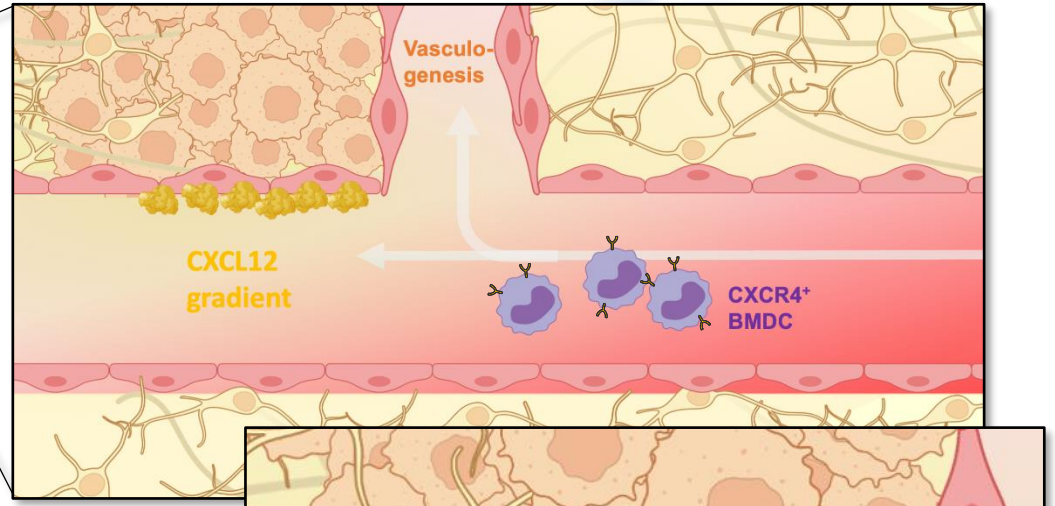
CXCL12 ↑

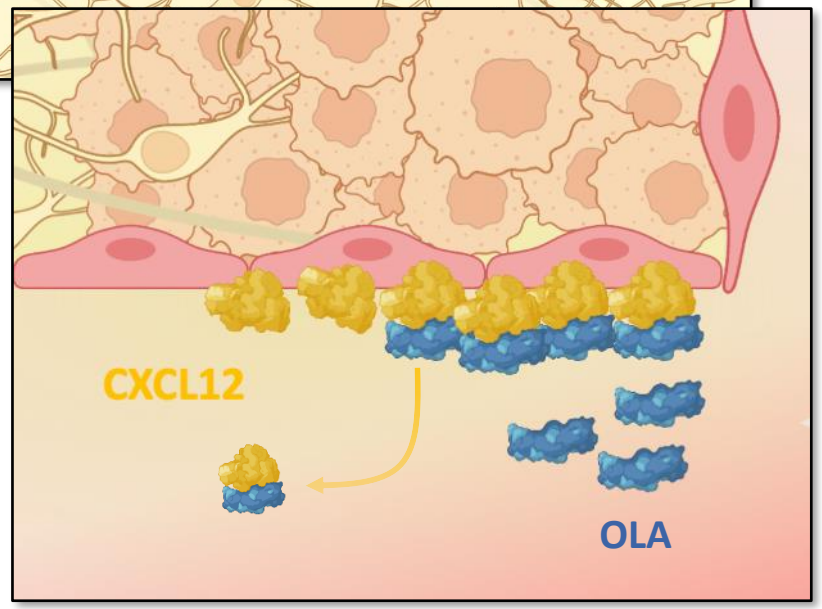
↓

Vasculogenesis | Immunosup-pressive TME

↓

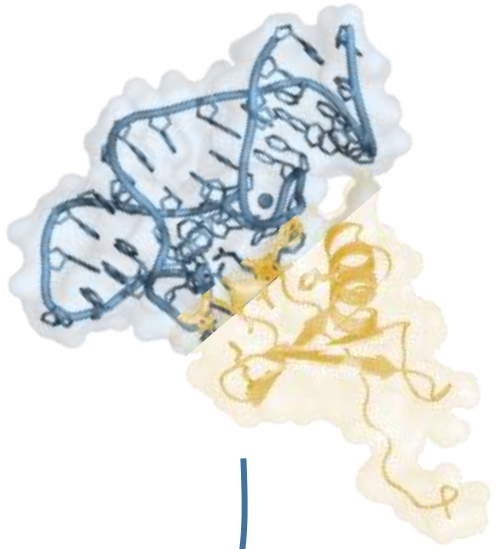
Tumor recurrence





Olaptesed pegol (OLA, NOX-A12)

RNA Spiegelmer (L-stereoisomer)



binds & neutralizes CXCL12

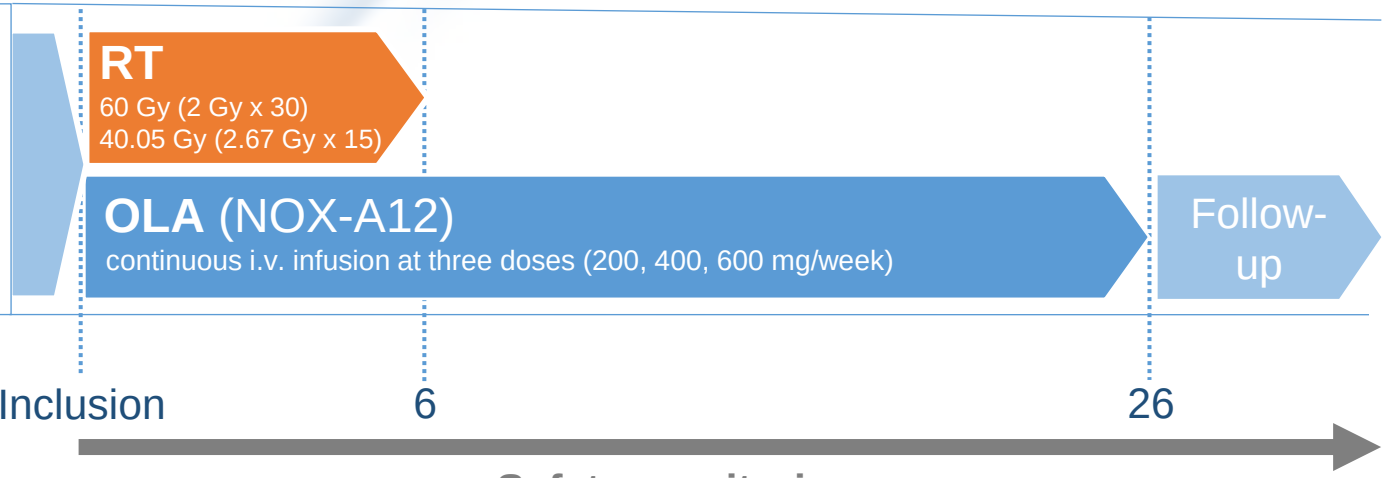
Ceradini, **Nat Med** 2004
Greenfield, **J Clin Invest.** 2010
Kioi, **J Clin Invest.** 2010
Liu, **Neuro Oncol.** 2014

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



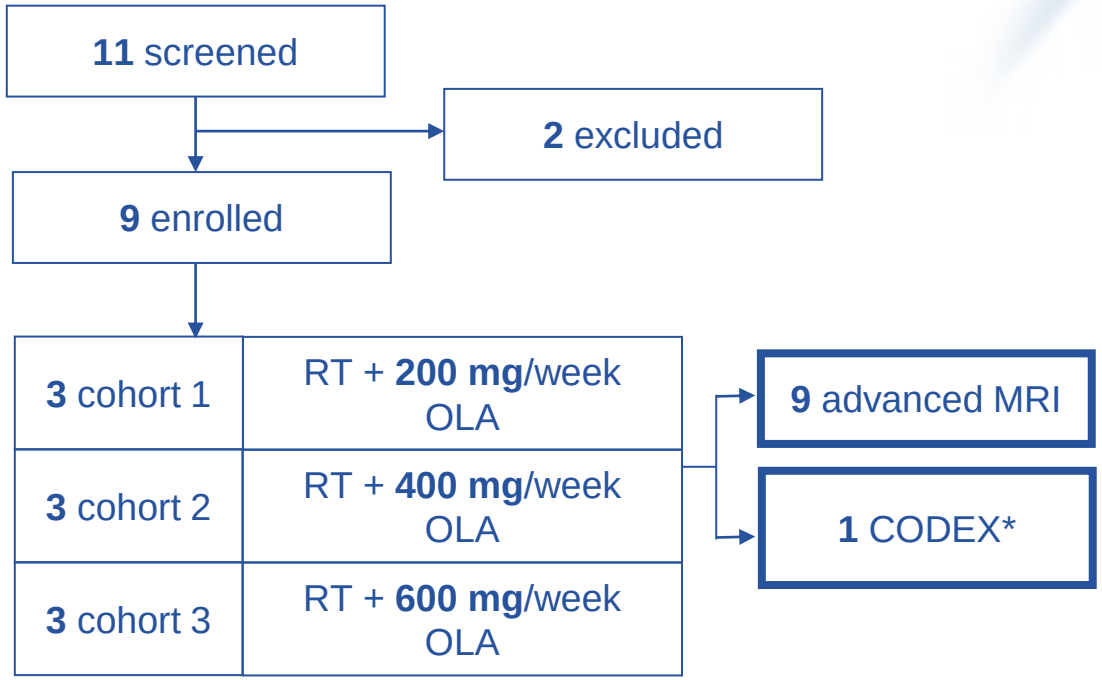
Safety monitoring
Advanced MRI (perfusion/diffusion)
CODEX® (multiplexed immunofluorescence imaging)

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

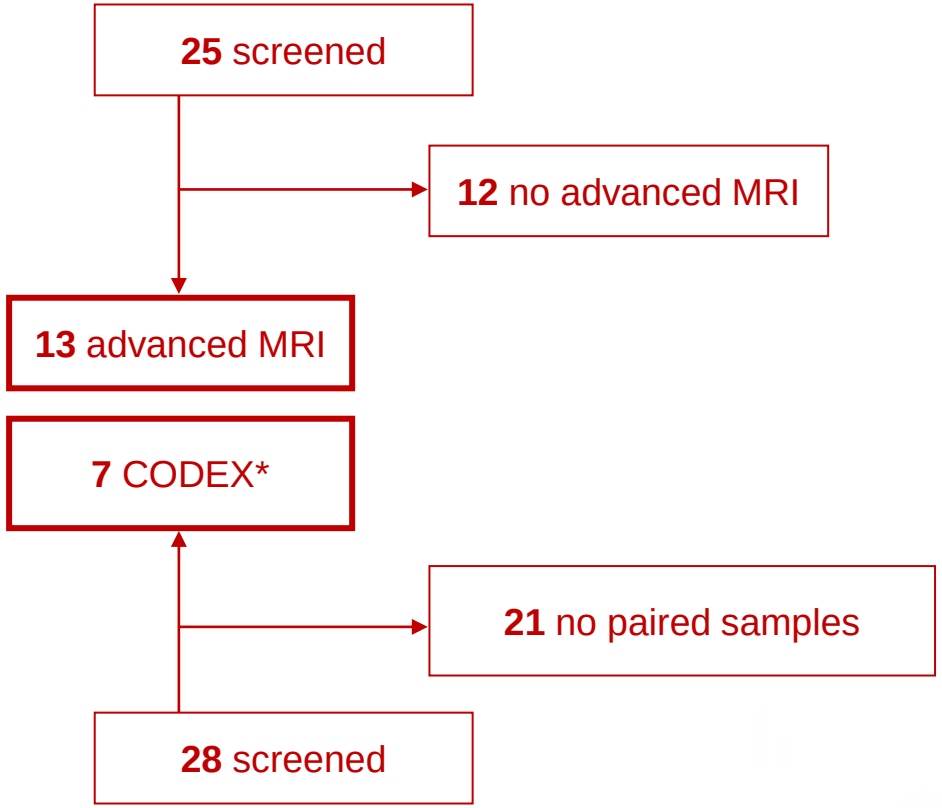
Secondary Endpoints: OLA/NOX-A12 plasma levels, tumor vascularization/perfusion (advanced MRI), PFS-6, mPFS, OS, QoL, NANO

CONSORT of GLORIA and controls

GLORIA



Matched Imaging Control Cohort**



CODEX Control Cohort

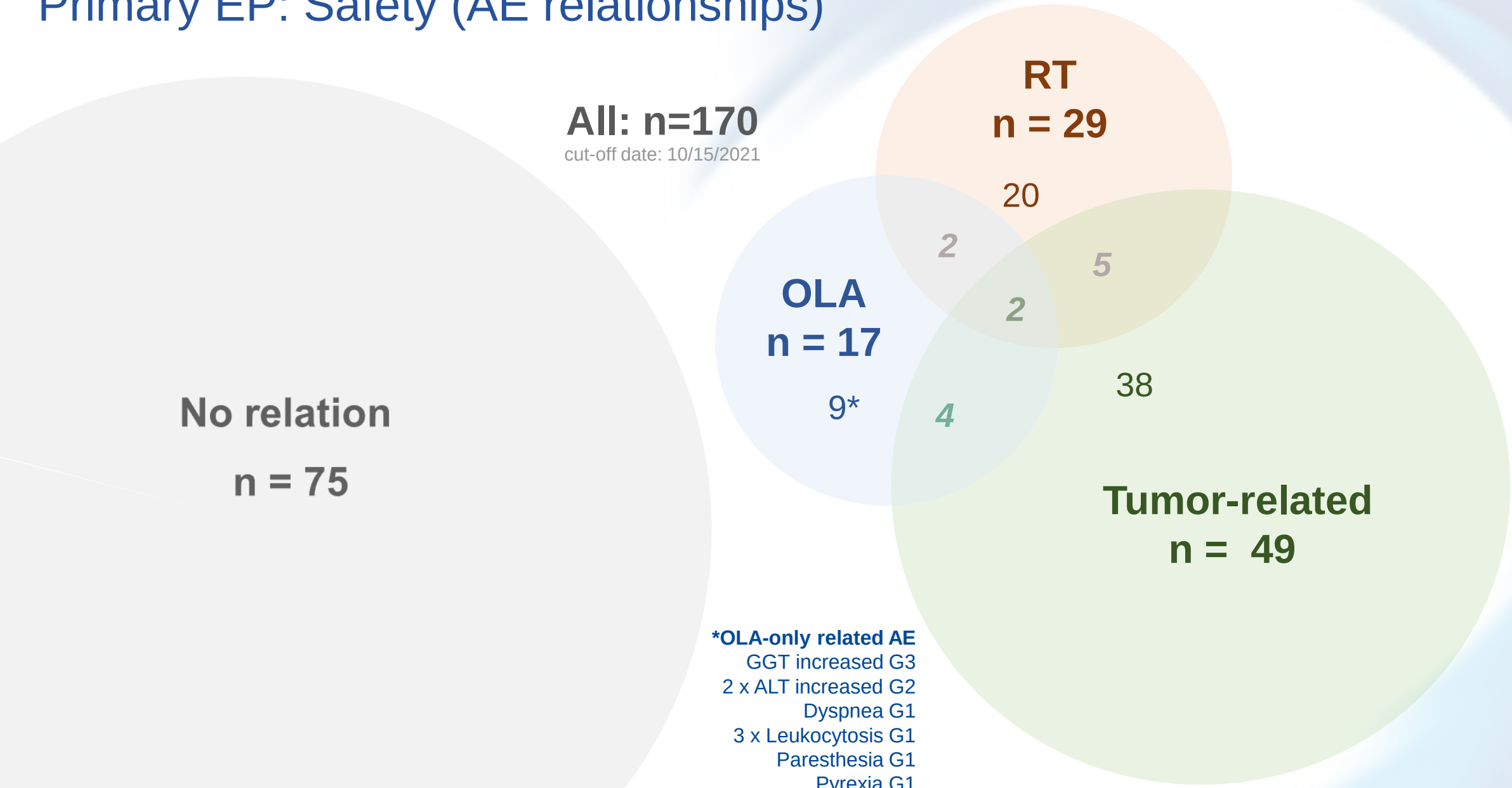
* Only performed for paired samples from 1st and 2nd surgery.

** 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)

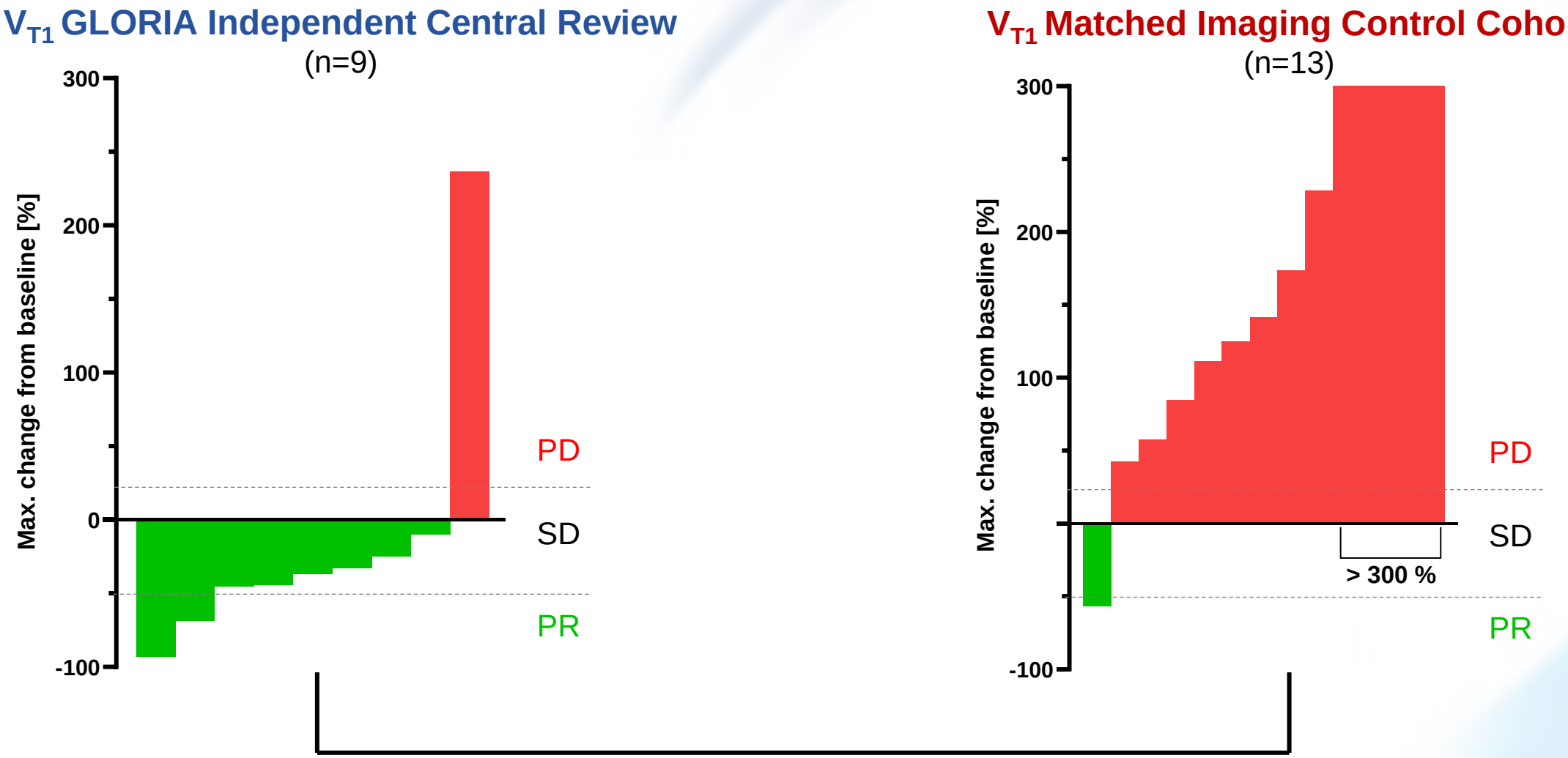
All: n=170

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

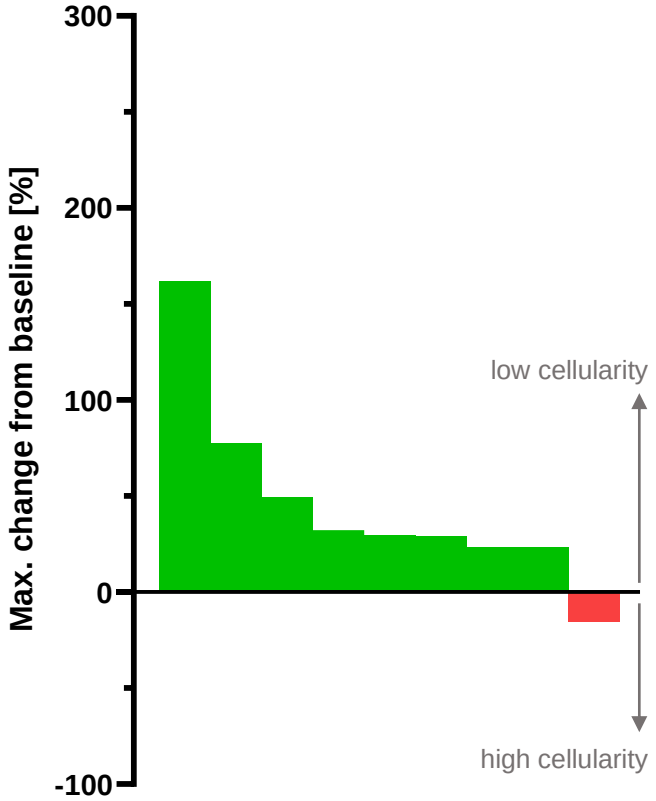
Best response under OLA (volume of T1 enhancing lesions)



Best response in cellularity and tumor perfusion under OLA

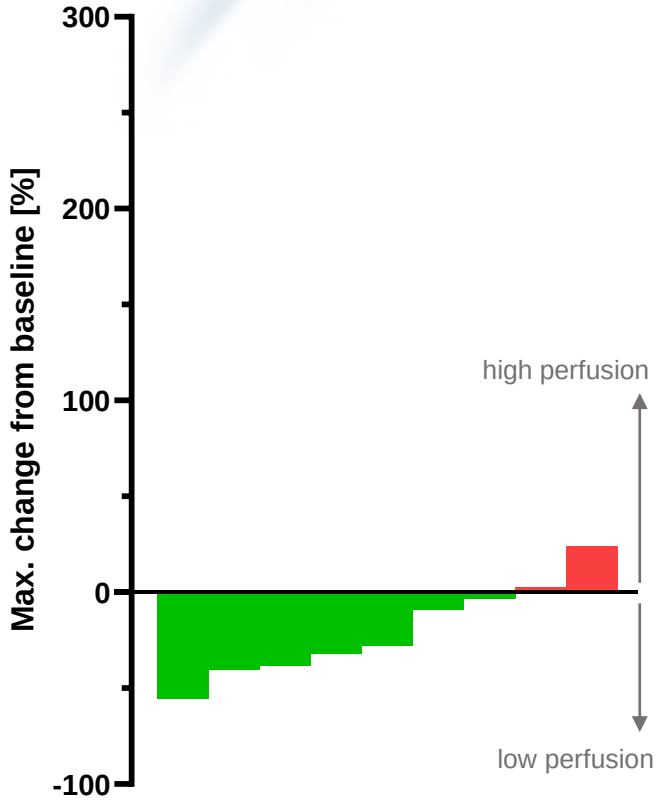
ADC mean

(Independent Central Review, n=9)



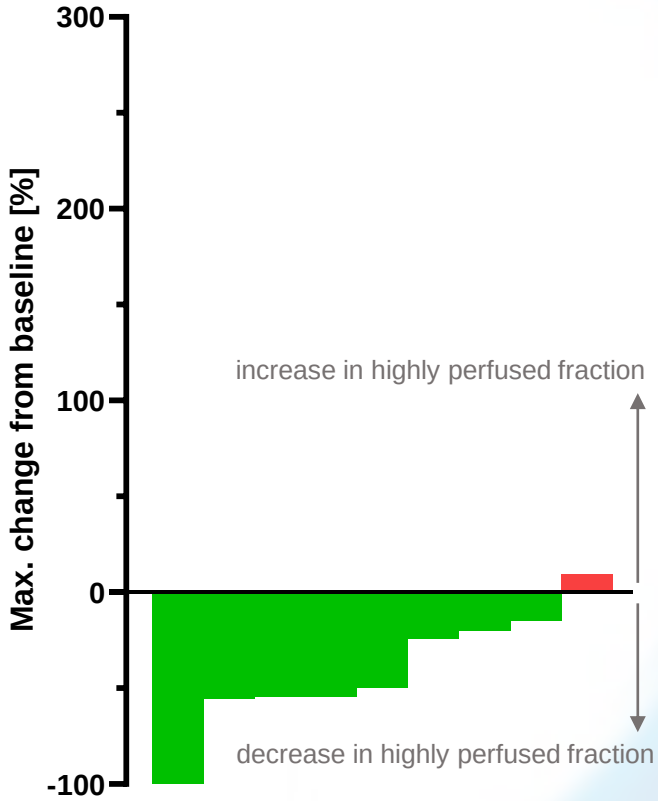
rCBV mean

(Independent Central Review, n=9)



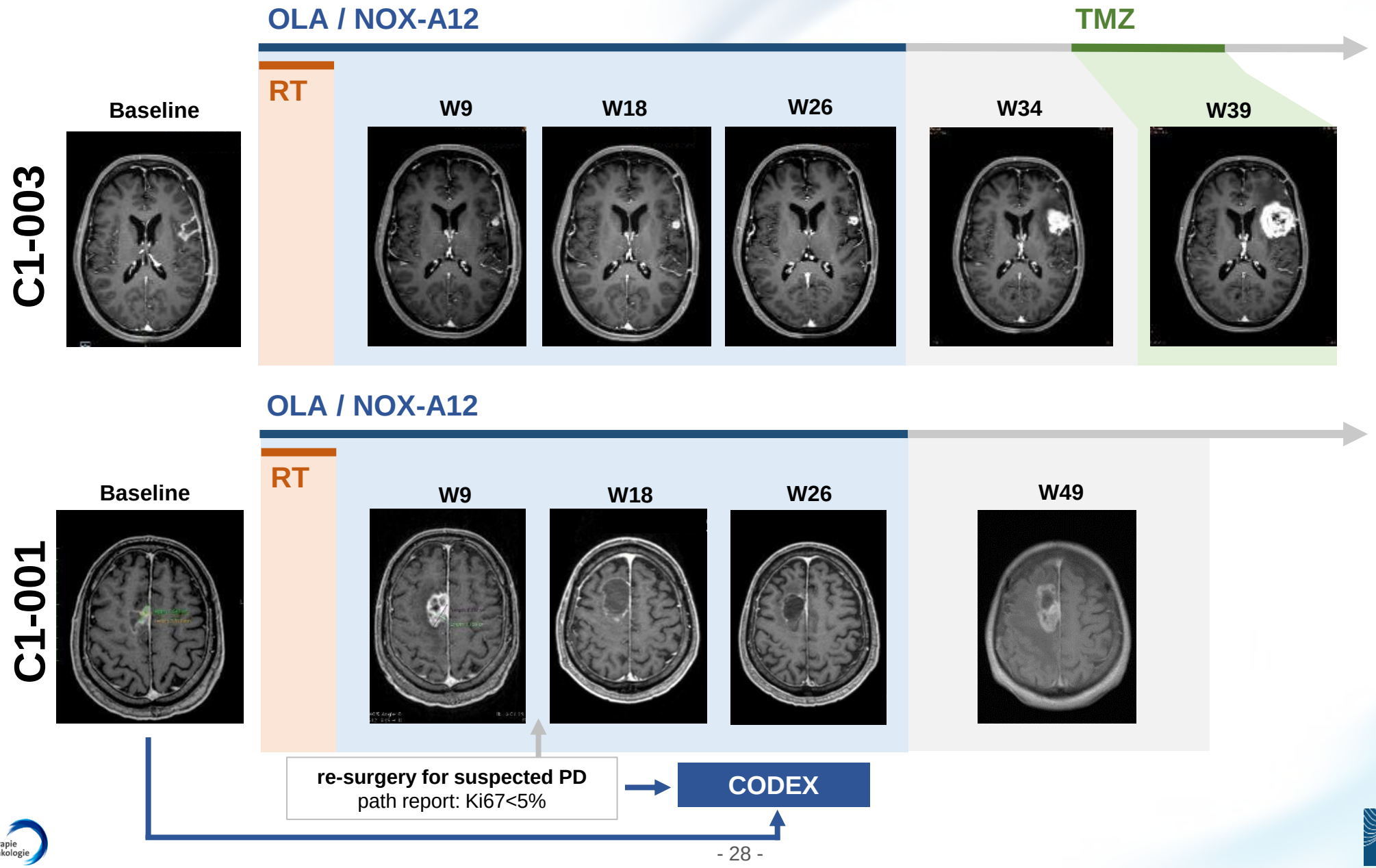
FTB^{high}

(Independent Central Review, n=9)



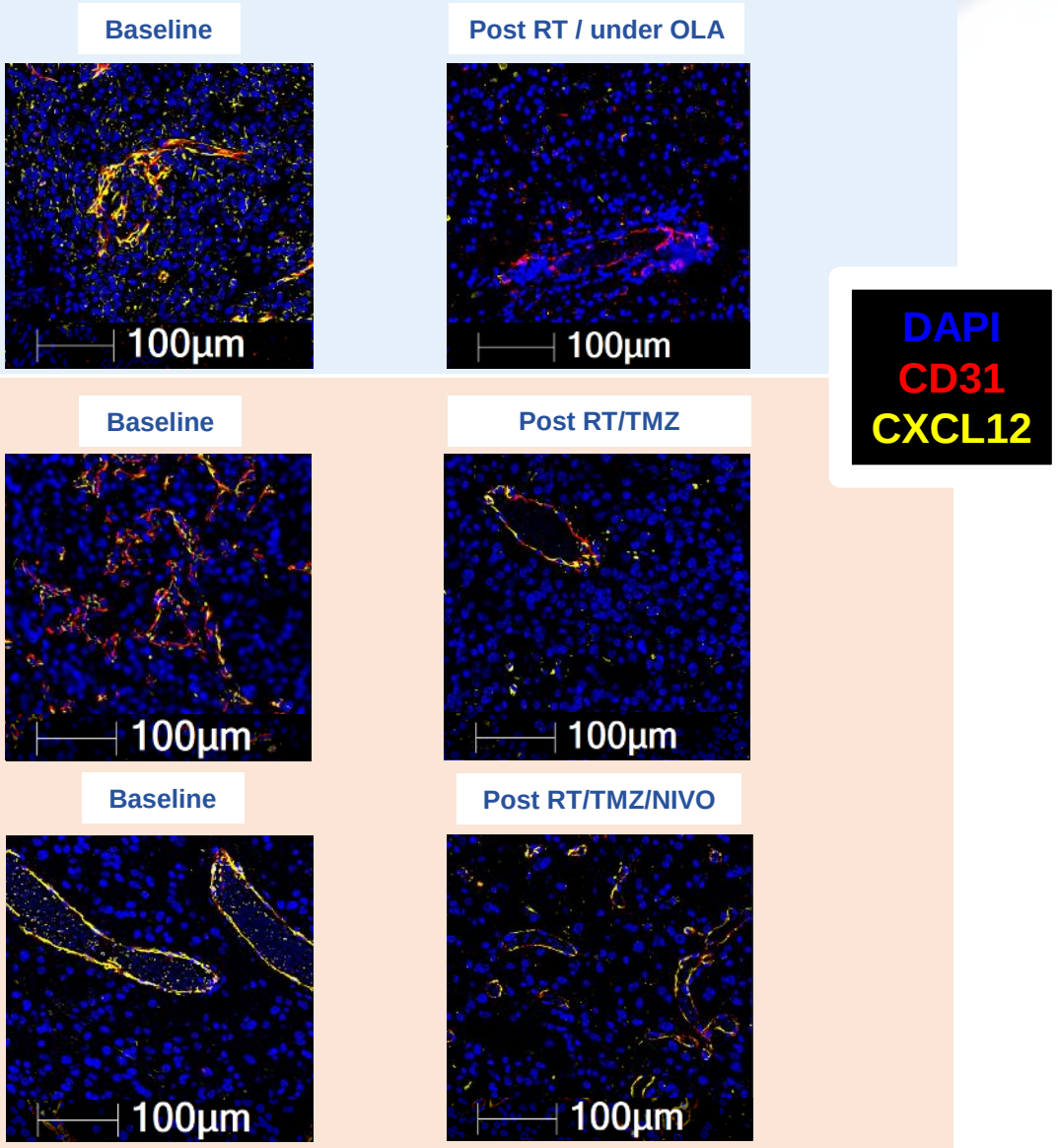
ADC, apparent diffusion coefficient (derived parameter from DWI sequences)
rCBV, standardized relative cerebral blood volume (derived parameter from DSC sequences)
FTB^{high} , fractional tumor burden with rCBV > 1.75

Exemplary response to RT/OLA

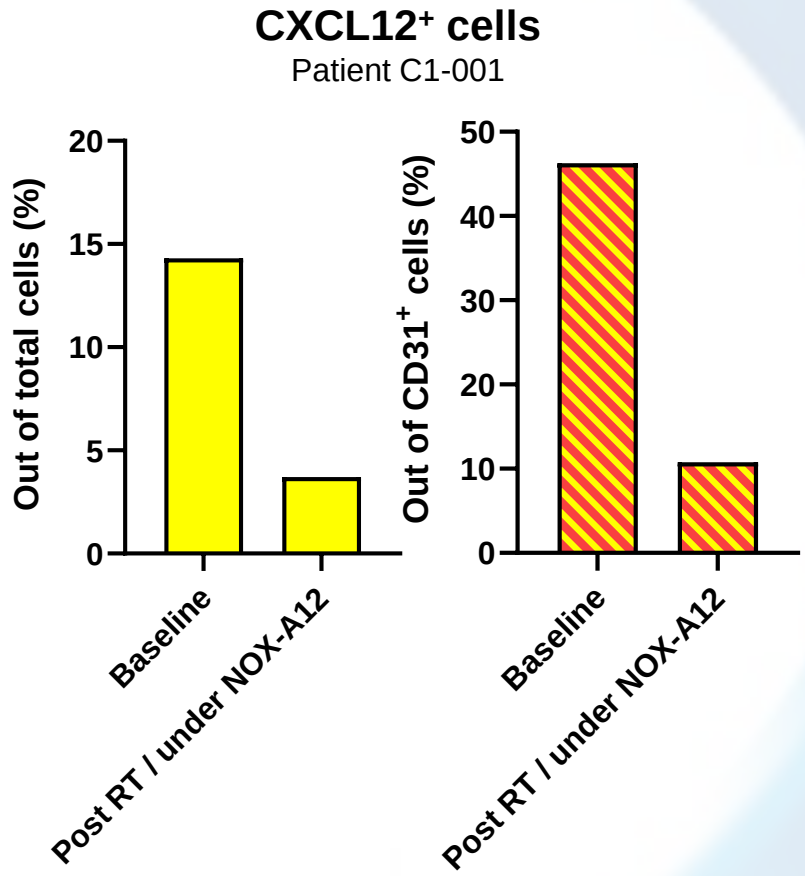


CODEX: RT/OLA reduces CXCL12 levels in the tumor endothelium

GLORIA
C1-001

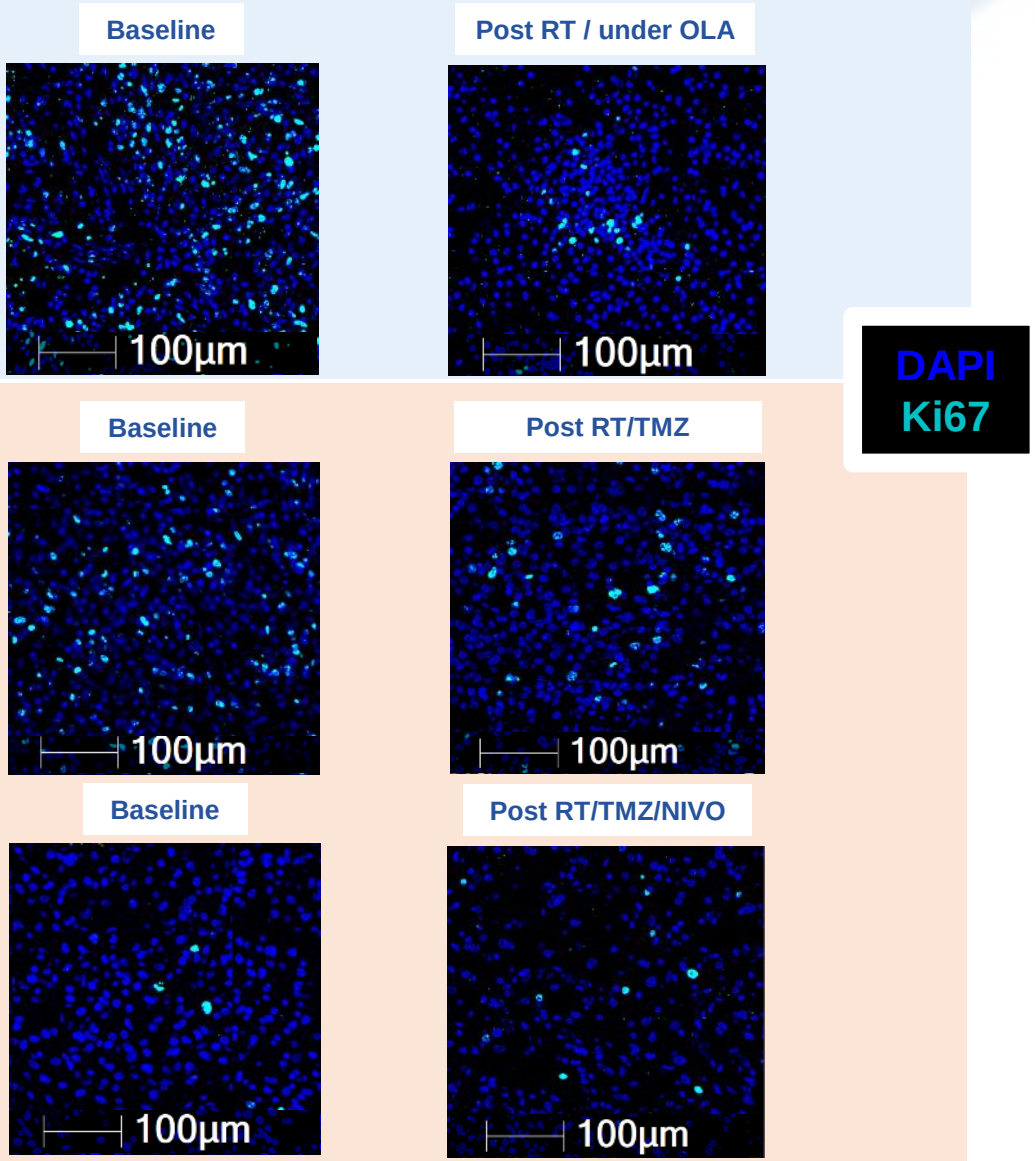


Images show areas of pathologist-confirmed tumor tissue

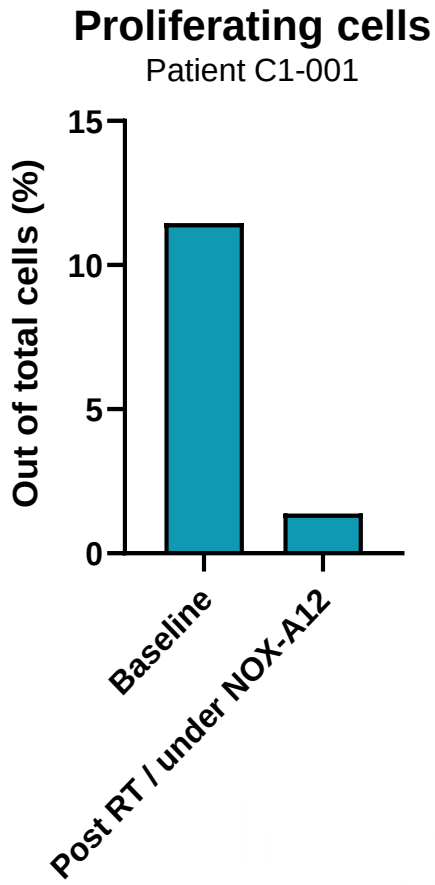


CODEX: RT/OLA reduces tumor cell proliferation

GLORIA
C1-001

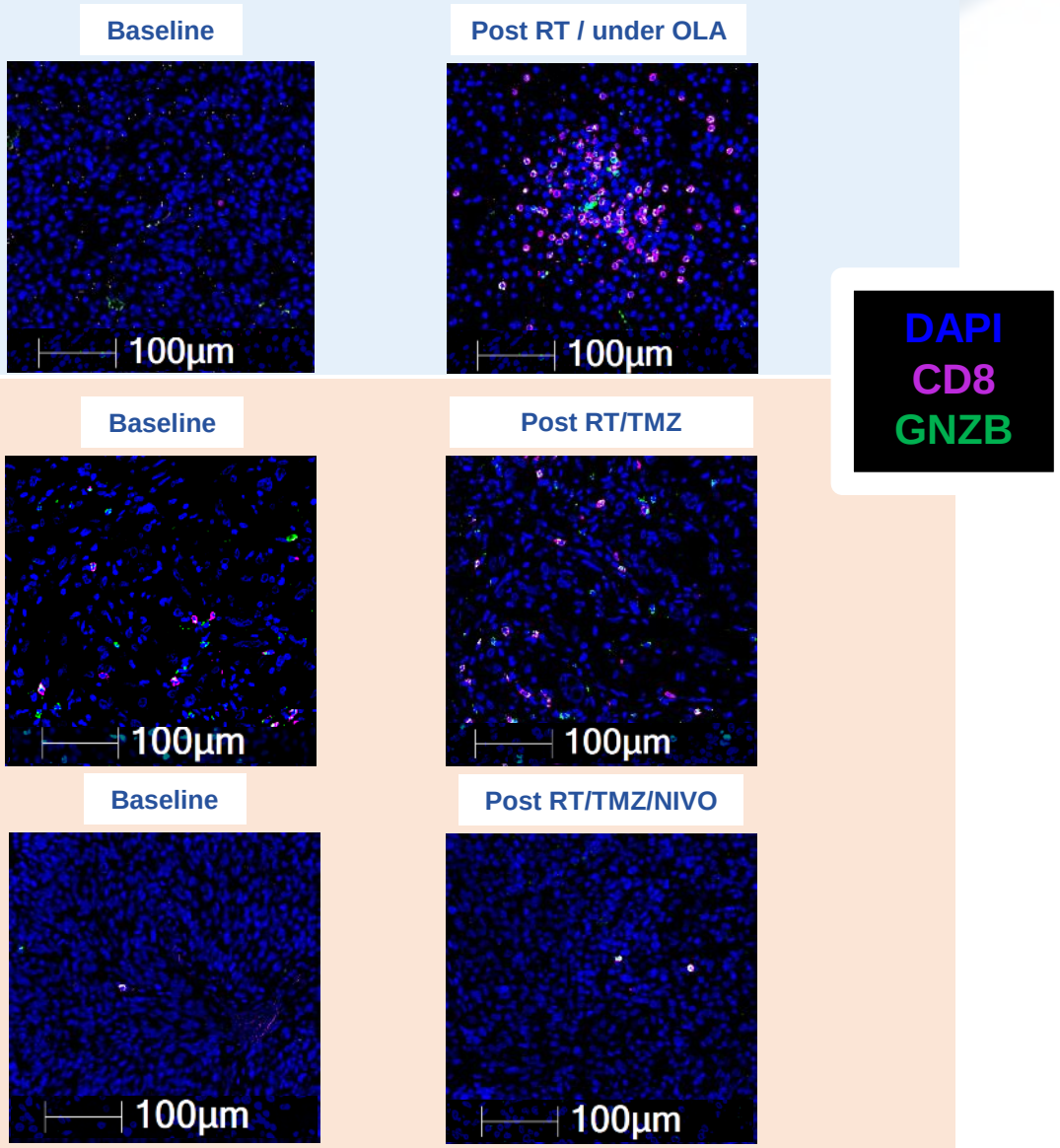


Images show areas of pathologist-confirmed tumor tissue



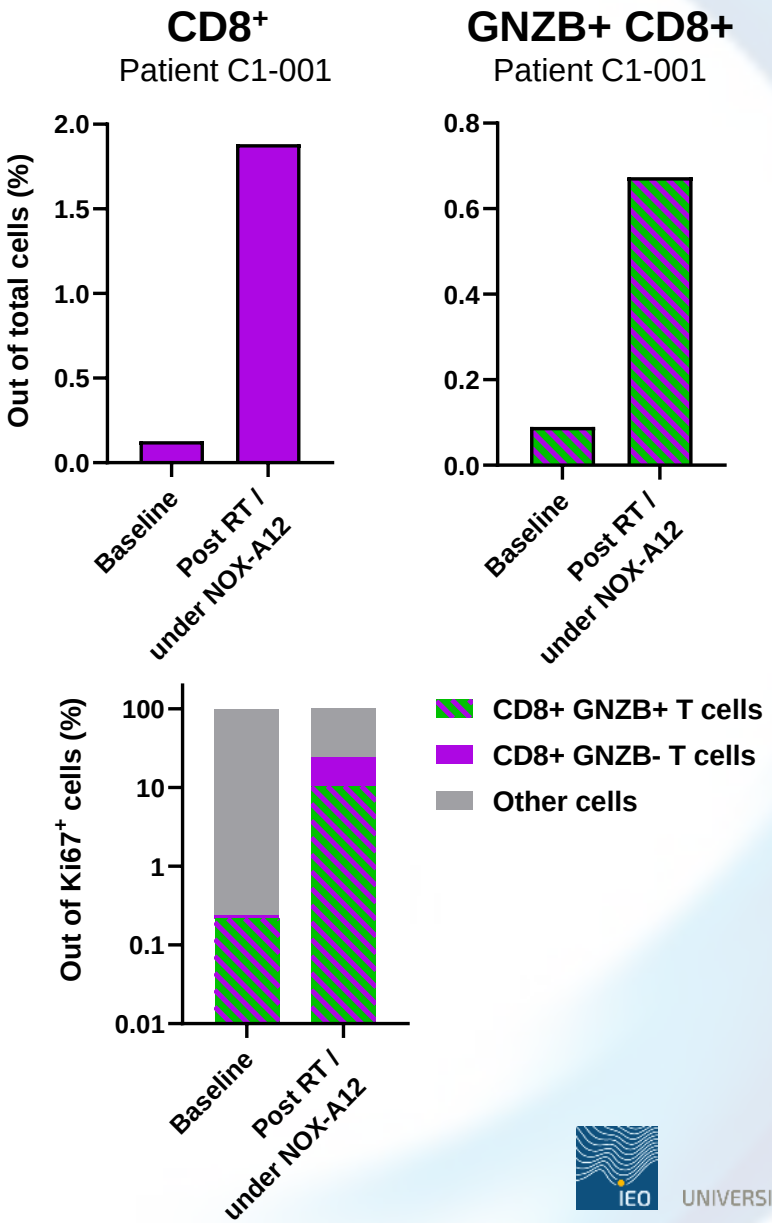
CODEX: Cytotoxic T cell infiltration and activation

GLORIA
C1-001



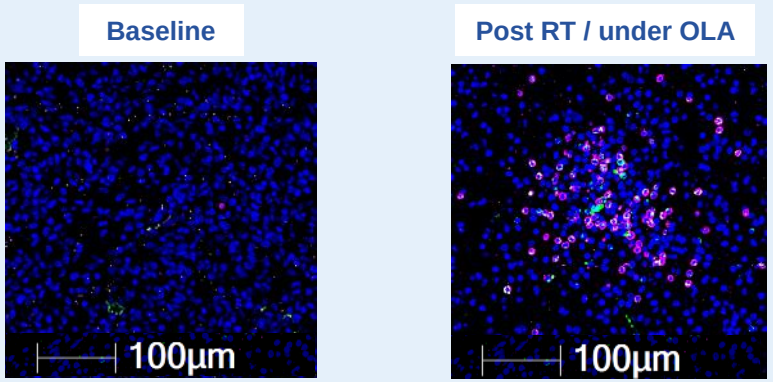
References

Images show areas of pathologist-confirmed tumor tissue

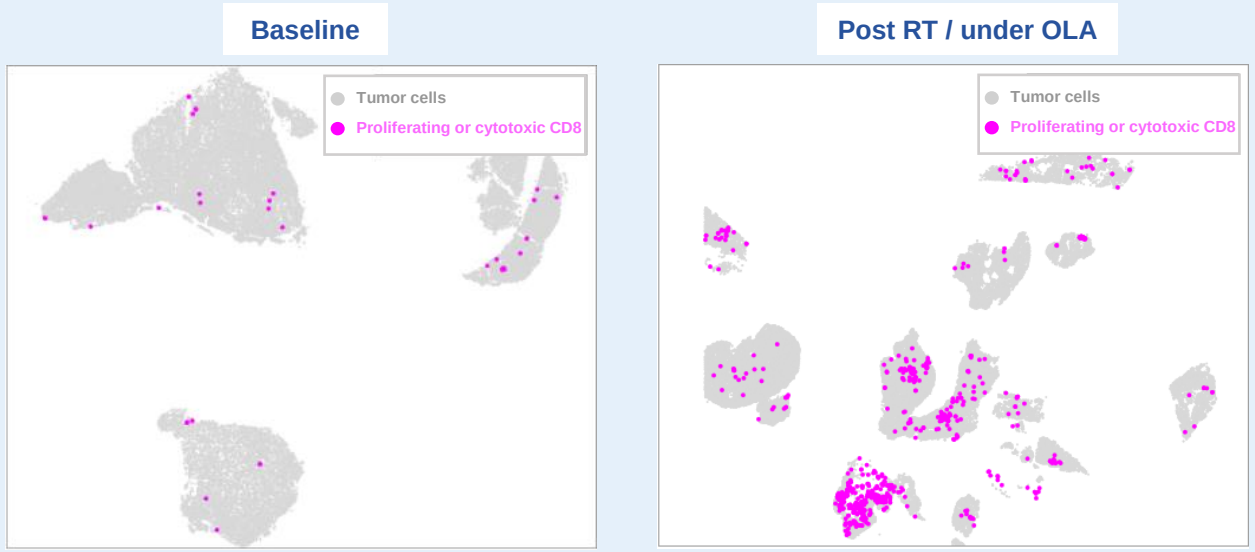


CODEX: Cytotoxic T cell infiltration and activation

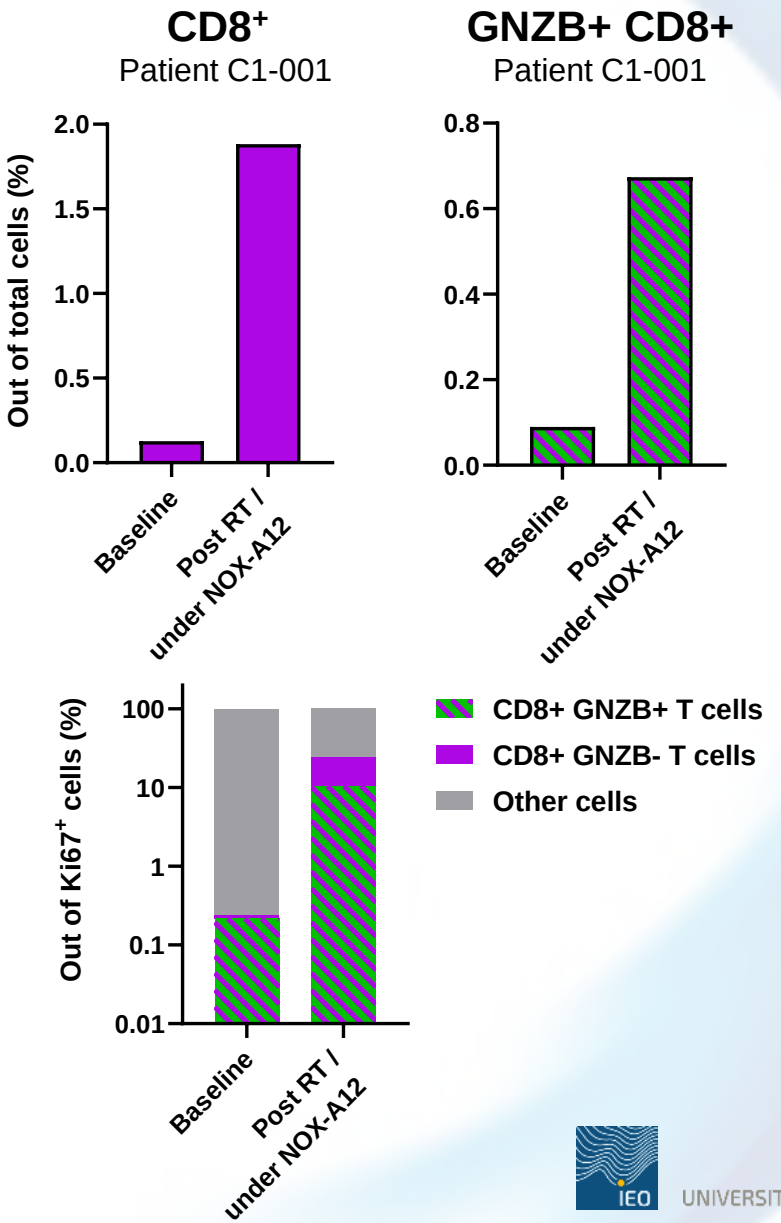
GLORIA
C1-001



Whole slide spatial Analysis



Images show areas of pathologist-confirmed tumor tissue



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**

Acknowledgements

UKB Radiation Oncology
Julian P. Layer
Katja Klever

UKB Exp. Oncology
Michael Hölzel
Sonia Leonardelli
Roberta Turiello

UKB Neuro-Oncology
Ulrich Herrlinger
Christiane Landwehr
Thomas Zeyen
Christina Schaub
Mirco Muscheid

UKB Neuropathology
Thorsten Pietsch
Lea Friker

UC London
Sotirios Bisdas

UKB Neuroradiology
Alexander Radbruch
Daniel Paech
Franziska Grau

ImmunoSensation^2
the immune sensory system Bonn cluster of excellence

Frank.Giordano@ukbonn.de

Uni Heidelberg
UH Mannheim
Elena Sperk
Katharina Sahm
Michael Platten

UH Leipzig
Clemens Seidel
Peter Hambsch
Nadja Talhi

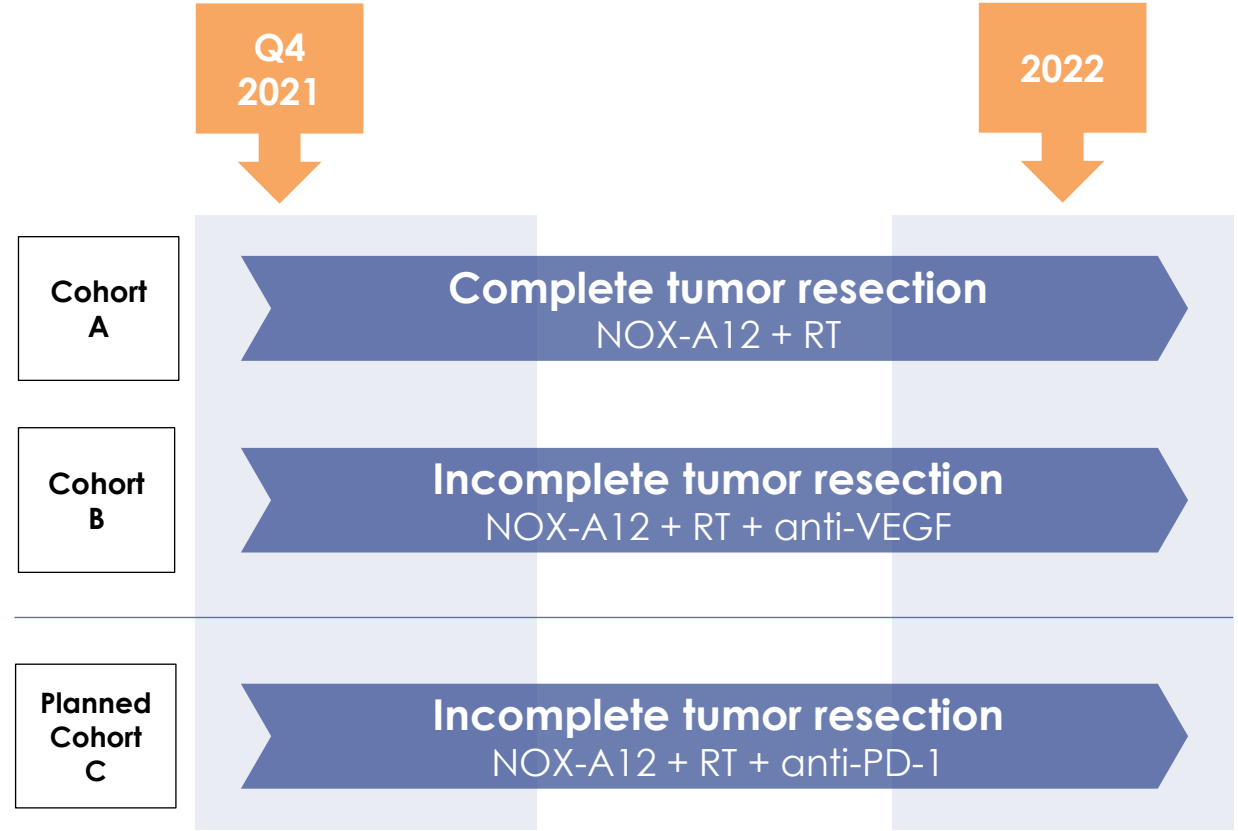
UH Essen
Martin Glas
Sied Kebir
Sarina Agkatsev

Expansion Cohorts of Phase 1/2 Trial in Brain Cancer

Newly diagnosed brain cancer (glioblastoma)

MGMT promoter unmethylated population: chemotherapy will be ineffective, so not used

NOX-A12 dose: 600mg/week



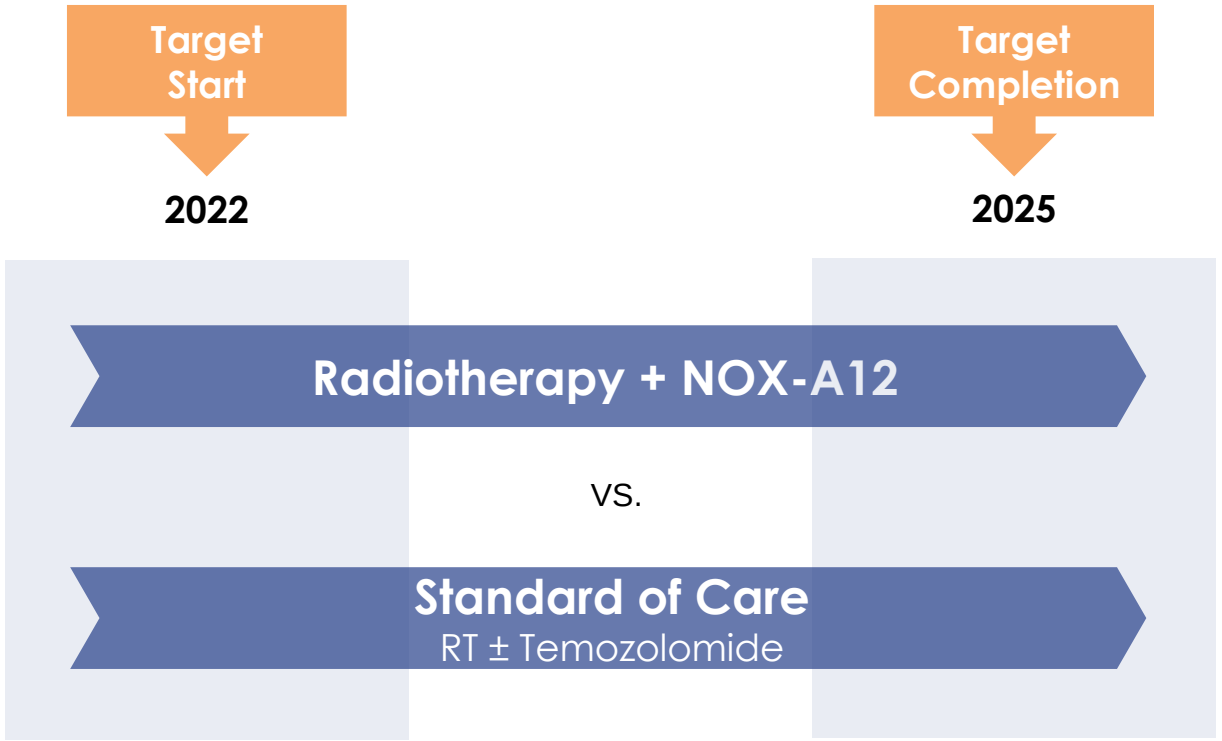
Expansion cohorts aim to provide additional clinical data to support the pivotal study trial design and discussions with the regulators

Next Step: Pivotal Trial in 1st line MGMT Promoter Unmethylated Patients – 2025 Read-out

Pivotal Study in newly diagnosed brain cancer (glioblastoma)

MGMT promoter unmethylated population: chemotherapy known to be ineffective[1]

Centers in EU & US



Treatment until progression to assess:

PFS, OS, other efficacy endpoints

1. Hegi et al. (2005) NEJM 352:997

Q&A Session

Dr. Frank Giordano
Chair & Director
Radiation Oncology Dept.
University Hospital Bonn

Lead investigator of NOX-A12
GLORIA Phase 1/2 study

Aram Mangasarian
CEO
NOXXON Pharma

Thank you!

Contact Us:

noxxon@noxxon.com

NOXXON PHARMA