KOL Webinar with Dr Frank Giordano

NOX-A12 Combination Therapies in First-Line Glioblastoma – The Key to the Tumor Microenvironment?
Analysis of Maturing Data from the Ongoing GLORIA Trial

November 22, 2022 | 12 PM ET / 6 PM CET

WEBINAR PRESENTERS

Dr. Frank Giordano
Professor and Chair of the Dept. of Radiation Oncology at the University Medical Center Mannheim
and Lead Investigator of NOX-A12 GLORIA Phase 1/2 Study

Aram Mangasarian
CEO
TME Pharma

Webinar moderated by:
Guillaume van Renterghem, Managing Director at LifeSci Advisors

Glioblastoma is a Devastating Orphan Brain Cancer where the TME Plays a Significant Role

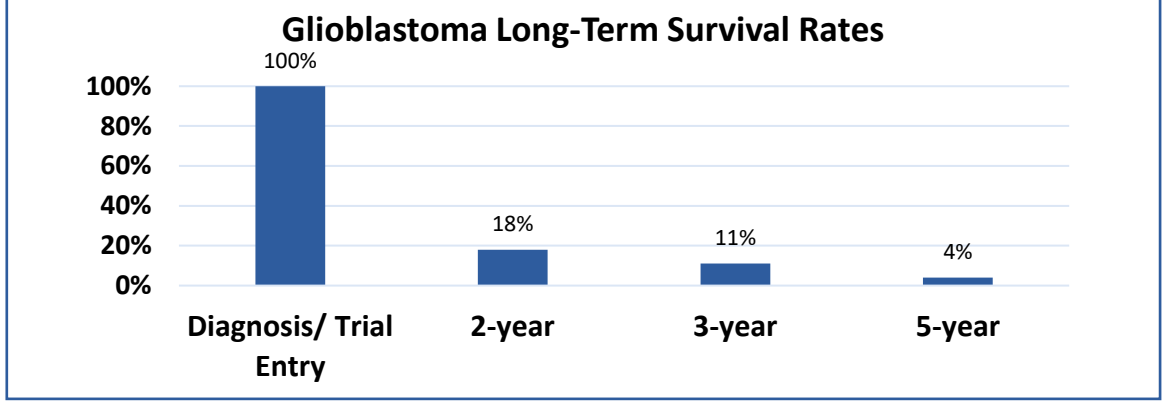
LACK OF EFFECTIVE THERAPIES & LOW OVERALL SURVIVAL

Orphan Status
29,000 New Cases per year[1]

4%

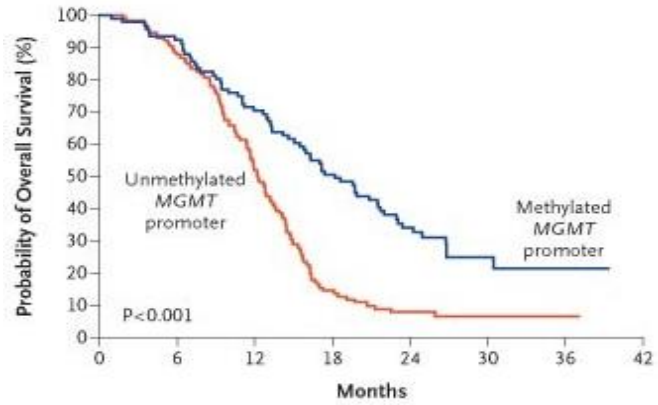
mOS
12-15 months

~ 160 active clinical trials



HIGH UNMET NEED PATIENT SEGMENTS

- MGMT unmethylated promoter – chemotherapy ineffective
- NOX-A12 to focus on MGMT unmethylated patients
- Incomplete resection – poor prognosis & therapeutic responses

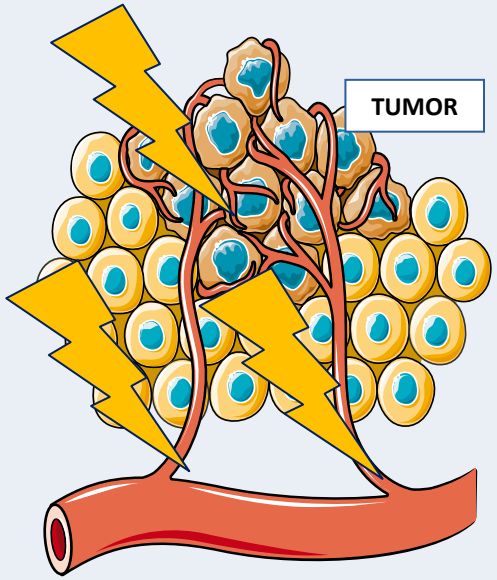


1. In the US, UK, FR, ES, DE & IT, Global Data April 2022

Sources: Poon MTC, et al., Scientific Reports 2020 Vol. 10 Issue 1; Hegi ME et al. N Engl J Med 2005;352:997-1003; Global Data, ClinicalTrials.gov & TME Pharma analysis, April 2022

NOX-A12's MOA is Relevant to GBM: Attacking Key Survival Mechanisms Following Radiotherapy

RADIOTHERAPY



RADIOTHERAPY kills many tumor cells and destroys blood vessels in irradiated zone leading to lack of oxygen (hypoxia) in the tumor making a more hostile environment for the tumor

Vessel destruction triggers **HYPOXIA**

SUPERIOR NOX-A12 PHARMACOLOGY
Direct targeting of CXCL12 provides more complete inhibition of axis than CXCR4 or CXCR7 antagonists

VASCULOGENESIS
Main driver of new vessel formation after radiotherapy is driven by CXCL12 and blocked by NOX-A12

HIF-1

HIF-1 triggers the two main pathways to re-grow blood vessels: **Vasculogenesis & Angiogenesis.**

CXCL12 chemokine

NOX-A12

Attraction to CXCL12

Monocytes

Endothelial cells

CXCR4 receptor

CXCR7 receptor

VEGF

ANGIOGENESIS
Limited role in new vessel formation post-RT in brain, significant role in other oncology settings

No survival benefit of anti-VEGF in GBM[1]

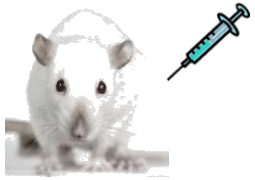
Inhibition of the CXCL12/CXCR4/CXCR7 axis can block tumor vasculogenesis

Source: Figure Adapted from Liu 2014, Neuro-Oncology 16:21 and Kioi 2010 J. Clin. Invest, 120:3
1. Gilbert et al., (2014) NEJM 30:8 & Chinot et al., (2014) NEJM 30:8

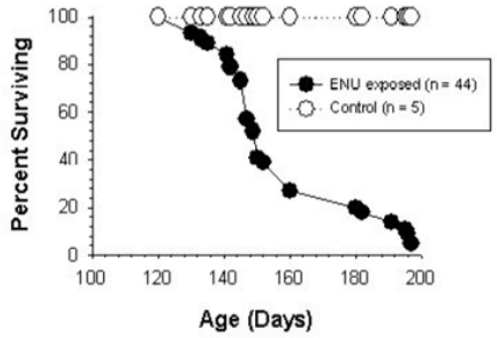
NOX-A12 + Radiotherapy Significantly Increases Survival and Demonstrates Complete Regression of Brain Tumors

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

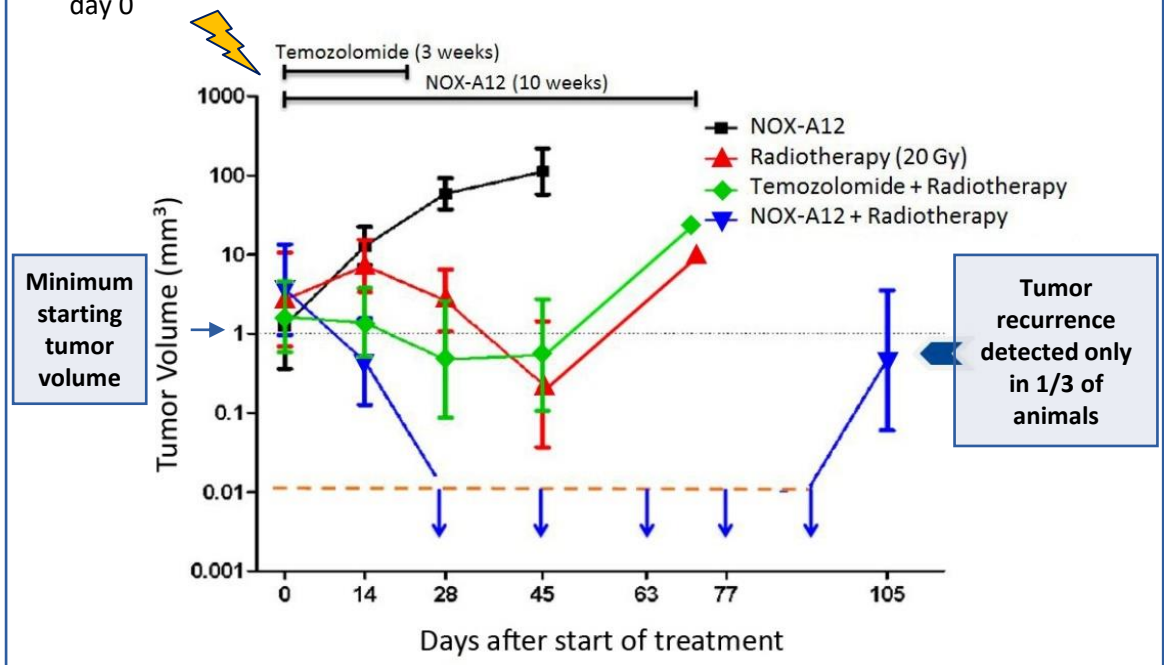


Pregnant rats:
ENU (carcinogen) on gestational age day 17 - 18



EFFECTS OF TREATMENTS

Radiotherapy at day 0



NOX-A12 + radiotherapy resulted in 100% complete response (66% durable) in brain cancer rat model

Source: Liu 2014, Neuro-Oncology 16:21

GLORIA Phase 1/2 Dose Escalation Study & Expansion Arms

Dose Escalation Cohort NOX-A12 + RT

NOX-A12 Doses tested:

200, 400 & 600 mg/week

Expansion Arms

NOX-A12 at 600 mg/week + Radiotherapy + anti-VEGF or anti-PD-1

1st line brain cancer (glioblastoma) with extremely poor prognosis due to:

- Incomplete surgical resection or biopsy only
- MGMT promoter unmethylated: chemotherapy ineffective

Standard of care in this population[1]:

- PFS of 6 months
- OS of 10 months

Radiotherapy

+

NOX-A12

Wearable pump[2] Continuous IV weekly refill

NOX-A12 + RT + anti-VEGF

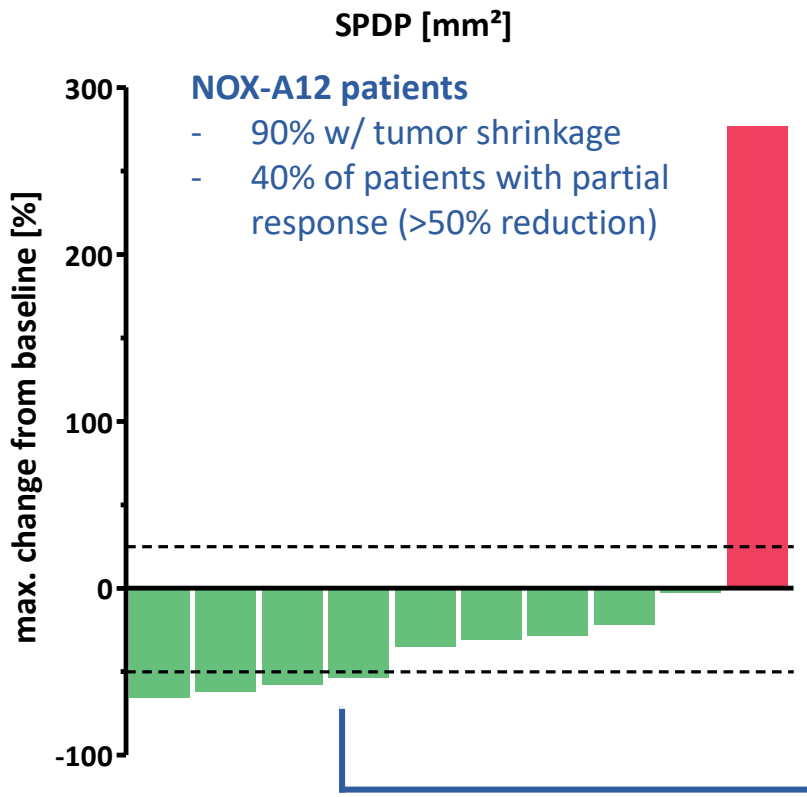
NOX-A12 + RT + anti-PD-1

1. Kreth 2013, Annals of Oncology 24:3117
2. CADD®-Solis VIP Ambulatory Infusion Pump by Smiths Medical

Best Response Under NOX-A12 + Radiotherapy (RT) vs. Matched Reference Cohort

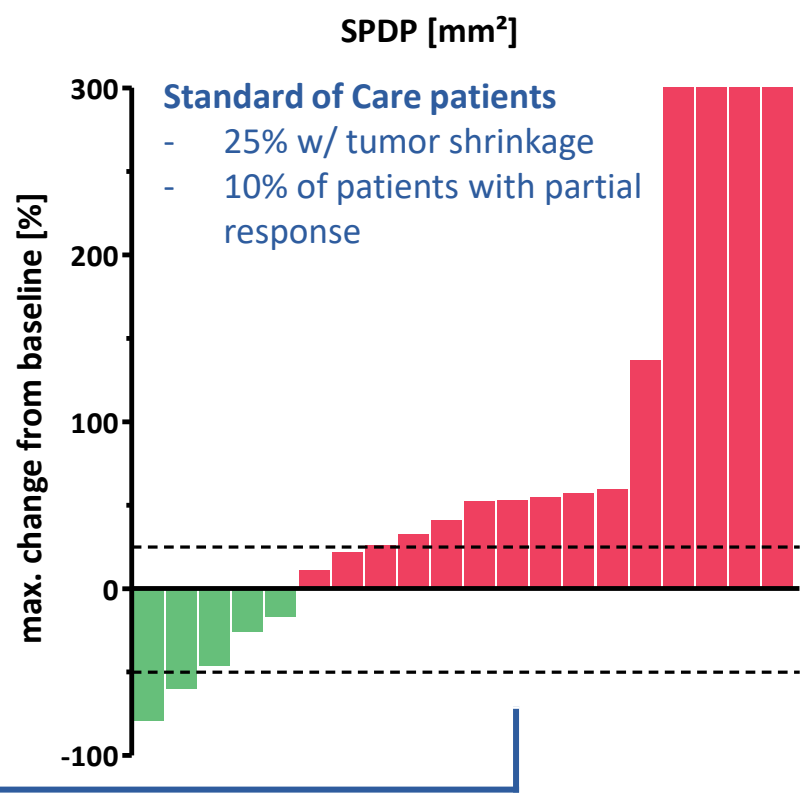
GLORIA MRI Assessment NOX-A12 + RT by Independent Central Reader

(n=10)



MRI Assessment of Standard of Care Matched Reference Cohort

(n=20)



p = 0.0044

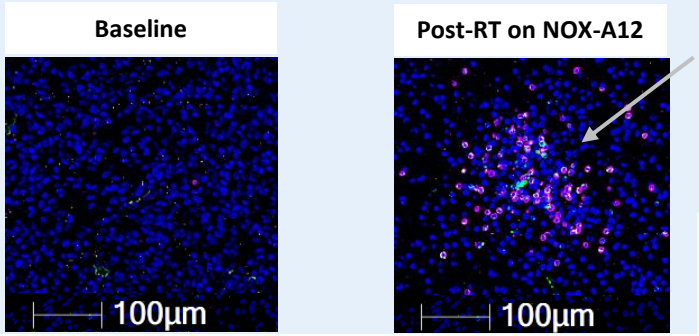
Non-parametric Mann Whitney U Test

2022 ASCO ANNUAL MEETING

Source: Giordano (2022) American Society for Clinical Oncology 2022 Annual Meeting Abstract of Poster #2050 of phase I/II GLORIA trial (NCT04121455), presented on June 5, 2022 & TME Pharma Press Release 26 May 2022

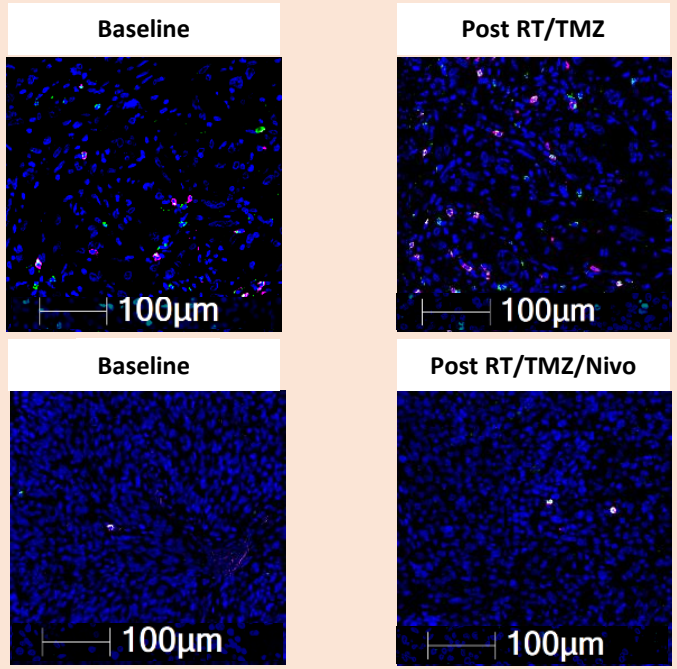
Multiplex-IF in On-therapy GBM Patient vs. References: Shows Extensive Infiltration of Activated Cytotoxic T Cells

GLORIA
C1-001

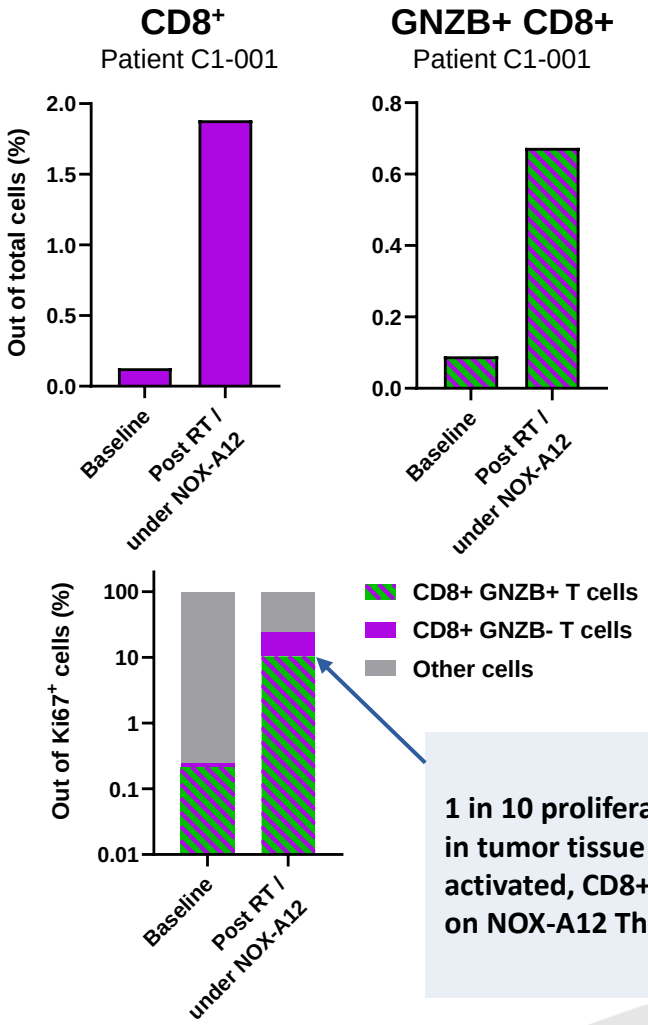


Clusters of Granzyme B positive, cytotoxic T cells consistent with coordinated immune response

References



DAPI
CD8
GNZB



1 in 10 proliferating cells in tumor tissue are activated, CD8+ T-cells on NOX-A12 Therapy

Images show areas of pathologist-confirmed tumor tissue

Source: Giordano (2021) Society for Neuro-Oncology 2021 Annual Meeting Presentation CTNI-43 – of phase I/II GLORIA trial (NCT04121455)

GLORIA Dose-Escalation Cohorts – Results

Toxicity

- Treatment was safe with no dose-limiting toxicity

Clinical Efficacy

- 9/10 patients achieved SD or better
- 4/10 patients achieved PR
- 3/4 of the responses occurred after completion of RT
- Signs of clinical efficacy despite 3+3 design with escalating doses, learning curve in handling the drug and low rates of 6-month drug exposure (mOS 12.7 months)
- Most striking is NOX-A12's ability to shrink tumors in nearly all patients when combined with radiotherapy

Translational Research

- CODEX revealed histopathological evidence of CXCL12 blockade by NOX-A12

GLORIA Phase 1/2 Dose Escalation Study & Expansion Arms

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Radiotherapy

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Wearable pump[2] Continuous IV weekly refill

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NOX-A12 + RT + anti-VEGF

NOX-A12 + RT + anti-PD-1

1. Kreth 2013, Annals of Oncology 24:3117
2. CADD®-Solis VIP Ambulatory Infusion Pump by Smiths Medical

Dr. Frank A. Giordano

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UMM UNIVERSITÄTSMEDIZIN MANNHEIM

DKFZ -Hector Krebsinstitut

dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

Medizinische Fakultät Mannheim der Universität Heidelberg

Universitätsklinikum Mannheim

Data from the GLORIA trial presented at the SNO on November 18 and further updates

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dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT

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DUAL INHIBITION OF POST-RADIOGENIC ANGIO- VASCULOGENESIS BY OLAPTESED PEGOL (NOX-A12) AND BEVACIZUMAB IN GLIOBLASTOMA – INTERIM DATA FROM THE FIRST EXPANSION ARM OF THE GERMAN PHASE 1/2 GLORIA TRIAL.

Frank A. Giordano[1], Julian P. Layer[1,2], Sonia Leonardelli[2], Lea L. Friker[3], Christina Schaub[4], Roberta Turiello[2], Elena Sperk[5], Iris Mildenberger[6], Franziska Grau[7], Daniel Paech[7], Torsten Pietsch[3], Wolf Mueller[8], Oliver Grauer[9], Mirjam Renovanz[10], Ghazaleh Tabatabai[10], Sied Kebir[11], Martin Glas[11], Sotirios Bisdas[12], Peter Hambsch[13], Clemens Seidel[13], Michael Hölzel[2] , Ulrich Herrlinger[4]

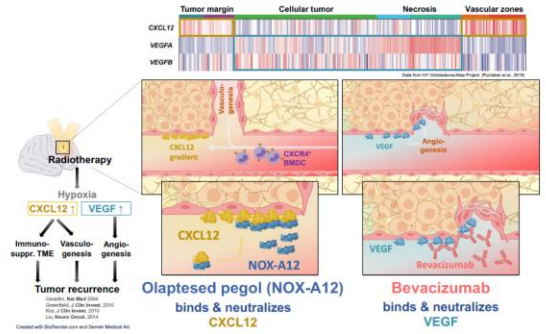
[1] Department of Radiation Oncology, University Hospital Bonn; [2] Institute of Experimental Oncology, University Hospital Bonn; [3] Department of Neuropathology, University Hospital Bonn; [4] Department of Neurology, University Hospital Bonn; [5] Department of Radiation Oncology, University Hospital Mannheim, University of Heidelberg; [6] Department of Neurology, University Hospital Mannheim, University of Heidelberg; [7] Department of Neuroradiology, University Hospital Bonn; [8] Institute of Neuropathology, University Hospital Leipzig; [9] Department of Neurology, University Hospital Münster; [10] Department of Neurology, University Hospital Tübingen; [11] Department of Neurology, University Hospital Essen; [12] Department of Neuroradiology, National Hospital for Neurology London; [13] Department of Radiotherapy, University Hospital Leipzig

SNO Annual Meeting 2022
CTNI-67

1 RATIONALE & STUDY DESIGN

Dual inhibition of the CXCL12- and VEGF-axes after radiotherapy (RT) of glioblastoma (GBM)

- abrogates CXCL12-dependent recruitment of pro-vasculogenic/tumorigenic bone marrow-derived cells (BMDC)
- prevents VEGF-driven angiogenesis within the tumor compartments



Key inclusion criteria:

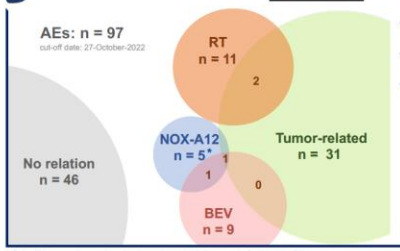
- Newly-diagnosed supratentorial GBM CNS WHO grade 4
- MGMT promoter unmethylated
- Incomplete resection
- ECOG ≤ 2

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

Secondary Endpoints: NOX-A12 plasma levels, tumor vascularization/perfusion as per advanced MRI, PFS-6, mPFS, OS, QoL (Quality of Life), NANO (Neurologic Assessment in Neuro-Oncology)

Exploratory Endpoint: Translational characterization of TME by CODEX®

2 SAFETY



- Triple treatment well-tolerated and safe
- Of all G≥2 AEs (n = 66), 3 (4.5%) NOX-A12-related (all G2)
- No dose limiting toxicities (DLT) and no treatment-related deaths

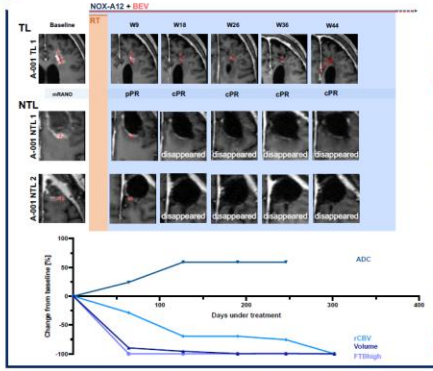
***NOX-A12-only related AE**

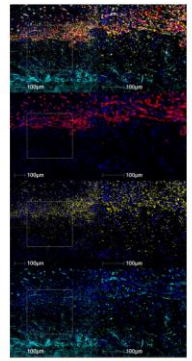
Extravasation	G2
Infusion site reaction	G2
Peripheral edema	G2

3 TREATMENT COURSE

- 5/6 patients achieved partial responses (PRs) as per mRANO in week 9
- All PRs remained durable at a median follow-up (FU) of 7.6 months
- Longitudinal NANO assessment revealed stable neurologic functioning in 5/6 patients
- PD in A-006 due to CSF metastases while target lesion control was maintained

4 EXEMPLARY PATIENT





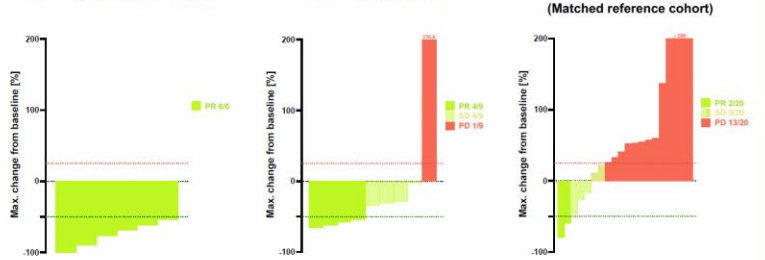
Left panel:
Radiographic treatment course of patient A-001 with target lesion (TL), non target lesions (NTLs) and MRI volumetric, diffusion (ADC) and perfusion (rCBV, FTBhigh) parameters (treatment ongoing)

Right Panel:
Multiplexed immunofluorescence (CODEX®) analysis of pretherapeutic tumor tissue of the same patient confirms distinct spatial distribution of CXCL12 and VEGFB in tumor compartments

DAPI
CD31
CXCL12
VEGFB

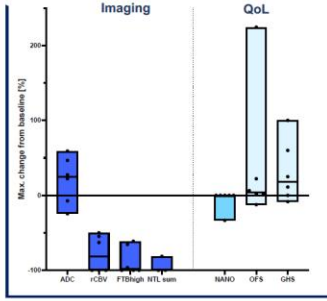
Radiotherapy + NOX-A12 + Bevacizumab in chemotherapy refractory **GBM**
Safe | No DLT | Encouraging efficacy of dual inhibition of angio-vasculogenesis
Treatment and follow up ongoing

5 TARGET LESION RESPONSE



- Trial results (left) were compared to the previously reported dose escalation cohorts (center) and a matched imaging reference cohort (right) treated with standard of care (SOC)
- The mean best sum of perpendicular diameters (SPD) response was -74.9% (-53.8% to -99.9%) for TL sums
- In 3/3 patients with NTL at least one lesion disappeared (not shown)

6 ADVANCED IMAGING & QoL



Mean best changes from baseline

Advanced imaging:

- Apparent Diffusion Coefficient (ADC) 20.6% (-24.5% to 59.1%)
- relative Cerebral Blood Volume (rCBV) -77.9% (-50 to -100%)
- Highly perfused-tumor fraction (FTB_{high}) -87.2% (-61.3% to -100%)
- SPD response of NTL sums -93.8% (-81.4% to -100%)

Clinician reported outcome:

- NANO response -5.6% (0% to -33.3%)

Patient reported outcome:

- Overall Function Score (OFS) 40.7% (-12.4% to 224.4%)
- Global Health Score (GHS) 31.3% (-8.3% to 100%)

REGISTRATION & CONTACT

Trial sponsored by TME Pharma AG
Registered with clinicaltrials.gov, ID: NCT04121455
Frank.Giordano@umm.de

UMM UNIVERSITÄTSMEDIZIN MANNHEIM
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dkfz. DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT
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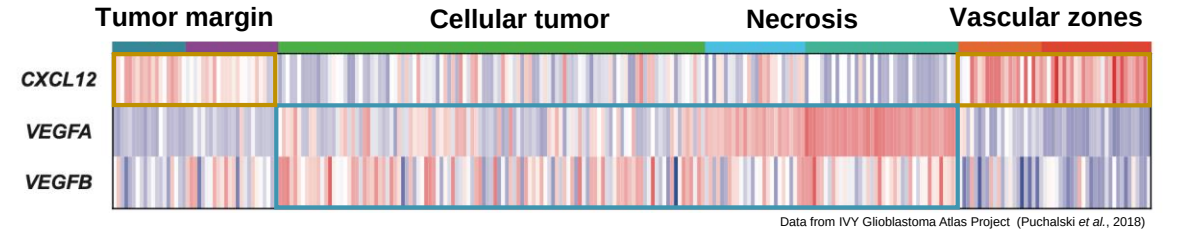
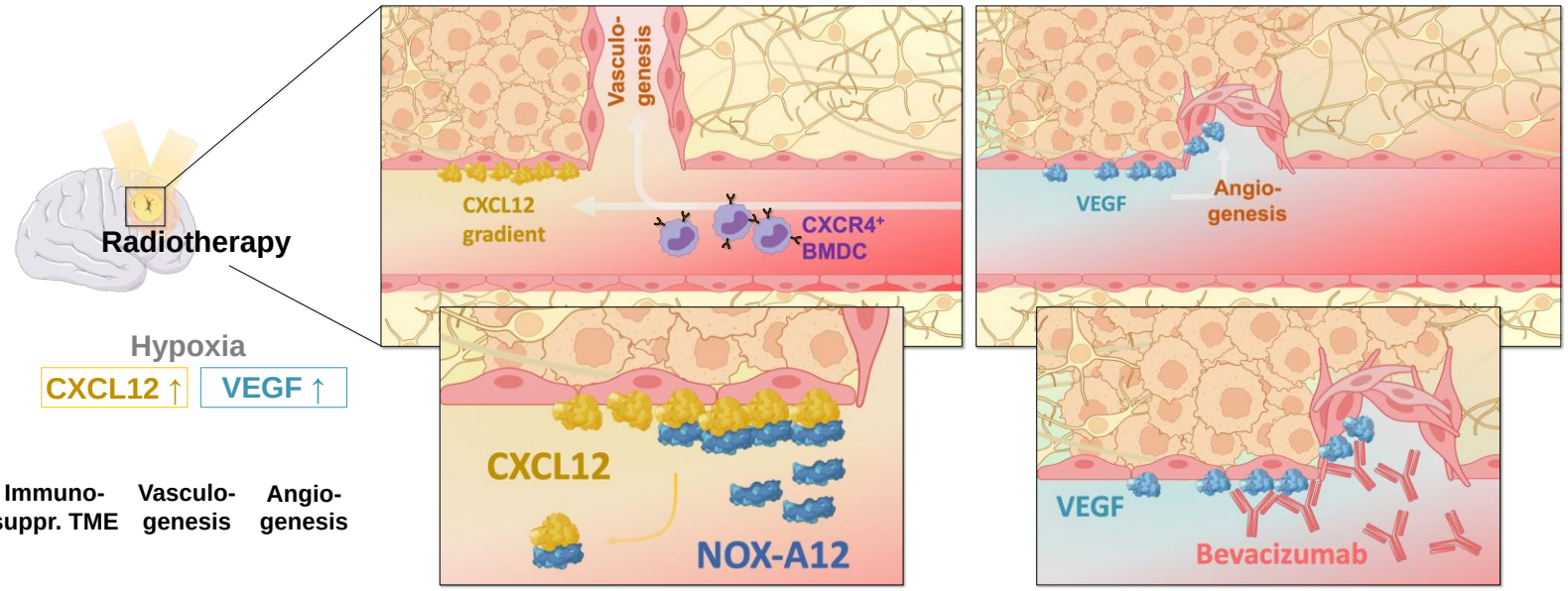


Data from IVY Glioblastoma Atlas Project (Puchalski *et al.*, 2018)



Tumor recurrence

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

Created with BioRender.com and Servier Medical Art.

Olaptesed pegol (NOX-A12)
binds & neutralizes
CXCL12

Bevacizumab
binds & neutralizes
VEGF

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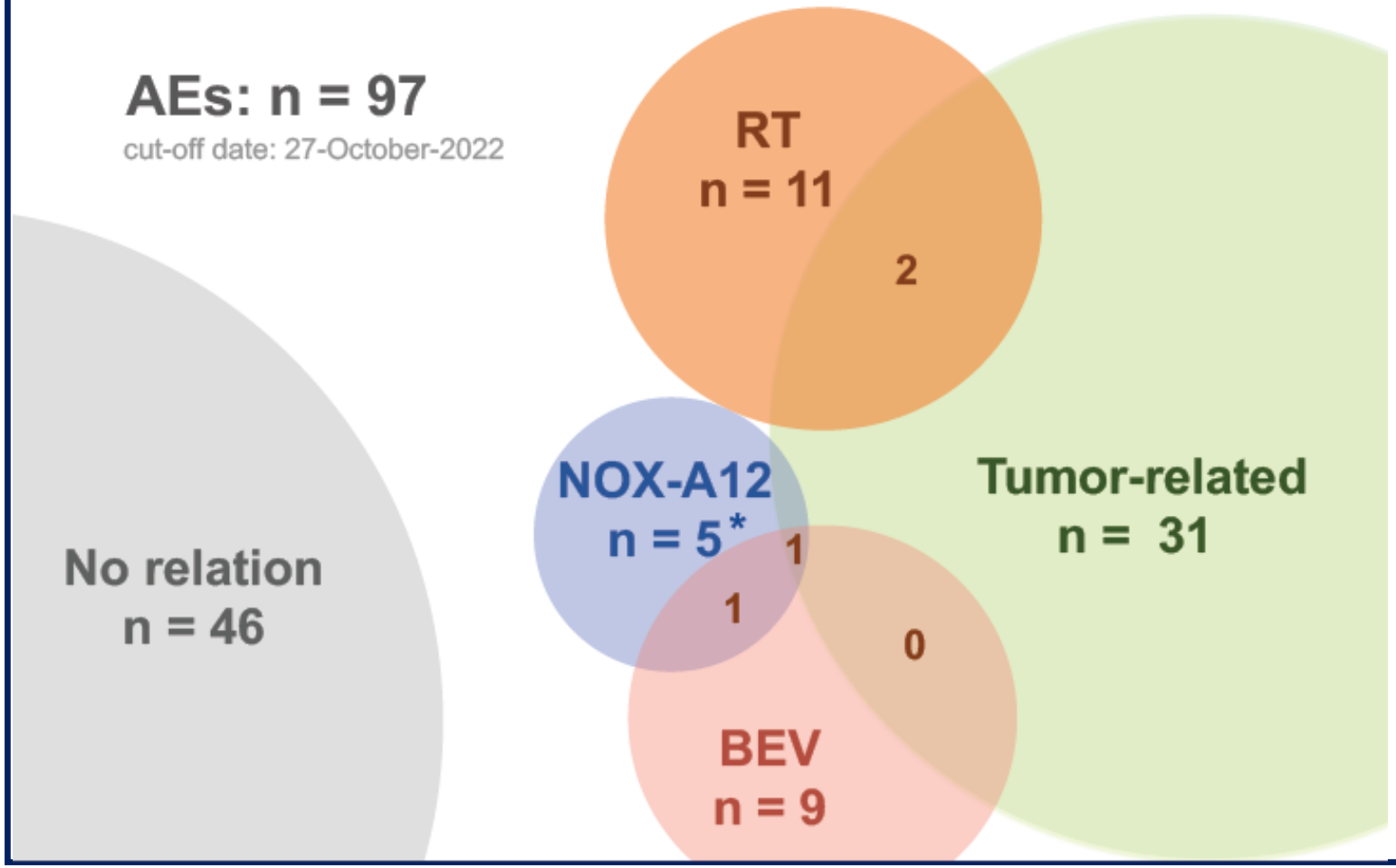
SAFETY



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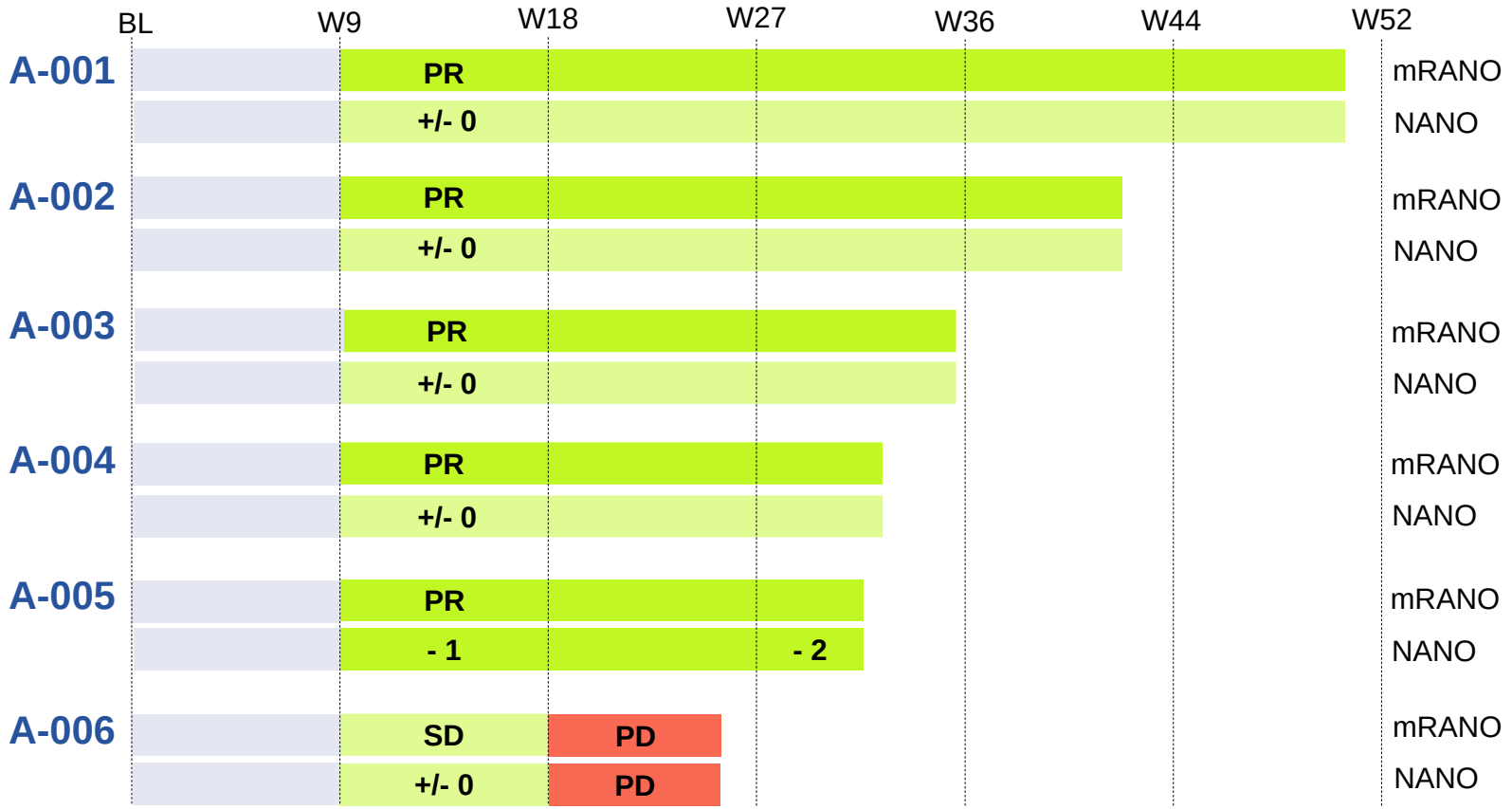
TREATMENT COURSE



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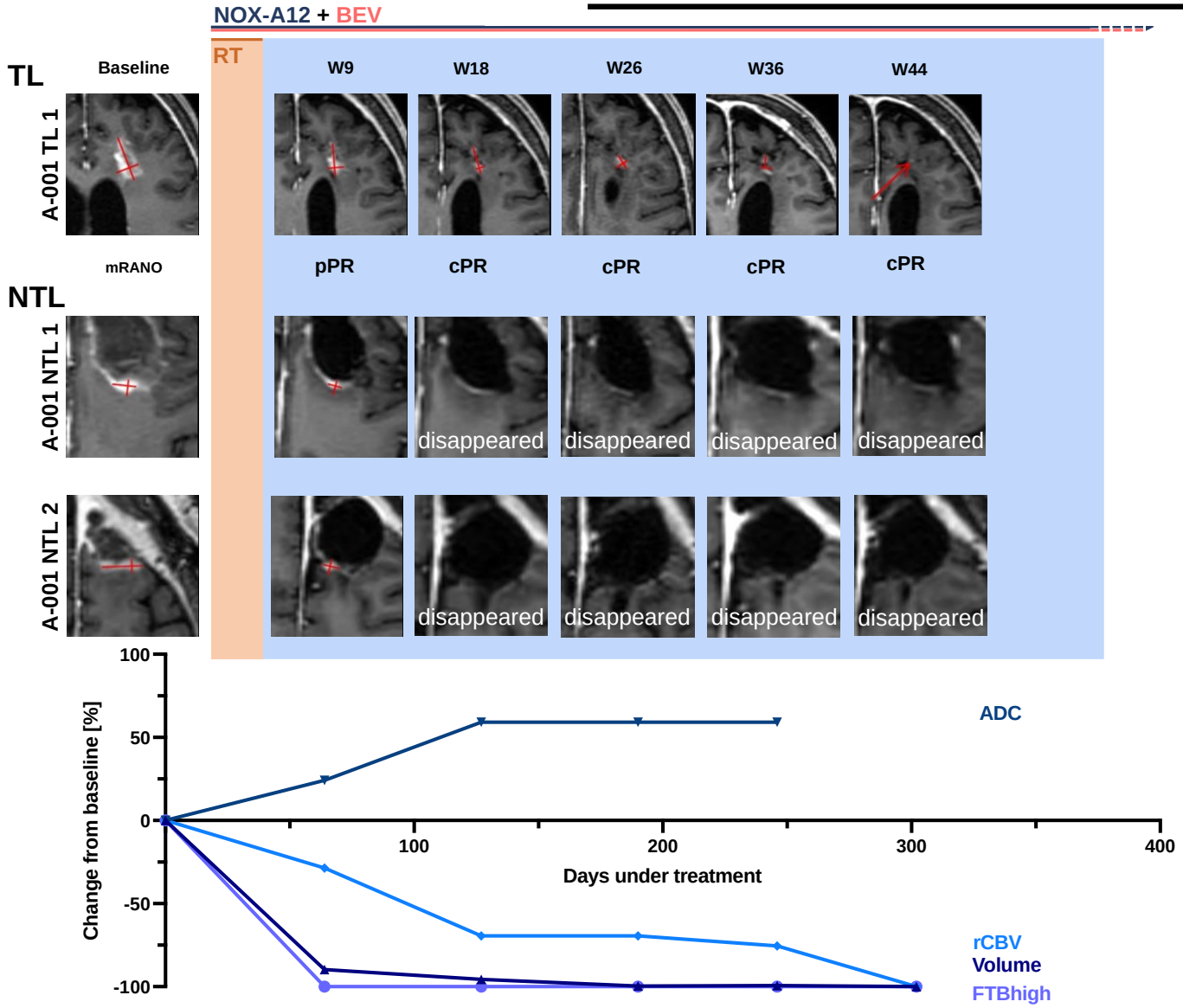
NANO: decrease in score represents improvement

EXEMPLARY PATIENT



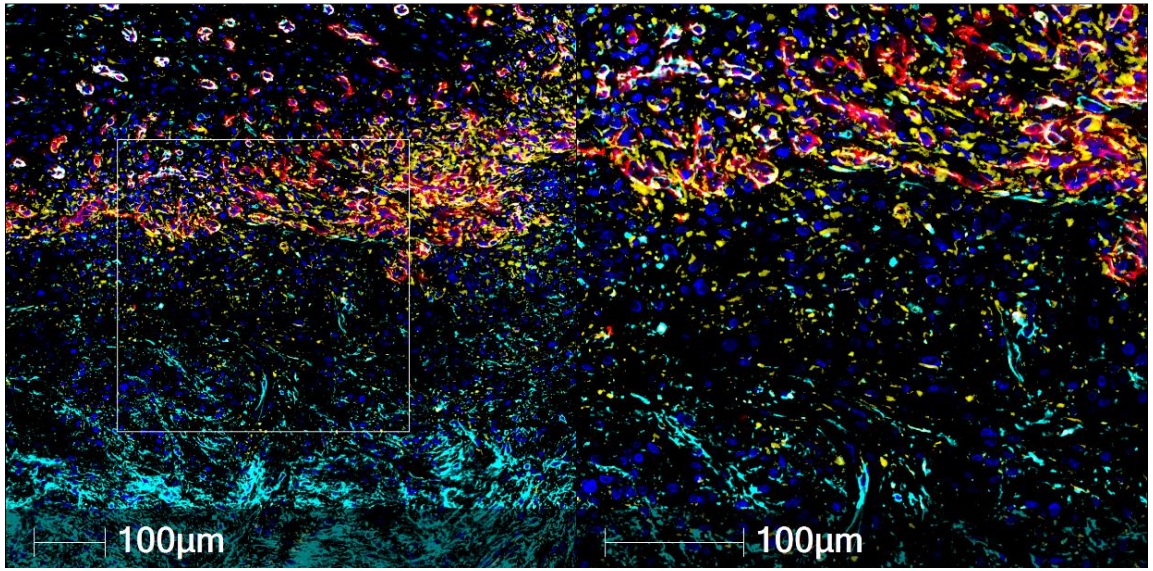
Radiographic treatment course of patient A-001 with target lesion (TL), non target lesions (NTLs) and MRI volumetric, diffusion (ADC) and perfusion (rCBV, FTBhigh) parameters (treatment ongoing)

Changes from baseline:
ADC: increase in change represents improvement
rCBV, Volume, FTBhigh: decrease in change represents improvement

4

EXEMPLARY PATIENT

Multiplexed immuno-fluorescence (CODEX®) analysis of pretherapeutic tumor tissue of the same patient confirms distinct spatial distribution of CXCL12 and VEGFB in tumor compartments



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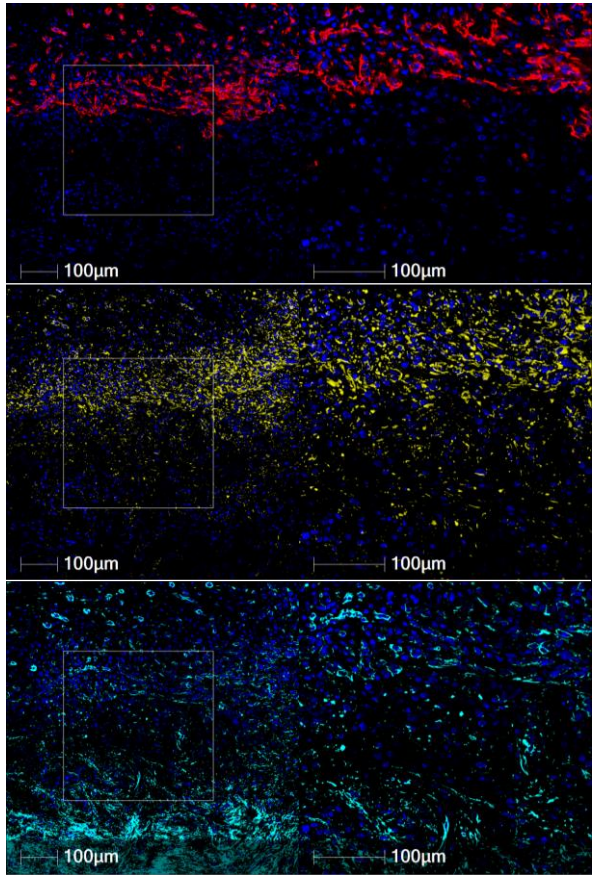

CD31

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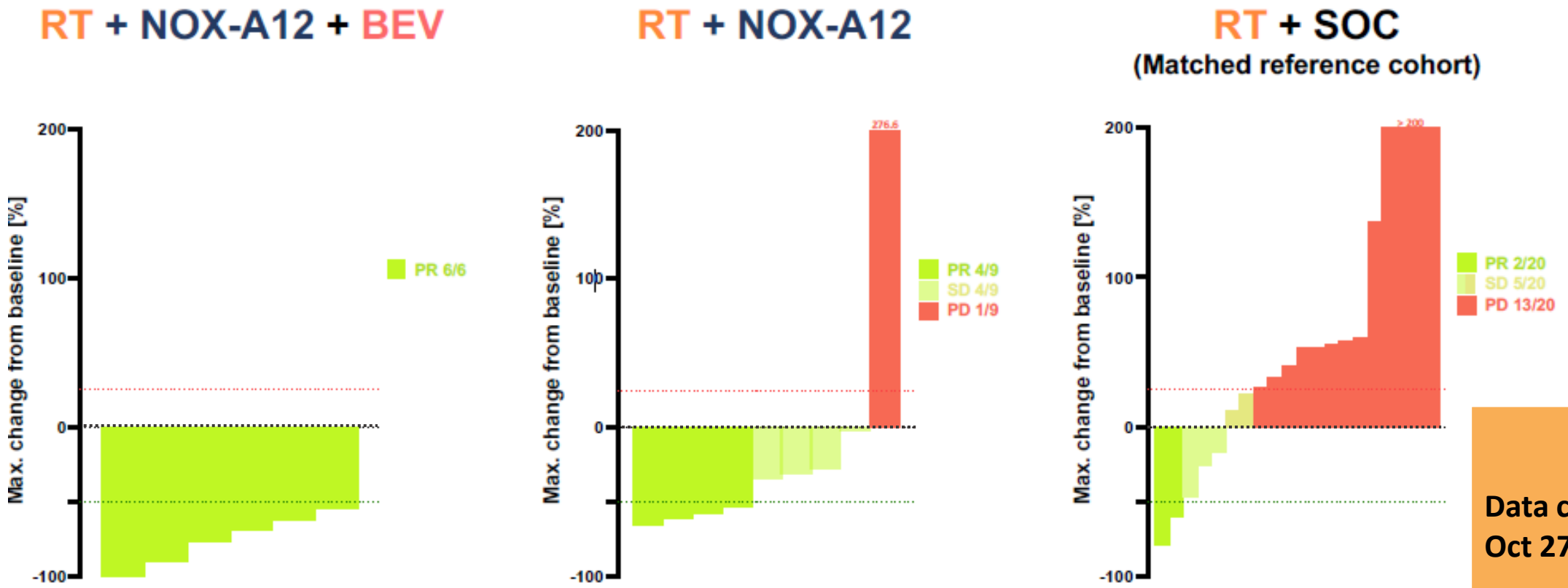
TARGET LESION RESPONSE



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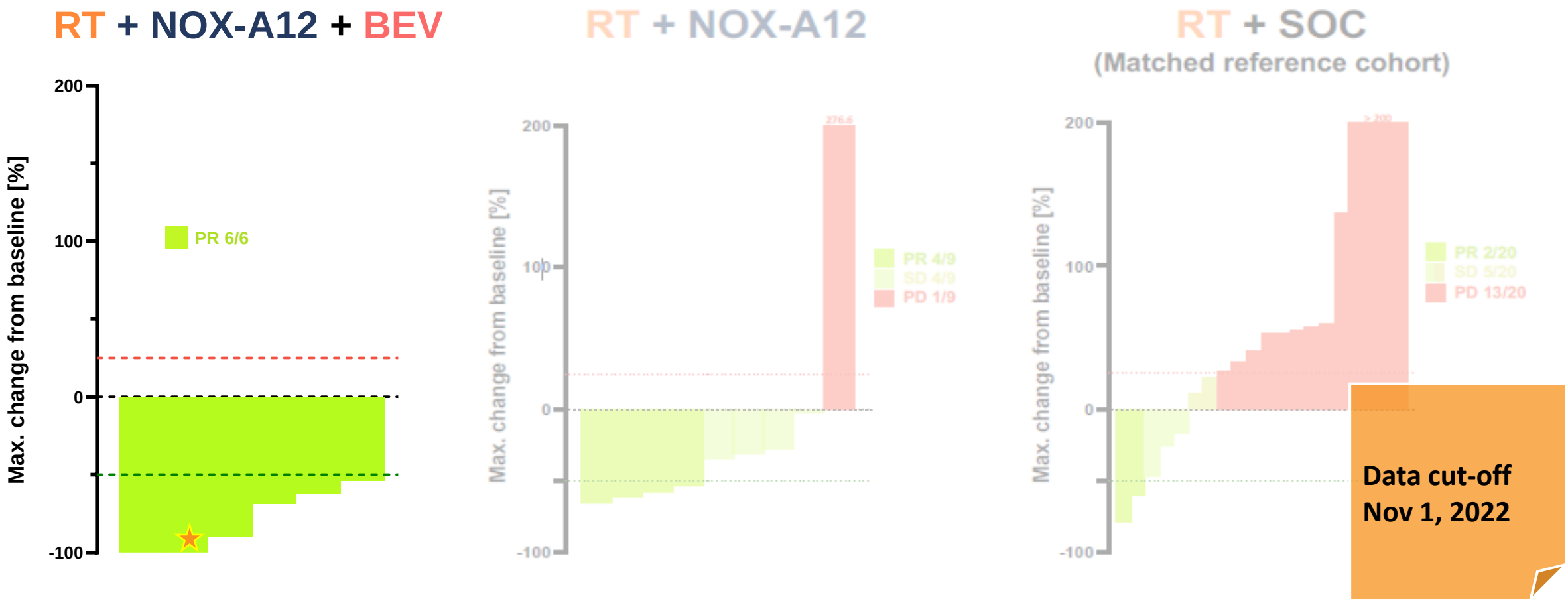
UPDATE: TARGET LESION RESPONSE



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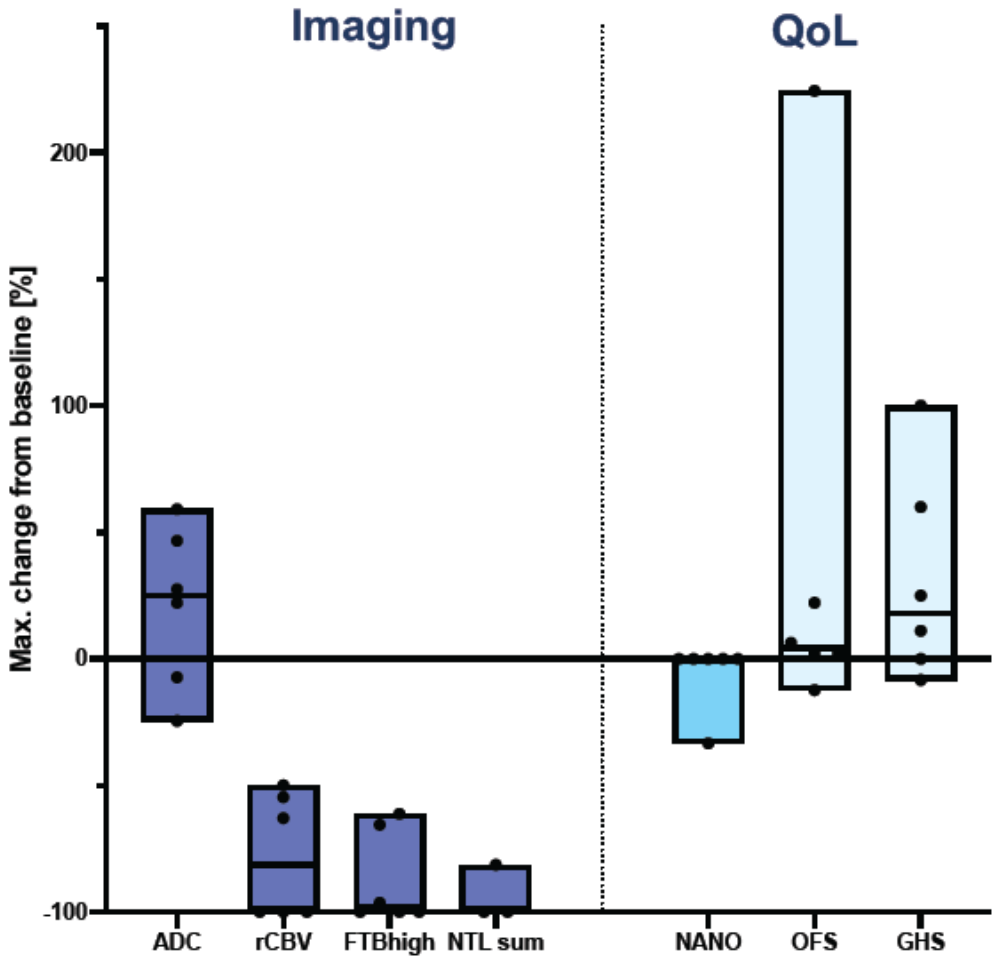

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- Apparent Diffusion Coefficient (ADC)
  20.6% (-24.5% to 59.1%)
- relative Cerebral Blood Volume (rCBV)
  -77.9% (-50 to -100%)
- Highly perfused-tumor fraction (FTB_{high})
  -87.2% (-61.3% to -100%)
- SPD response of NTL sums
  -93.8% (-81.4% to -100%)

Clinician reported outcome:

- NANO response -5.6% (0% to -33.3%)

Patient reported outcome:

- Overall Function Score (OFS)
  40.7% (-12.4% to 224.4%)
- Global Health Score (GHS)
  31.3% (-8.3% to 100%)

Conclusions:

- **Radiotherapy** + **NOX-A12** + **Bevacizumab** in chemotherapy refractory GBM is safe
- No DLT
- Encouraging efficacy of dual inhibition of angio-vasculogenesis
- Treatment and follow up ongoing

Q&A SESSION

Thank you.

Contact us:

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