KEY OPINION LEADER WEBINAR

The new biomarker with potential to select brain cancer patients most likely to respond best to NOX-A12 treatment

June 26, 2023 | 4 PM CET / 10 AM ET

WEBINAR PANEL

Key Opinion Leaders:

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

Prof. Michael Hölzel
Director at the Institute for Experimental Oncology at University Hospital Bonn, Germany, and lead researcher of the GLORIA trial companion diagnostics program

Joined by:

Aram Mangasarian
CEO
TME Pharma

Guillaume van Renterghem
Managing Director
LifeSci Advisors

TME Pharma Pipeline

Therapy & Indication	Preclinical	Phase 1/2	Phase 2	Phase 3	Next Inflection Point	Partner/ Collaborator
NOX-A12 + Radiotherapy **Brain cancer / Glioblastoma** Orphan Drug Status US & EU Expansion arms +anti-VEGF, +anti-PD1			FDA/EMA discussions when OS data mature		15-month OS from anti-VEGF expansion arm expected mid-2023	
NOX-A12 + Immunotherapy **Pancreatic Cancer**			Protocol approved in FR, ES & US			Scientific Collaborator MSD
NOX-E36 Combinations **Solid Tumors**						

Trial completed Trial ongoing or in preparation

All timelines subject to financing and patient recruitment

NOX-A12 (olaptesed pegol) is an injectable PEG-conjugated L-stereoisomer RNA aptamer that directly binds and neutralizes the chemokine CXCL12, preventing signaling through its two receptors CXCR4 & CXCR7. NOX-A12 also de-anchors the chemokine, destroying its gradient forming capacity.

NOX-E36 (emapticap pegol) is an injectable PEG-conjugated L-stereoisomer RNA aptamer conjugated to 40kD PEG that directly binds and neutralizes the chemokine CCL2, preventing signaling through its receptor CCR2. NOX-E36 also de-anchors the chemokine, destroying its gradient forming capacity.

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

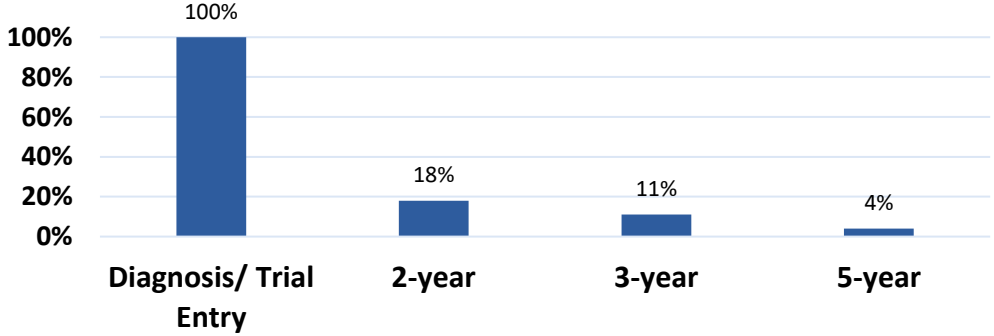
LACK OF EFFECTIVE THERAPIES & LOW OVERALL SURVIVAL

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

5Y
4%

mOS
12-15 months

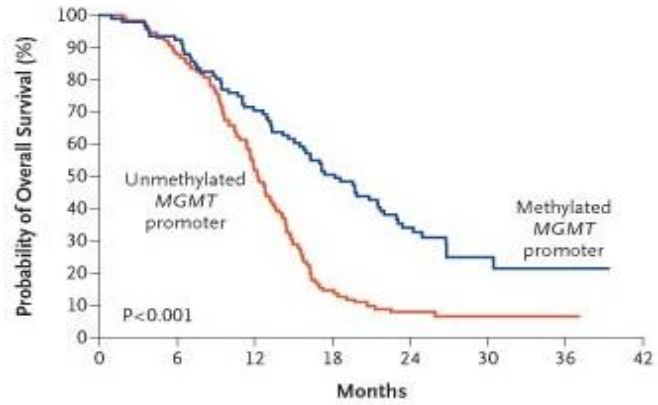
~ 160 active clinical trials



HIGH UNMET NEED PATIENT SEGMENTS

- MGMT unmethylated promoter – chemotherapy ineffective
- Incomplete surgical removal of tumor tissue – poor prognosis

NOX-A12 GLORIA trial recruits glioblastoma patients with MGMT unmethylated tumor remaining after surgery



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

Biomarkers – Prognostic vs Predictive

- **Prognostic Biomarkers**

A prognostic biomarker provides information about which outcomes are likely/unlikely based on markers present in the patient's tumor.

- **Predictive biomarkers**

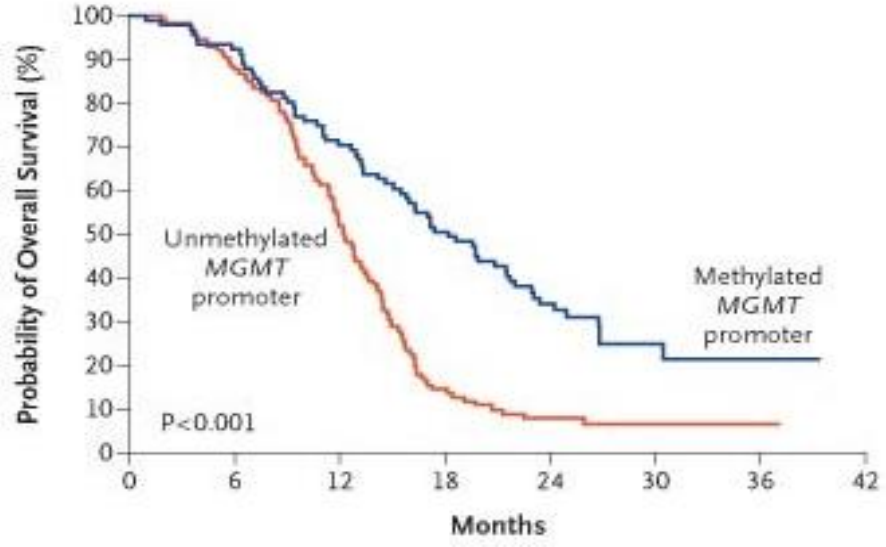
A predictive biomarker provides information about the benefit of a specific treatment for an individual patient.

Established Predictive Biomarker in Glioblastoma

MGMT promoter methylation status

- **MGMT unmethylated promoter = chemotherapy ineffective**
- Incomplete surgical removal of tumor tissue – poor prognosis

NOX-A12 GLORIA trial focuses on MGMT unmethylated patients with residual tumor after surgery



Sources: Poon MTC, et al., Scientific Reports 2020 Vol. 10 Issue 1; Hegi ME et al. N Engl J Med 2005;352:997-1003

Study Arms

Dose Escalation Cohorts

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

RT
60 Gy (2 Gy x 30)
40.05 Gy (2.67 Gy x 15)

NOX-A12
continuous i.v. infusion at three doses (200, 400, 600 mg/week)

FU

1 6

NOX-A12 + BEV Cohort

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

RT
60 Gy (2 Gy x 30)

NOX-A12
continuous i.v., 600 mg/week

BEV
10 mg/kg, q2w i.v.

FU

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NOX-A12 + PEM Cohort

Key inclusion criteria:
- Newly-diagnosed supratentorial glioblastoma WHO IV
- MGMT promoter unmethylated
- Incomplete resection < 5cm
- ECOG ≤ 2
- no immunosuppression

RT
60 Gy (2 Gy x 30)

NOX-A12
continuous i.v., 600 mg/week

PEM
200 mg, q3w i.v.

FU

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2023 ASCO ANNUAL MEETING

Potential predictive biomarker for response to radiotherapy and CXCL12-inhibition in glioblastoma in the phase I/II GLORIA trial.

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ASCO ANNUAL MEETING
Abstract #405

1 Study design

Inclusion criteria
- Newly-diagnosed supratentorial GBM (WHO CNS grade 4)
- MGMT promoter unmethylated
- Incomplete resection/biopsy only
- ECOG ≤ 2

RT
60 Gy (2 Gy x 30)
40.05 Gy (2.67 Gy x 15)
+
NOX-A12
Continuous i.v. infusion at three DLs (200, 400, 600 mg/week)
Follow-up

Week 1 | Week 6 | Week 26*

Safety monitoring
Advanced MRI (incl. perfusion/diffusion)

Primary endpoint:	Safety (incidence of adverse events)
Secondary endpoint:	NOX-A12 plasma levels, radiographic response, PFS, OS
Exploratory endpoints:	Multiplexed immunofluorescence imaging (CODEX®) - assessment of tissue biomarkers

- 10 patients with newly diagnosed incompletely resected (n=8) or biopsied (n=2) GBM with ECOG≤2, age≥18 and without MGMT promoter methylation were enrolled
- All patients received standard RT (60 Gy in 30 fractions or 40.05 Gy in 15 fractions) and escalating dose levels of continuous (24/7) i.v. infusions of NOX-A12 for 26 weeks

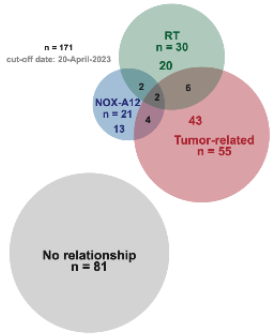
* End of treatment: 26 weeks; continuation beyond 26 weeks per investigator's decision

2 Trial outcomes

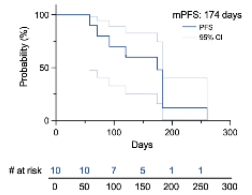
Patient characteristics (n=10)

Variable	n (%)	Median (range)
Gender		
Male	7 (70)	
Female	3 (30)	
Age (years)		65 (43-79)
ECOG Score		
0	7 (70)	
1	3 (30)	
Baseline NANO score		0 (0-4)
Resection status		
Incomplete	8 (80)	
Biopsy	2 (20)	
Residual volume (cc)		4.3 (2.5-34.1)
Weeks post surgery		4.6 (3.9-7.1)
Tumor localization		
Frontal lobe	4 (40)	
Temporal lobe	5 (50)	
Parietal lobe	3 (30)	
Occipital lobe	2 (20)	
Radiotherapy		
Normofractionated	7 (70)	
Hypofractionated	3 (30)	

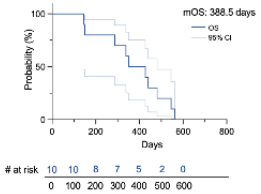
Adverse Events



Progression-free survival GLORIA



Overall survival GLORIA

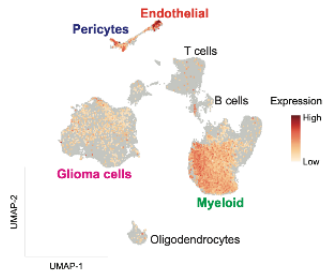


- Treatment was safe with no dose-limiting toxicities
- Of all G≥2 adverse events (n=84), 4 (4.7%) were considered to be solely NOX-A12-related, including 1 G3 AE at DL 3 (elevation of GGT)
- Median PFS of the GLORIA cohort was 5.7 (range 1.9–8.5) months and the median OS was 12.7 (4.7–18.4) months

* authors contributed equally

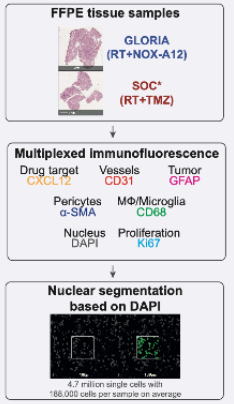
3 scRNAseq and tissue analysis

CXCL12 expression in scRNAseq from human GBM
Abdelfattah et al. 2022

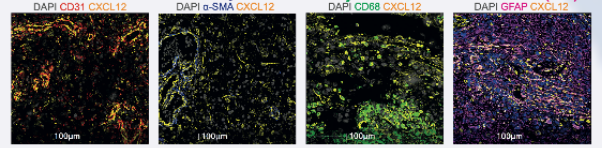


- Highest CXCL12 mRNA expression in endothelial cells, followed by pericytes, myeloid (macrophages, microglia) and glioma cells

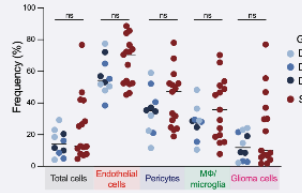
Workflow



Multiplexed immunofluorescence for CXCL12 positivity



Frequency of CXCL12⁺ cells

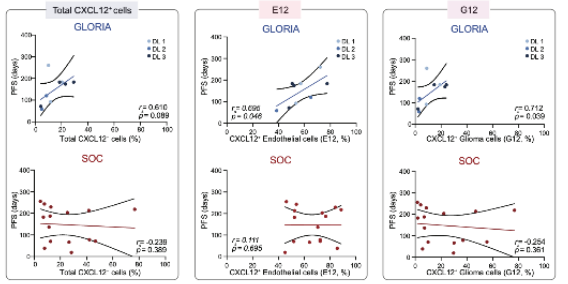


- Cell-type specific CXCL12 protein expression assessed in pre-treatment tumor samples from:
  - GLORIA patients (n=10)
  - SOC cohort (n=15)*
- Tissue analysis confirms cell type-specific expression of CXCL12 seen in scRNAseq
- No signifcant differences in CXCL12⁺ cell frequency between GLORIA and SOC

*SOC cohort: external control with incompletely resected or biopsied GBM (WHO CNS grade 4) lacking MGMT promoter methylation and treated with standard of care (SOC) (n=15).

High frequency of CXCL12⁺ endothelial / glioma cells is predictive for clinical efficacy of RT + CXCL12-inhibition in GBM

4 CXCL12 positivity and PFS



- Positive trend between frequency of total CXCL12⁺ cells and PFS in the GLORIA cohort
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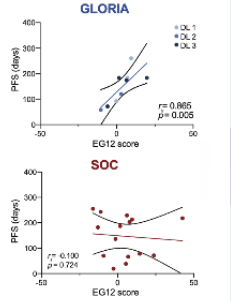
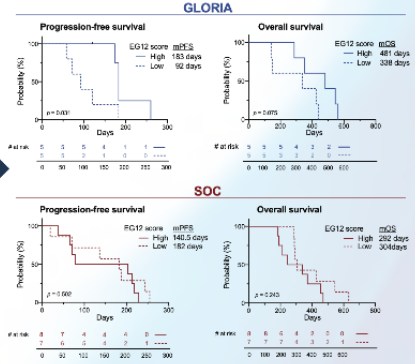
5 EG12 score



- Creation of a combined EG12 score incorporating endothelial and glioma cells (mean of the median-centered values of E12 and G12)

6 Stratified Survival



frank.giordano@umm.de

Registered with clinicaltrials.gov, ID: NCT04121455.

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IEO
UNIVERSITÄT BONN

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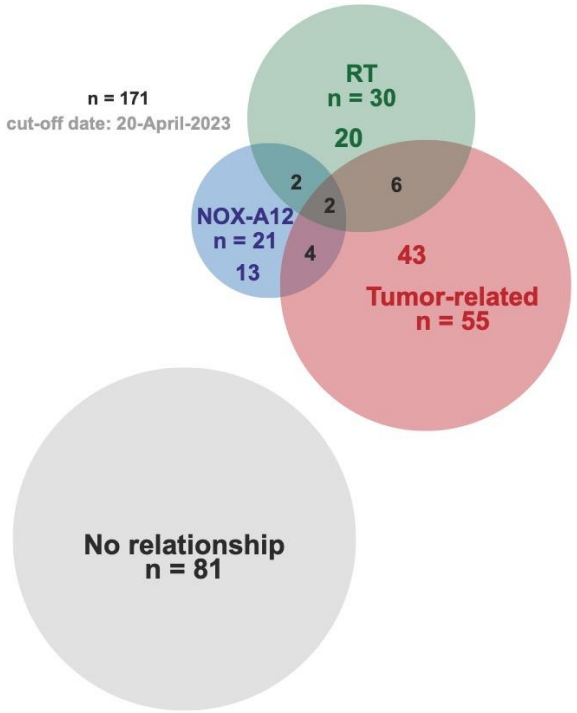

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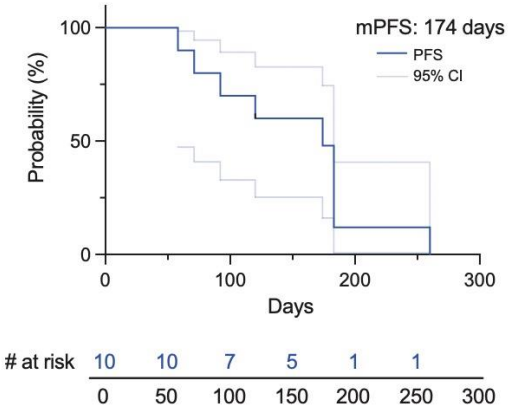
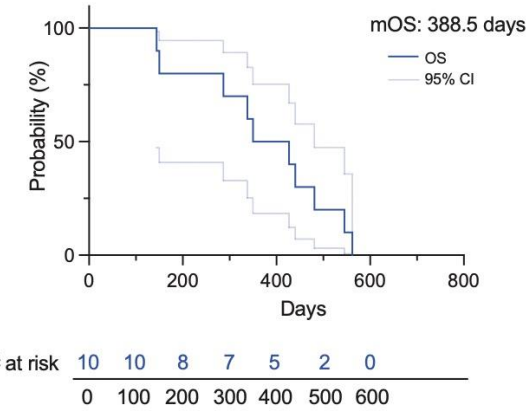


Overall survival GLORIA



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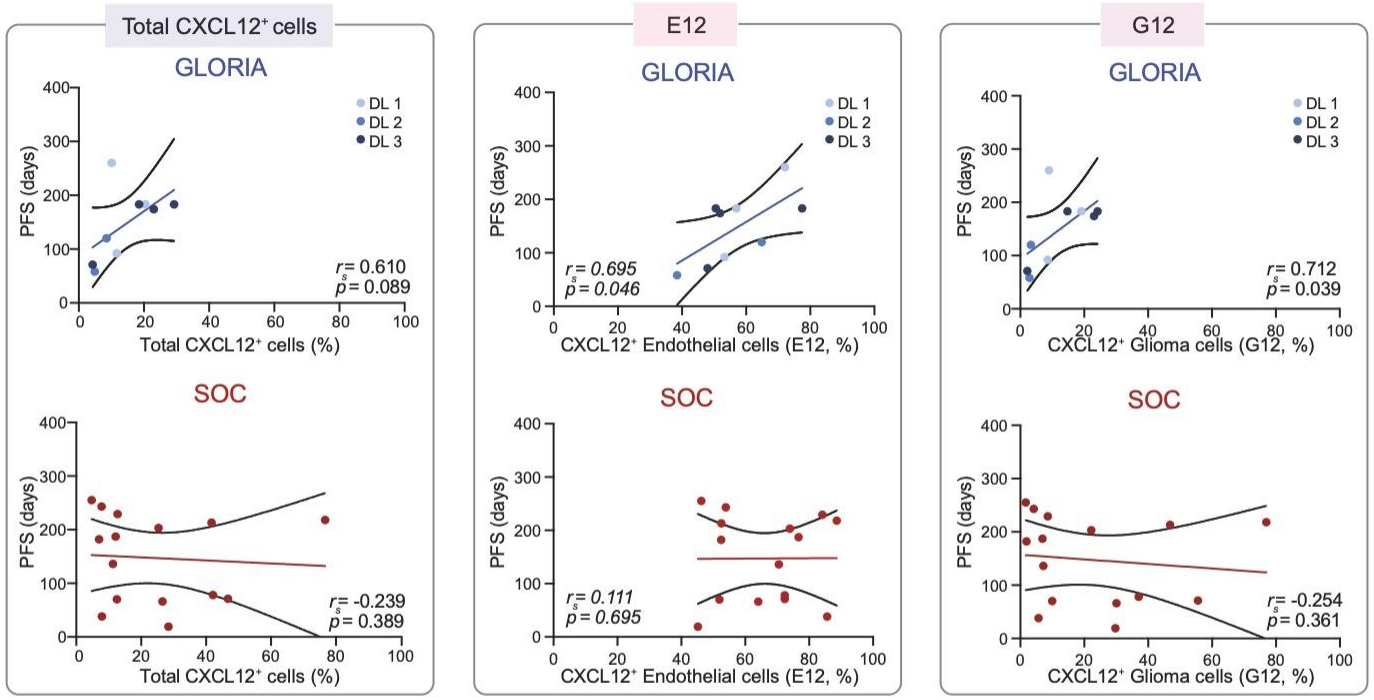
4 CXCL12 positivity and PFS



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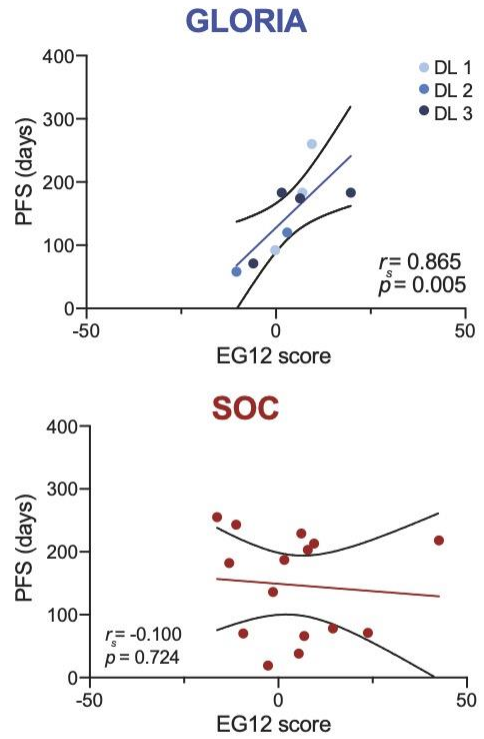

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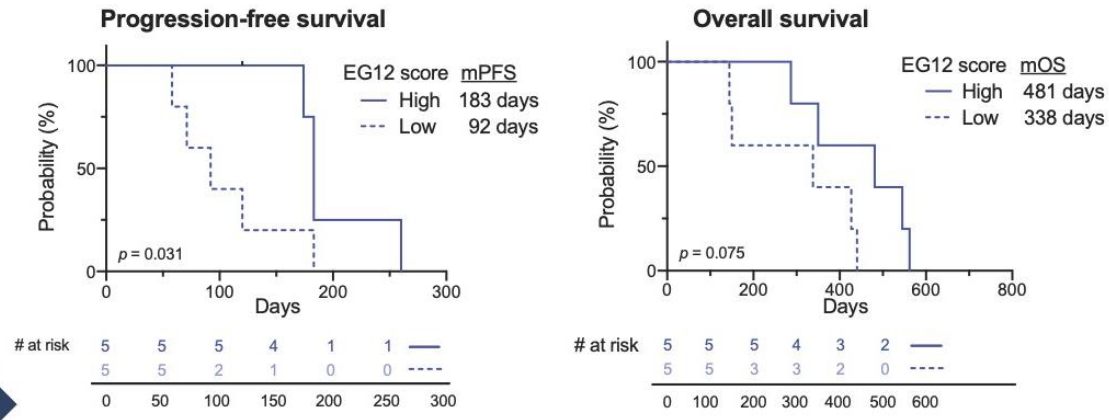
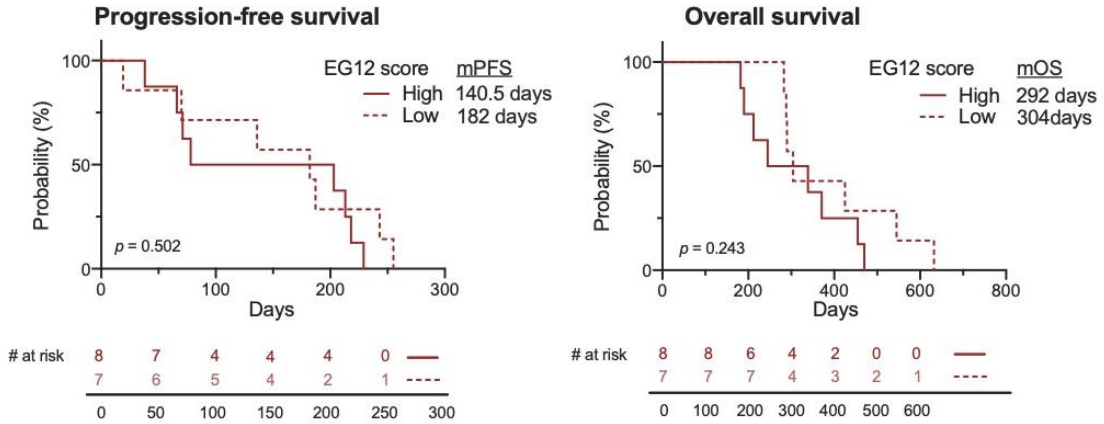
6 Stratified Survival

GLORIA



SOC



Value of Predictive Biomarkers

A **predictive biomarker** is a measurable biological characteristic that provides information about the likelihood of an individual patient to respond to a specific treatment.

Significance of a Predictive Biomarker:

- **Clinical Development:** helps to **identify target populations for clinical trials** thereby **enhancing the statistical power** of the trial and **reducing the risk of failure**
- **Personalized Medicine:** guides treatment decisions by **identifying patients who are more likely to respond** to a specific therapy
- **Health Economics: reduces healthcare costs** associated with ineffective treatments, minimizing adverse events, and optimizing resource allocation thus **supporting positive pricing and reimbursement decisions**

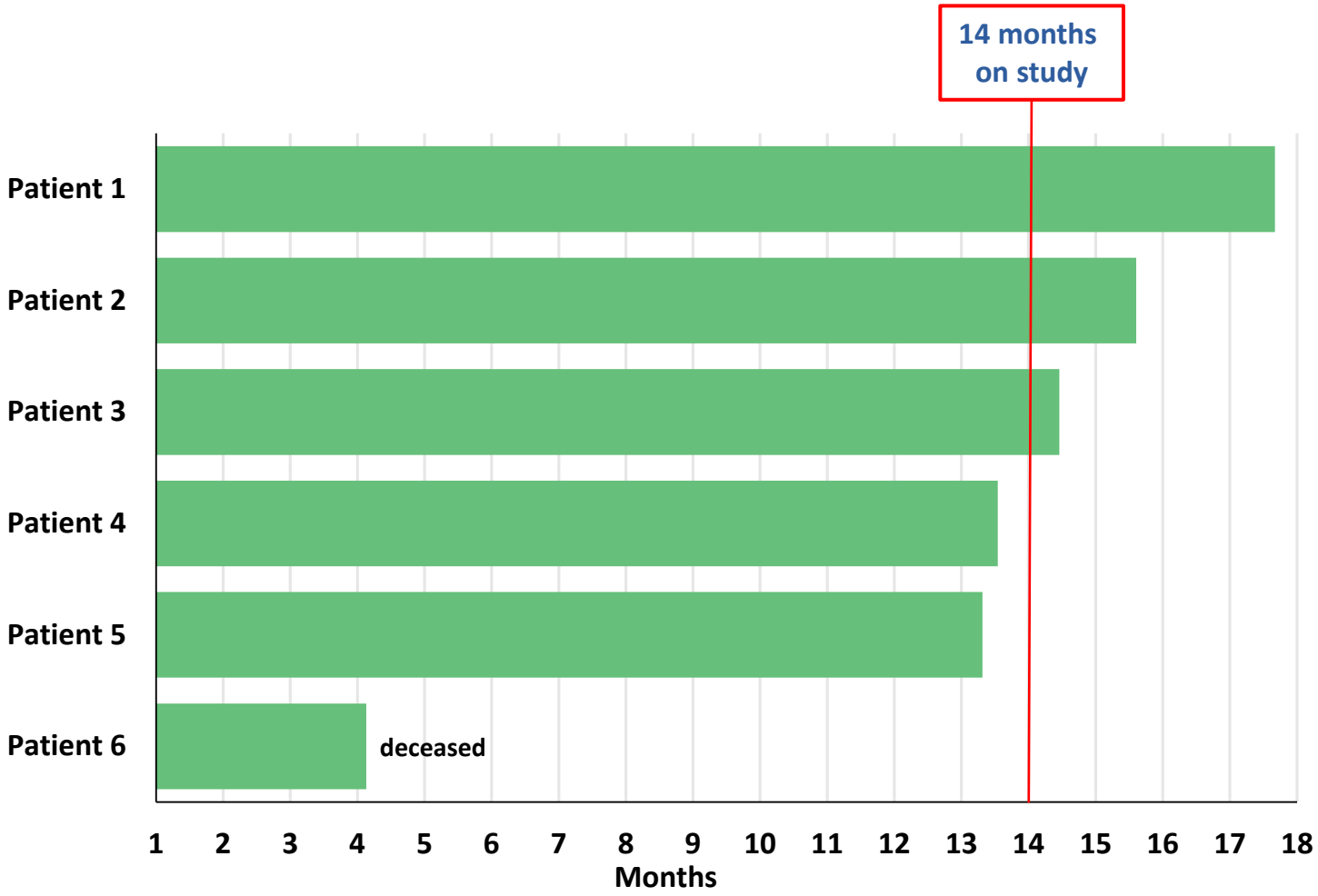
Questions?

Thank you.

Contact us:

tme@tmepharma.com

NOX-A12 + RT + Bevacizumab: Maturing Survival Data
83% OS with 14-month Median Time on Study



- **5 out of 6 patients alive** with **14-month** median time on study (cut-off date 21 May 2023)
- **Median overall survival (mOS) continues to improve**
- **5 out of 6 patients achieved durable mRANO responses >6 months**
- **15-month** survival data expected **mid-2023**
- PD in patient 6, which led to death, was due to cerebrospinal fluid (CSF) metastases while target lesion control was maintained

Sources: *TME Pharma* Press Release from 26 May 2023