

[www.tmepharma.com](http://www.tmepharma.com)

# Improving Therapeutic Outcomes by Targeting the Tumor Microenvironment

May 2024



# 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.

# Strong Value Proposition Through Differentiated Pipeline Targeting the Tumor Microenvironment

## MISSION

Develop **novel therapies** for **treatment of cancers** where the **Tumor Microenvironment** significantly impacts survival

## NOX-A12 LEVERAGEABLE TECHNOLOGY

**Dual MoA leverageable to solid tumors** as combinations with:

- Radiotherapy (RT)
- Anti-vascular agents VEGF-(R)
- Immunotherapies

## VERY PROMISING DATA

**Brain Cancer (1<sup>st</sup> line GBM)**  
**Phase 1/2 clinical trial**

**NOX-A12 + RT + bevacizumab<sup>1</sup>:**

- mOS 19.9 months in chemotherapy resistant patients with residual tumor
- 10-fold improvement in 21-month survival vs. standard of care (50% vs. 5%)
- 2 of 6 patients with survival >24 months
- 3 of 6 patients with >99% tumor size reduction including 1 complete response

## FOCUS ON ORPHAN CANCER INDICATIONS

**Brain Cancer (1<sup>st</sup> line GBM)**  
**Orphan Drug Designation Granted in US & EU, and Fast Track designation awarded by FDA**  
~\$2.5 bn Addressable Market

**Pancreatic Cancer (2<sup>nd</sup> line)**  
~\$6 bn Addressable Market

## UPCOMING CATALYSTS

**Financing and Initiation of Randomized Phase 2 Trial in GBM (IND open in US)**

- **TME Pharma is listed on Euronext Growth Paris – ALTME**
- Highly efficient structure with 14 employees and key expertise in-house
- Cash & equivalents:
  - **€2.2 million** (31 December 2023)
  - **€2.55 million** gross additional raised in 2024
  - Financial visibility into July 2024

## FINANCIALS AND SHAREHOLDING STRUCTURE

Public listing	2016
ISIN Code	NL0015000YE1
Ticker	ALTME
Market	Euronext Growth Paris
Market Cap*	€7 M
Shares outstanding**	28,453,373
Warrants Z ISIN	NL0015001SR3
Warrants Z outstanding**	3,326,104

\* As of April 25, 2024

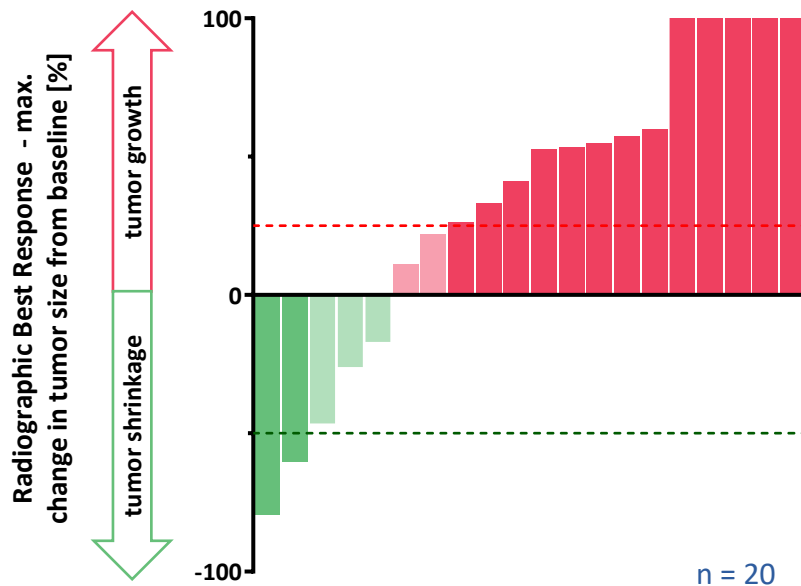
\*\*As of March 28, 2024, yielding up to 4,157,630 more shares

# NOX-A12 Combinations Improve Best Response Rates and Depth of Tumor Shrinkage vs. Standard of Care

## Standard of Care

### Radiotherapy + Chemotherapy

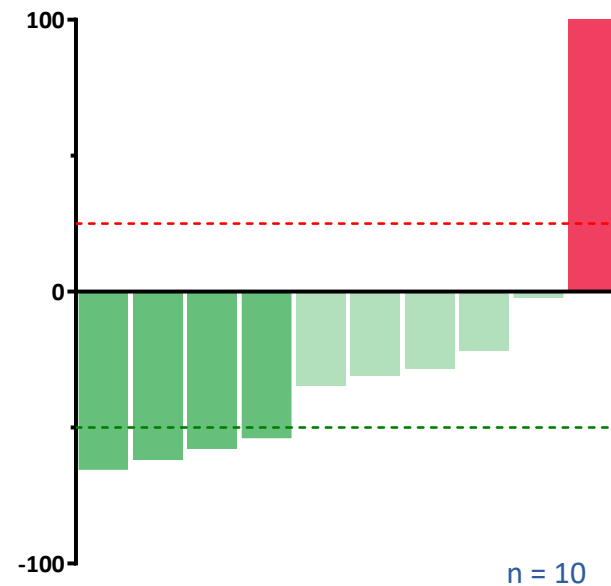
(Matched reference cohort from center participating in trial: MGMT Unmethylated & incomplete surgical resection or biopsy only)



Median Overall Survival (mOS)

10.5 months

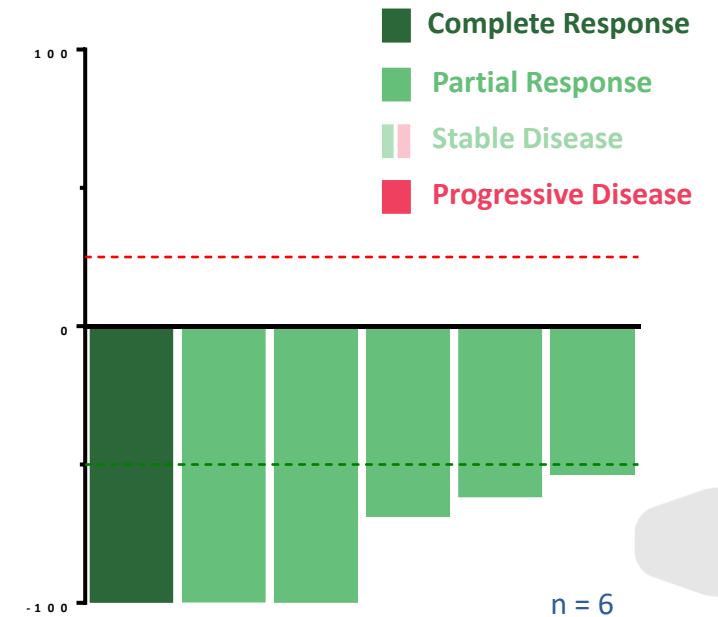
## Radiotherapy + NOX-A12



12.7 months

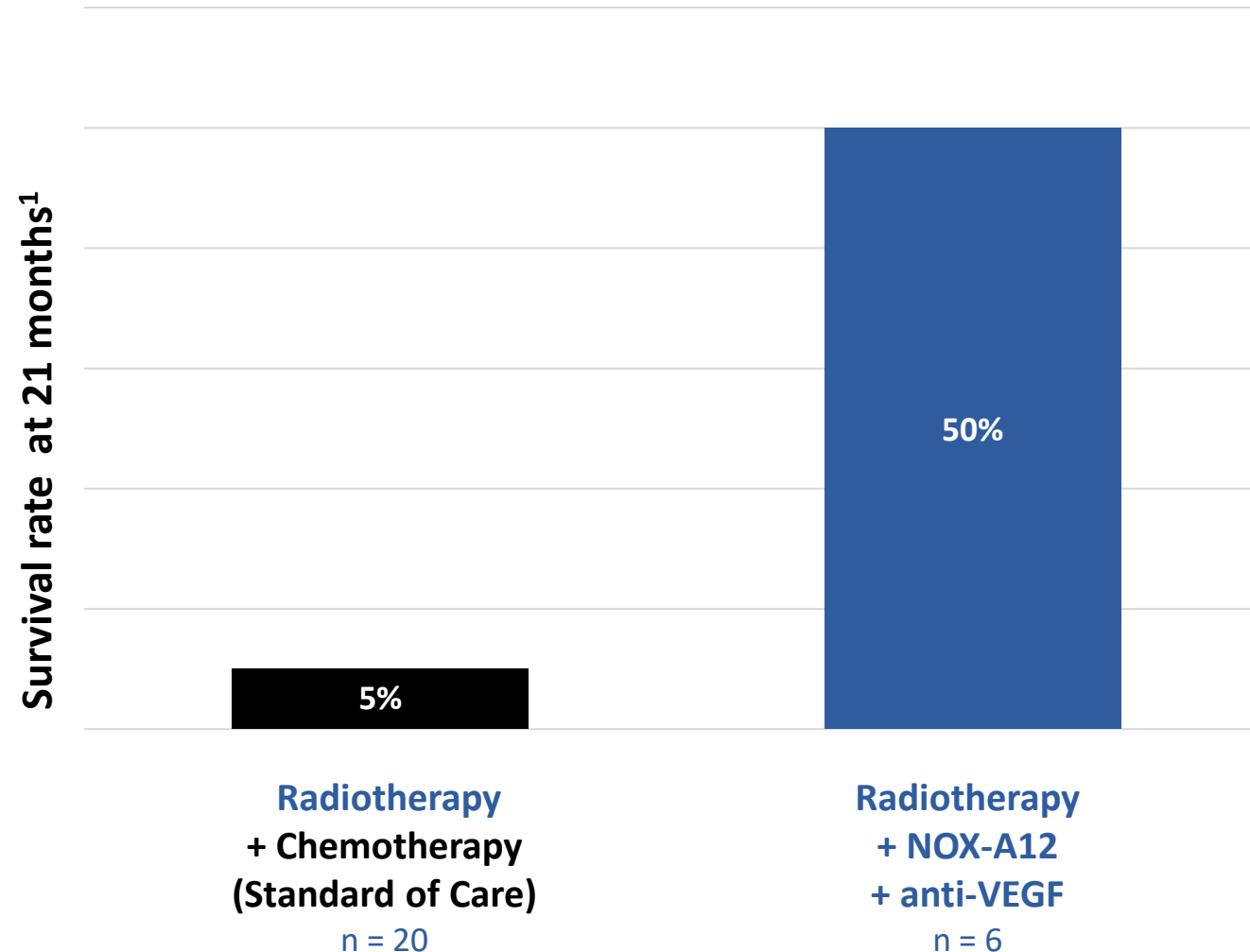
15.8 months biomarker high

## Radiotherapy + NOX-A12 + anti-VEGF



19.9 months

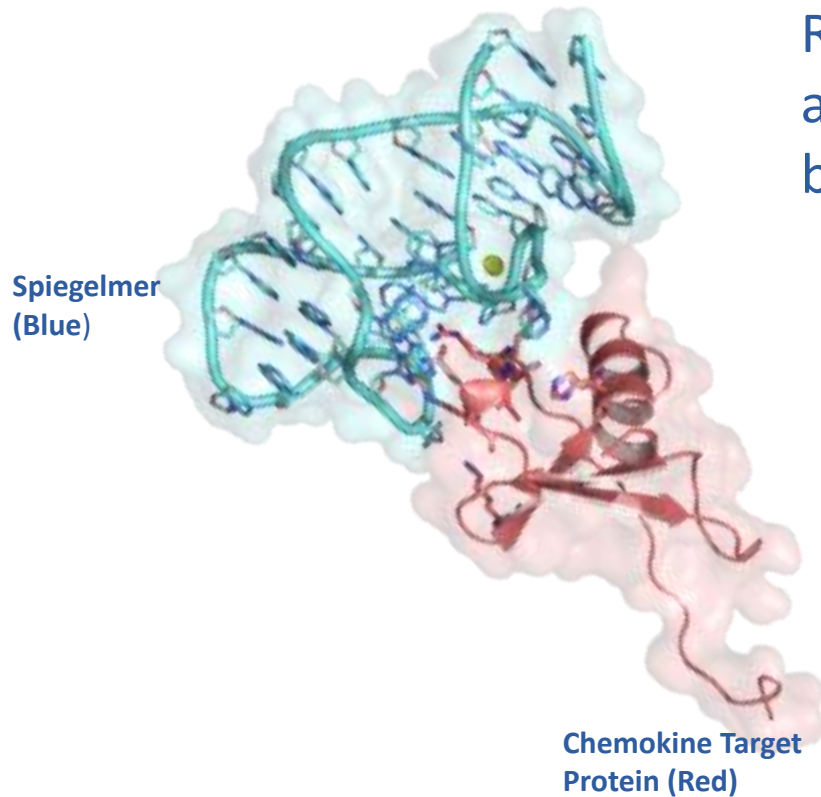
# 10-Fold Improvement in 21-month Survival for NOX-A12 + RT + anti-VEGF vs. Standard of Care



Since neither bevacizumab (anti-VEGF) alone, nor bevacizumab plus radiotherapy have previously been shown to extend survival<sup>2</sup>, the **strong increase in survival can be attributed to the complementary mechanism of action of NOX-A12 with bevacizumab and radiotherapy**

1. Standard of care data from 20-patient matched reference cohort of newly diagnosed glioblastoma with MGMT unmethylated, incompletely resected or biopsy-only tumors; Giordano (2022) ASCO Annual Meeting Pres. #2050. NOX-A12 survival data from TME Pharma Press Release 2 February 2024; 2. Chinot (2014) NEJM, Gilbert (2014) NEJM, Herrlinger (2016) J Clin Oncology

# Spiegelmer® Platform: Next-Generation RNA Aptamers



**Chemokines** are like street-signs in the body for moving cells, they are anchored (location information) and display instructions e.g. (“enter here”) for moving cells that can “see” them with the appropriate receptors.

RNA aptamers made with L-stereoisomer bind their targets with affinity similar or higher than antibodies and come with key benefits:

- Natural resistance to nuclease degradation - no chemical modification of backbone needed
- Large interaction surface enables complete inhibition of both key chemokine domains: receptor activation & anchoring for location

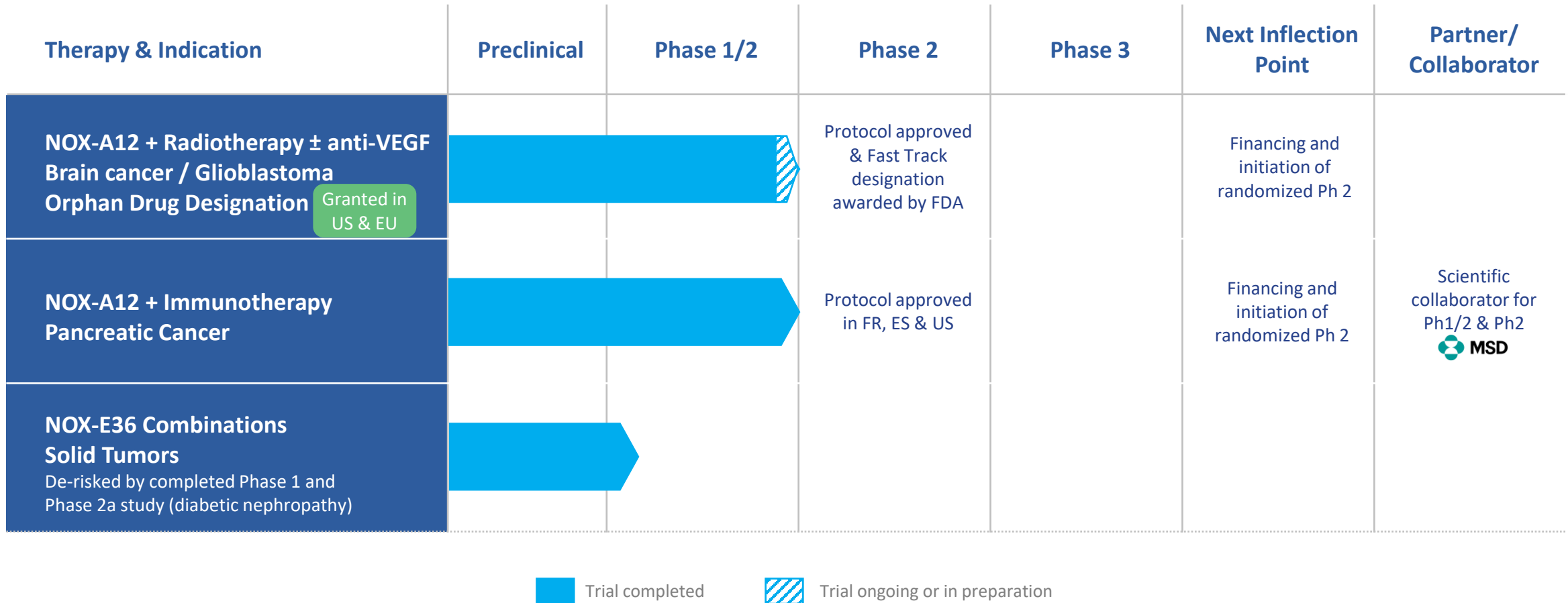
## FDA Approved RNA Aptamers

**izervay™**  
(avacincaptad pegol  
intravitreal solution)

**MACUGEN®**  
PEGAPTANIB SODIUM INJECTION

Iveric  
bought by  
Astellas  
for \$5.9b

# Pipeline Assets Complement Anti-Cancer Therapies to Enhance Treatment Efficacy



All timelines subject to financing and patient recruitment

**NOX-A12 (olaptased 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.



# Experienced Biopharma Team

## MANAGEMENT



**Aram Mangasarian**  
Chief Executive Officer

- 20+ years experience in biotech
- ~€65m raised for TME Pharma
- Novexel: €150m license with Forest & \$505m acquisition by AZ
- ExonHit: \$30m alliance with Allergan



**Ewelina Staniuk**  
Sr Director, IR & BD

- 10+ years in international projects
- Portfolio of financing & partnering opportunities
- Design and execution of corporate communication



**Jarl Ulf Jungnelius, MD**  
Chief Medical Officer

- Oncologist with 25+ years clinical & research experience
- Isofol, Celgene, Takeda, Pfizer, Eli Lilly
- Approvals of Alimta®, Revlimid®, Abraxane® & Gemzar®



**Heike Balzer**  
SVP Finance

- 20+ years experience in corporate finance
- Execution of investments for over €190m
- Lecturer at the Potsdam University



**Dirk Eulberg**  
SVP Project Management

- 20+ years experience in biotech
- Development of 3 drugs from discovery to clinic
- Lead role in big pharma and academic collaborations



**Karen Ophoff**  
VP HR & Legal, General Counsel

- 20+ years experience in legal & corporate matters, incl. Euronext Growth listing
- Negotiation & execution of transactions for over €190m

## SUPERVISORY BOARD



**Chairman of the Board**  
**Maurizio Petitbon**  
Senior Advisor, BlackRock

- Advisor, entrepreneur and investor in healthcare space



**Susan Coles**  
Vivet Therapeutics  
General Counsel & Head of Finance

- 25+ years experience in international collaborations and corporate/commercial activities



**Oscar Izeboud**  
Scenic Biotech  
CEO

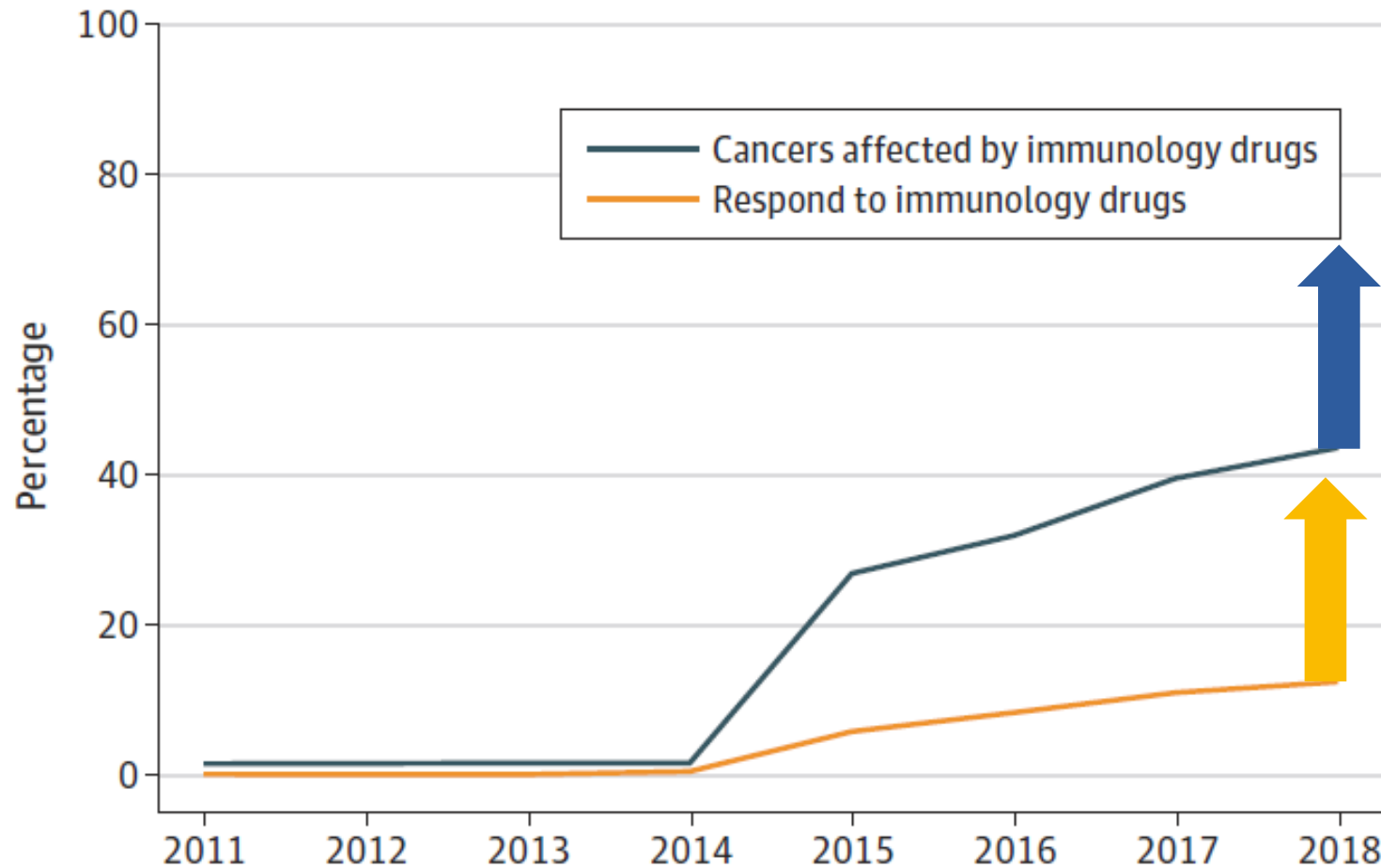
- 20+ years of experience in biotech, including 14 years in investment banking



UNIQUE APPROACH:

Modulating Tumor Microenvironment  
Chemokines to Improve Cancer Therapy

# The Tumor Microenvironment (TME) is a Key Hurdle to Solid Tumor Treatments



**Efficacy of cancer therapy has been limited by the TME of both solid and hematological cancers.**

**Targeting the TME can address key hurdles**

Sources: Haslam A. & Prasad V., JAMA Network Open. 2019;2(5):e192535. doi:10.1001/jamanetworkopen.2019.2535, Update suggests reduction to 36.1% eligibility and 10.9% response due to failed confirmatory trials in A.

Haslam, J. Gill and V. Prasad JAMA Netw Open 2020 Vol. 3 Issue 3 Pages e200423

Cancers affected by immunology drugs = percentage of the total US cancer patient population eligible for an approved checkpoint immunotherapy

Respond to immunology drugs = the overall response rate (complete plus partial) projected as a percentage of all US cancer patients

# TME Pharma's Drug Candidates Allow the Immune System to Penetrate Solid Tumor Defenses and Block Repair of Damaged Tumors


## NOX-A12 effects

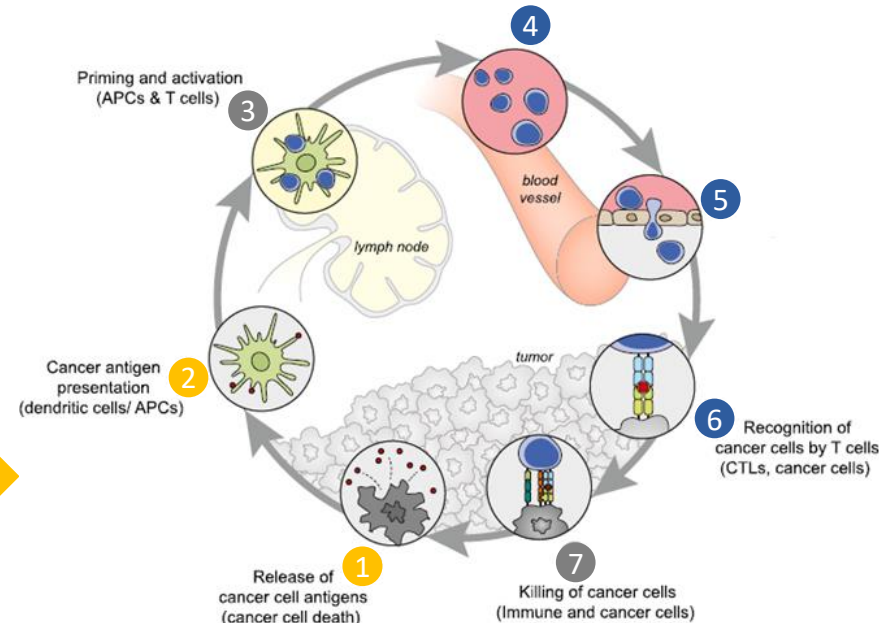
**Blocks repair of damaged tumors**

**Prevents entry of immuno-suppressive cells**


**Enables infiltration of anti-cancer immune cells into the TME**

## NOX-A12<sup>a</sup>

 **Decrease in neovascularization of damaged tumors by bone-marrow-derived cells**



## NOX-A12<sup>b</sup> & NOX-E36<sup>c</sup>

 **Decrease in suppressive myeloid cells to tumors**


 **Increase in trafficking & infiltration of immune effector cells**

Figure adapted from Chen & Mellman 2013, Immunity 39:1.

(a) Liu 2014, Neuro-Oncology 16:21. Chernikova S et al., AACR-NCI-EORTC Int. Conf. on Molecular Targets and Cancer Therapeutics 2013. Deng L et al., Neoplasia (2017) 19, 1–7;

(b) Giordano (2021) Society for Neuro-Oncology 2021 Annual Meeting Presentation CTNI-43 – of phase I/II GLORIA trial (NCT04121455). Giordano (2022) American Society for Clinical Oncology 2022 Annual Meeting Poster #2050 of phase I/II GLORIA trial (NCT04121455).

(c) Bartneck 2019, Cell Mol Gastroenterol Hepatol 7:371. Lazarus 2017, Poster PT165 Soc Surg Oncol 70th Annual Cancer Symposium.

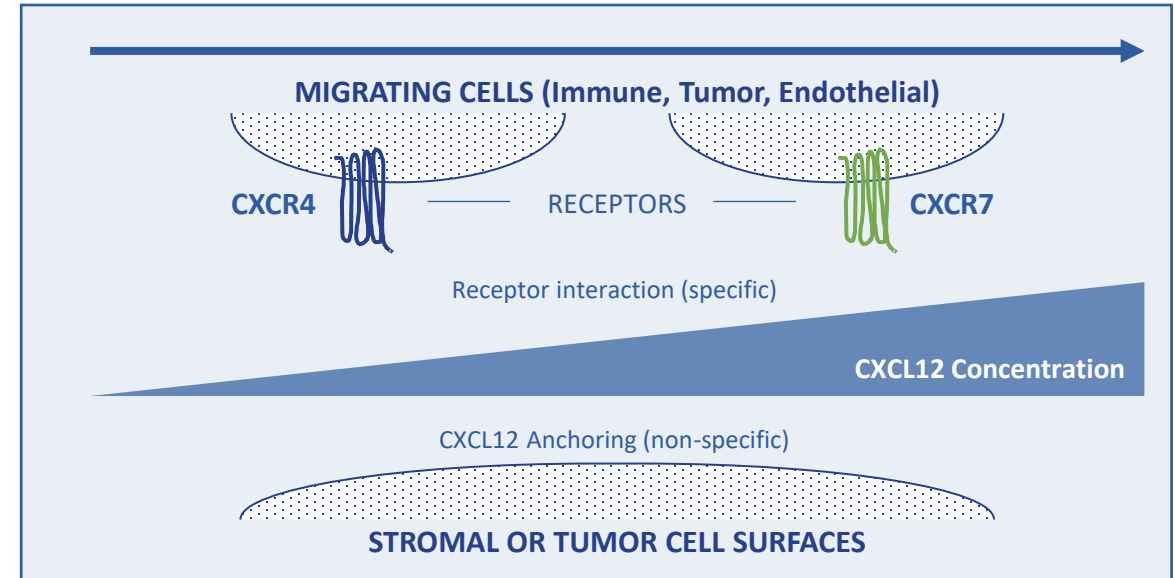
# Role of CXCL12 Chemokine Axis in Cancer

## NOX-A12 Inhibition of CXCL12 Provides Strong Differentiation

### Roles of CXCL12 / CXCR4 / CXCR7 Axis

- Establishment of tumor-promoting microenvironment excluding / sequestering effector T-cells and recruitment of immuno-suppressive cell populations
- Recruitment of endothelial progenitor cells (growth support, tumor vascularization)
- Stimulation of tumor growth
- Adhesion
- Chemotherapy resistance
- Spreading / metastasis

**Blocking only CXCR4 is not sufficient for adequate control of the TME and may be counter-productive in certain cancer therapy contexts. Blocking CXCR7 has shown to be crucial in solid tumors such as brain and pancreatic cancer.**



### NOX-A12 BINDING OF THE CHEMOKINE CXCL12:

- 1) blocks receptor interaction with both CXCL12 receptors (CXCR4 and CXCR7) and down-stream signalling
- 2) neutralizes anchor domain detaching chemokine & destroying the location information of the chemokine concentration gradient

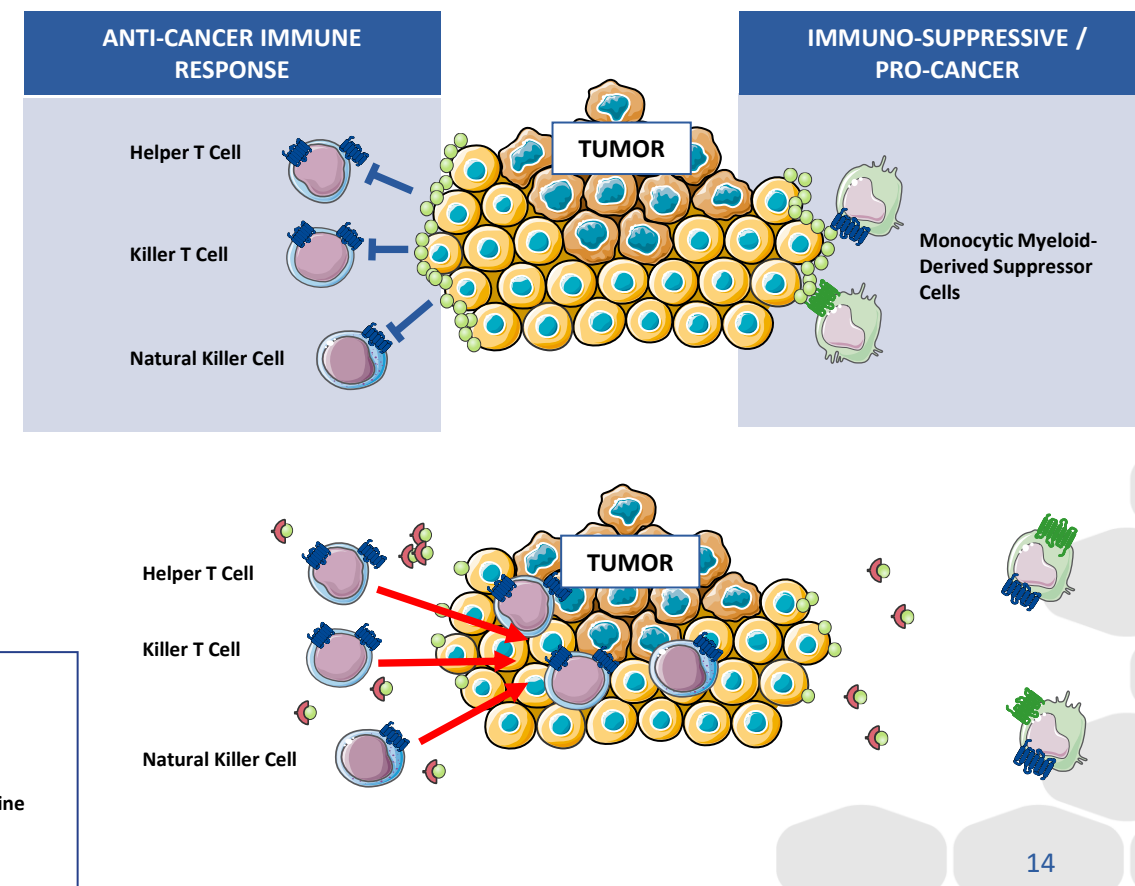
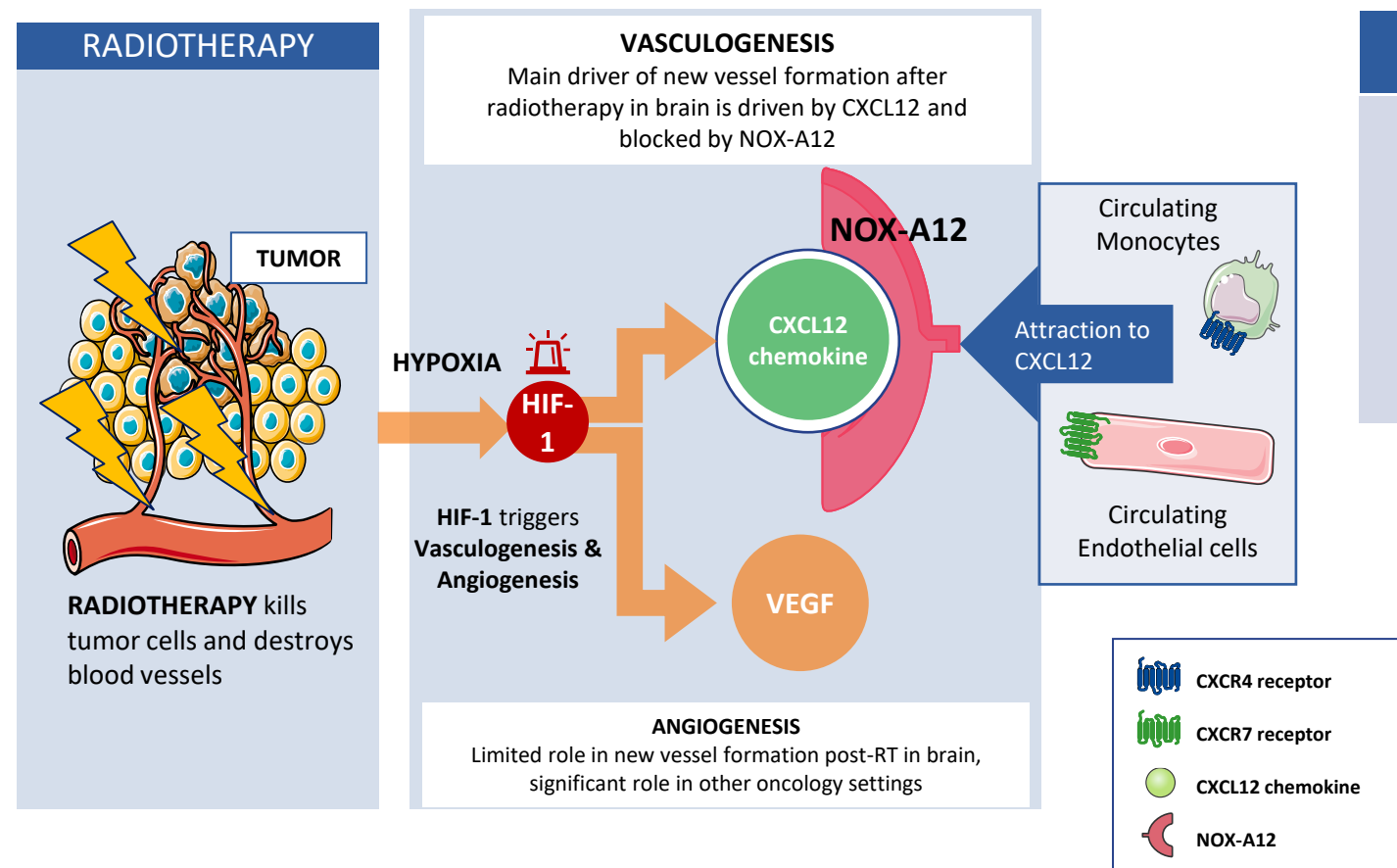
# NOX-A12 – Dual Mechanism of Action

## Blockage of Vasculogenesis:

Use in combination with anti-vascular agents such as radiotherapy or anti-VEGF-(R)

Overcome immune exclusion & prevent recruitment of immune-suppressive cells

Combos with CPIs, Bi-Specifics, Cell Therapies

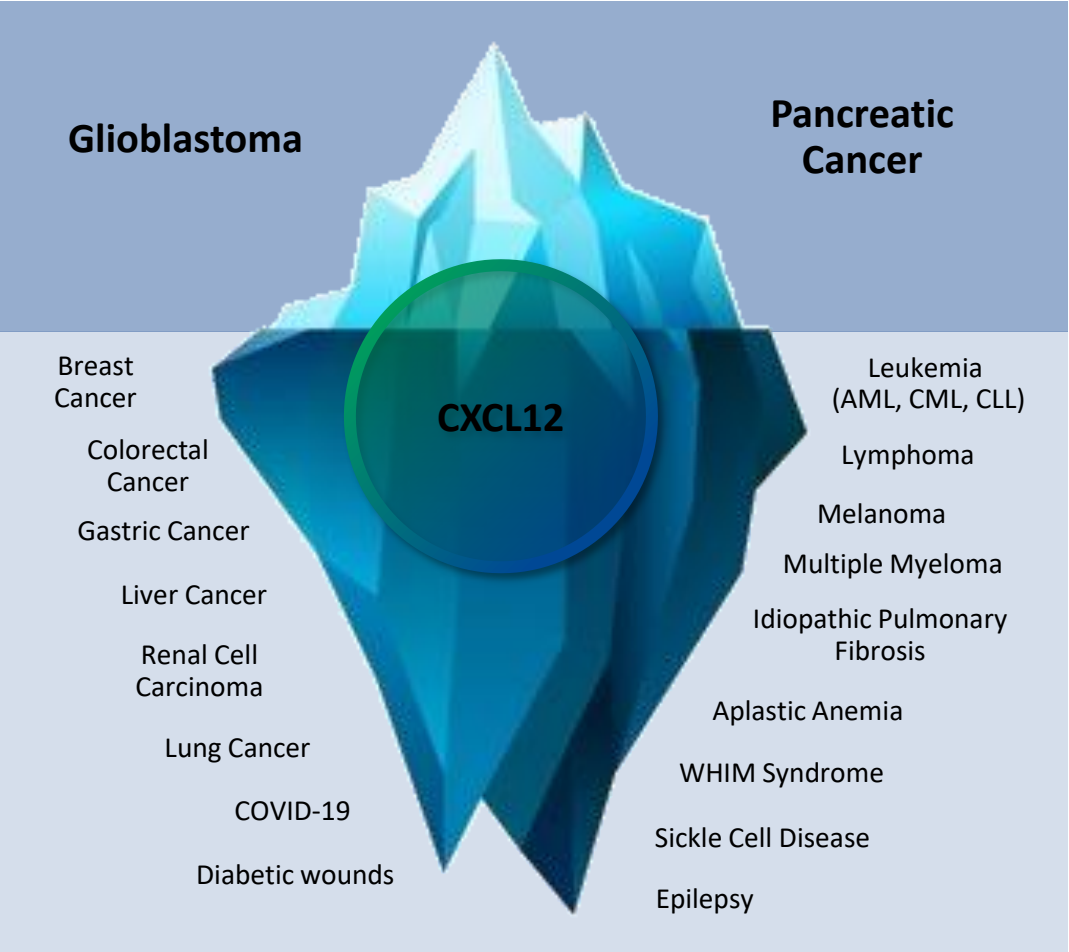
























# TME Pharma at the Forefront of Chemokine Development for Cancer with Limited Direct Competition in Brain & Pancreatic Cancer



The CXCL12/CXCR4/CXCR7 axis involved in many cancers and other indications



	Blocks CXCL12 interaction w/		Developed in	
	CXCR4 receptor 	CXCR7 receptor 	Pancreatic Cancer 	Glioblastoma 
<b>NOX-A12</b> TME Pharma				
Motixafortide BioLineRx				
Plerixafor <sup>1</sup> Sanofi				
Mavorixafor <sup>2</sup> X4 /Abbisko				

Includes assets in development worldwide from preclinical phase to registration.  
 Source: Citeline Clinical Intelligence Reports, TME Pharma analysis, February 2024  
 1. The IIT by L.D. Recht at Stanford studying whole brain radiation therapy (WBRT) with temozolomide and plerixafor in GBM has been resumed in H1 2023; 2. X4 Pharma outlicensed mavorixafor to Abbisko with the exclusive rights in Greater China to develop and commercialize mavorixafor in oncology indications – including pancreatic cancer. However, no clinical development in pancreatic cancer has been initiated by Abbisko since the deal announcement in 2019.



# NOX-A12 + Radiotherapy $\pm$ Bevacizumab in Chemotherapy Refractory Glioblastoma



# 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 US + Eur-5<sup>1</sup>



5-year Survival  
6,9%<sup>2</sup>



mOS  
8 months<sup>2</sup>



~ 315 active clinical  
trials in US & Europe<sup>3</sup>

## NOX-A12 OFFERS CHEMO-FREE REGIMEN FOR HIGH UNMET NEED PATIENT SEGMENTS

### CHEMO-RESISTANT

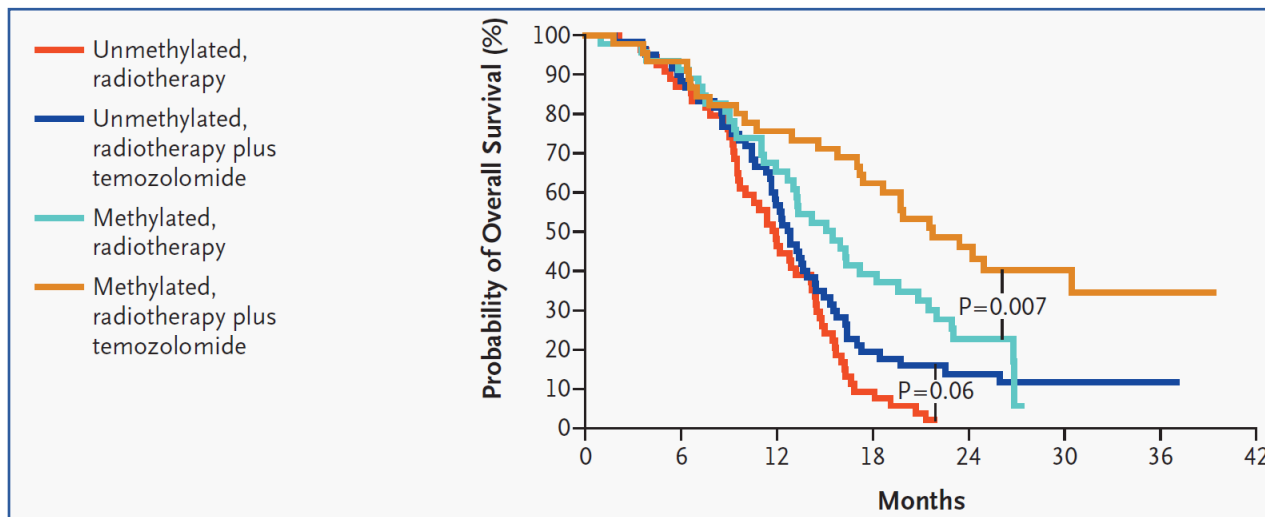
- >50% of GBM patients have **unmethylated MGMT** promoter leading to **no significant benefit from chemotherapy** and worse prognosis
- NOX-A12 trial omits chemotherapy** improving overall safety profile and offers immune-friendly regimen

### PARTIAL TUMOR RESECTION

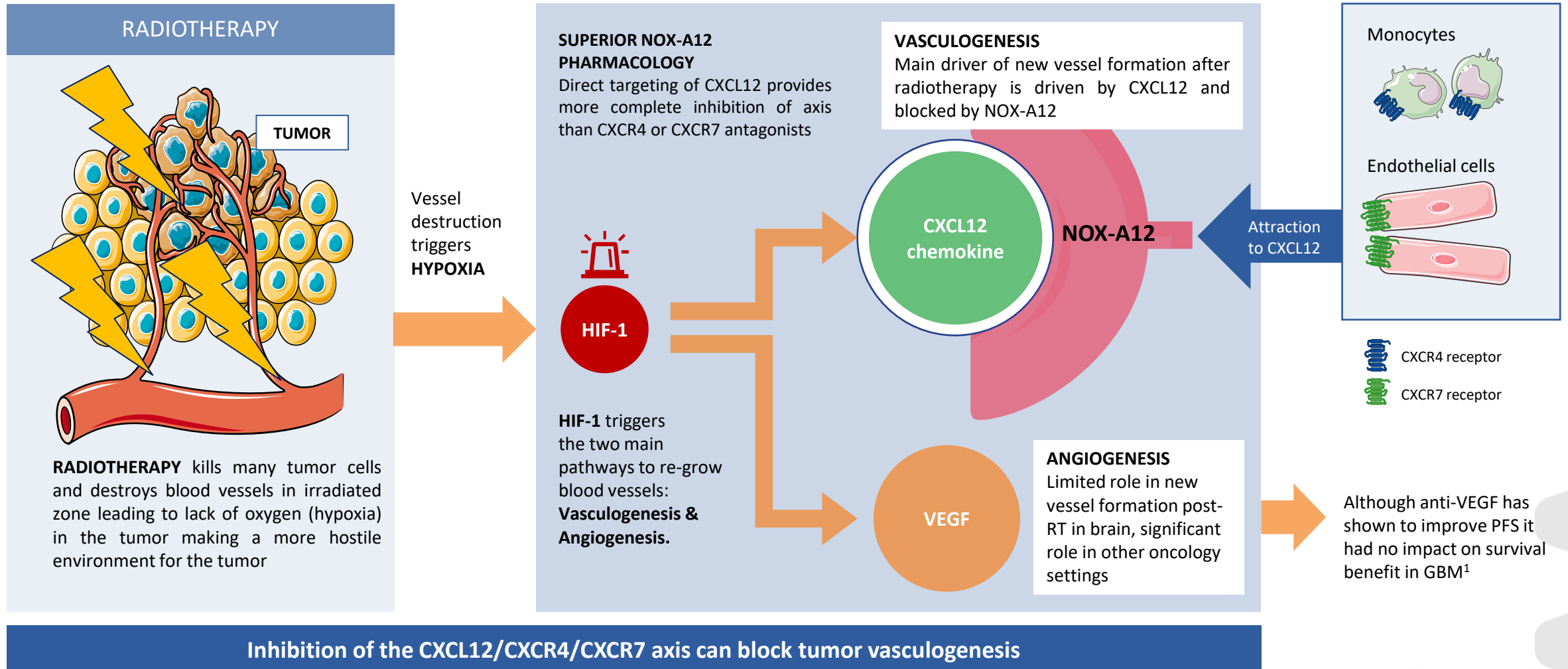
- Patients with measurable **tumor remaining** after maximal safe surgical removal of cancer have worse prognosis vs. patients with complete tumor resection



**NOX-A12 GLORIA study focuses on patients with tumor detectable after surgery that is chemotherapy resistant – the most difficult to treat patient population in GBM whose expected survival is approx. 10 months.**



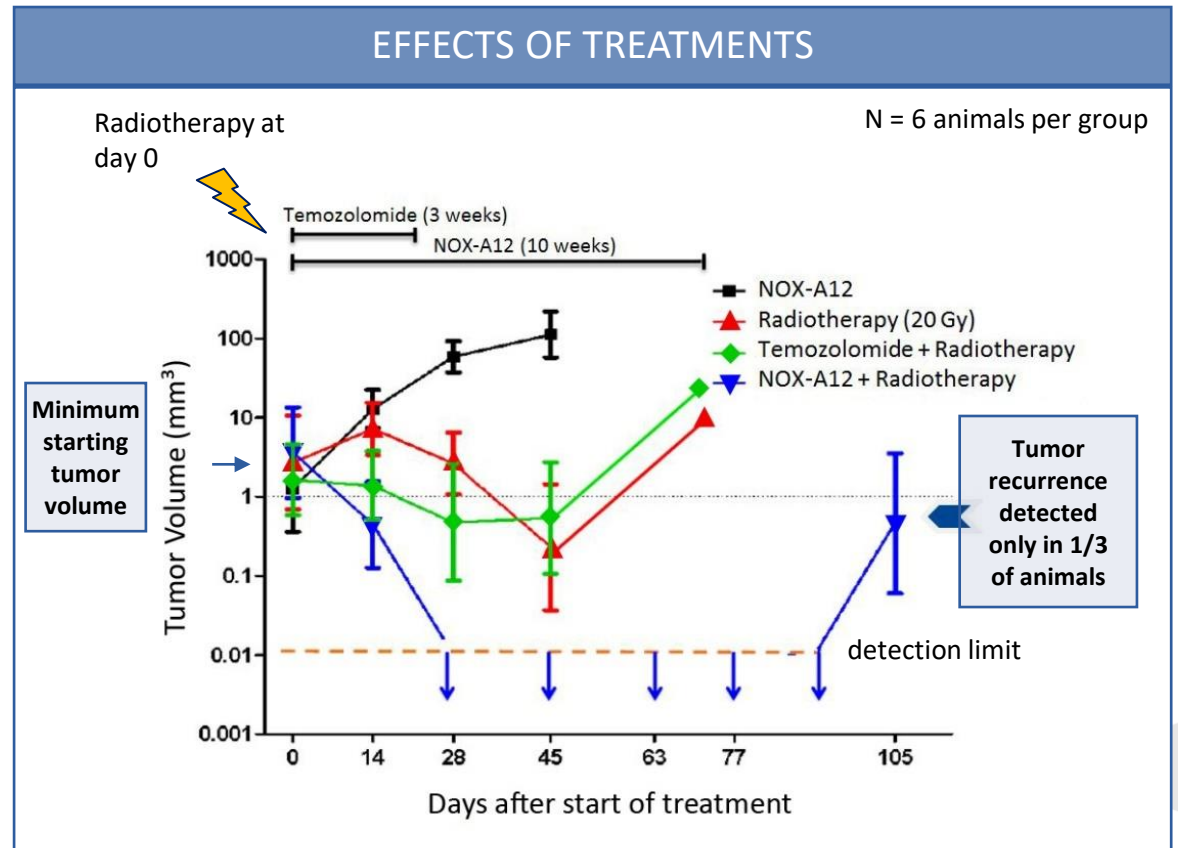
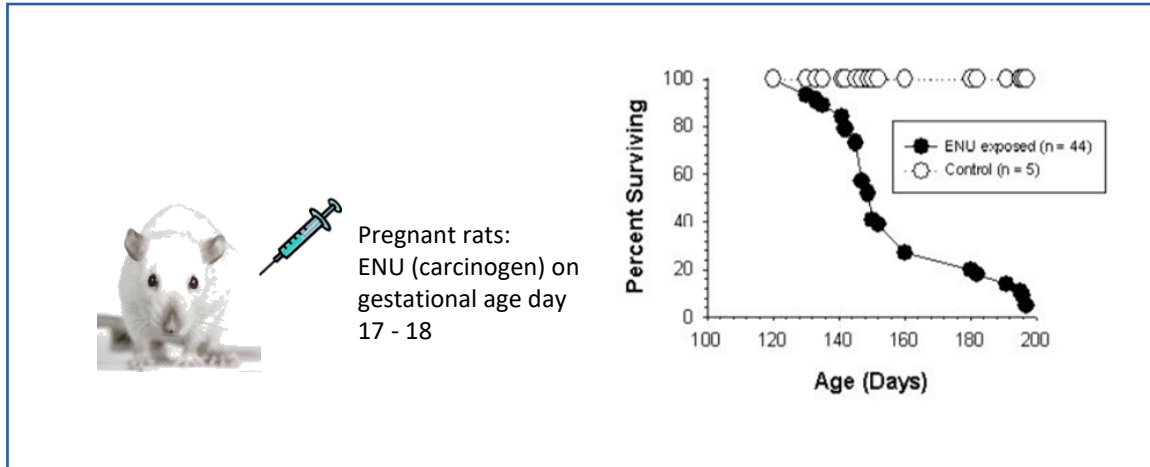
# NOX-A12's MOA is Relevant to GBM: Attacking Key Survival Mechanisms Following Radiotherapy



# NOX-A12 + Radiotherapy Increases Survival and Demonstrates Complete Regression of Brain Tumors in Animal Models

## 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



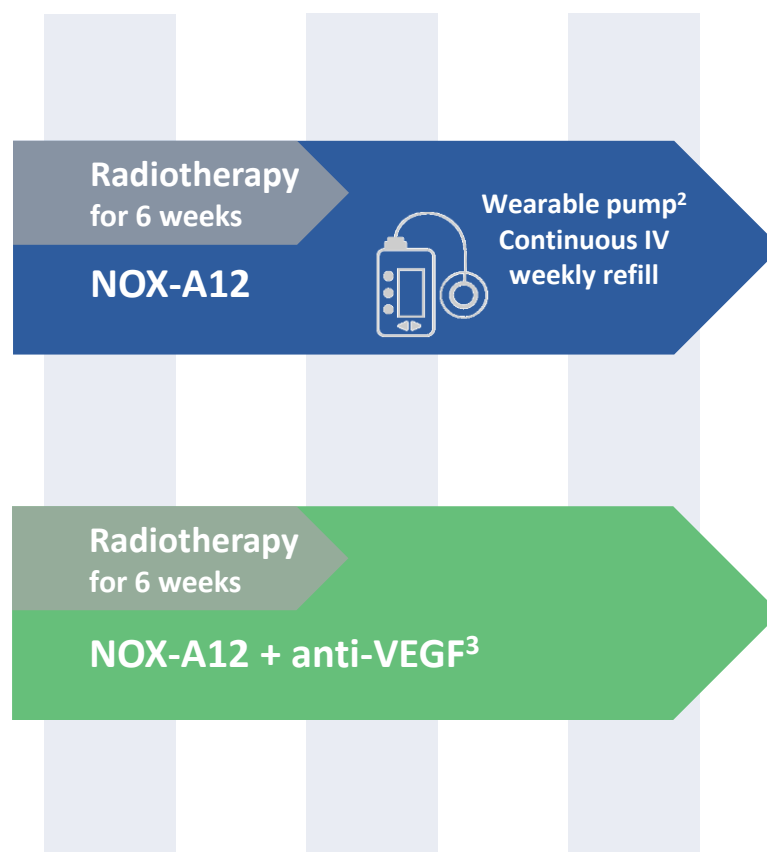
**NOX-A12 + radiotherapy resulted in 100% complete response (66% durable) in brain cancer rat model**

# GLORIA Phase 1/2 Dose Escalation Study & Expansion Arm

**1<sup>st</sup> line brain cancer  
(glioblastoma) with extremely  
poor prognosis due to:**

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

Expected median survival in this population receiving standard of care is approx. 10 months<sup>1</sup>



## **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

1. Standard of care data from 20-patient matched reference cohort of newly diagnosed glioblastoma with MGMT unmethylated, incompletely resected or biopsy-only tumors; Giordano (2022) ASCO Annual Meeting Pres. #2050

2. CADD®-Solis VIP Ambulatory Infusion Pump by Smiths Medical

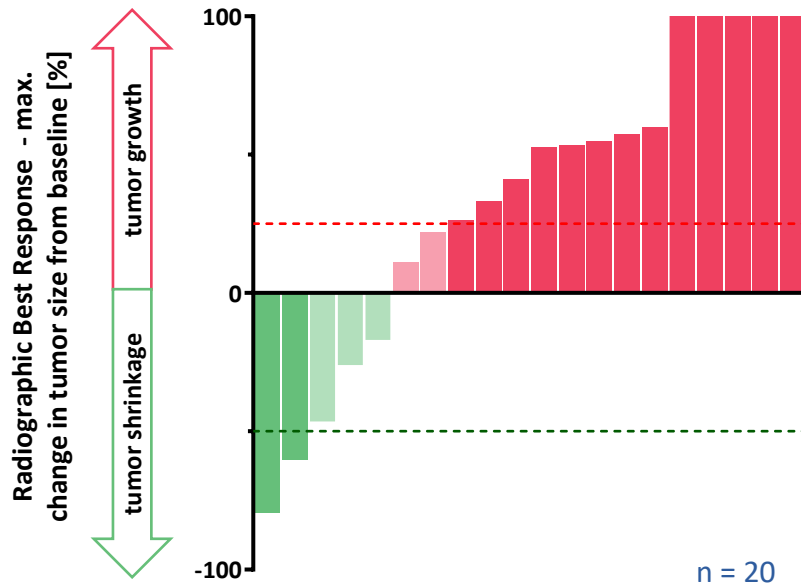
3. Bevacizumab (BEV).

# NOX-A12 Combinations Improve Best Response Rates and Depth of Tumor Shrinkage vs. Standard of Care

## Standard of Care

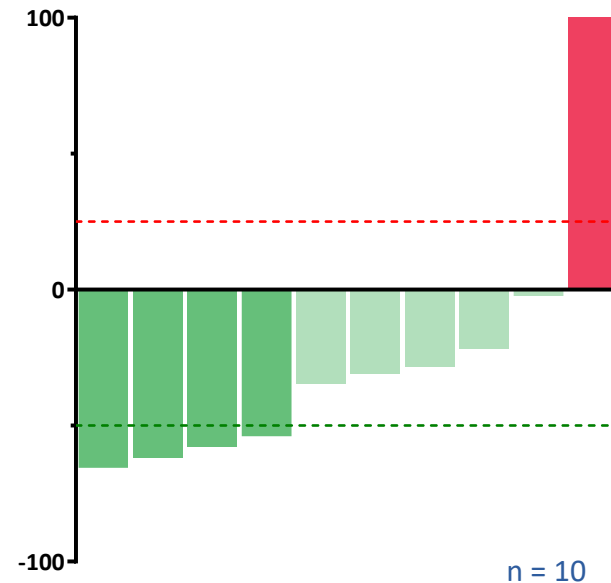
### Radiotherapy + Chemotherapy

(Matched reference cohort from center participating in trial: MGMT Unmethylated & incomplete surgical resection or biopsy only)



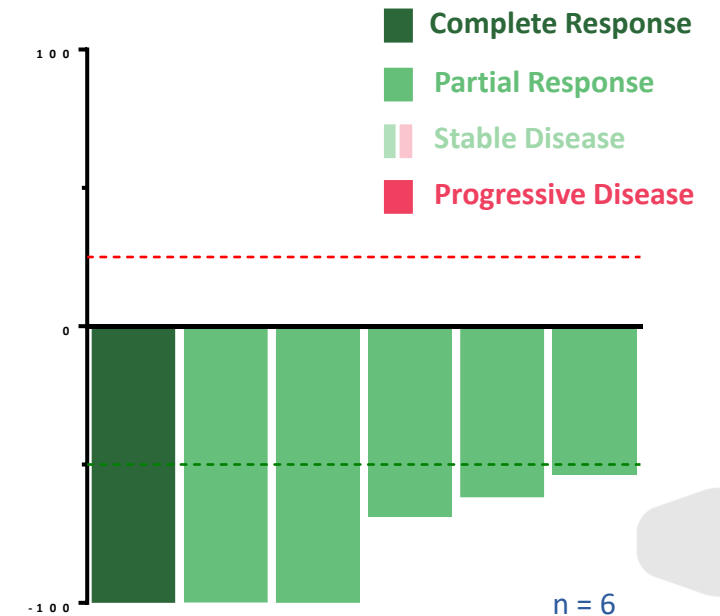
Median Overall Survival (mOS) **10.5 months**

## Radiotherapy + NOX-A12



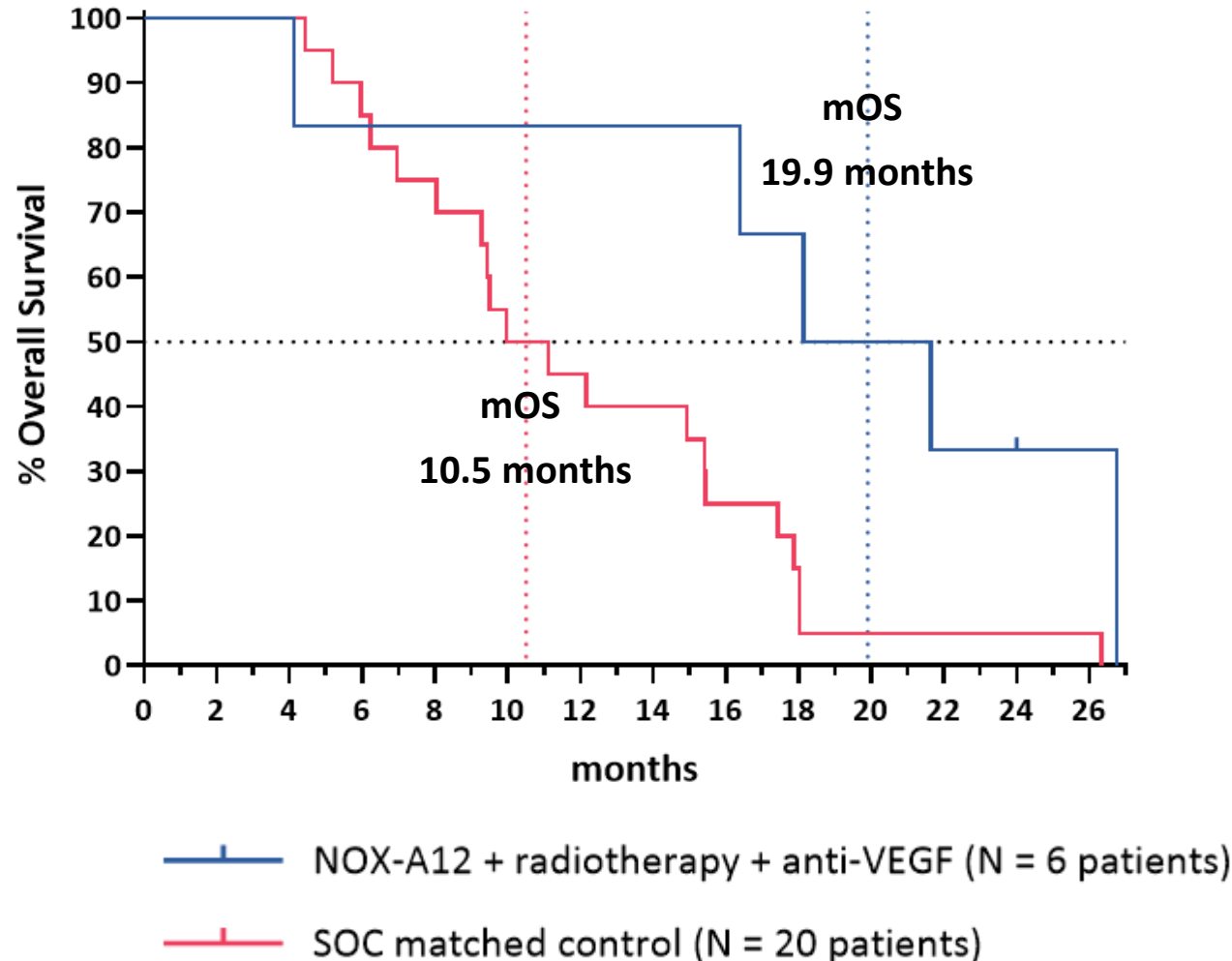
**12.7 months**  
15.8 months biomarker high

## Radiotherapy + NOX-A12 + anti-VEGF



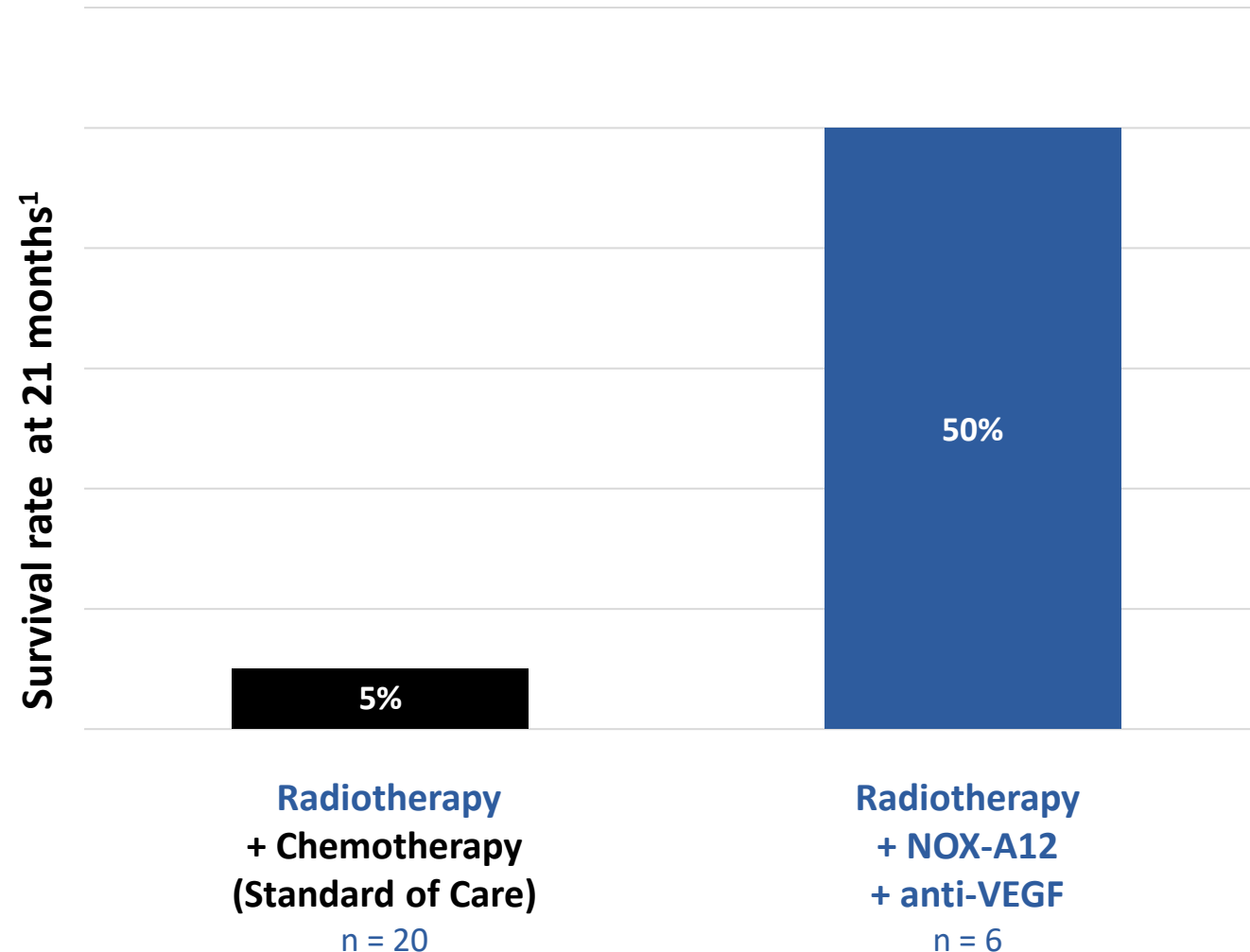
**19.9 months**

# NOX-A12 + anti-VEGF + RT: Improves median Overall Survival vs Standard of Care Reference Cohort



- Median overall survival (mOS): 19.9 months for NOX-A12 combo vs. 10.5 months for Standard of Care
- 2 out of 6 patients survived longer than >24 months
- 50% overall survival at 21 months
- 5 out of 6 patients achieved durable mRANO responses >6 months

# 10-Fold Improvement in 21-month Survival for NOX-A12 + RT + anti-VEGF vs. Standard of Care



Since neither bevacizumab (anti-VEGF) alone, nor bevacizumab plus radiotherapy have previously been shown to extend survival<sup>2</sup>, the **strong increase in survival can be attributed to the complementary mechanism of action of NOX-A12 with bevacizumab and radiotherapy**

1. Standard of care data from 20-patient matched reference cohort of newly diagnosed glioblastoma with MGMT unmethylated, incompletely resected or biopsy-only tumors; Giordano (2022) ASCO Annual Meeting Pres. #2050. NOX-A12 survival data from TME Pharma Press Release 2 February 2024; 2. Chinot (2014) NEJM, Gilbert (2014) NEJM, Herrlinger (2016) J Clin Oncology

# Relevant Benchmark Studies in Chemotherapy Resistant Glioblastoma from US and EU

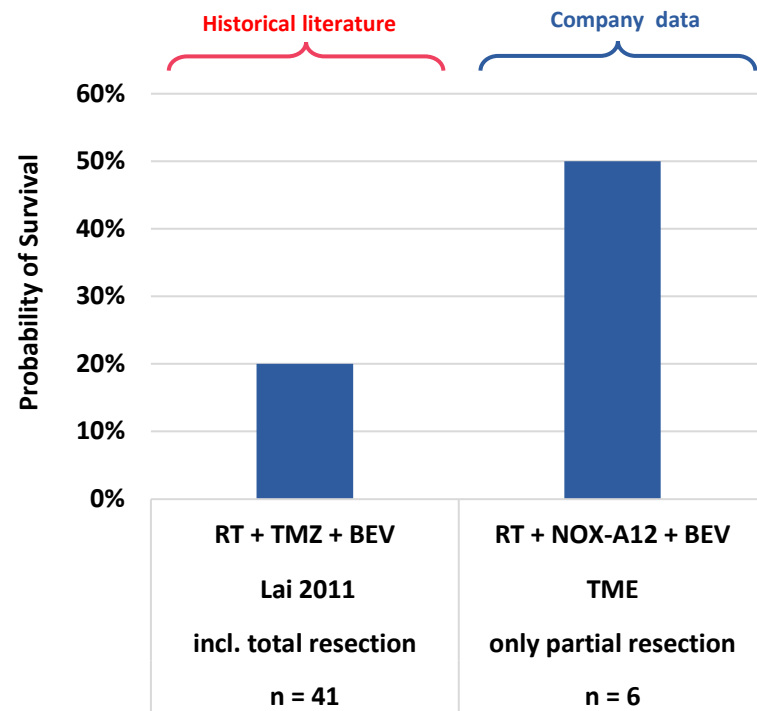
Experimental Agent (Company)	Surgical removal of detectable tumor (T=total; P=partial; B=biopsy only)	Patient number	Response criteria	Overall Response Rate (ORR)	Median Overall Survival (mOS) in months	Status	Reference
<b>NOX-A12 + Radiotherapy + bevacizumab (TME Pharma)</b>	<b>0% T; 100% P</b>	<b>6</b>	<b>RANO</b>	<b>83%</b>	<b>19.9</b>	<b>Ph 1/2 ongoing, Orphan Drug Designation &amp; Fast Track Designation granted</b>	<b>TME Pharma Internal Data</b>
Tumor Treating Fields (TTF) + Radiotherapy + Temozolomide (Novocure)	53% T; 34% P; 13% B	209	Macdonald	n.a.	16.9	Approved	Stupp R (2017), JAMA
Val-083 after Radiotherapy + Temozolomide chemotherapy (Kintara)	information not provided	36	RANO	n.a.	16.5	Failed pre-defined criteria for GBM AGILE trial Ph 3	O'Brien (2021), Society for Neuro-Oncology Annual Meeting
Paxalisib + Radiotherapy (Kazia)	77% T; 17% P; 10% B	30	RANO	3%	15.7	Failed pre-defined criteria for GBM AGILE trial Ph 3	Wen P (2022); J Clin Oncol.
Enzastaurin + Radiotherapy (Denovo)	43.9% T; 40.4% P; 15.8 B	57	Macdonald	7%	15	Orphan Drug Designation & Fast Track Designation granted; Ph 3 ongoing	Wick W (2013), Neuro Oncol.
Temozolomide chemotherapy + Radiotherapy + bevacizumab (Roche)	63% T; 34% P; 3% B #	215	Macdonald	n.a.	14.3	Failed in Ph 3	Gilbert MR (2014), NEJM
Nivolumab anti-PD-1 immunotherapy + Radiotherapy (BMS)	54% T; 46% P	280	RANO	7.8%	13.4	Failed in Ph 3	Omuro A (2022); Neuro Oncol.
Temozolomide chemotherapy + Radiotherapy	information not provided	60	n.a.	n.a.	12.7	Approved (current standard of care)	Hegi ME (2005) NEJM



# Higher Survival at 21 Months with NOX-A12 + BEV Than Seen in Benchmark BEV Studies Enrolling Patients with Better Prognosis

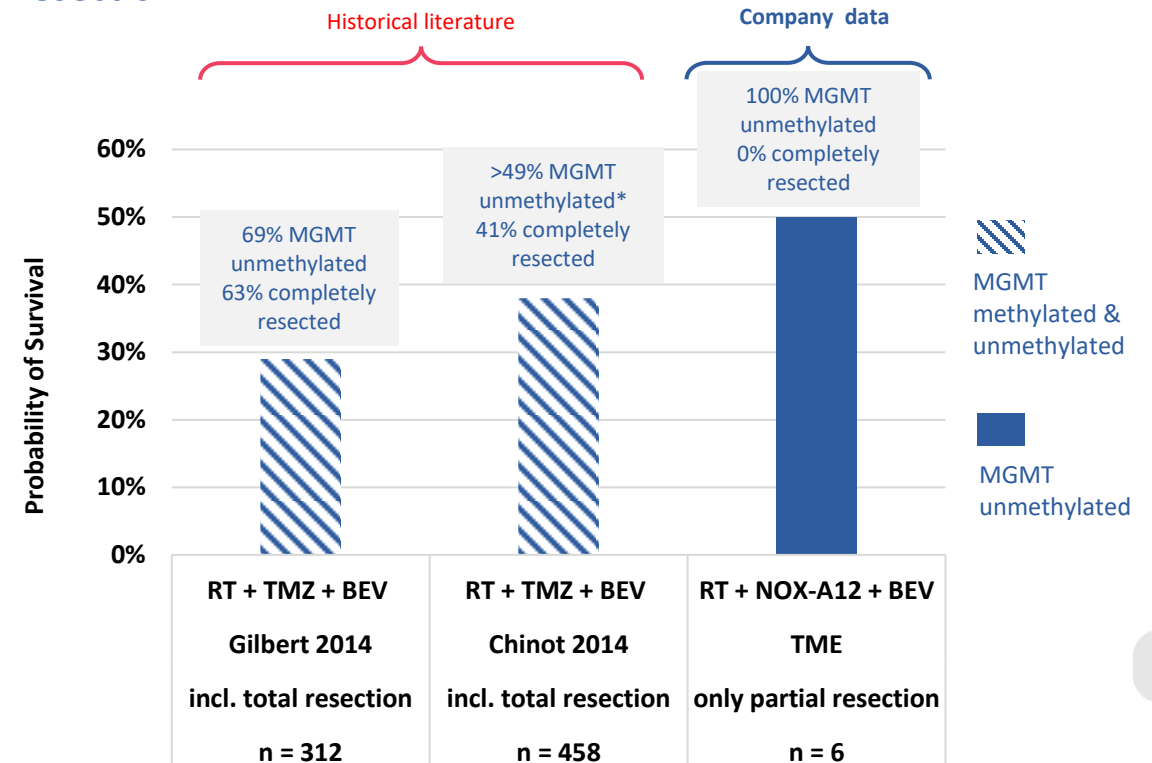
## OS at 21 months:

Benchmark Phase 2 study with only MGMT unmethylated patients but incl. gross total resection



## OS at 21 months:

Benchmark Phase 3 studies with mixed populations in terms of MGMT and resection



**Superior survival signal of NOX-A12 + BEV vs. TMZ + BEV even when tested in patients with worse prognosis**

# FDA-Approved Phase 2 Study Design in GBM: 5-arm Randomized Controlled Study, 20 Patients / Arm

- Newly diagnosed glioblastoma patients with extremely poor prognosis:
- Incomplete surgical resection
- MGMT promoter unmethylated: chemotherapy ineffective
- Randomized-controlled enrollment
- Treatment duration 1 to 2 years

Expected survival in this population receiving standard of care<sup>1</sup>:

- mOS of approx. 10 months

Orphan Drug and Fast Track Designations awarded by FDA

**Arm 1**

RT - 6 weeks

**NOX-A12 – 200mg/week + bevacizumab**

**Arm 2**

RT - 6 weeks

**NOX-A12 – 400mg/week + bevacizumab**

**Arm 3**

RT - 6 weeks

**NOX-A12 – 600mg/week + bevacizumab**

**Arm 4**

RT - 6 weeks

**NOX-A12 – 600 mg/week**

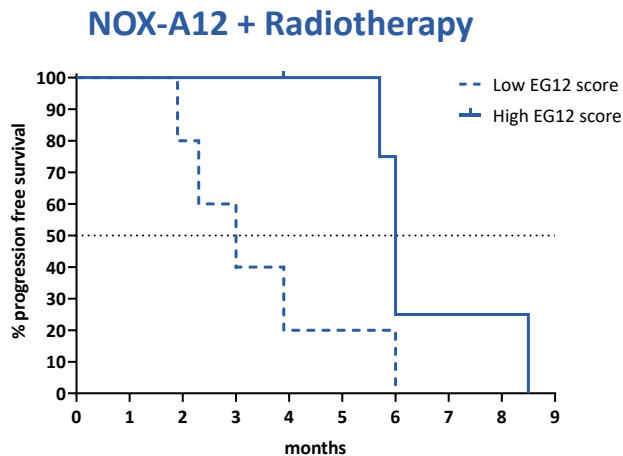
**Arm 5**

RT - 6 weeks

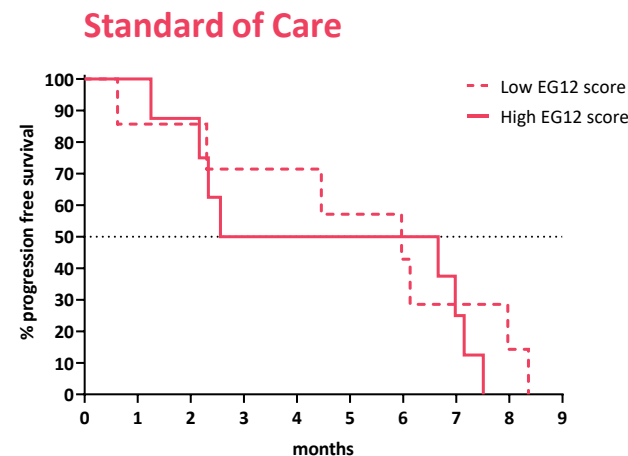
**temozolomide**

# The EG12 Score: A Potential Predictive Biomarker for Clinical Outcome

- A predictive biomarker is a measurable biological characteristic that provides information about the **likelihood of an individual patient to respond to a specific treatment**
- Analysis of tumor tissue revealed that the EG12 score **strongly and significantly correlated with PFS** in GLORIA patients receiving NOX-A12 + RT ( $p=0.005$ ) but not in patients treated with standard of care ( $p=0.724$ )
- The **EG12 score predicts PFS for NOX-A12-treated patients** with statistical significance ( $p=0.031$ )



**EG12<sup>high</sup> patients with significantly longer PFS**  
( $p=0.031$ ; mPFS = 6.0 vs. 3.0 months for EG12<sup>high</sup> vs EG12<sup>low</sup>)

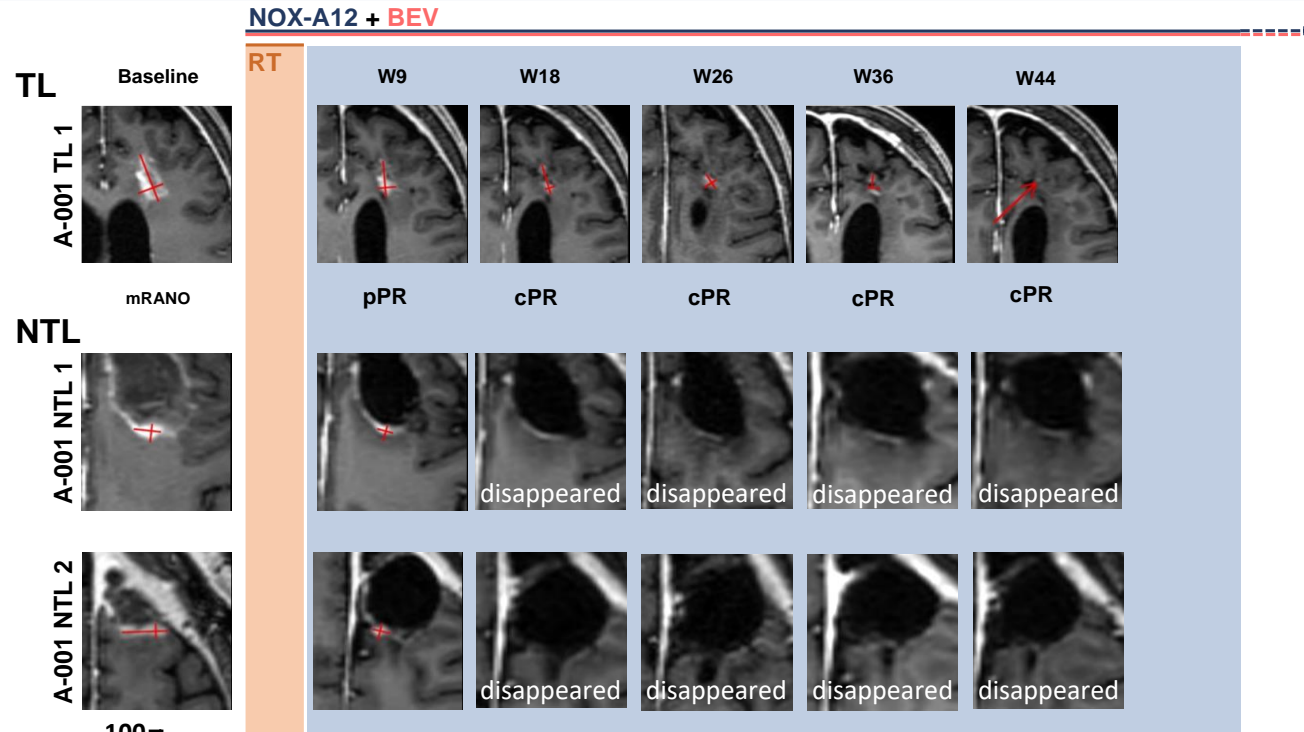


**No significant difference in PFS**  
( $p=0.502$ ; mPFS 4.6 vs. 6.0 months for EG12<sup>high</sup> vs EG12<sup>low</sup>)

- There is also a **strong trend for the EG12 score to predict OS for NOX-A12 treated patients** ( $p=0.075$ )

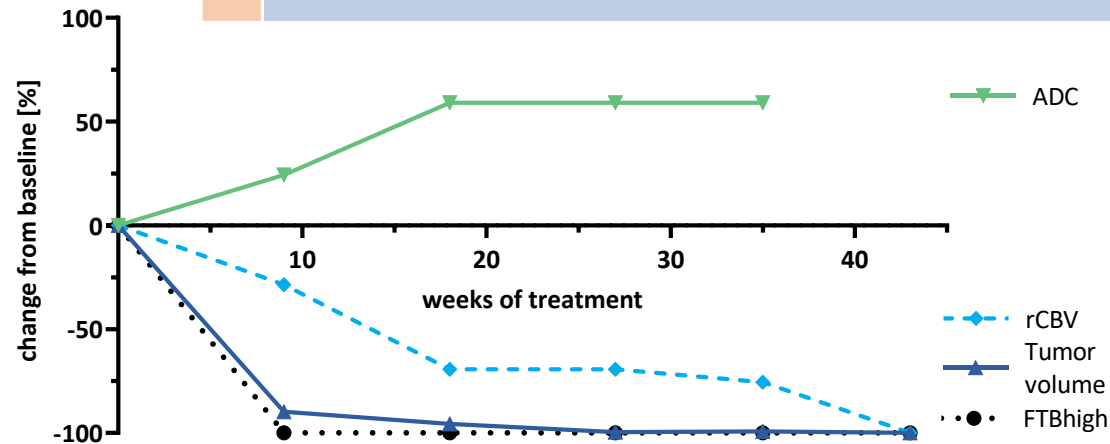
➤ The EG12 score might be a **predictive biomarker for OS** in patients treated with NOX-A12 + RT

# NOX-A12 + RT + Bevacizumab: Near-Complete Response in Exemplary Patient



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

pPR – preliminary partial response  
cPR – confirmed partial response

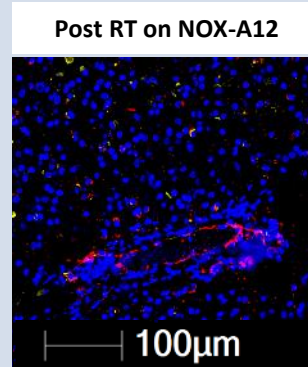
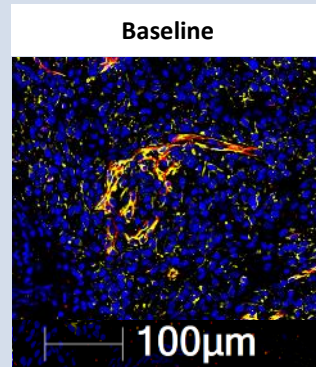


Changes from baseline  
ADC: increase in change represents improvement  
rCBV, Volume, FTBhigh: decrease in change represents improvement

cut off date: 01-Nov-2022

# NOX-A12 Neutralizes the CXCL12 Chemokine on Blood Vessel Walls in GBM Patient

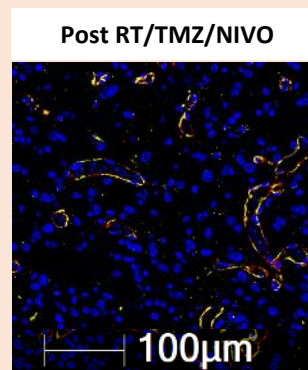
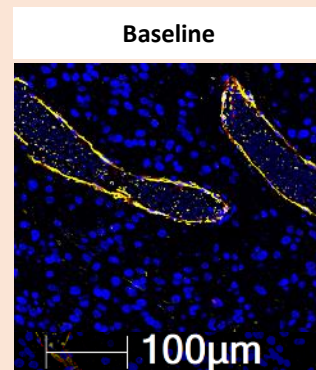
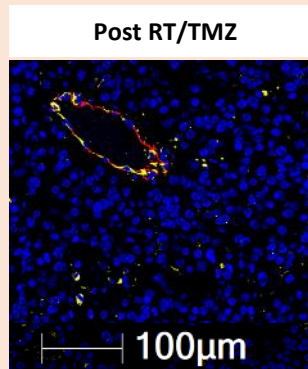
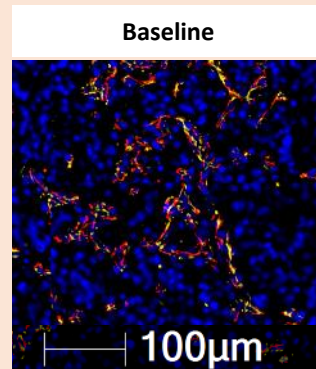
GLORIA  
C1-001



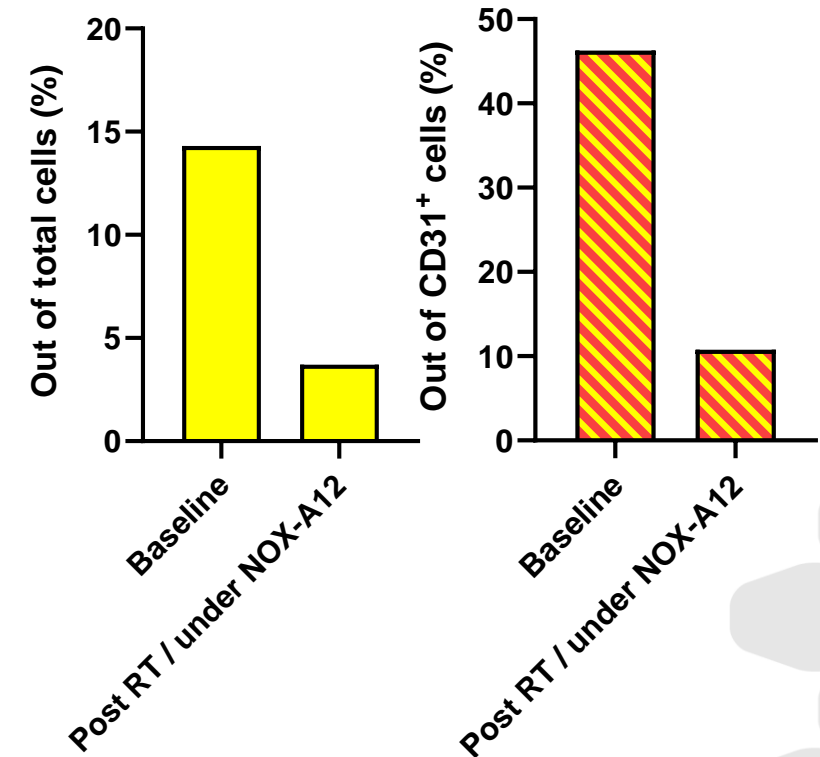
DAPI  
CD31  
CXCL12

Images show  
areas of  
pathologist-  
confirmed  
tumor tissue

Reference  
patients



CXCL12<sup>+</sup> cells  
Patient C1-001

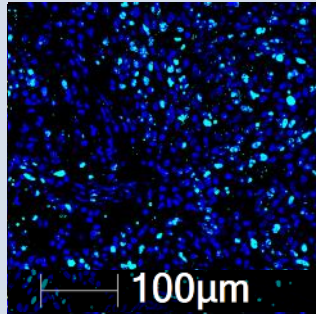




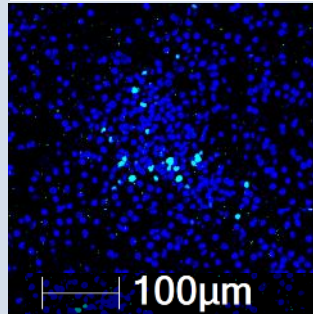
# NOX-A12 + RT Reduce Tumor Cell Proliferation in GBM Patient

GLORIA  
C1-001

Baseline



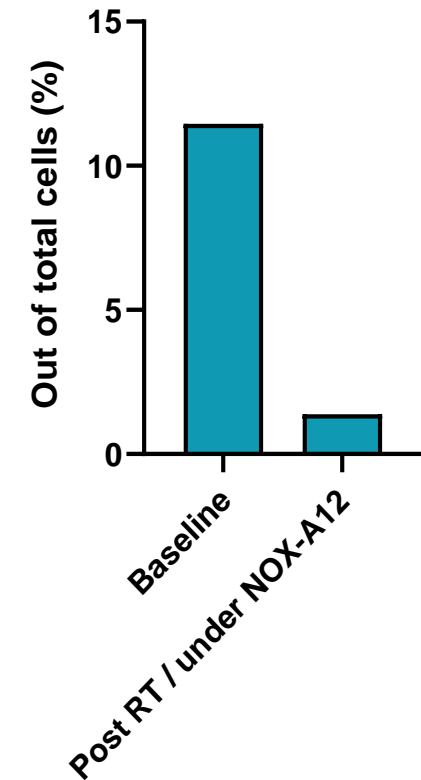
Post-RT on NOX-A12



DAPI  
Ki67

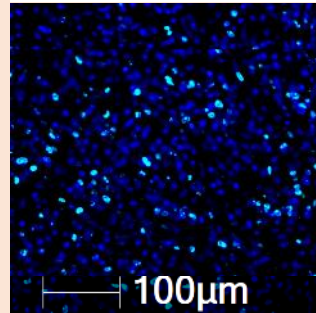
Images show  
areas of  
pathologist-  
confirmed  
tumor tissue

Proliferating cells  
Patient C1-001

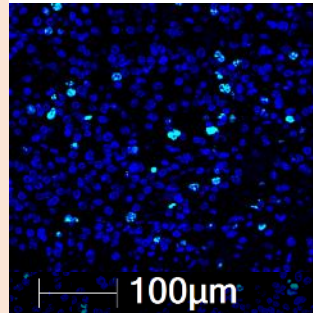


Reference  
patients

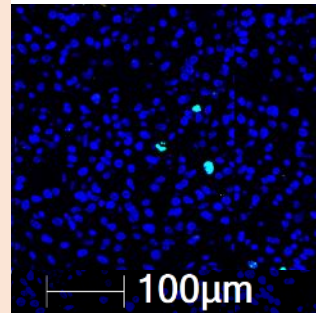
Baseline



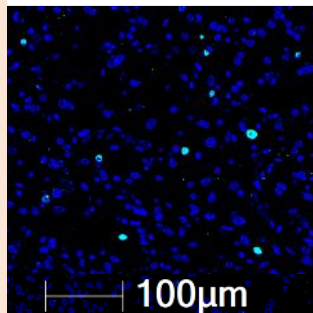
Post RT/TMZ



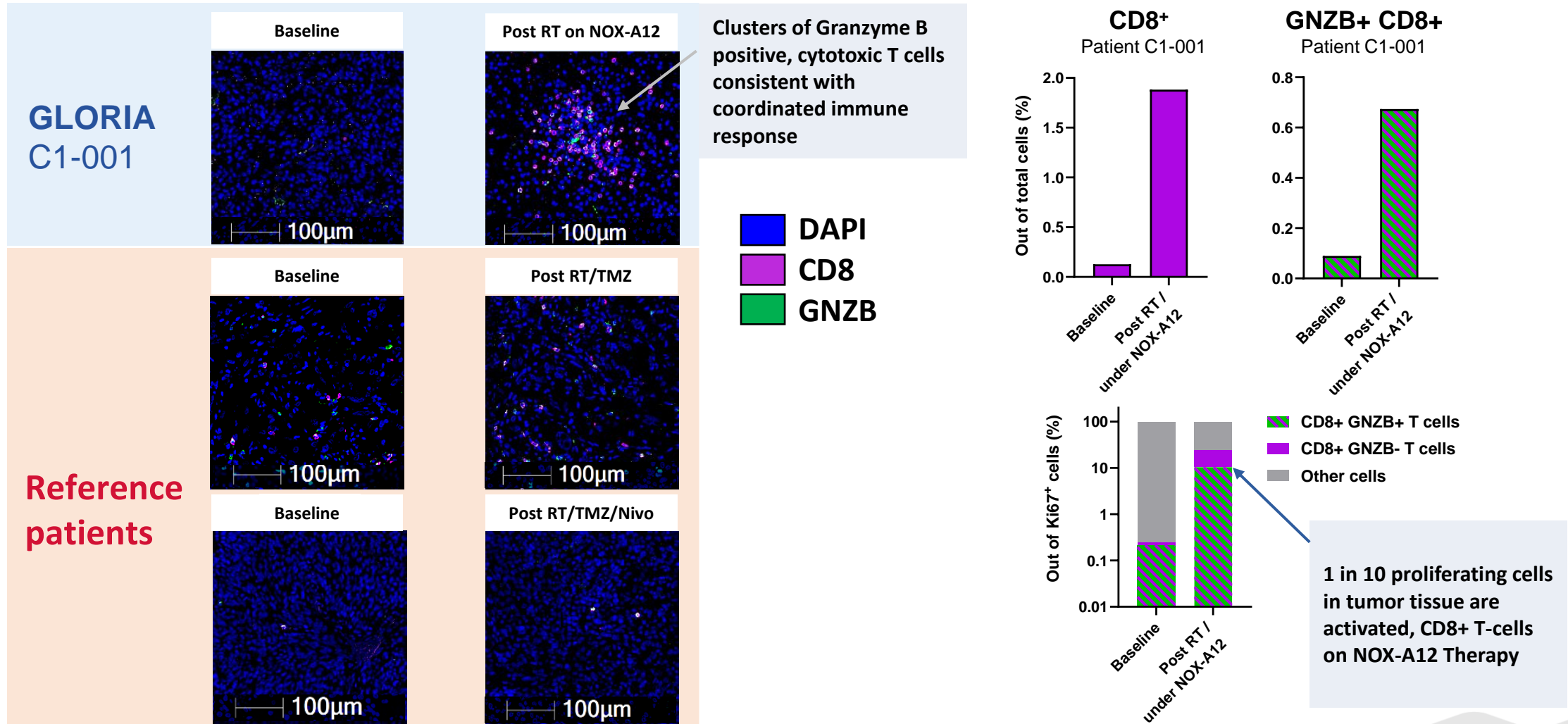
Baseline



Post RT/TMZ/NIVO



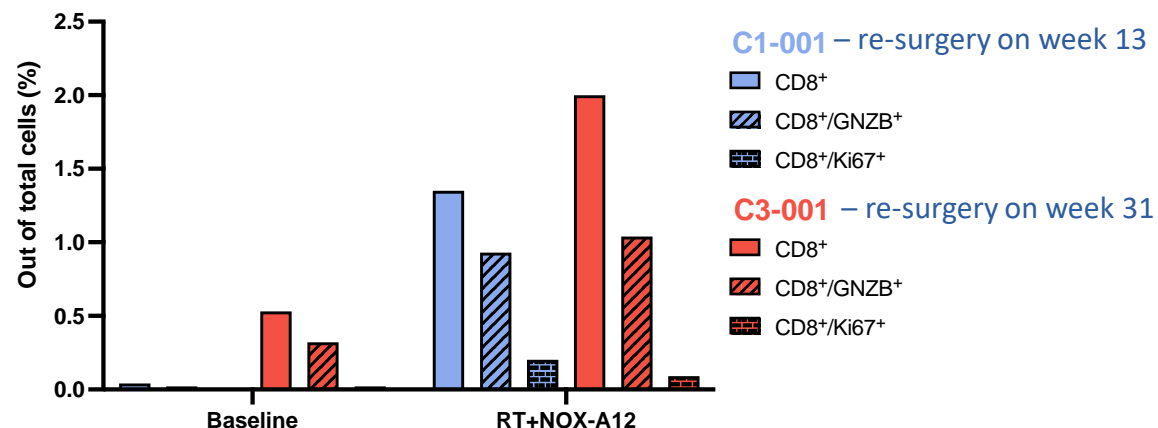
# NOX-A12 + RT Lead to Extensive Penetration of Immune System (Cytotoxic T Cells) in the Tumor of GBM Patient



Images show areas of pathologist-confirmed tumor tissue

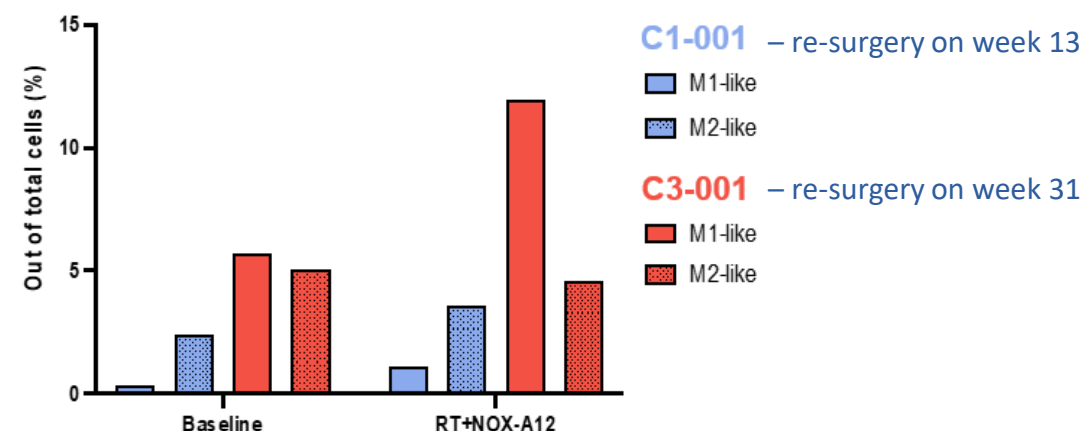
# NOX-A12 + RT = ↗ Anti-Cancer Cells + ↘ Pro-Cancer Cells

## T cells



- Substantial increase in cytotoxic T cells in two patients under treatment with NOX-A12
- Increased proportion of activated and proliferating cytotoxic T cells as well as T cell cluster formation in two patients under treatment with NOX-A12

## Macrophages



### Increased anti-cancer macrophages in two patients under treatment with NOX-A12

- Increase in anti-cancer macrophages (M1-like)
- No consistent change in pro-cancer macrophages (M2-like)



# Good Safety, Tolerability and Promising Efficacy Data in NOX-A12 and NOX-A12 + Bevacizumab Arms

- **Good safety and tolerability** profile of all combinations
- Tissue analysis **confirms mode(s) of action**<sup>1,2</sup>
- **Potential biomarker identified** which is **predictive for PFS** in patients treated with NOX-A12 + RT<sup>3</sup>
- **Promising response rates** for the combination of NOX-A12 + RT and for NOX-A12 + RT + BEV<sup>2,4</sup>
- **Clinical outcome beyond expectation for the study population**
- NOX-A12 + RT + BEV:<sup>5</sup>
  - **19.9 months mOS vs. 10.5 months for Standard of Care**
  - **10-fold improvement of 21-month survival vs. Standard of Care (50% vs. 5%)**
- **Regulatory status:**<sup>6</sup>
  - **Open IND for upcoming Phase 2** in newly diagnosed, chemotherapy-resistant glioblastoma w/residual tumor post-surgery, **Fast Track Designation** awarded by the FDA
  - **Orphan Drug Designation** in the EU and US
- **Future development potential**
  - The MoA of NOX-A12 also supports development of NOX-A12 in MGMT methylated patients, in recurrent glioblastoma as well as in brain metastases from other cancer types (e.g. breast and lung)

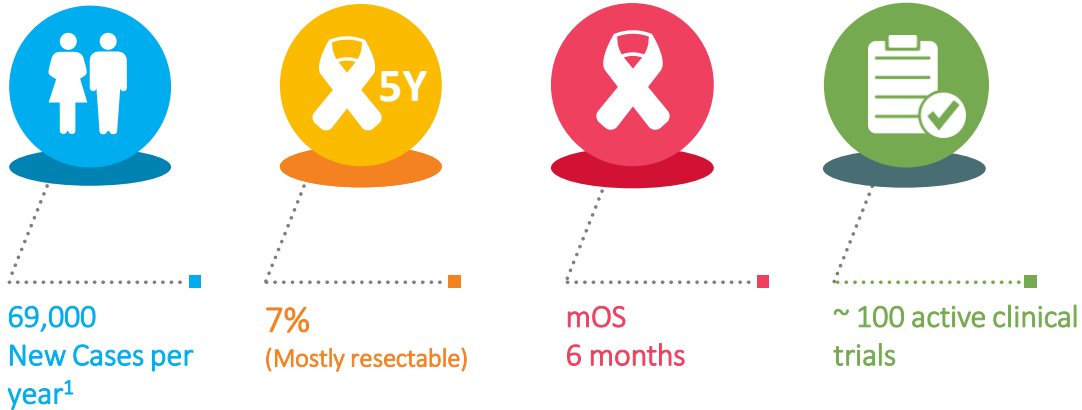


# NOX-A12 + Immunotherapy in Pancreatic Cancer



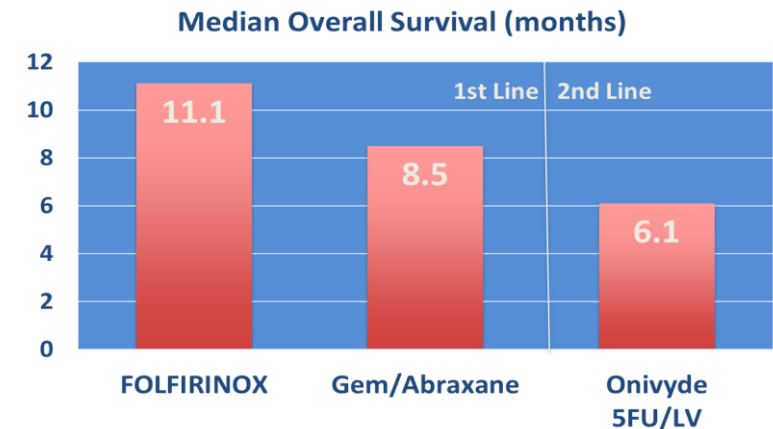
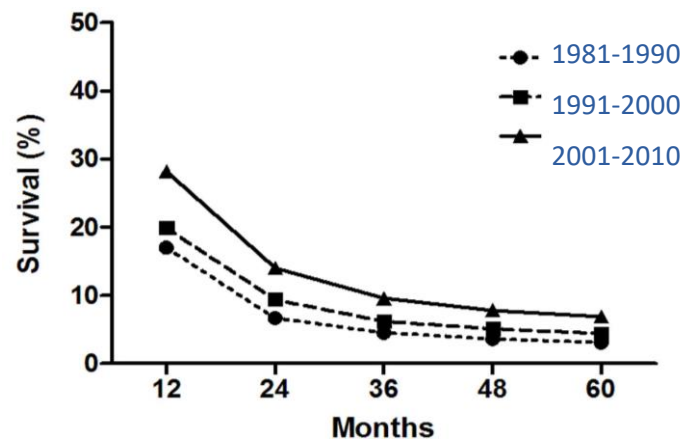
# Pancreatic Cancer – Extremely Low Overall Survival and Limited Treatment Options

## LACK OF EFFECTIVE THERAPIES & LOW OVERALL SURVIVAL



## HIGH UNMET NEED IN RELAPSED & REFRACTORY PATIENT SETTINGS

- Pancreatic cancer stroma sequesters T cells preventing engagement with tumor cells – many immuno-suppressive cells: TAMs, MDSCs
- NOX-A12 is ideally positioned for combination with checkpoint inhibitors and other MoAs to improve long-term outcomes



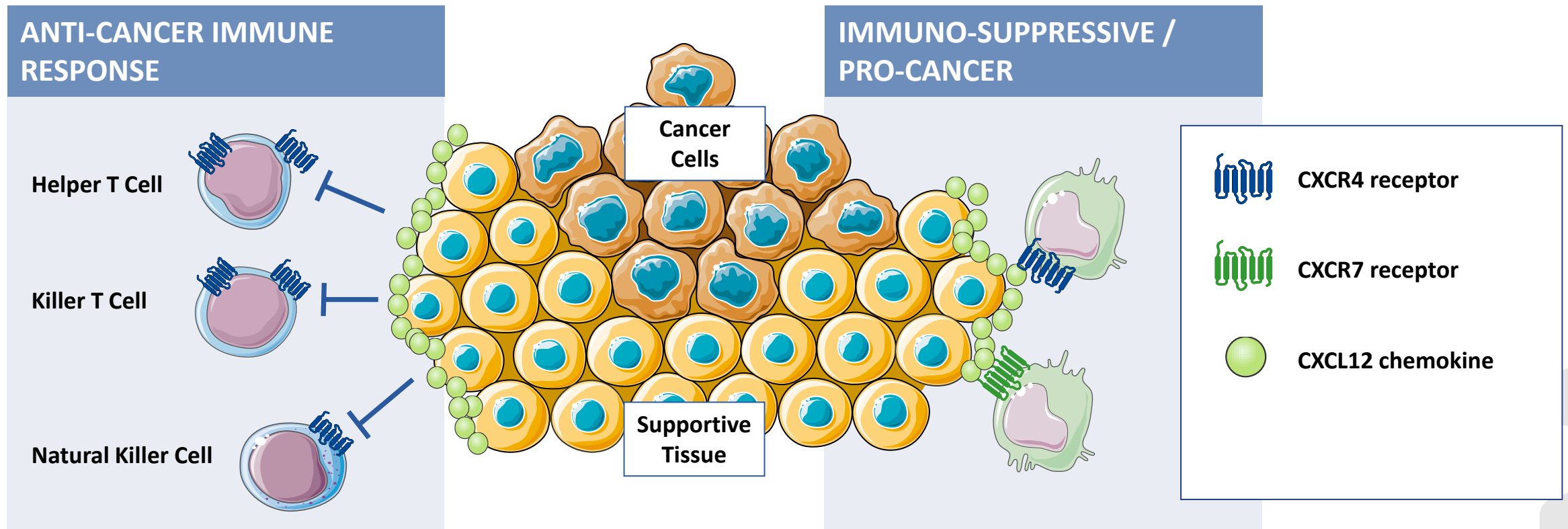
1. Second-line in the US, UK, FR, ES, DE & IT, 107k first-line. Global Data April 2022

Sources: Sun, H. (2015) Scientific Reports 4, 6747.doi:10.1038/srep06747; S. Pusceddu, M, et al. (2019) Cancers Vol. 11 Issue 4; Seo YD, et al., (2019) Clin Cancer Res; 25(13); Global Data, ClinicalTrials.gov & TME Pharma analysis, April 2022

# NOX-A12 + Immunotherapy: Mode of Action

## CXCL12:

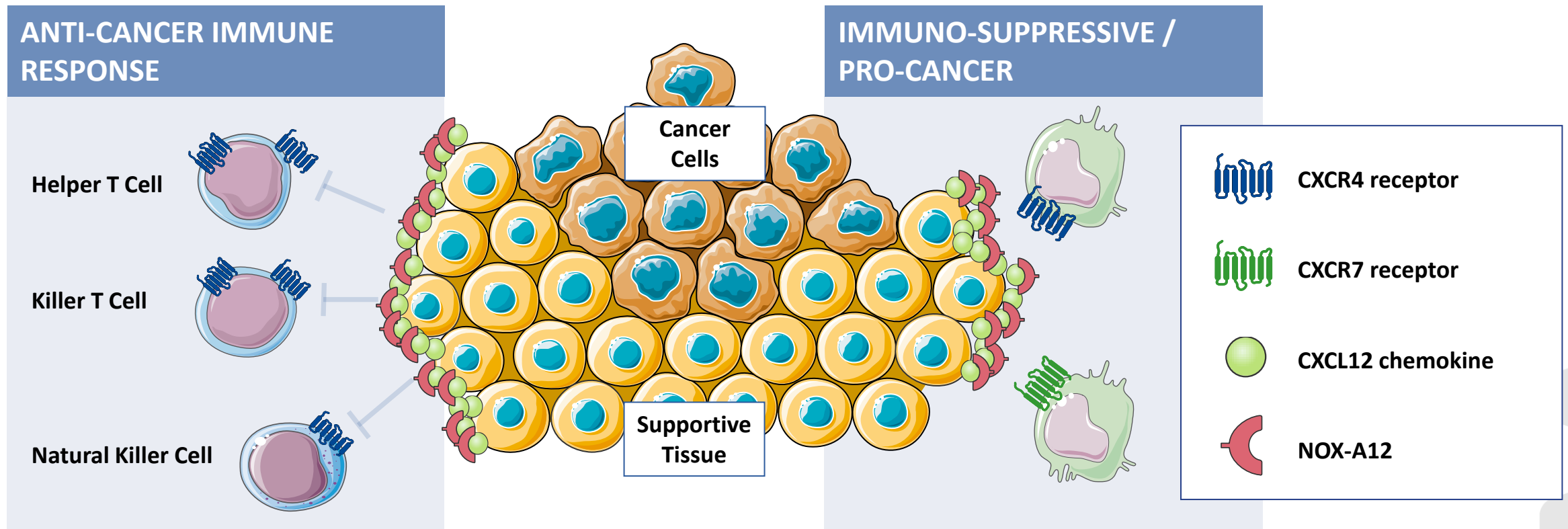
- excludes effector immune cells from entering the tumor
- attracts bone-marrow derived immuno-suppressive / pro-cancer cells to region of tumor



# NOX-A12 + Immunotherapy: Mode of Action

## NOX-A12:

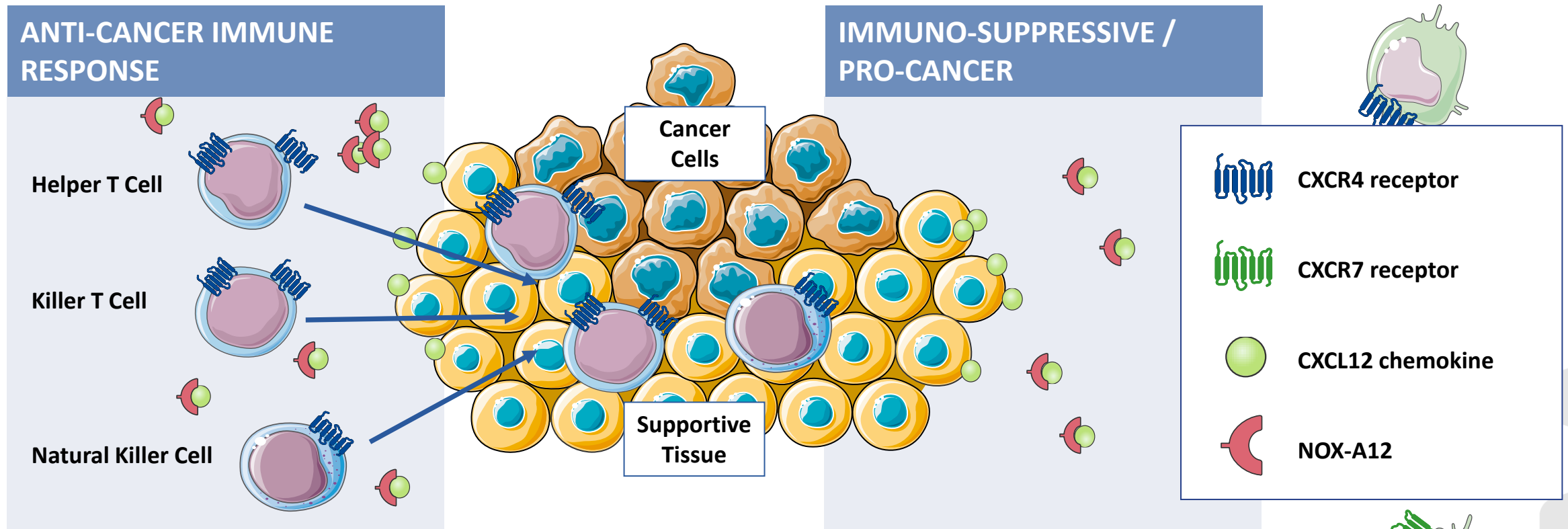
- reduces CXCL12 “wall” around solid tumors, which
- allows Killer T Cells to enter, eliminates attraction of immuno-suppressive / pro-cancer cells<sup>1</sup>



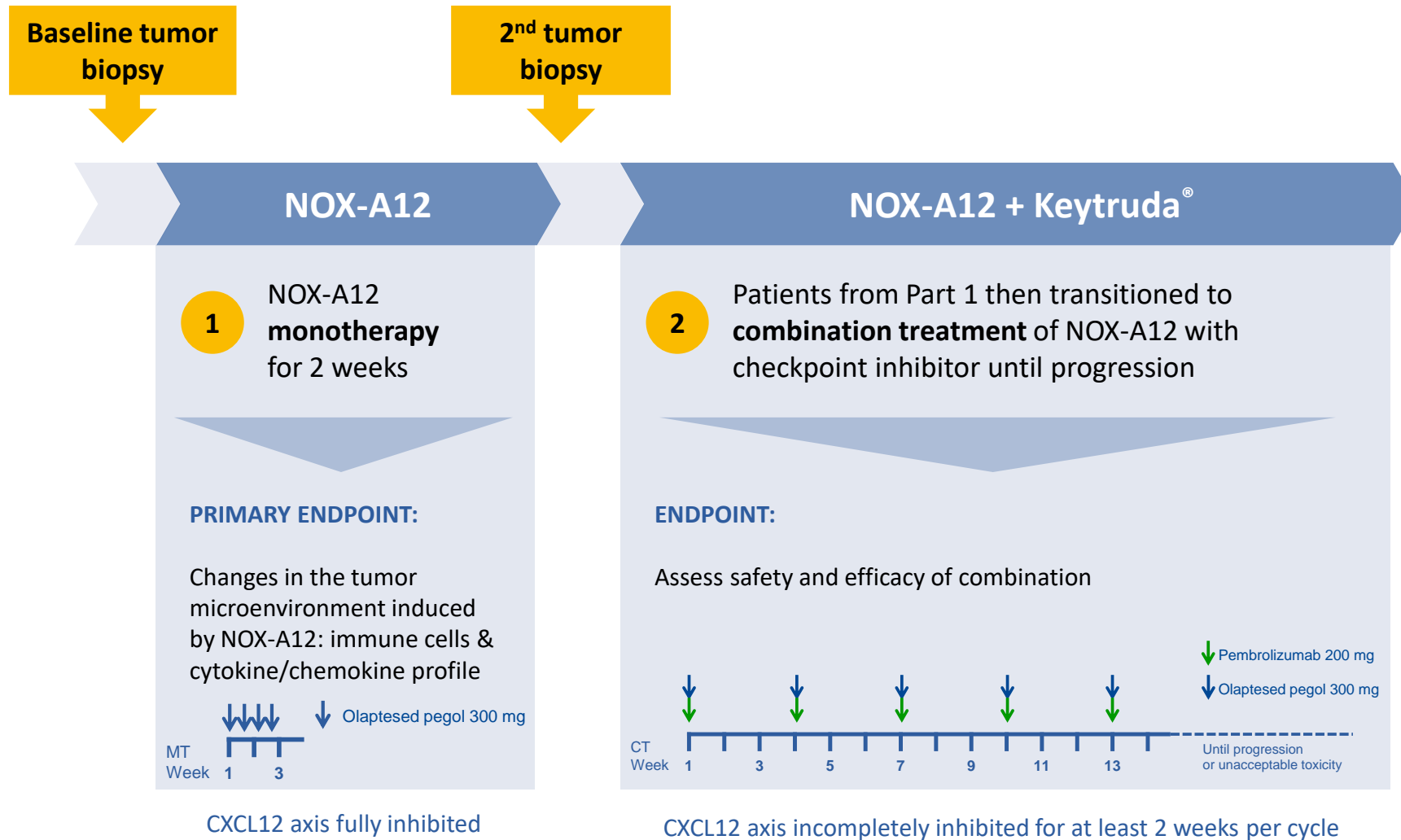
# NOX-A12 + Immunotherapy: Mode of Action

## NOX-A12:

- reduces CXCL12 “wall” around solid tumors, which
- allows Killer T Cells to enter, eliminates attraction of immuno-suppressive / pro-cancer cells<sup>1</sup>



# Phase 1/2 Trial Completed in 9 Pancreatic Cancer and 11 Metastatic Colorectal Cancer Patients



Clinical Trial a Scientific Collaboration with:

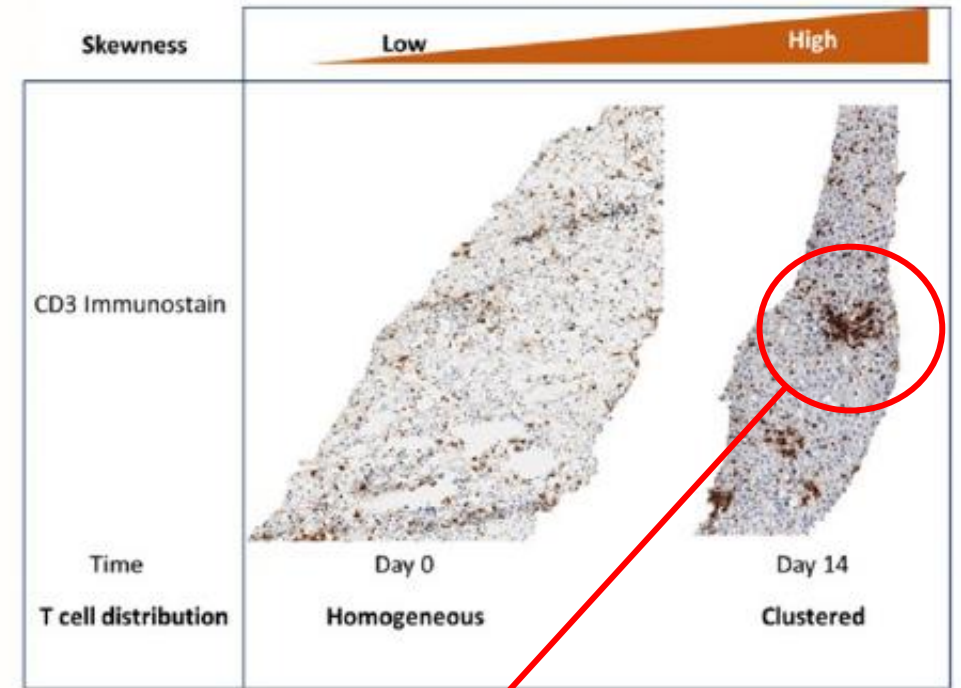
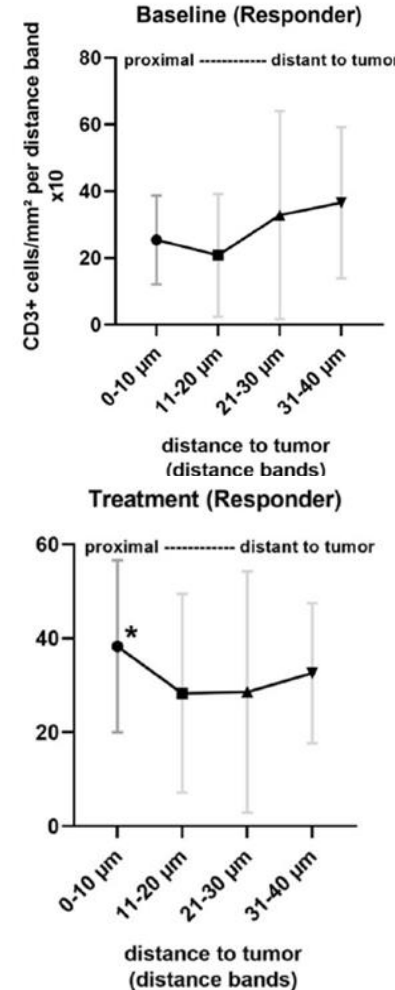
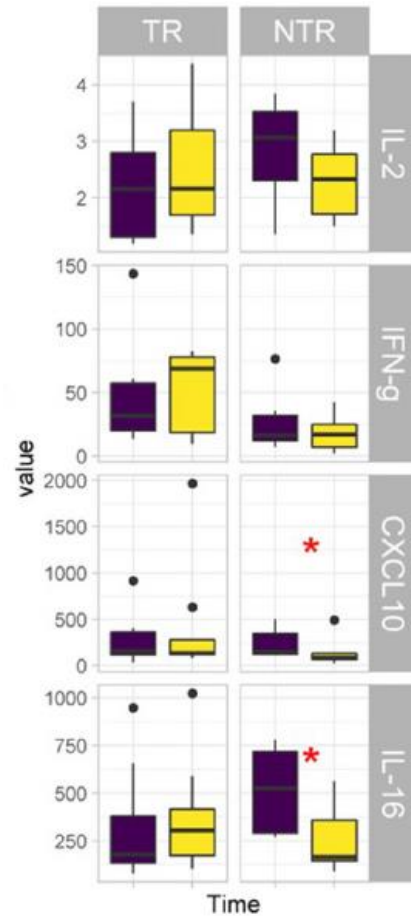




# In PDAC / CRC Patients NOX-A12 Monotherapy Induces Integrated Immune Response and T Cell Clustering

## Cytokine profile

Unsupervised clustering of patients based on relative changes in the molecular immune landscape at the end of NOX-A12 monotherapy. Concentrations of the most affected cytokines before and at the end of the monotherapy in patients clustered in tissue responders (TR) and tissue non-responders (TNR).



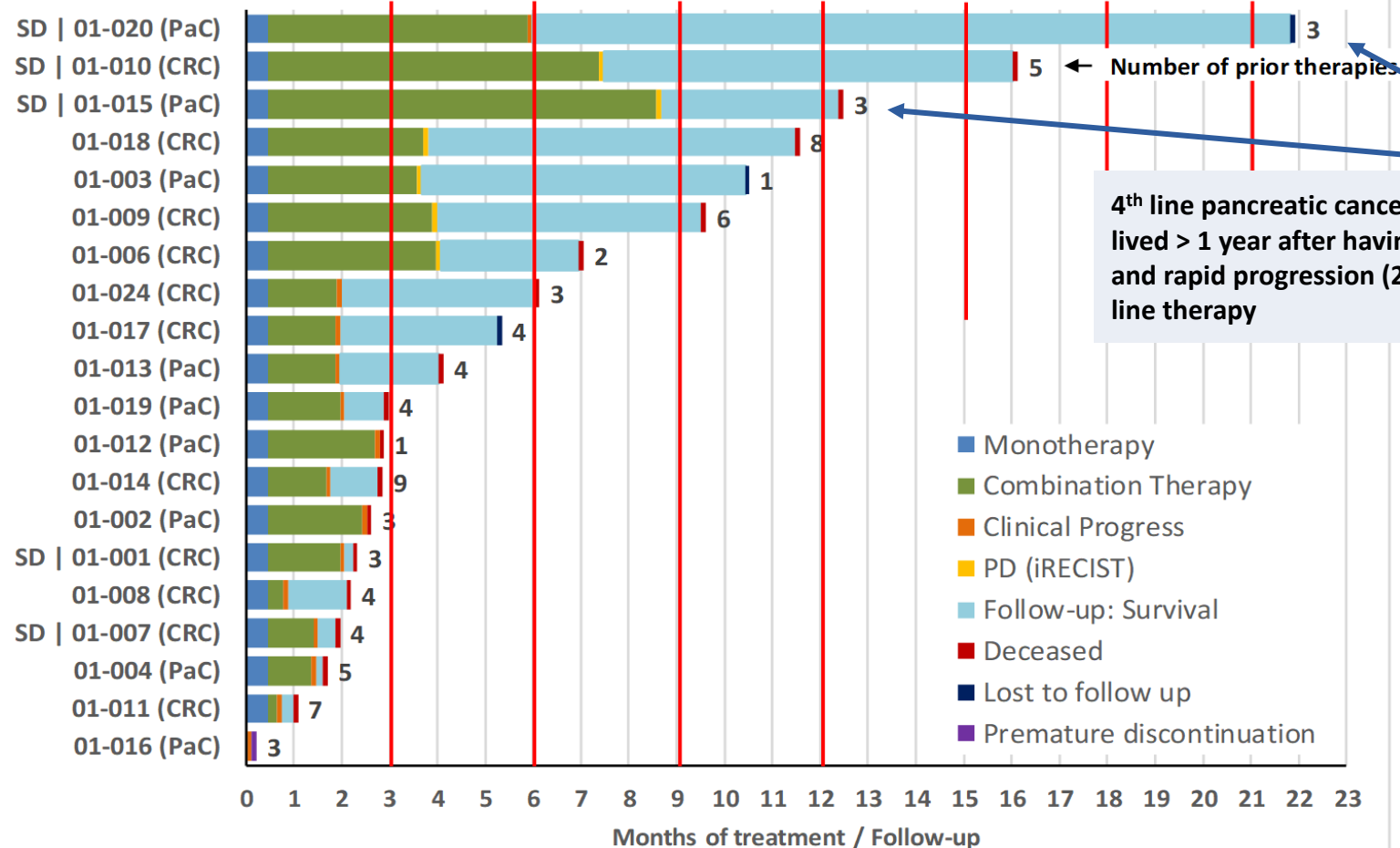
T-cell clustering in PaC/CRC patients on NOX-A12 monotherapy similar to that seen in glioblastoma patients while on NOX-A12 therapy post-RT with infiltration of proliferating GNZB+/CD8+ cells



# Impressive Survival in Heavily Pre-Treated Patients

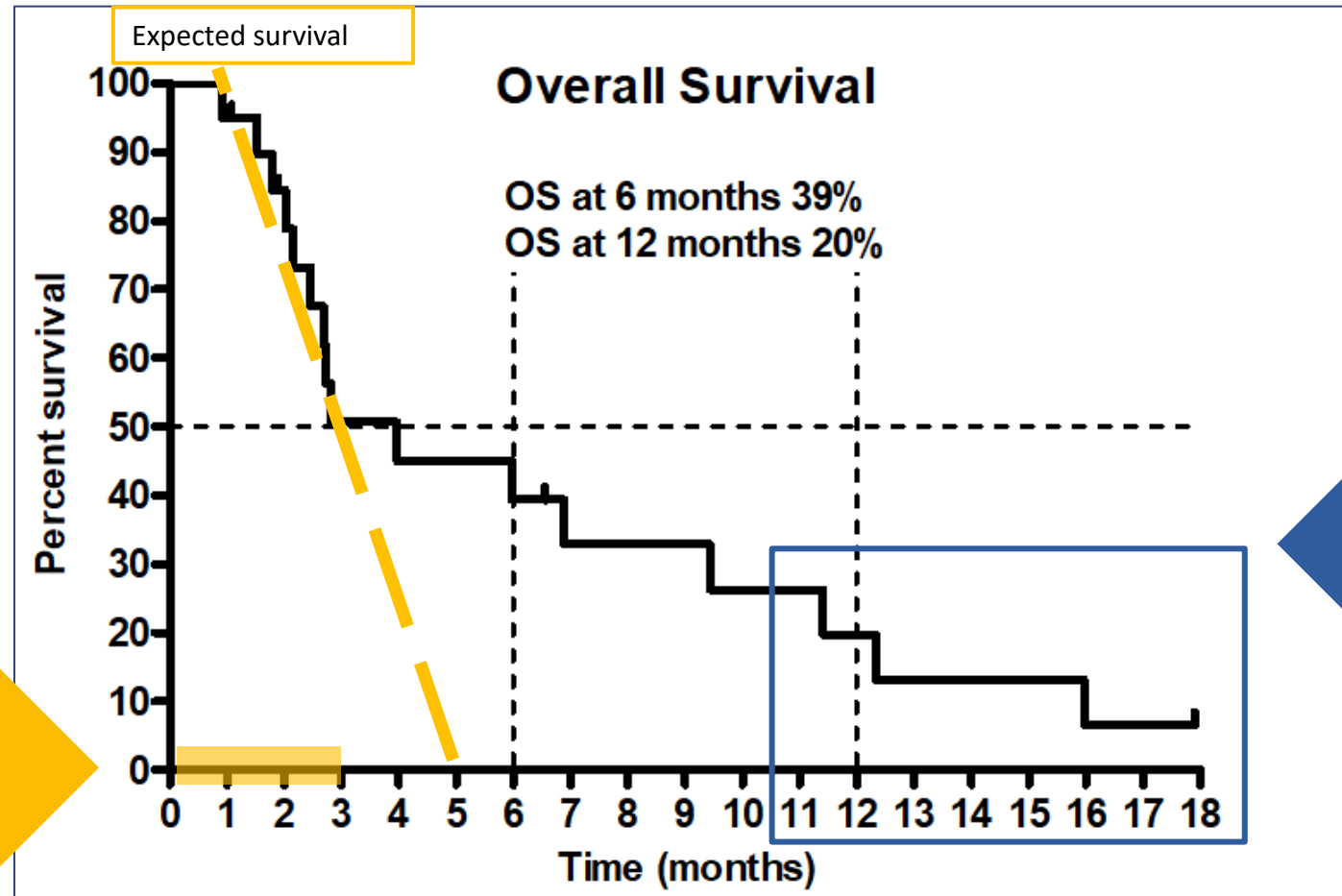
- **Pancreatic  
4<sup>th</sup> line of therapy on  
average**

- **CRC  
6<sup>th</sup> line of therapy on  
average**



4<sup>th</sup> line pancreatic cancer patients who lived > 1 year after having no response and rapid progression (2 months) on 3<sup>rd</sup> line therapy

# Overall Survival Longer Than Expected for this Heavily Pre-Treated Population



Responses to immunotherapy can take **3-6 months** to observe and many advanced patients don't have that time

Pancreatic cancer patients receiving on average their 4th line of therapy

Colorectal cancer patients receiving on average their 6th line of therapy

Of the 5 stable disease patients (25% of the study population) **3 survived for more than a year**

# Status and Next Steps in Development of NOX-A12 in Pancreatic Cancer

- Phase 2 designed to position NOX-A12 + immunotherapy as Standard of Care in 2<sup>nd</sup> line pancreatic cancer
- Design tests 2 arms, each with NOX-A12 + pembrolizumab combined with either gemcitabine/Abraxane<sup>®</sup> or Onivyde<sup>®</sup>/5FU/LV
- Protocol approved by regulators in France and Spain and by US FDA

# NOX-A12: Two Orphan Indications with ~\$8.5bn Total Addressable Market



**Target population US & EU –  
New cases per year**



**Expected duration of treatment  
based on median OS**



**Total Addressable Market<sup>1</sup>**



**Next inflection points**

## **NOX-A12 Brain Cancer Fast Track & Orphan Drug Status Granted**

## **NOX-A12 Pancreas Cancer**

<b>29,000</b>	<b>69,000 (2<sup>nd</sup> line) 107,000 (1<sup>st</sup> line)</b>
<b>&gt;12 months</b>	<b>&gt;12 months</b>
<b>\$2.5 bn (1<sup>st</sup> line)</b>	<b>\$6bn (2<sup>nd</sup> line) \$9.3bn (1<sup>st</sup> line)</b>
<b>Financing &amp; initiation of randomized Phase 2</b>	<b>Financing &amp; initiation of randomized Phase 2</b>

1. Based on potential pricing of US\$10,000 per month in the US and US\$5,000 in Europe



Thank you.

Contact us:

[tme@tmepharma.com](mailto:tme@tmepharma.com)