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Improving Therapeutic Outcomes by Targeting the Tumor Microenvironment

June 2025



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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 DATA¹

Brain Cancer (1st line GBM)
Phase 1/2 clinical trial with
NOX-A12 + RT + Bevacizumab:

- **Statistically significant increase in survival vs. standard of care in chemotherapy resistant patients with residual tumor (mOS 19.9 vs 9.5 months; p=0.003) and an HR of 0.30**
- 3 of 6 patients with >99% tumor size reduction including 1 complete response
- 2 of 6 patients with survival >24 months

FOCUS ON ORPHAN CANCER INDICATIONS

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

Pancreatic Cancer
(2nd line)
~\$6 bn Addressable
Market

UPCOMING CATALYSTS

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

Phase 1b trial initiation of spin-out ophthalmology program for front & back-of-eye diseases

FINANCIAL OVERVIEW

- **TME Pharma is listed on Euronext Growth Paris – ALTME**
- Cash & equivalents:
 - **€3.2 million** (31 Dec 2024)
 - **€1.7 million** raised in 2025
 - Financial visibility into **May 2026**

SHAREHOLDING STRUCTURE

Public listing	2016
ISIN Code	NL0015000YE1
Ticker	ALTME
Market	Euronext Growth Paris
Market Cap*	€7.3 M
Shares outstanding*	94,188,981

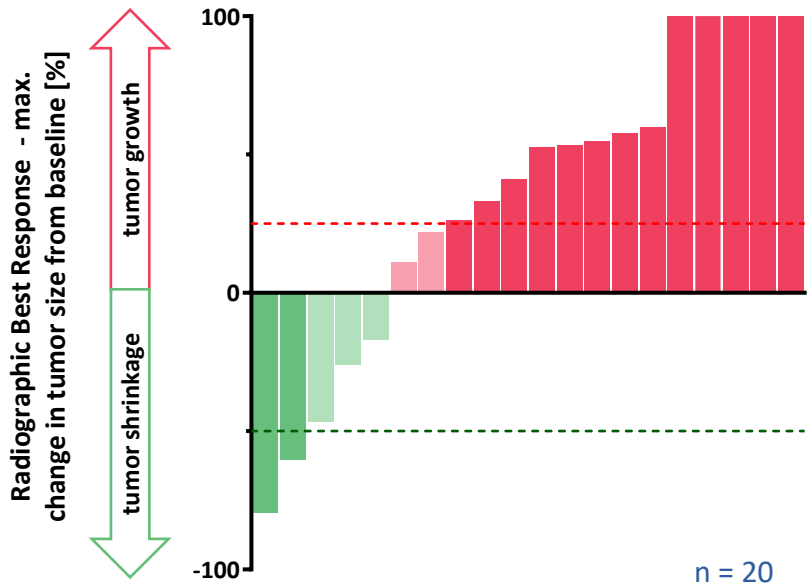
*As of June 27, 2025

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

Standard of Care

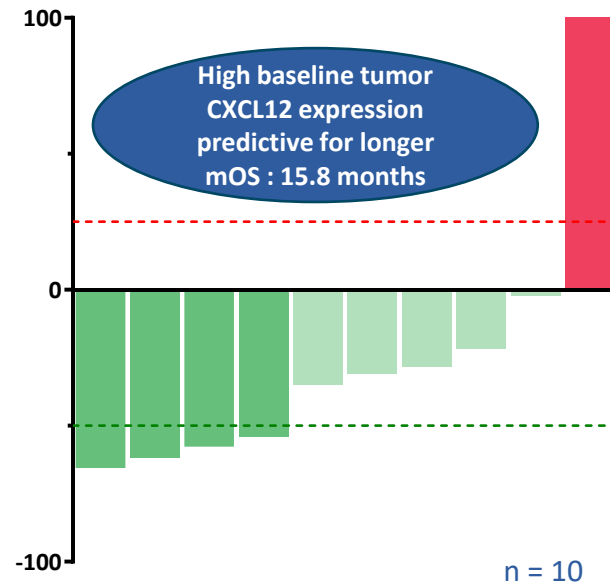
Radiotherapy + Chemotherapy

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



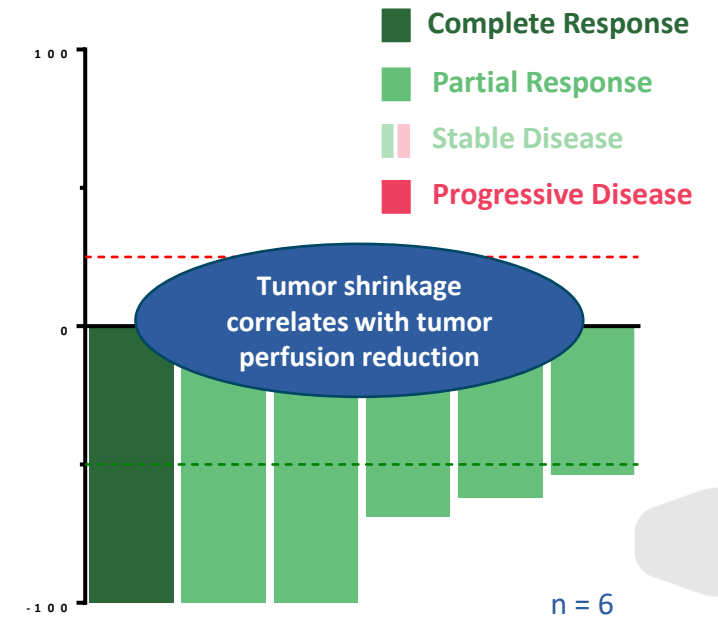
Median Overall Survival (mOS) **9.5 months**
n = 22

Radiotherapy + NOX-A12



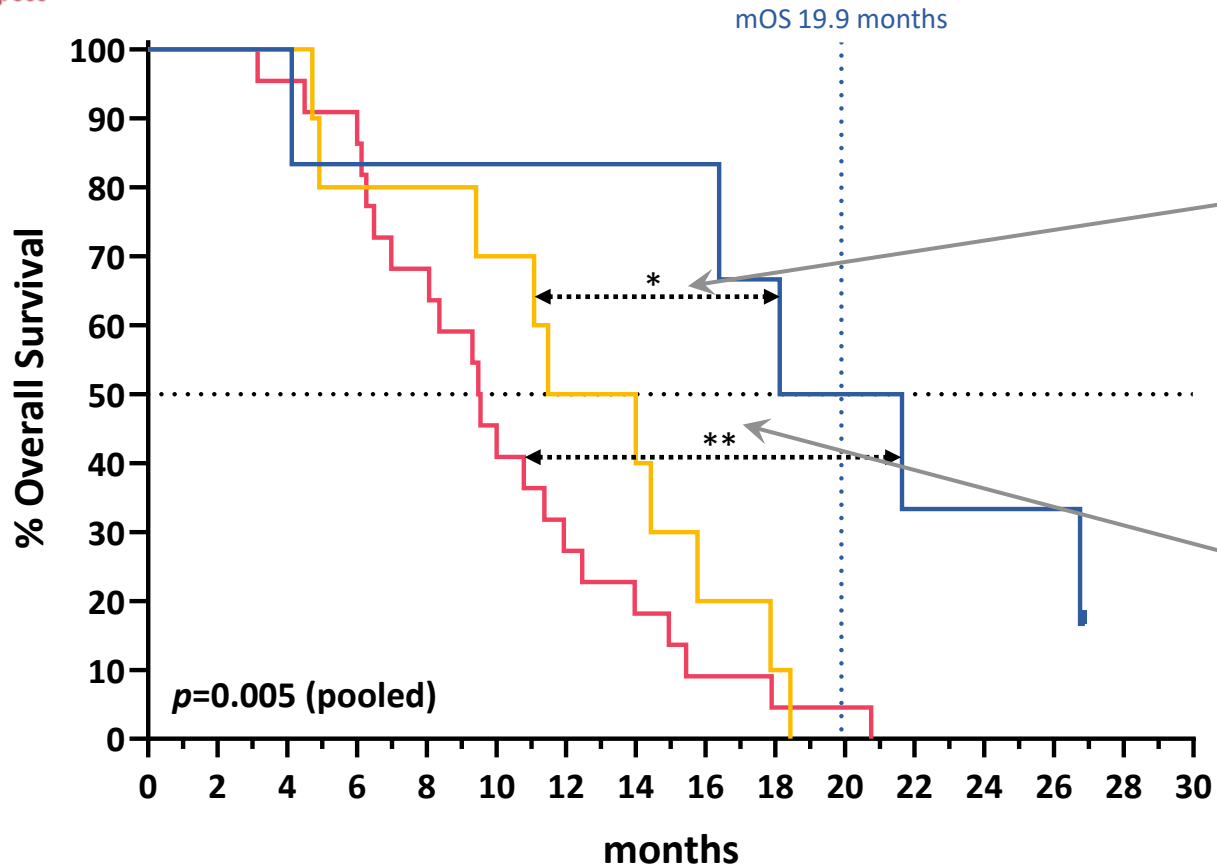
12.7 months

Radiotherapy + NOX-A12 + anti-VEGF



19.9 months

OS significantly increased for NOX-A12 + anti-VEGF + RT over standard of care and NOX-A12 + RT



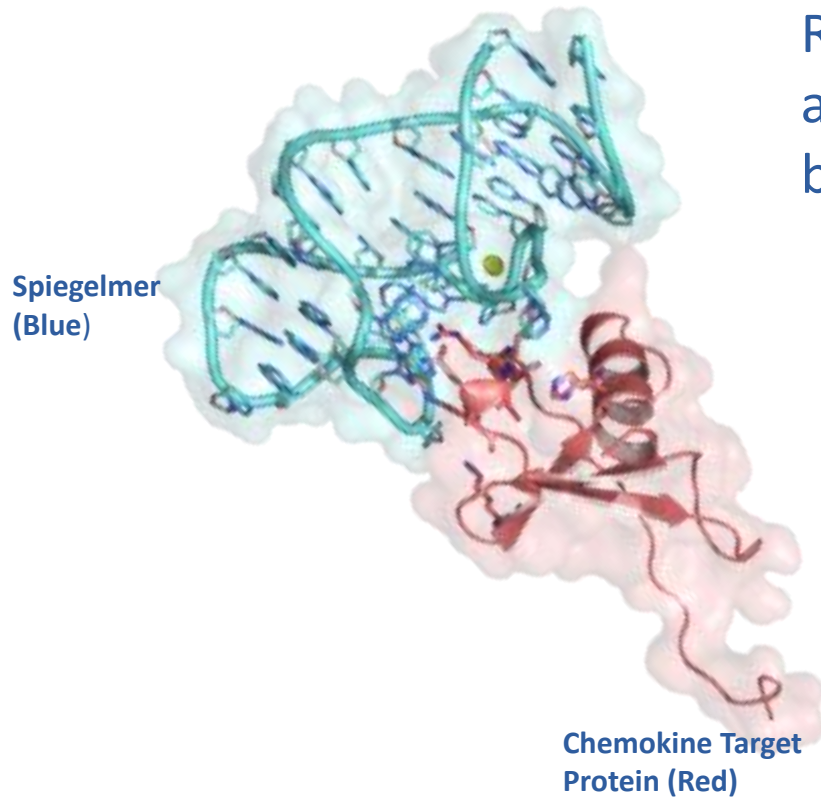
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p=0.021
HR: 0.34

Statistically significant improvement in overall survival for NOX-A12 + anti-VEGF + RT vs. Standard of Care (SOC)
p=0.003
HR: 0.30

Patients at risk	6	5	5	4	2	0
	10	8	5	1	0	0
	22	19	6	1	0	0

— NOX-A12 + anti-VEGF (bevacizumab) + RT (N = 6)
 — NOX-A12 + RT (N = 10)
 — SOC matched reference cohort (N = 22)

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

Therapy & Indication	Preclinical	Phase 1/2	Phase 2	Phase 3	Next Inflection Point	Partner/ Collaborator
NOX-A12 + Radiotherapy ± anti-VEGF Brain cancer / Glioblastoma Orphan Drug Designation Granted in US & EU			Phase 2 protocol approved; Fast Track awarded by FDA		Financing and initiation of randomized Ph 2	
NOX-A12 + Immunotherapy Pancreatic Cancer			Phase 2 protocol approved		Financing and initiation of randomized Ph 2	Scientific collaborator for Ph1/2 & Ph2

Planned external development

NOX-E36 to be Externalized and Monetized in Ophthalmology		Planned in Glaucoma Surgery Derisking: already tested in 175 subjects in Phase 1 & 2 in other indications				Clinical collaboration for Ph1 & option agreement
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■ Trial completed
 ▨ Trial ongoing or in preparation
 ▨ Preclinical ophthalmology animal studies completed & ongoing

All timelines subject to financing and patient recruitment

NOX-A12 (olaptosed 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 and Board

MANAGEMENT



Diede van den Ouden
Chief Executive Officer

- 20+ years professional investor experience
- Executive and advisory roles in EU listed companies
- Track record of corporate reorganization



Jarl Ulf Jungnelius, MD
Chief Medical Officer

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

SUPERVISORY BOARD



Chairman of the Board
Maurizio Petitbon
BlackRock

- Senior Advisor
- Advisor, entrepreneur & investor in healthcare space



Susan Coles
Vivet Therapeutics General Counsel & Head of Finance

- 25+ years experience in int'l collaborations & commercial activities



Lee Schalop
LSWorks

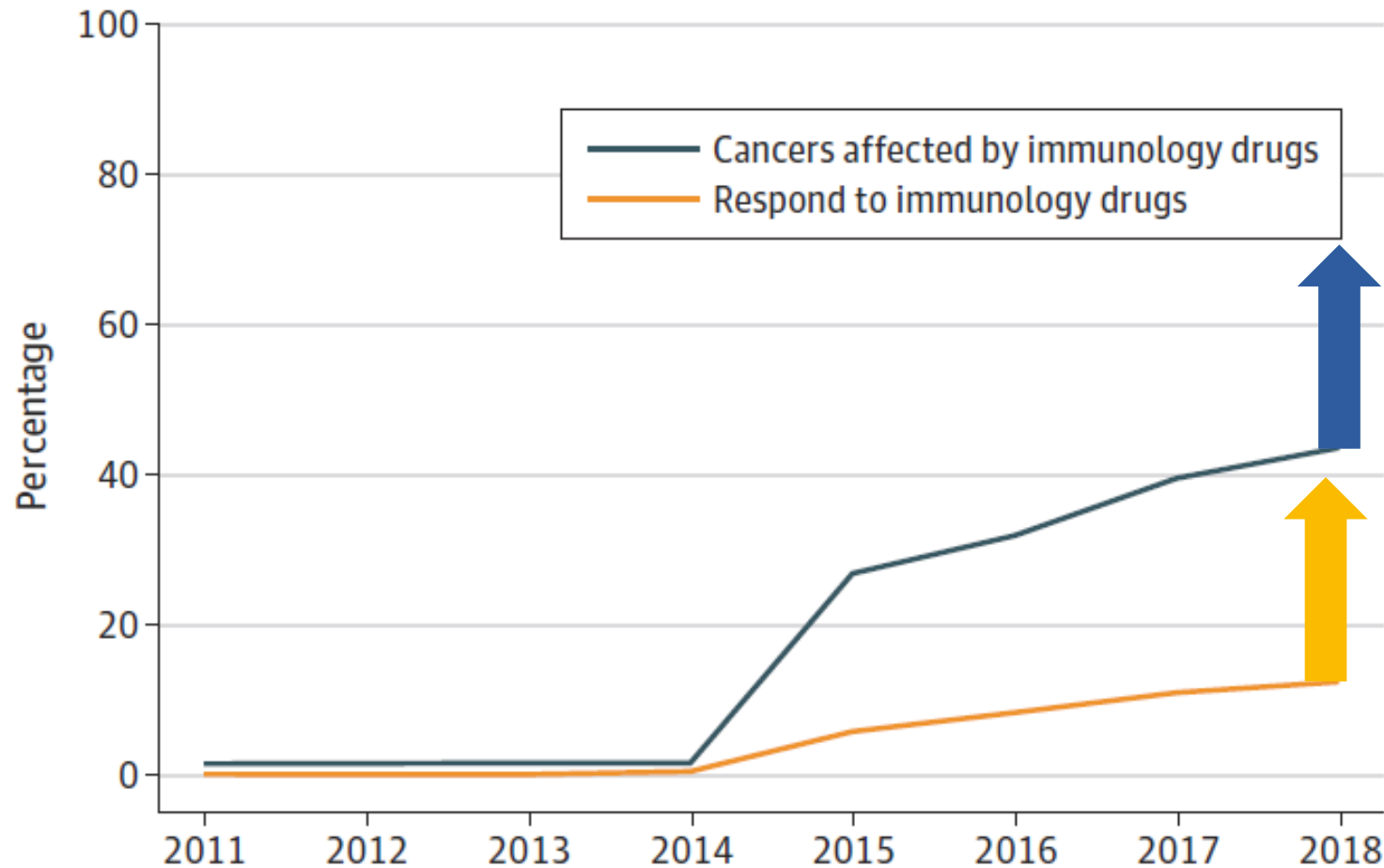
- Founder
- 35+ years in banking & biotech incl. successful sale of a brain cancer company



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

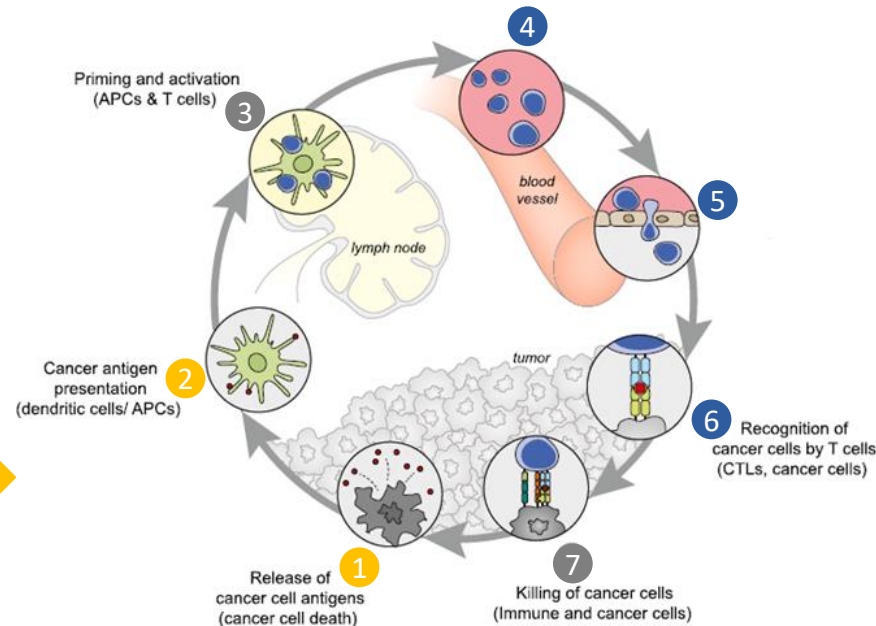
Blocks repair of damaged tumors

Prevents entry of immuno-suppressive cells

Enables infiltration of anti-cancer immune cells into the TME

NOX-A12^a

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



NOX-A12^b & NOX-E36^c

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.

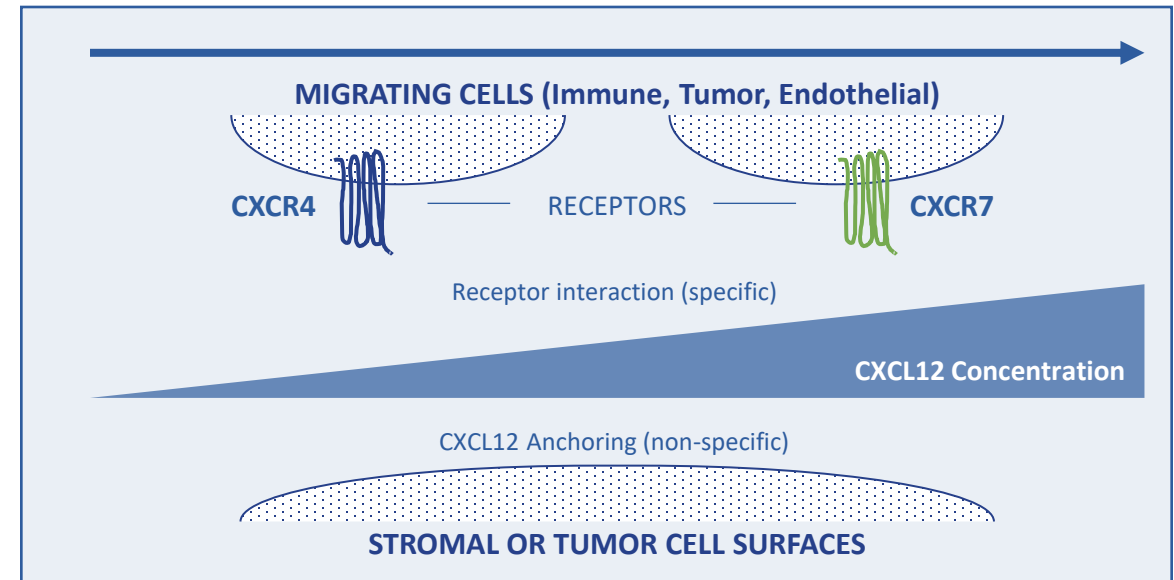
Role of CXCL12 Chemokine Axis in Cancer

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

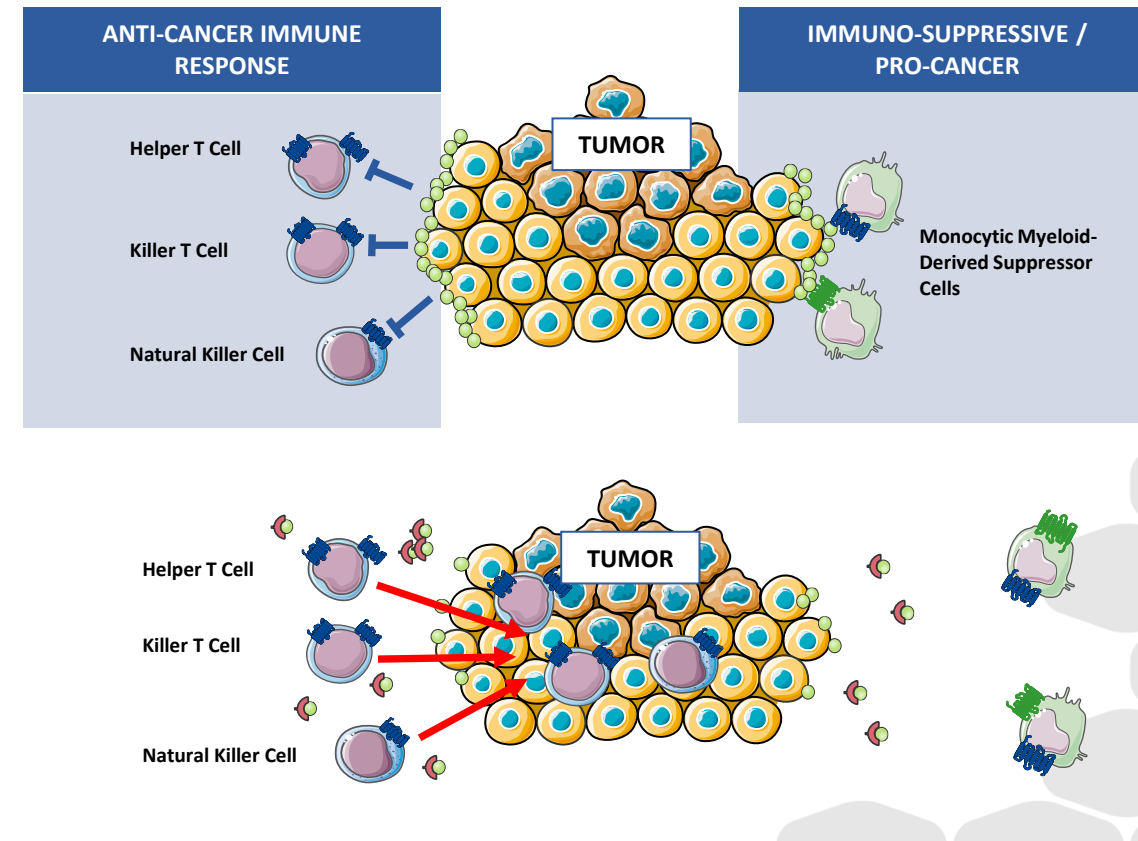
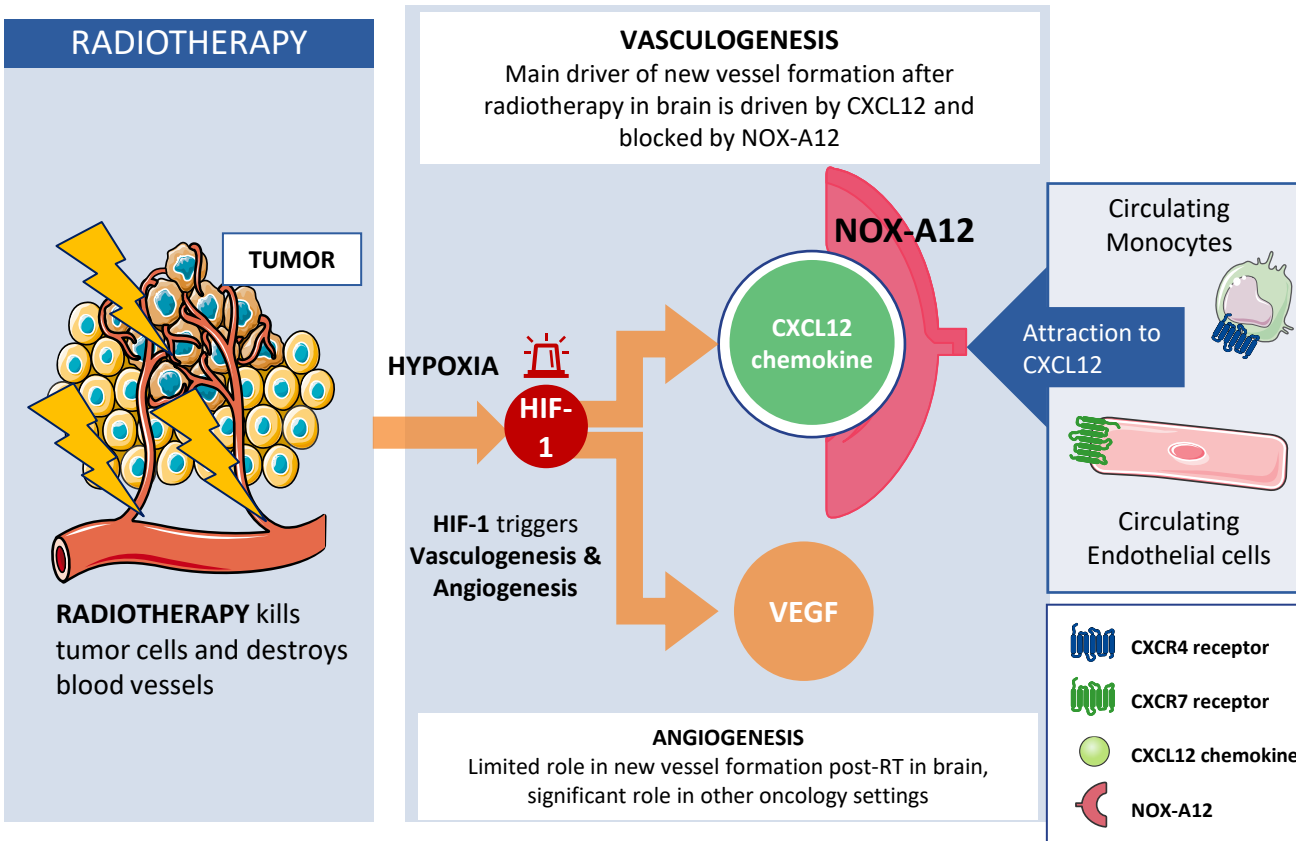
NOX-A12 – Dual Mechanism of Action

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

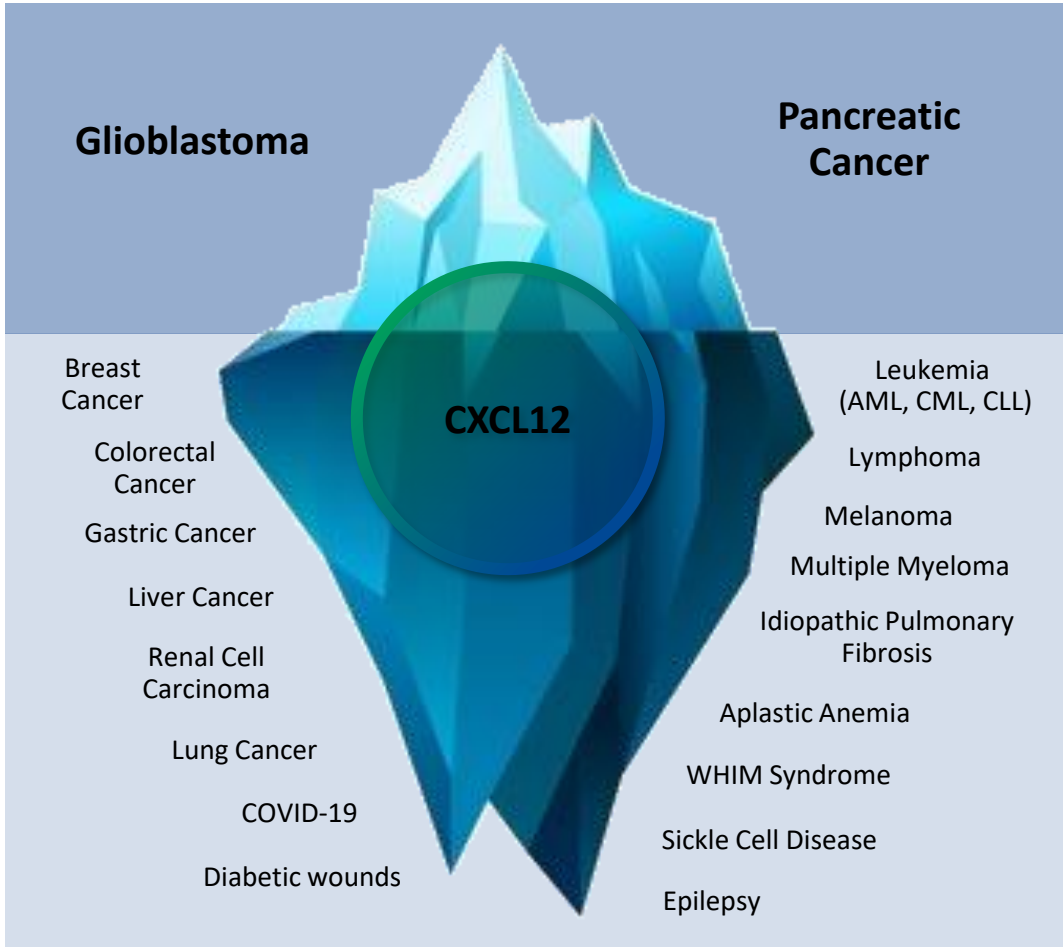
Combos with CPIs, Bi-Specifics, Cell Therapies



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
NOX-A12 TME Pharma	✓	✓	✓	✓
Motixafortide BioLineRx	✓	✗	✓	✗
Plerixafor ¹ Sanofi	✓	✗	✓	✓
Mavorixafor ² 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.

Brain Cancer is an Area of Active Pharma Interest

- **Servier** received **FDA approval** for Voranigo (vorasidenib) in **low grade, IDH mutant glioma** in Aug 2024 following its \$2 billion acquisition of **Agios'** oncology business in 2021¹
- **Royalty Pharma**, which earlier this year acquired a stake in Agios' royalty payments for Voranigo, has projected the **drug could reach more than \$1 billion in annual peak sales** in the U.S. based on around **1500 new diagnoses per year and prevalence of approximately 10,000 in the U.S.**¹
- **Day One Biopharma** out-licensed ex-U.S. rights for its BRAF-mutant pediatric low-grade glioma (pLGG) drug Ojemda/tovorafenib to **Ipsen in a \$461 million deal** including \$111 million upfront and \$350 million in milestone payments and double-digit tiered royalties²
- **GSK** is investing in the development for **Glioblastoma** as one of two focus indications for their PARP inhibitor **Zejula (niraparib)**³
- **MSD/Merck** acquired **ModifiBio** for **\$30 million upfront** and **up to \$1.3 billion** with potential future payments for development of MOD-246 a “precision chemotherapy” which was developed to target glioblastoma⁴
- **Jazz Pharmaceutical** to acquire **Chimerix** for a total consideration of **~\$935 million**, adding to their oncology pipeline Phase 3 dordaviprone program in **H3 K27M-mutant diffuse glioma**⁵



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-5¹



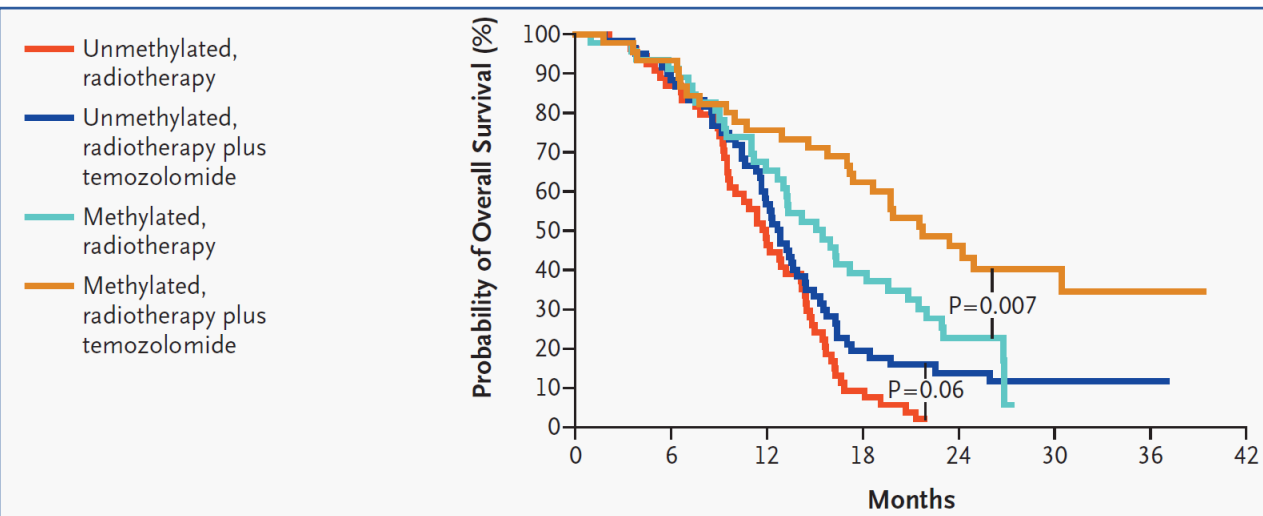
5-year Survival 6,9%²



mOS 8 months²



~ 315 active clinical trials in US & Europe³



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

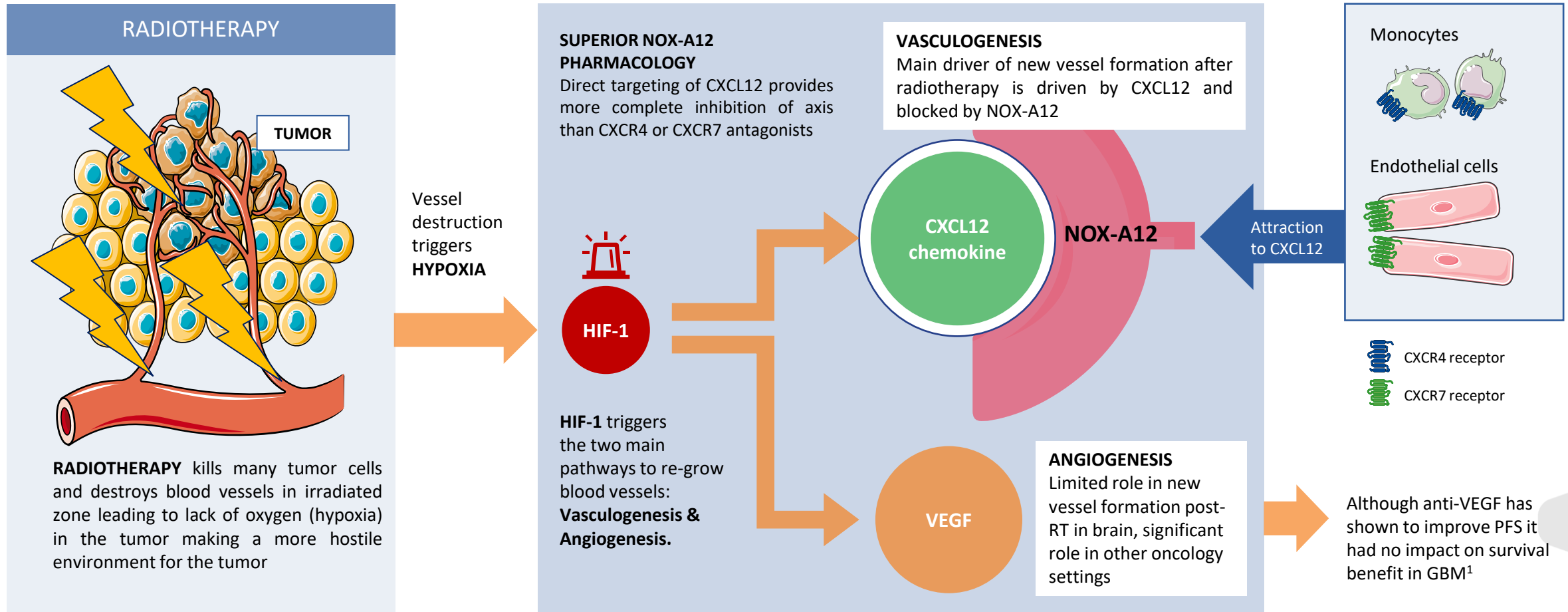
PARTIAL TUMOR RESECTION

- 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

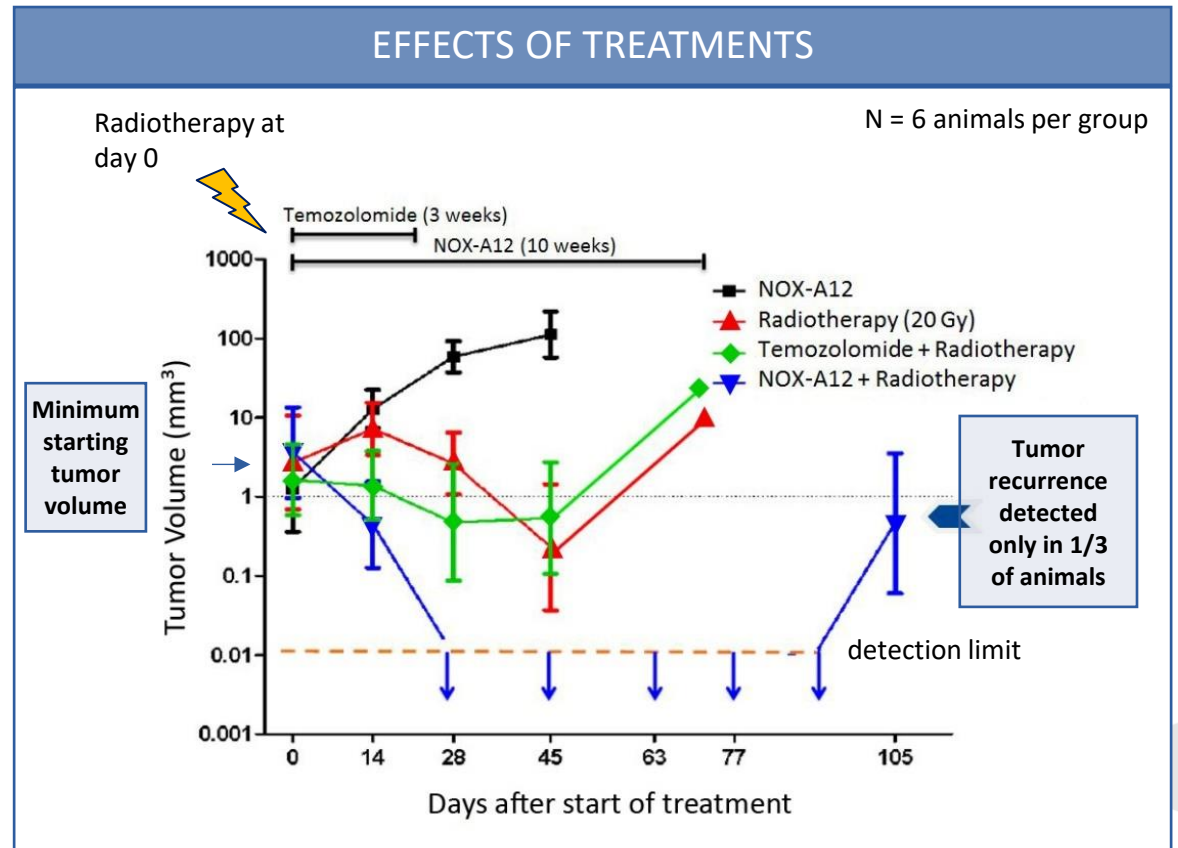
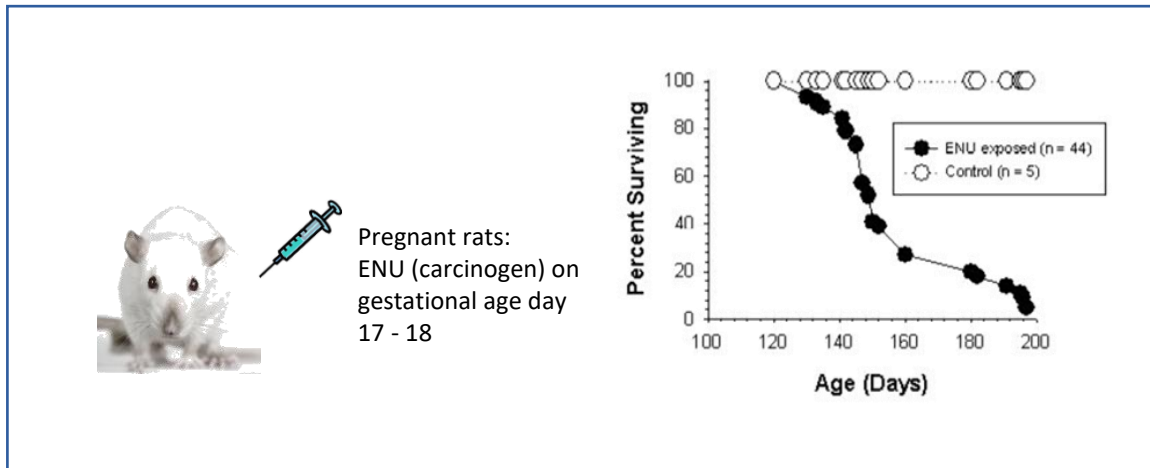


Inhibition of the CXCL12/CXCR4/CXCR7 axis can block tumor vasculogenesis

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



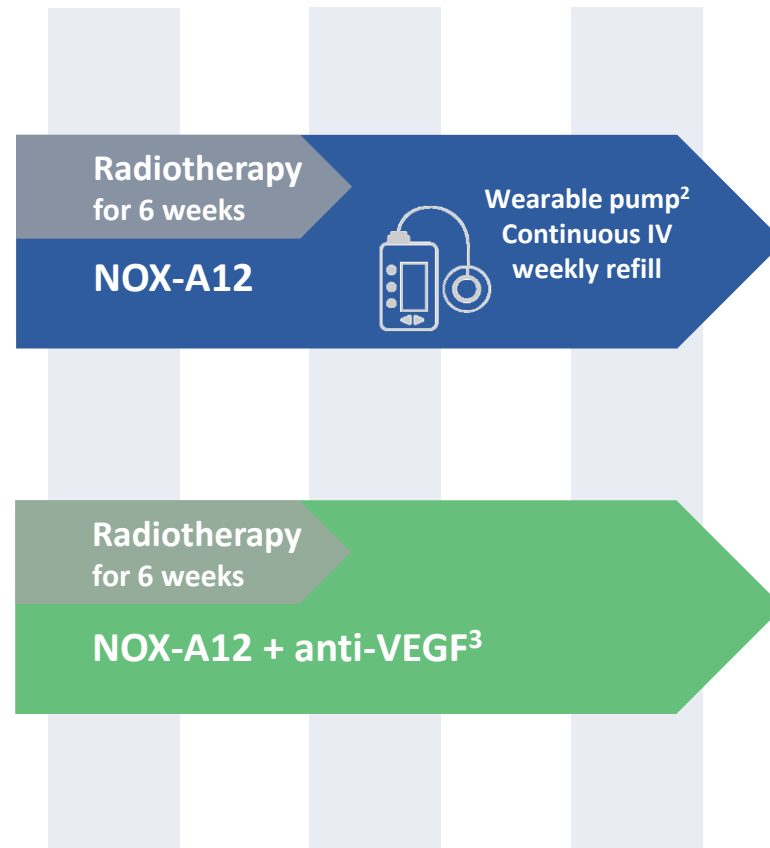
NOX-A12 + radiotherapy resulted in 100% complete response (66% durable) in brain cancer rat model

GLORIA Phase 1/2 Dose Escalation Study & Expansion Arm

1st 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 months¹



Dose Escalation Cohorts NOX-A12 + RT

NOX-A12 Doses tested:
200, 400 & 600 mg/week

Expansion Arm

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

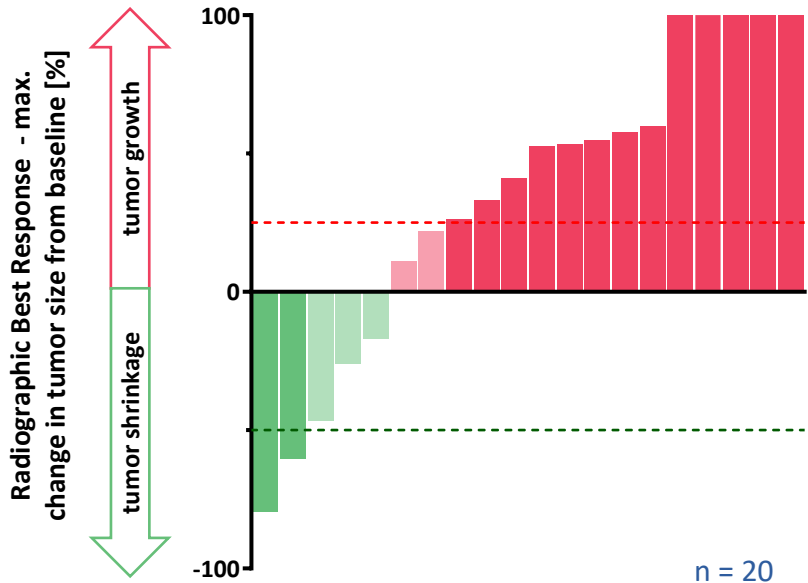
1. Standard of care data from 20-patient matched reference cohort of newly diagnosed glioblastoma with MGMT unmethylated, incompletely resected or biopsy-only tumors; Giordano (2022) ASCO Annual Meeting Pres. #2050
2. CADD[®]-Solis VIP Ambulatory Infusion Pump by Smiths Medical
3. Bevacizumab (BEV).

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

Standard of Care

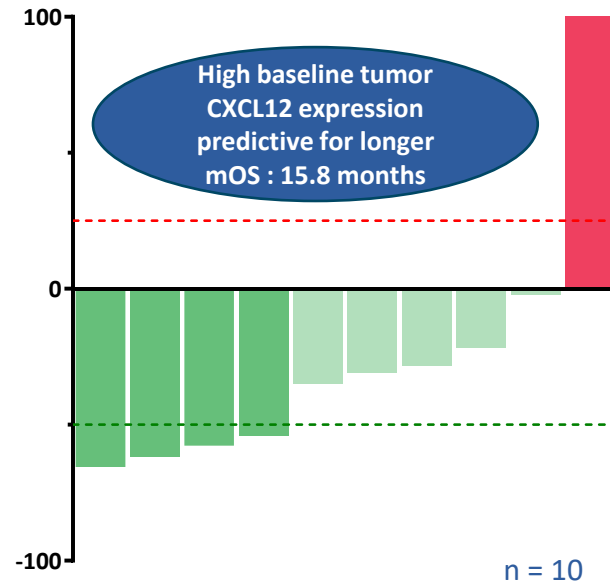
Radiotherapy + Chemotherapy

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



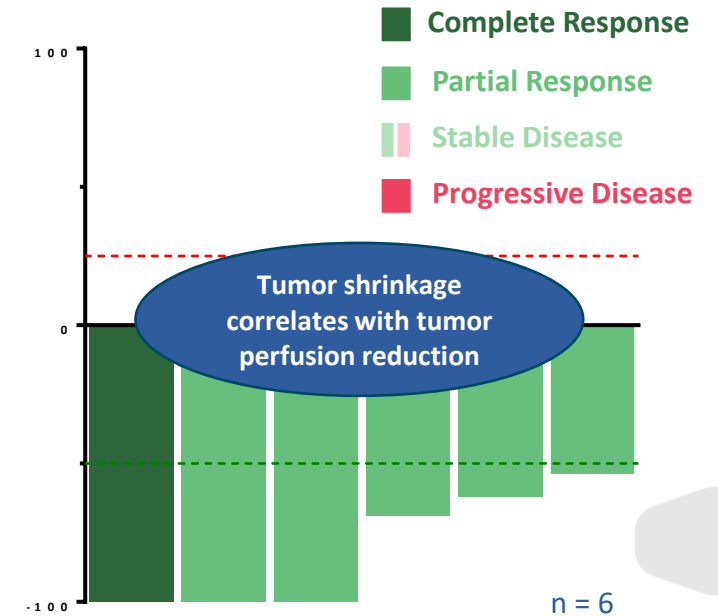
Median Overall Survival (mOS) **9.5 months**
n = 22

Radiotherapy + NOX-A12



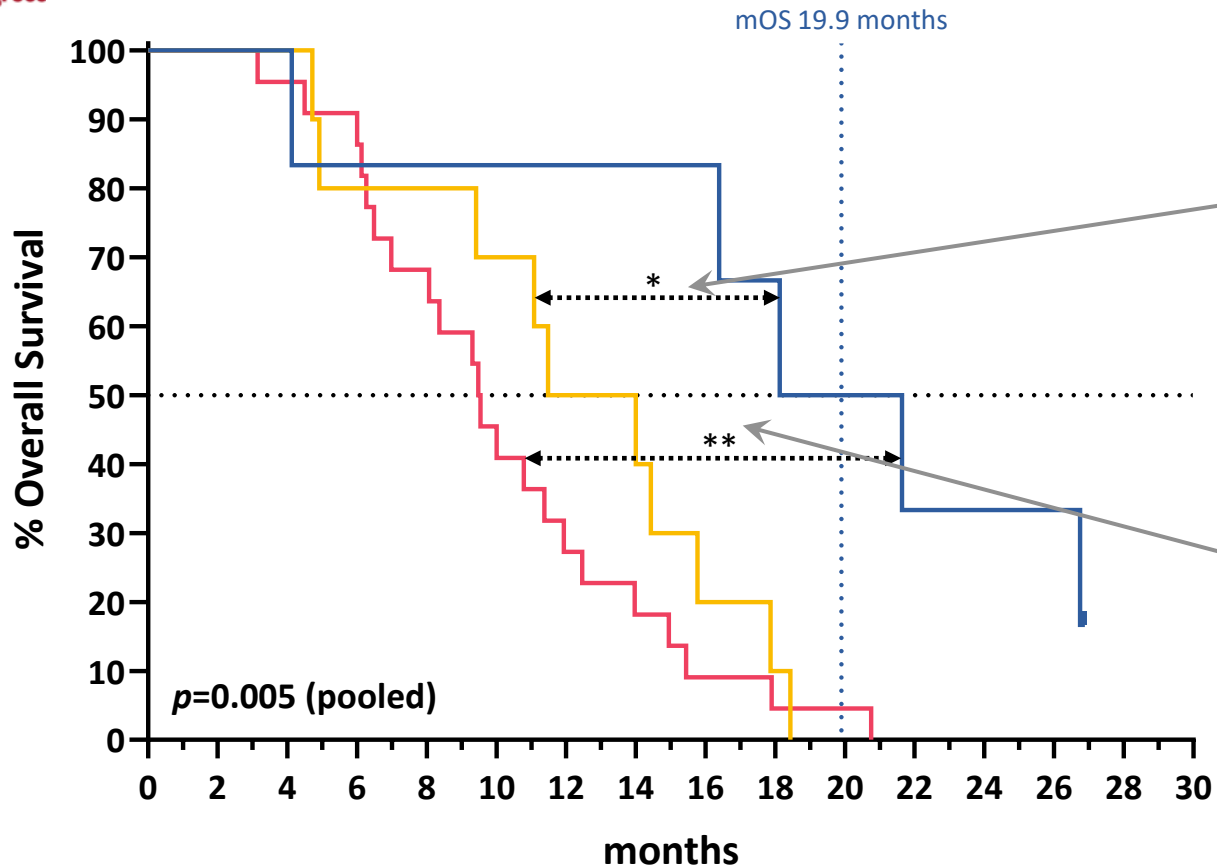
12.7 months

Radiotherapy + NOX-A12 + anti-VEGF



19.9 months

OS significantly increased for NOX-A12 + anti-VEGF + RT over standard of care and NOX-A12 + RT



Statistically significant improvement in overall survival for NOX-A12 + anti-VEGF + RT vs. NOX-A12 + RT
p=0.021
HR: 0.34

Statistically significant improvement in overall survival for NOX-A12 + anti-VEGF + RT vs. Standard of Care (SOC)
p=0.003
HR: 0.30

Patients at risk	6	5	5	4	2	0
	10	8	5	1	0	0
	22	19	6	1	0	0

— NOX-A12 + anti-VEGF (bevacizumab) + RT (N = 6)
 — NOX-A12 + RT (N = 10)
 — SOC matched reference cohort (N = 22)

4 Key Factors Affecting Glioblastoma Patient Survival to Consider when Benchmarking Survival Data

1. IDH status

- Since 2021 WHO guidelines¹, only tumors with wild-type IDH gene are recognized as glioblastoma
- For such 'true' GBM patients, only 1/3 of median survival time can be expected in comparison to patients with IDH-mutant tumors which are no longer considered as GBM: 1.2 vs. 3.6 years²
- Data from studies initiated before 2021 tend to be skewed towards over-estimation of survival

2. MGMT promoter methylation status

- This biomarker predicts sensitivity to SoC chemotherapy³ with temozolomide
- Slightly more than 50% of newly diagnosed patients have an unmethyated MGMT promoter making their tumors refractory to standard chemotherapy
- Median survival for patients with MGMT unmethyated tumors is approx. half that of methylated: 12.7 vs. 21.7 months³

3. Degree of surgical resection

- Complete ('gross total') surgical resection adds 5-8 months to median survival vs. partial resection/biopsy-only⁴

4. Patient ethnicity

- Asian patients live significantly longer (hazard ratio 0.75) than other ethnicities⁵
- Studies enrolling primarily Asian populations will show longer survival times than other studies

➤ **Benchmarking of survival is challenging as all comparative data come from mixed populations with divergent expected survival outcomes**

TME Pharma's study included only patients that combine unfavorable key factors

1. IDH wild-type

2. MGMT unmethylated

3. Partial resection

4. Caucasian patients

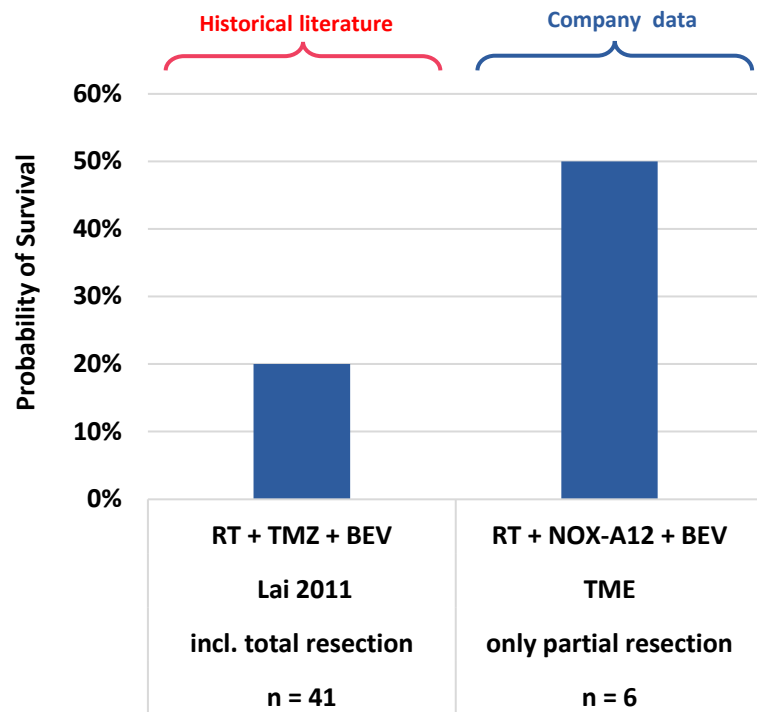
Relevant Benchmark Studies in Chemotherapy Resistant Glioblastoma from US and EU

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
NOX-A12 + Radiotherapy + bevacizumab (TME Pharma)	0% T; 100% P	6	RANO	83%	19.9	Ph 1/2 ongoing, Orphan Drug Designation & Fast Track Designation granted	TME Pharma Internal Data
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

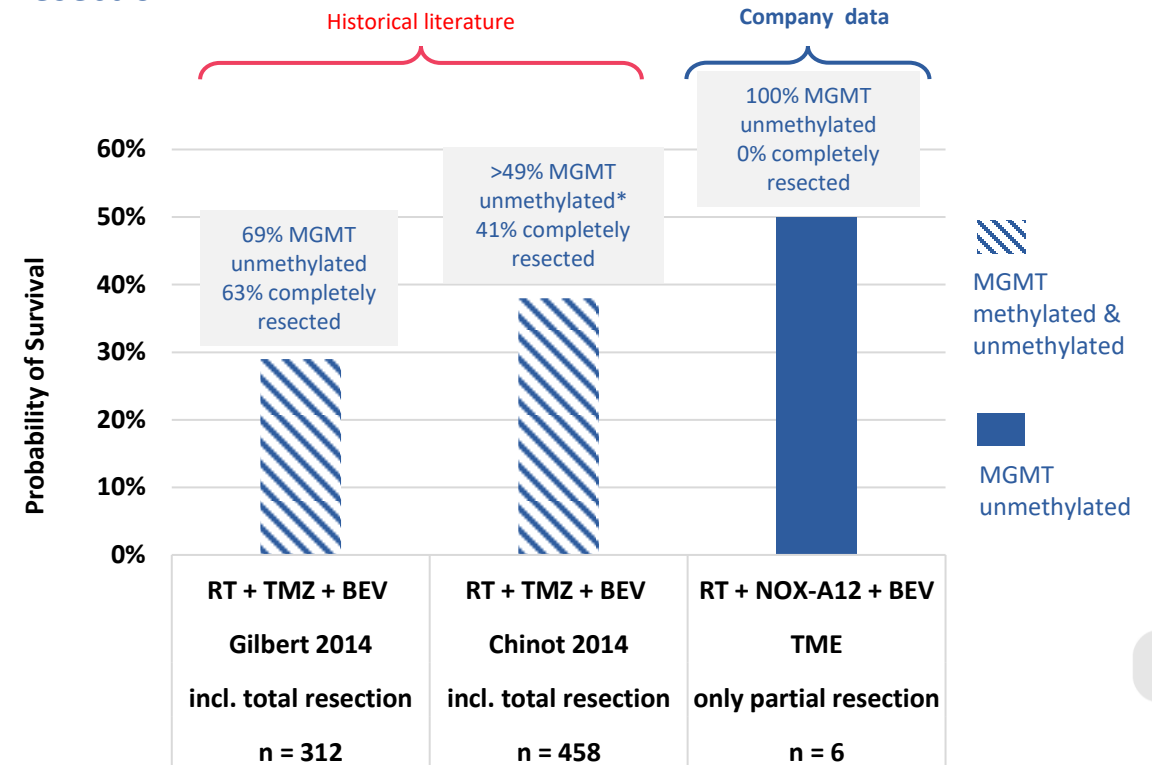
OS at 21 months:

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

Sources: Lai 2011, J Clin Oncol 29:142; Gilbert 2014, NEJM 370:699; Chinot 2014, NEJM 370:709

* MGMT status not available for 25% of patients; actual percentage of unmethylated patients thus expected to be higher

Approved Phase 2 Study Design in GBM in US and Germany: 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 care¹:

- 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

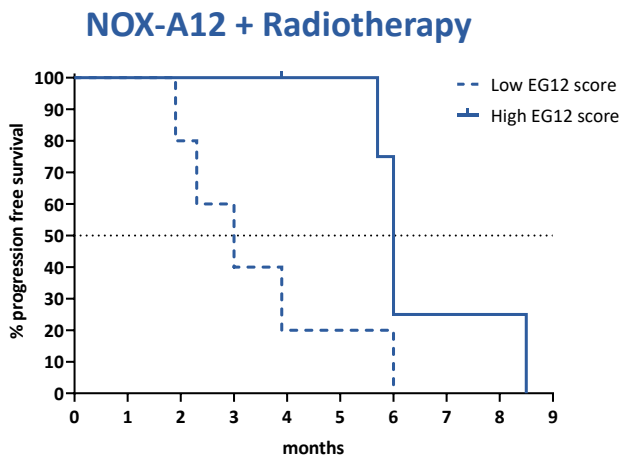
Arm 5

RT - 6 weeks

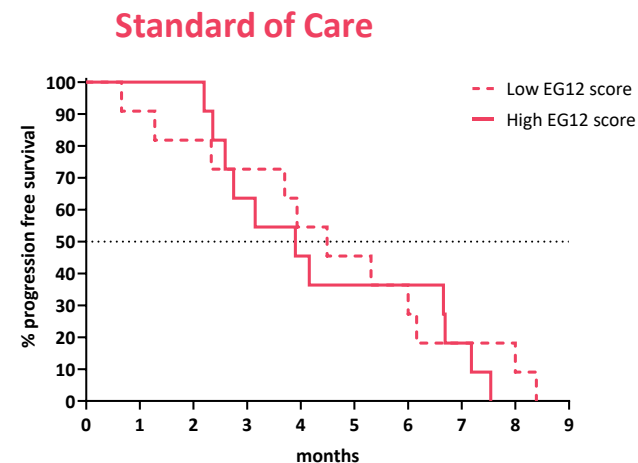
temozolomide

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 ($p=0.556$)
- The **EG12 score predicts PFS for NOX-A12-treated patients** with statistical significance ($p=0.031$)



EG12^{high} patients with significantly longer PFS
($p=0.031$; mPFS = 6.0 vs. 3.0 months for EG12^{high} vs EG12^{low})

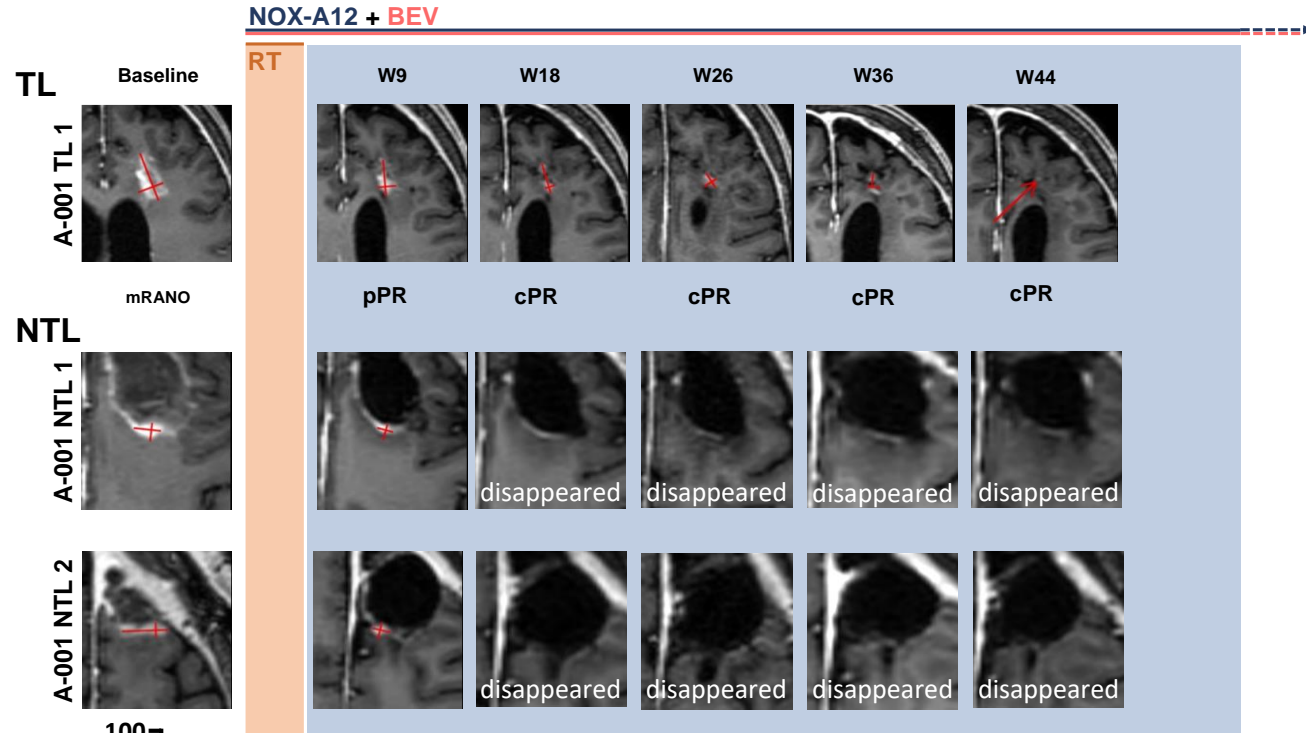


No significant difference in PFS
($p=0.628$; mPFS 3.9 vs. 4.5 months for EG12^{high} vs EG12^{low})

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

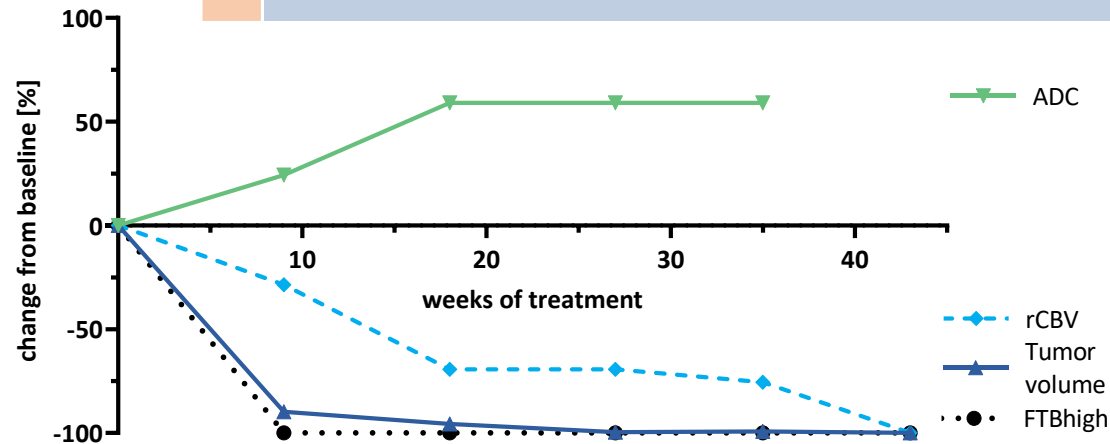
➤ The EG12 score might be a **predictive biomarker for OS** in patients treated with NOX-A12 + RT

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



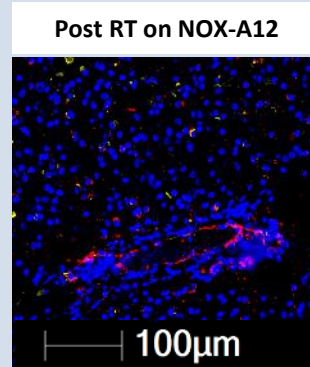
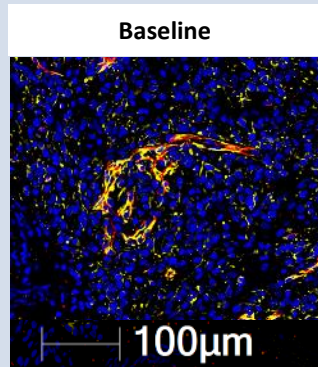
Changes from baseline
ADC: increase in change represents improvement
rCBV, Volume, FTBhigh: decrease in change represents improvement

→ >99% reduction

cut off date: 01-Nov-2022

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

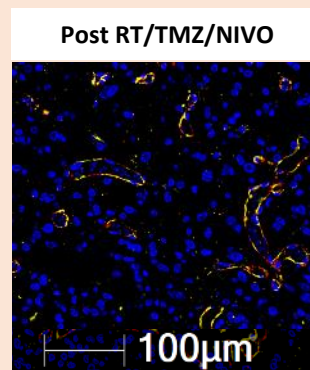
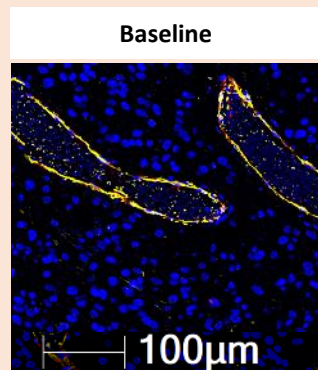
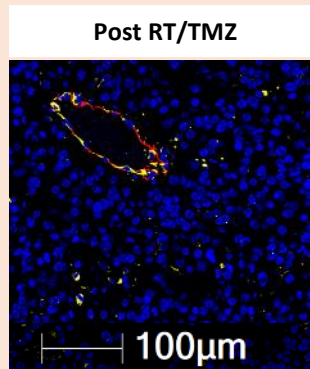
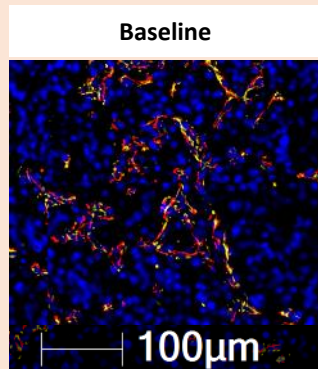
GLORIA
C1-001



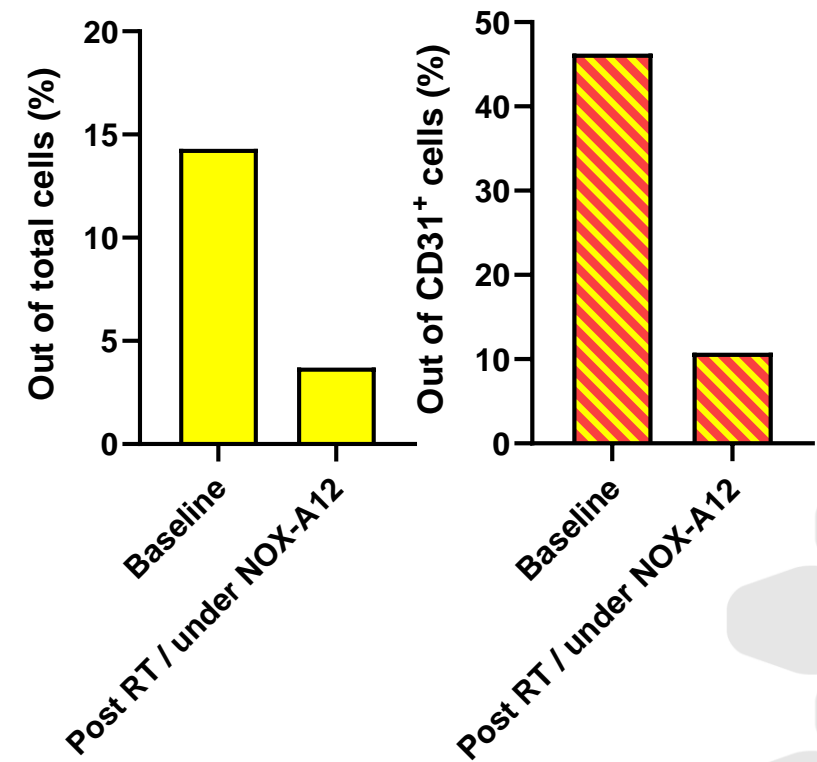
■ DAPI
■ CD31
■ CXCL12

Images show areas of pathologist-confirmed tumor tissue

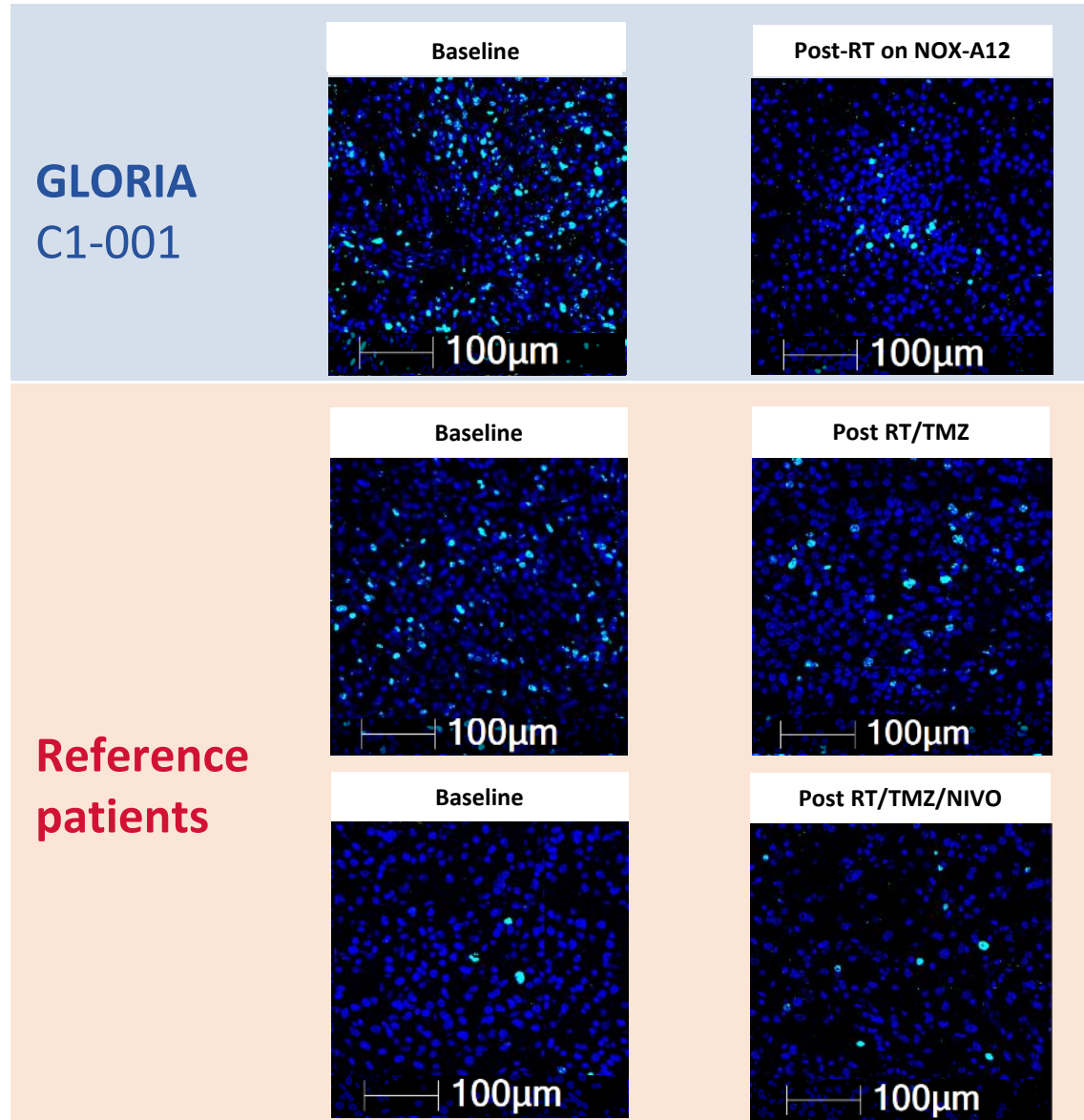
Reference
patients



CXCL12⁺ cells
Patient C1-001

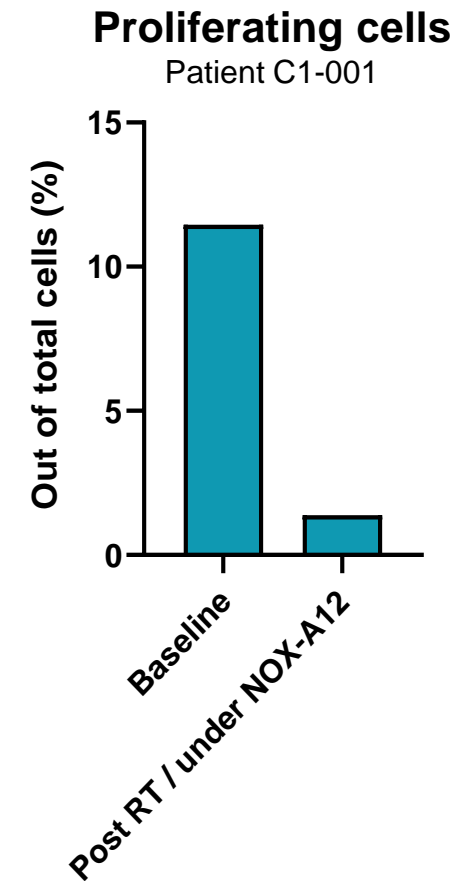


NOX-A12 + RT Reduces Tumor Cell Proliferation in GBM Patient

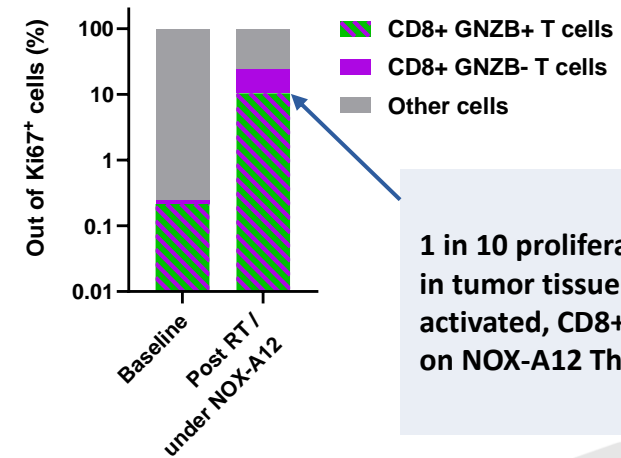
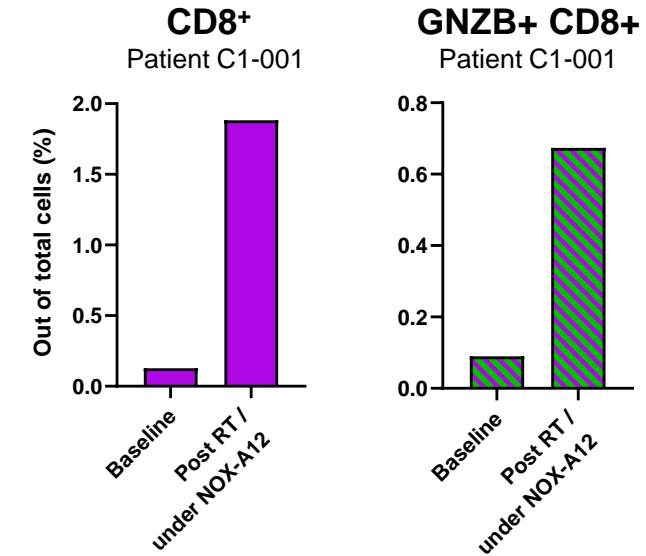
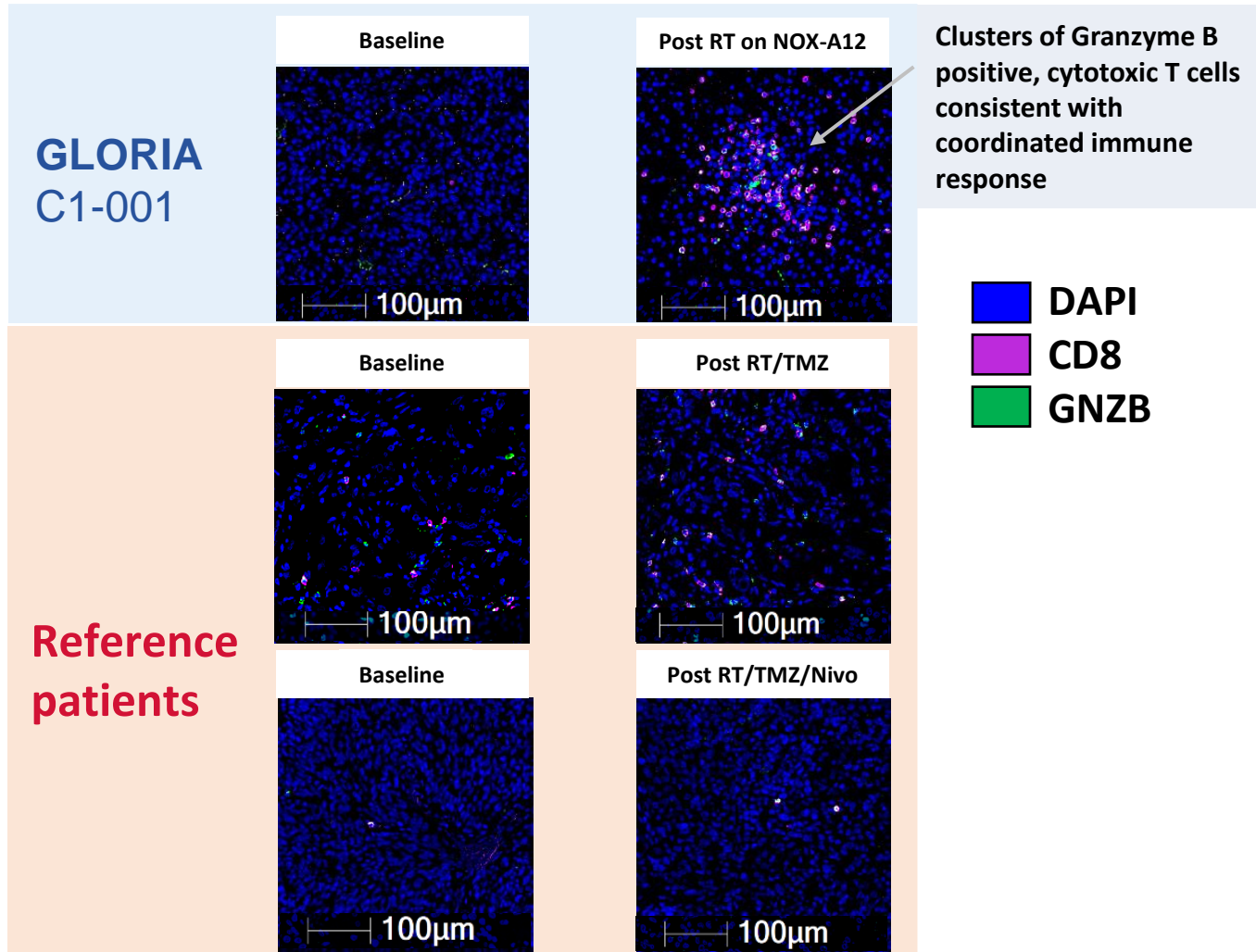


■ DAPI
■ Ki67

Images show areas of pathologist-confirmed tumor tissue



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

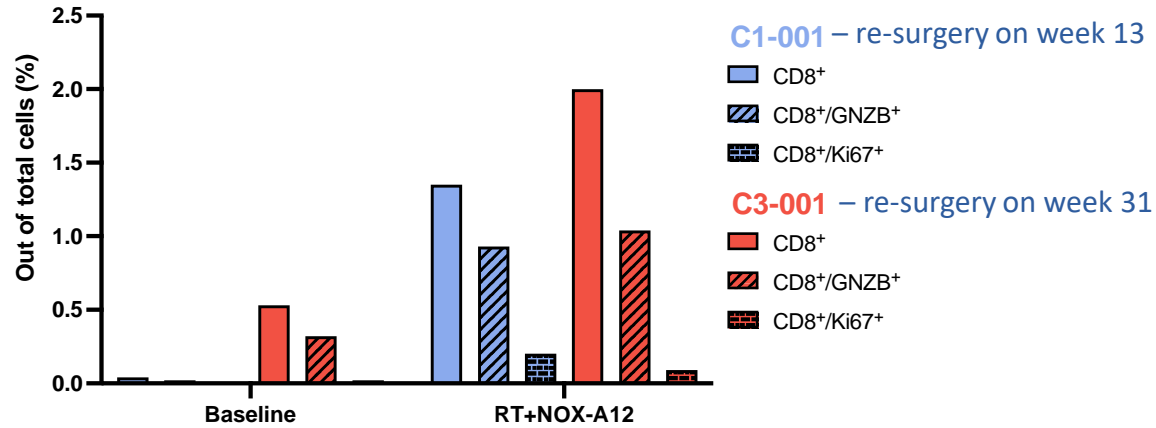


1 in 10 proliferating cells in tumor tissue are activated, CD8+ T-cells on NOX-A12 Therapy

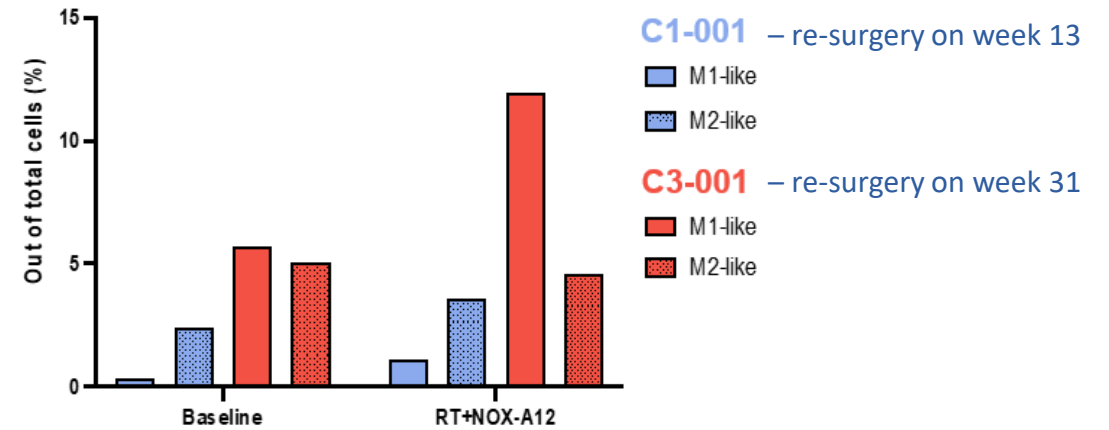
Images show areas of pathologist-confirmed tumor tissue

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

T cells



Macrophages



- 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

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)

Robust Protection Possible Through Foundational Method Claims on NOX-A12

Method of use patents offer protection nearly identical to that of a composition-of-matter patents for drugs where the first approval is under protection of a method of use patent¹:

- If using NOX-A12 proves to be therapeutically successful in a particular indication, FDA will approve the molecule only for that protected use.
- This prevents generic competitors from obtaining approval for the same indication through, for example, skinny labeling*.
- To commercialize the same molecule competitors will have to conduct independent clinical trials and show efficacy for an entirely different use, and even then, will face off-label competition from TME Pharma's original molecules.
- GLP-1 agonists such as Ozempic are clear examples of extended protection through method of use patents even after composition-of-matter patents expire with a median protection of 18.3 years from FDA approval and 31.9 years from first patent filing².

* Skinny labeling is when a generic drug development obtains approval for marketing of a known drug by arguing that the composition-of-matter patent has expired, and that the generic version is intended only for a non-patented use

1. Rai AK & Rice G (2014) Science Translational Medicine Vol 6 Issue 248
2. Alhiary R. et al (2023) Journal of the American Medical Association, Volume 330, Number 7

Patents

- **Core Method of Use claims on NOX-A12 + Irradiation + Bevacizumab for Glioblastoma will expire in 2043, before any extensions, if granted.**
- Granted patent covering use of NOX-A12 for therapy of cancer expiring 2031.
- Composition-of-matter patent on NOX-A12 expiring in 2027.

Regulatory

- **Orphan Drug Exclusivity is considered the minimum coverage for business planning :**
 - 10+2 years in EU (Granted for NOX-A12 in Glioma)
 - 7 years from approval in US (Granted for NOX-A12 in Glioblastoma)
 - 10 years in Japan
 - 7 years in China – Glioblastoma validated as orphan in China since Sept 2023

NOX-A12 Combination: Potential for Transformational Activity in GBM

- Unprecedented activity in MGMT unmethylated glioblastoma patients with residual tumor after surgery: **statistically significant improvement in survival** and **doubling of mOS¹**.
- High rates of tumor response: **83% mRANO responses durable > 6 months¹**.
- **Excellent safety and tolerability** in a chemotherapy-free regimen¹.
- **Commercial exclusivity** in glioblastoma market, estimated at €2.5 billion/yr², ensured by **Orphan Drug protection** in major markets. Additional **foundational method of use claims could provide robust protection well into 2040's³**.
- Commercial and scientific rationale to expand into other CNS indications with high unmet need where radiotherapy is routinely used and there are only limited good options available.

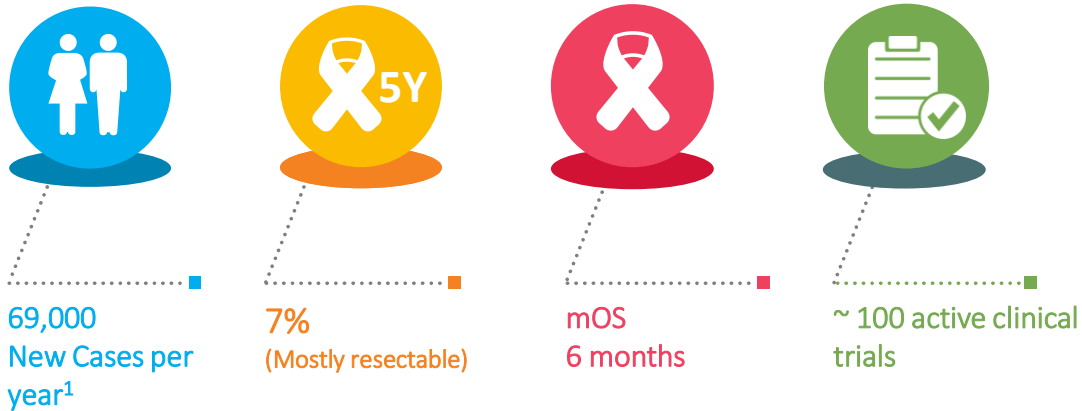


NOX-A12 + Immunotherapy in Pancreatic Cancer



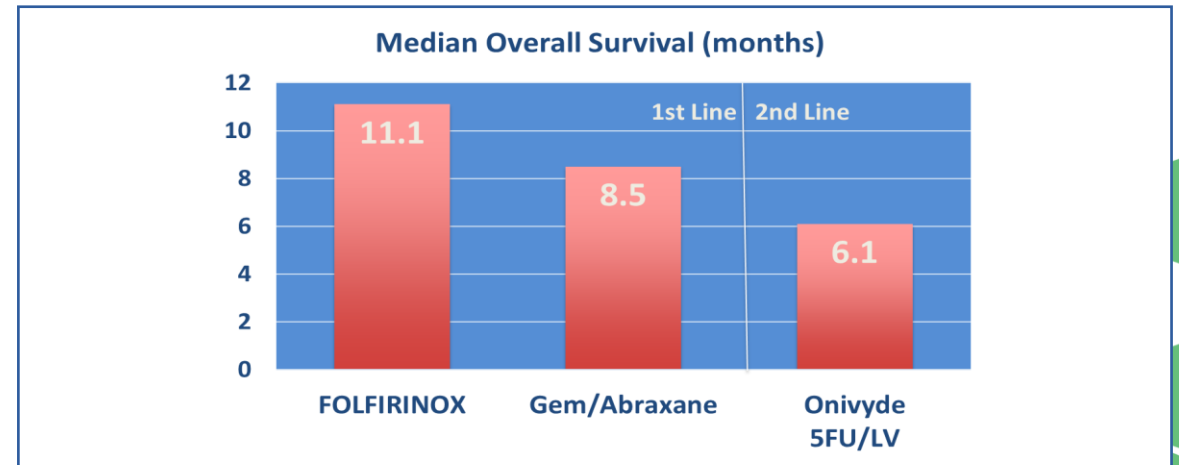
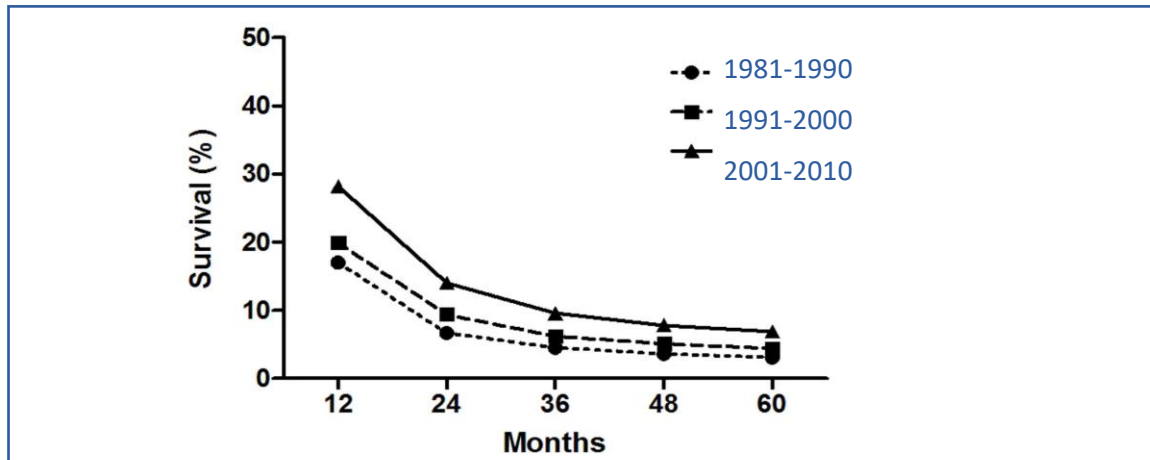
Pancreatic Cancer – Extremely Low Overall Survival and Limited Treatment Options

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



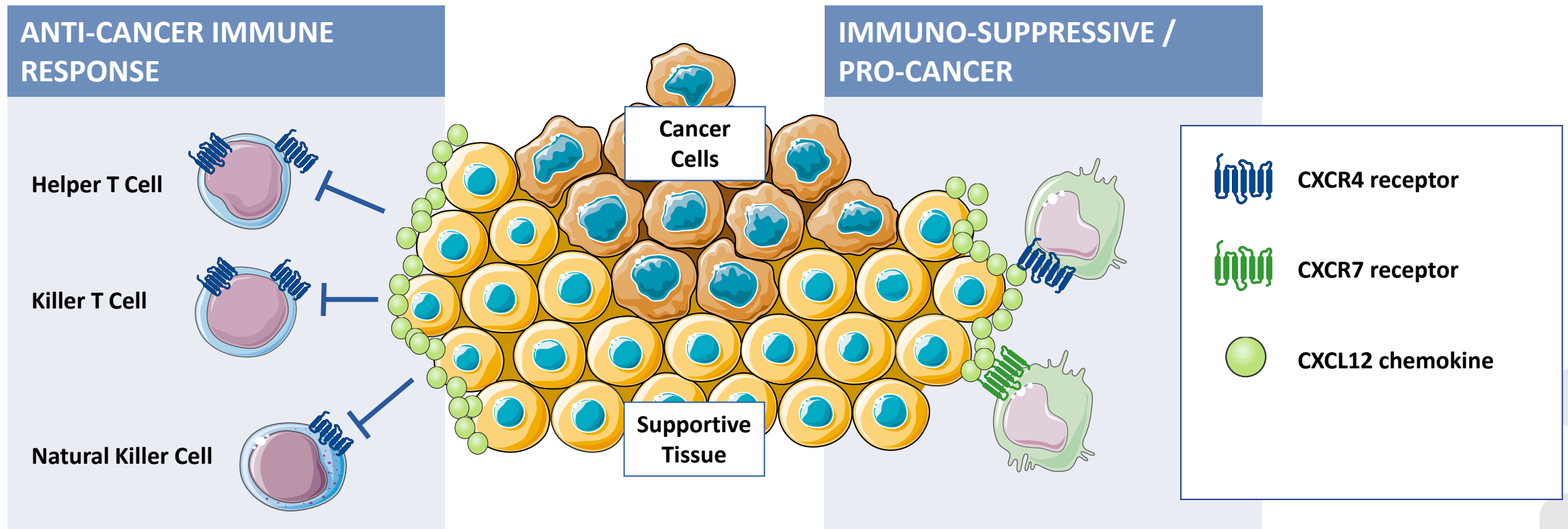
1. Second-line in the US, UK, FR, ES, DE & IT, 107k first-line. Global Data April 2022

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:

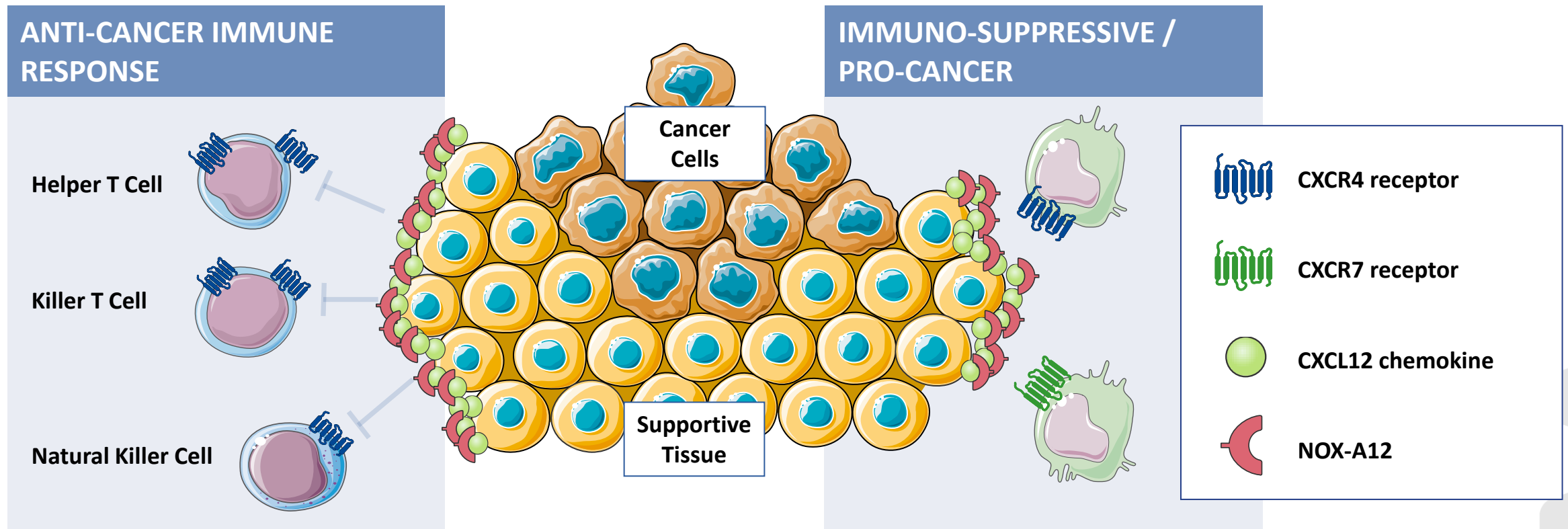
- excludes effector immune cells from entering the tumor
- attracts bone-marrow derived immuno-suppressive / pro-cancer cells to region of tumor



NOX-A12 + Immunotherapy: Mode of Action

NOX-A12:

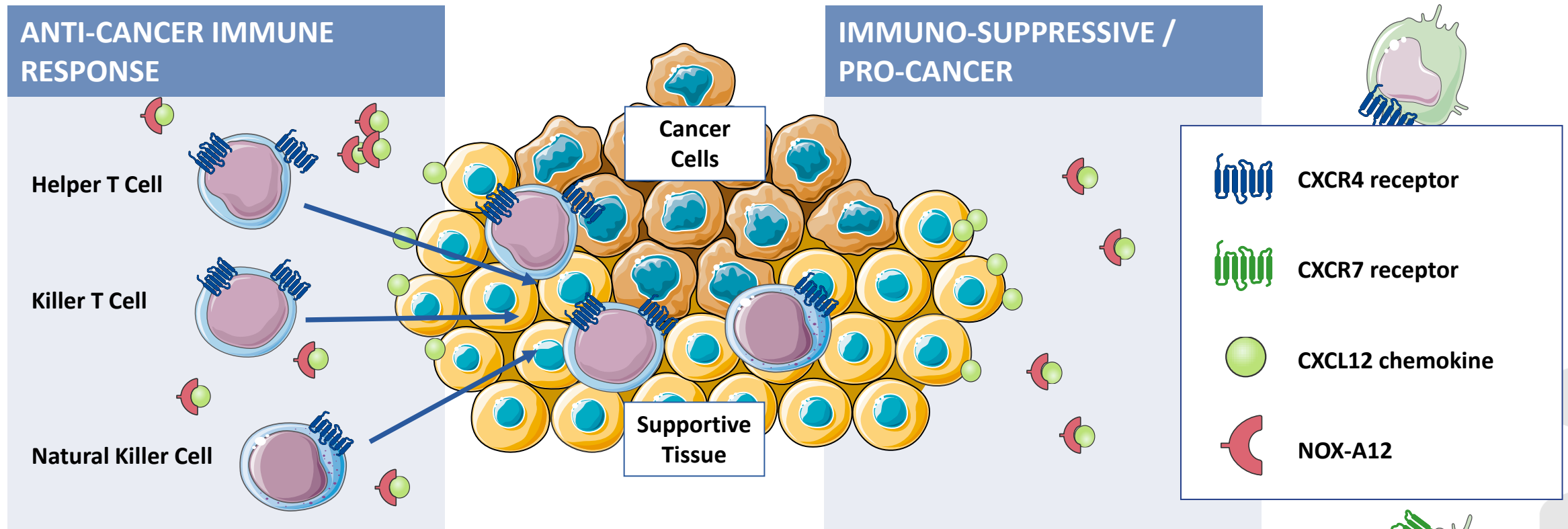
- reduces CXCL12 “wall” around solid tumors, which
- allows Killer T Cells to enter, eliminates attraction of immuno-suppressive / pro-cancer cells¹



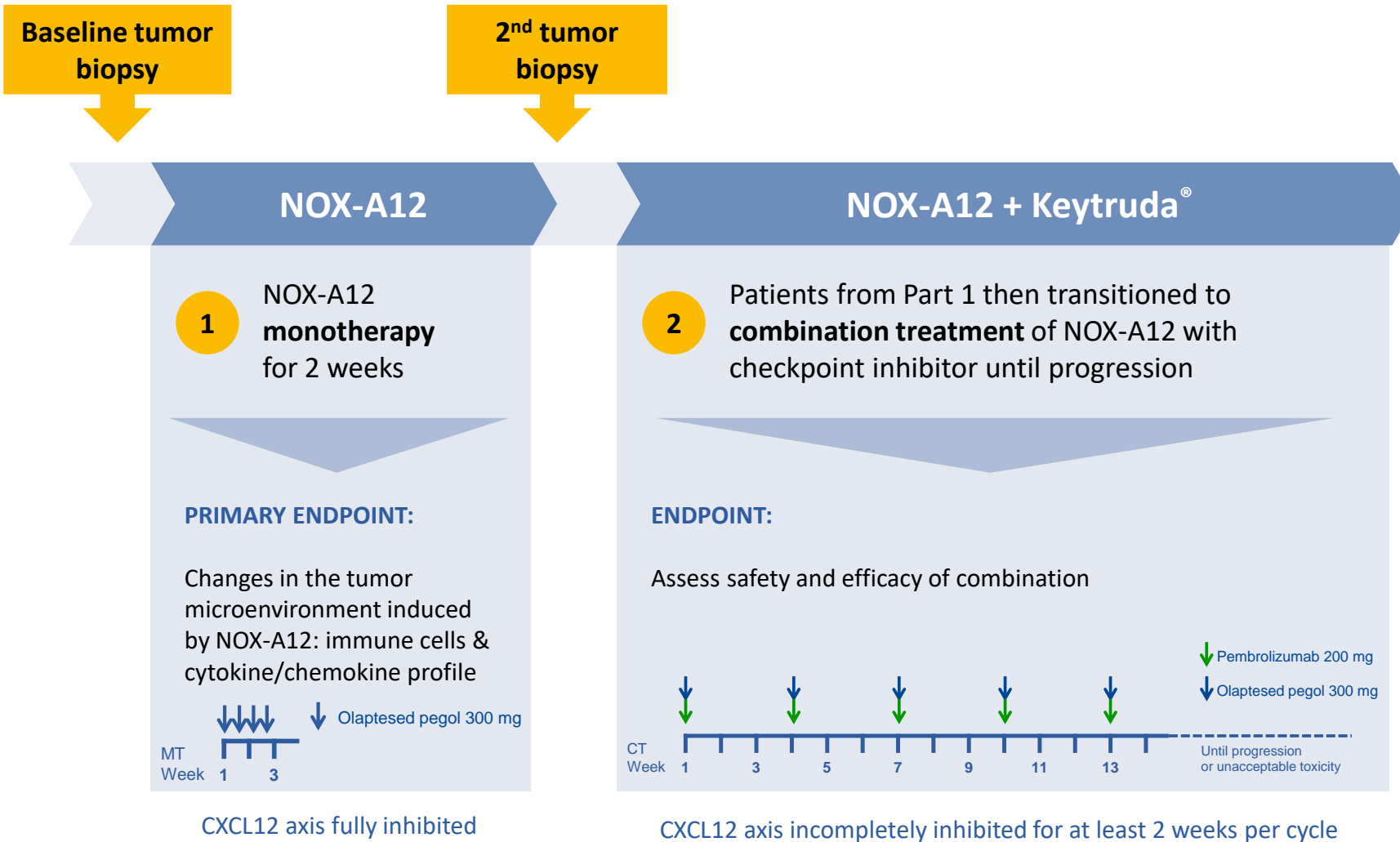
NOX-A12 + Immunotherapy: Mode of Action

NOX-A12:

- reduces CXCL12 “wall” around solid tumors, which
- allows Killer T Cells to enter, eliminates attraction of immuno-suppressive / pro-cancer cells¹



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



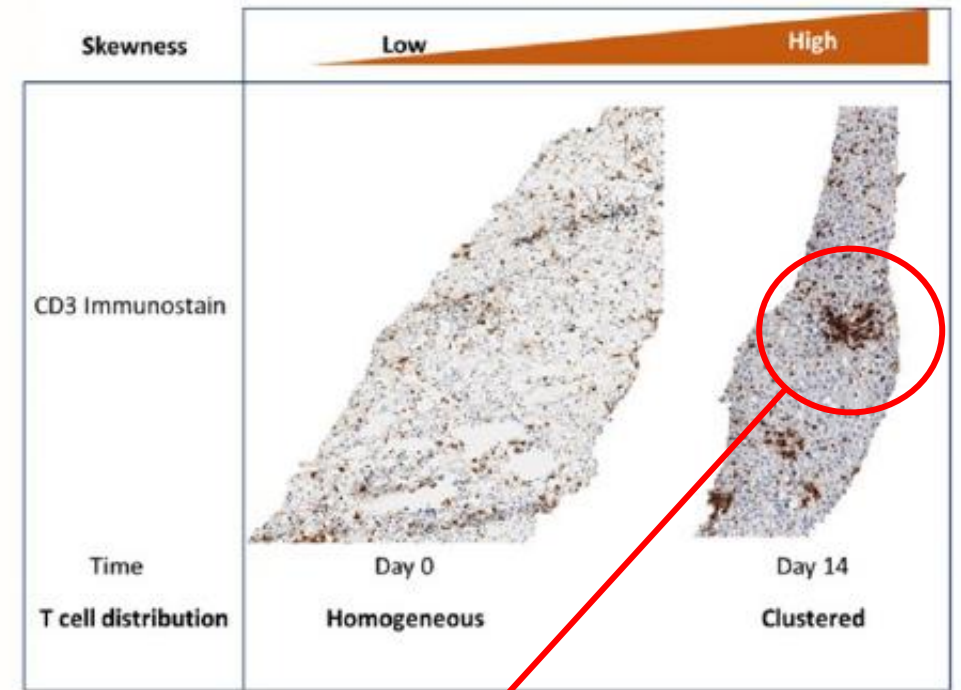
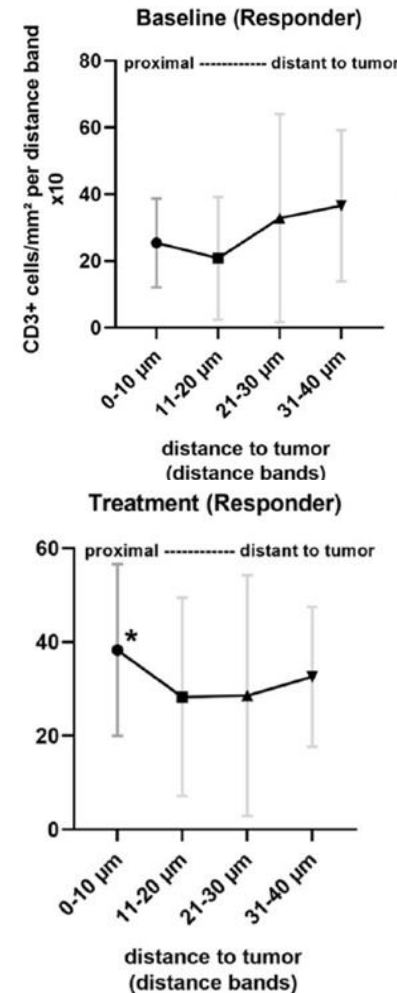
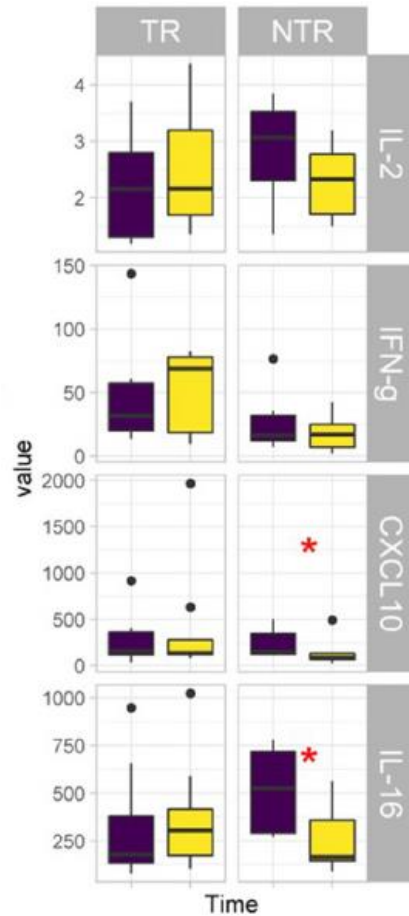
Clinical Trial a Scientific Collaboration with:



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

Cytokine profile

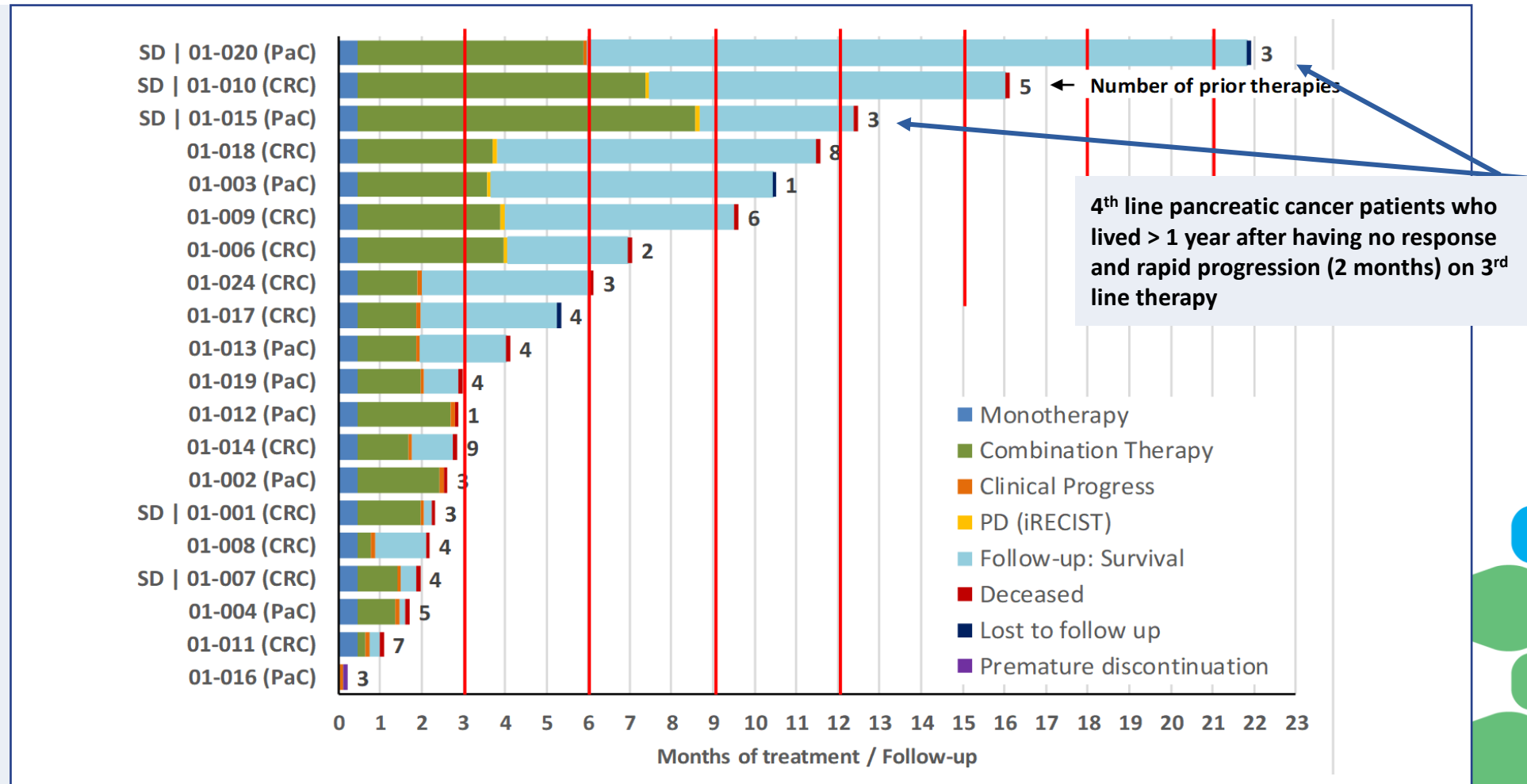
Unsupervised clustering of patients based on relative changes in the molecular immune landscape at the end of NOX-A12 monotherapy. Concentrations of the most affected cytokines before and at the end of the monotherapy in patients clustered in tissue responders (TR) and tissue non-responders (TNR).



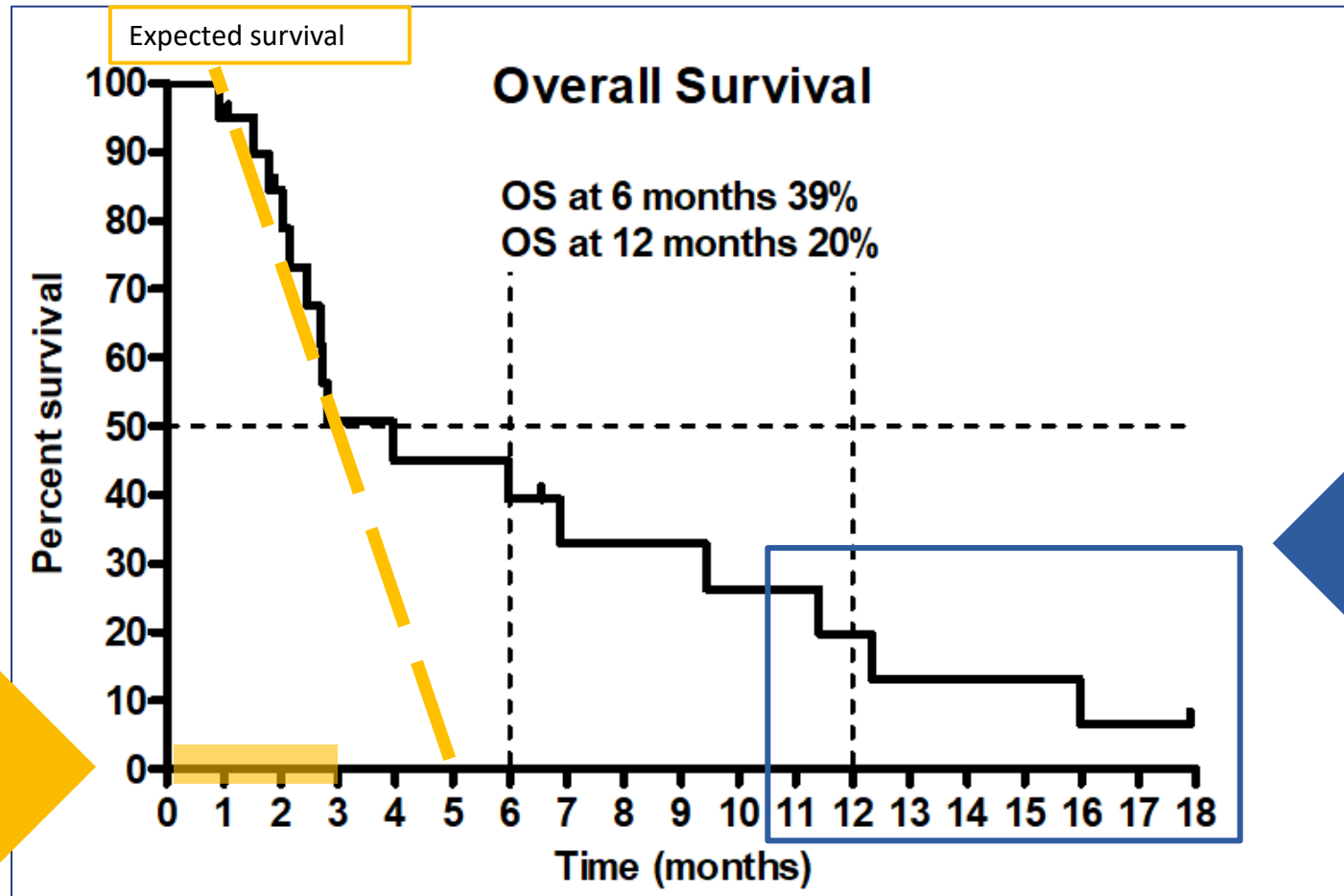
T-cell clustering in PaC/CRC patients on NOX-A12 monotherapy similar to that seen in glioblastoma patients while on NOX-A12 therapy post-RT with infiltration of proliferating GNZB+/CD8+ cells

Impressive Survival in Heavily Pre-Treated Patients

- Pancreatic 4th line of therapy on average
- CRC 6th line of therapy on average



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 2nd line pancreatic cancer
- Design tests 2 arms, each with NOX-A12 + pembrolizumab combined with either gemcitabine/Abraxane[®] or Onivyde[®]/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 Market¹



Next inflection points

	NOX-A12 Brain Cancer Fast Track & Orphan Drug Status Granted	NOX-A12 Pancreas Cancer
	29,000	69,000 (2nd line) 107,000 (1st line)
	>12 months	>12 months
	\$2.5 bn (1st line)	\$6bn (2nd line) \$9.3bn (1st line)
	Financing & initiation of randomized Phase 2	Financing & initiation of randomized Phase 2

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