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Improving Therapeutic Outcomes by Targeting the Tumor Microenvironment

April 2024

Forward Looking Statements

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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 DATA

Brain Cancer (1st line GBM)
Phase 1/2 clinical trial

NOX-A12 + RT + bevacizumab[1]:

- 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%)
- 83% durable partial responses as per mRANO
- 3 of 6 patients with >99% tumor size reduction including 1 complete response

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)

1. Giordano (2022) SNO Annual Meeting Poster Presentation #CTNI-67 & *TME Pharma* Press Releases from 19 November 2022, 13 July 2023, 2 February 2024, 2 April 2024

Financial Profile

- ***TME Pharma* is listed on Euronext Growth Paris – ALTME**
- Highly efficient structure with 14 employees and key expertise in-house
- Cash & equivalents:
  - **€3 million** (30 June 2023)
  - **~€5.15 million** gross additional raised since 30 June 2023
  - Financial visibility into July 2024

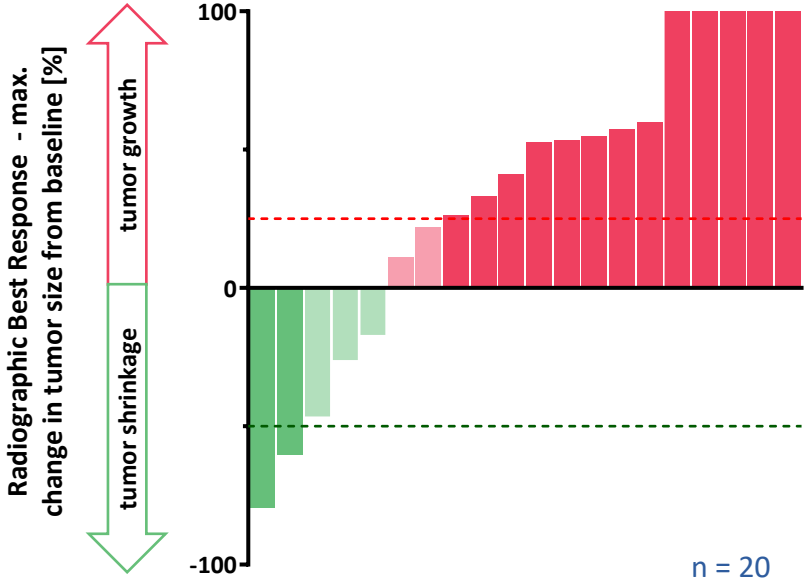
FINANCIALS AND SHAREHOLDING STRUCTURE	
Public listing	2016
ISIN Code	NL0015000YE1
Ticker	ALTME
Market	Euronext Growth Paris
Market Cap*	€8.9 M
Shares outstanding*	28,453,373
Warrants Z ISIN	NL0015001SR3
Warrants Z outstanding*	3,326,104

*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

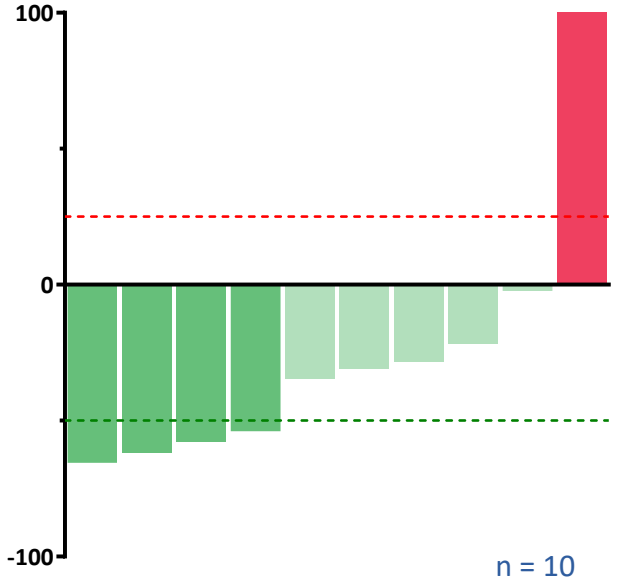
(Matched reference cohort from center participating in trial: MGMT Unmethylated & incomplete surgical resection or biopsy only)



Median Overall Survival (mOS)

10.5 months

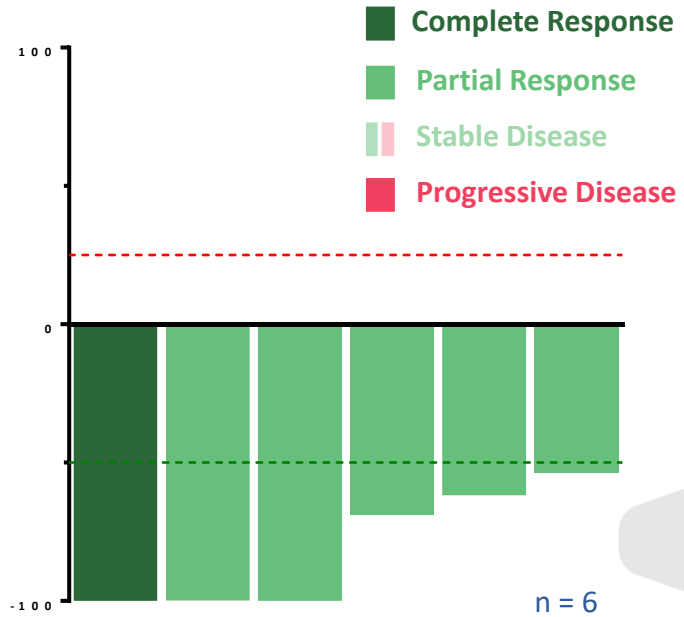
Radiotherapy + NOX-A12



12.7 months

15.8 months biomarker high

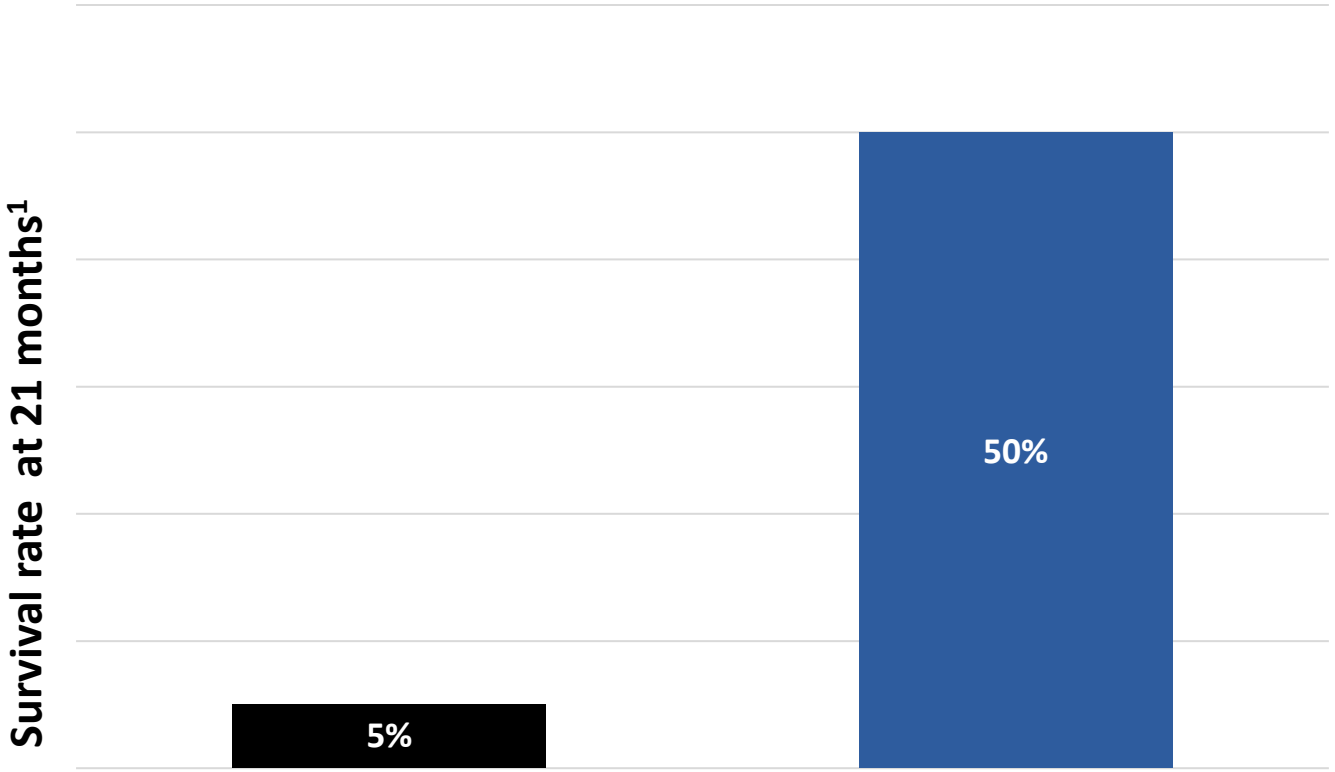
Radiotherapy + NOX-A12 + anti-VEGF



19.9 months

Sources: Giordano (2022) ASCO Annual Meeting Presentation #2050; Giordano (2022) SNO Annual Meeting Poster Presentation #CTNI-67, Giordano (2023) ASCO Annual Meeting Poster Presentation #405 & *TME Pharma* Press Release from 19 November 2022, 26 May 2023, 13 July 2023, 2 February 2024

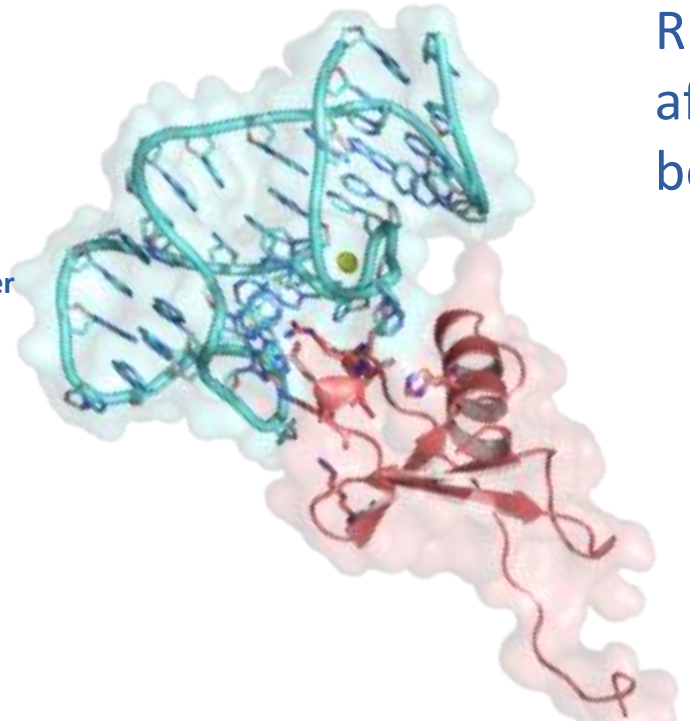
10-Fold Improvement in 21-month Survival for NOX-A12 + RT + anti-VEGF vs. Standard of Care



Since neither bevacizumab (anti-VEGF) alone, nor bevacizumab plus radiotherapy have previously been shown to extend survival [2], 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



Spiegelmer (Blue)

Chemokine Target Protein (Red)

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)

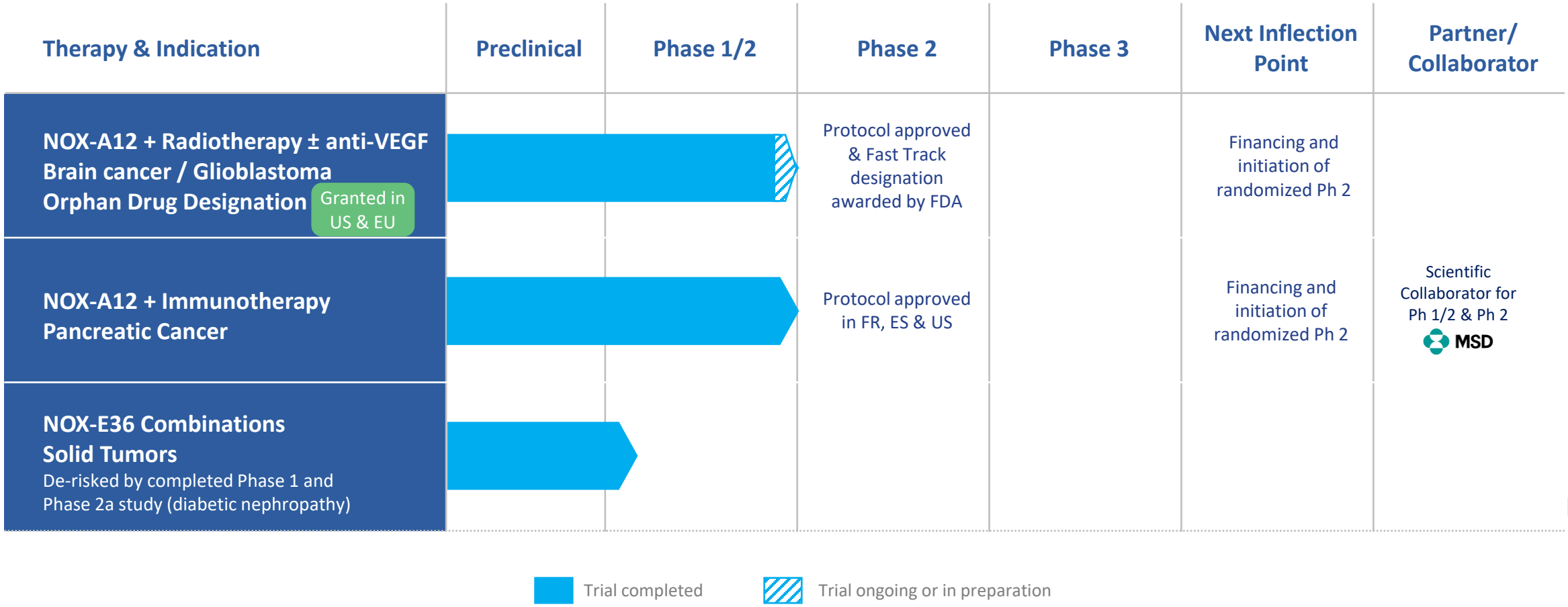
MACUGEN® PEGAPTANIB SODIUM INJECTION

Iveric bought by Astellas for $5.9b

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.

Crystal structure of the Spiegelmer NOX-E36 bound to chemokine CCL2 from Oberthür, D. et al. Nat Commun 6.6923 (2015)

Pipeline Assets Complement Anti-Cancer Therapies to Enhance Treatment Efficacy



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.

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

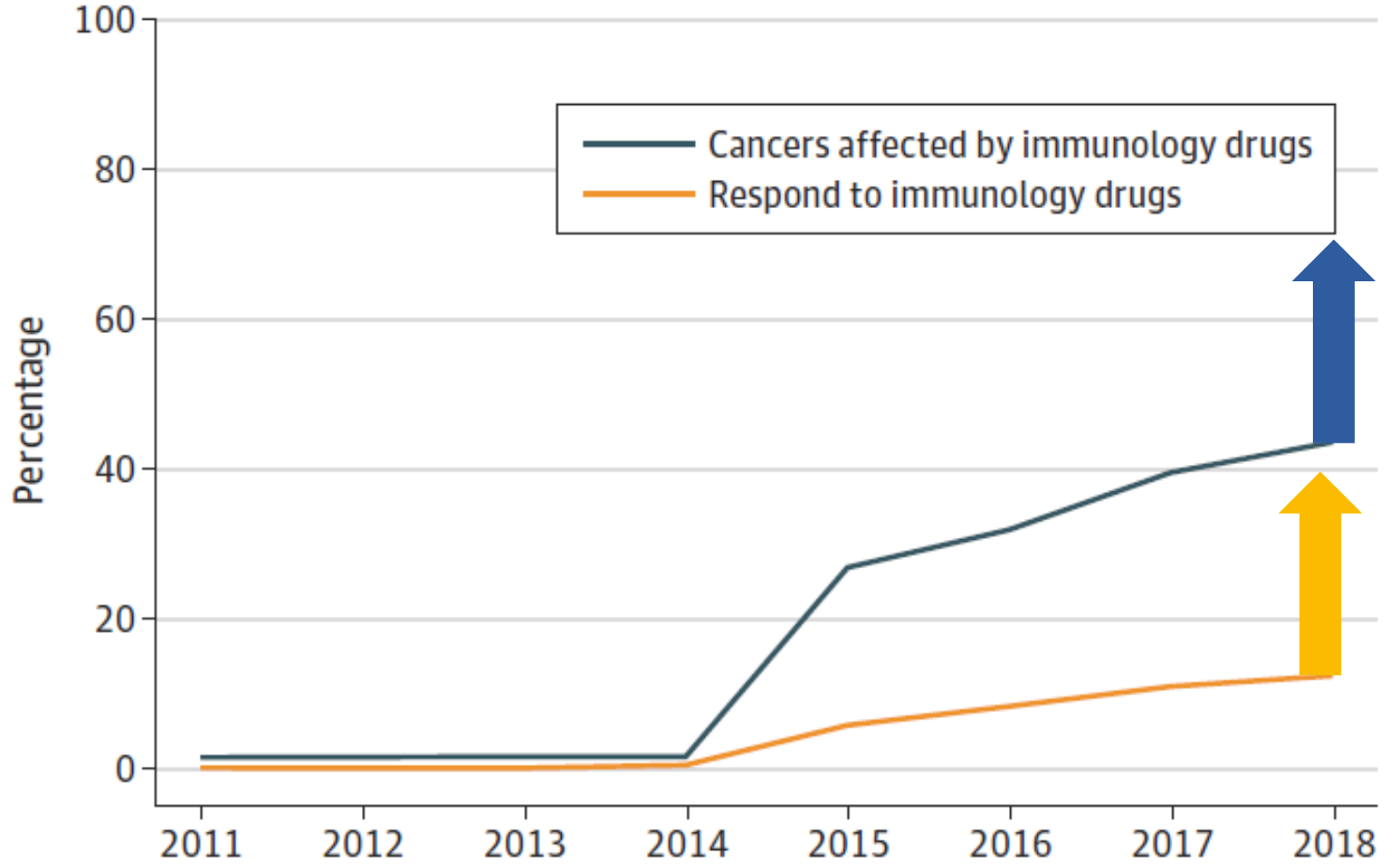
- 20+ years of experience in biotech, including 14 years in investment banking

TME pharma

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

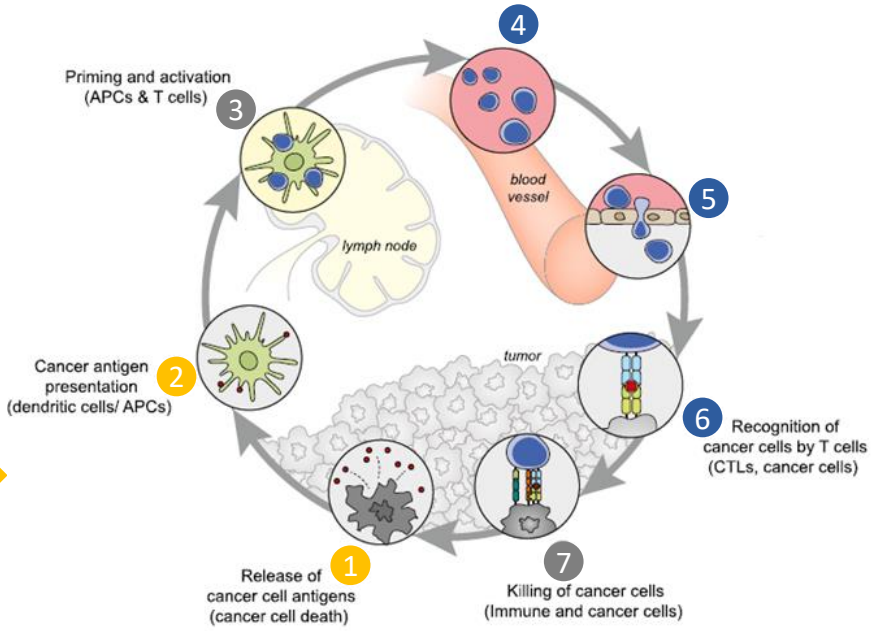
Blocks repair of damaged tumors

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).

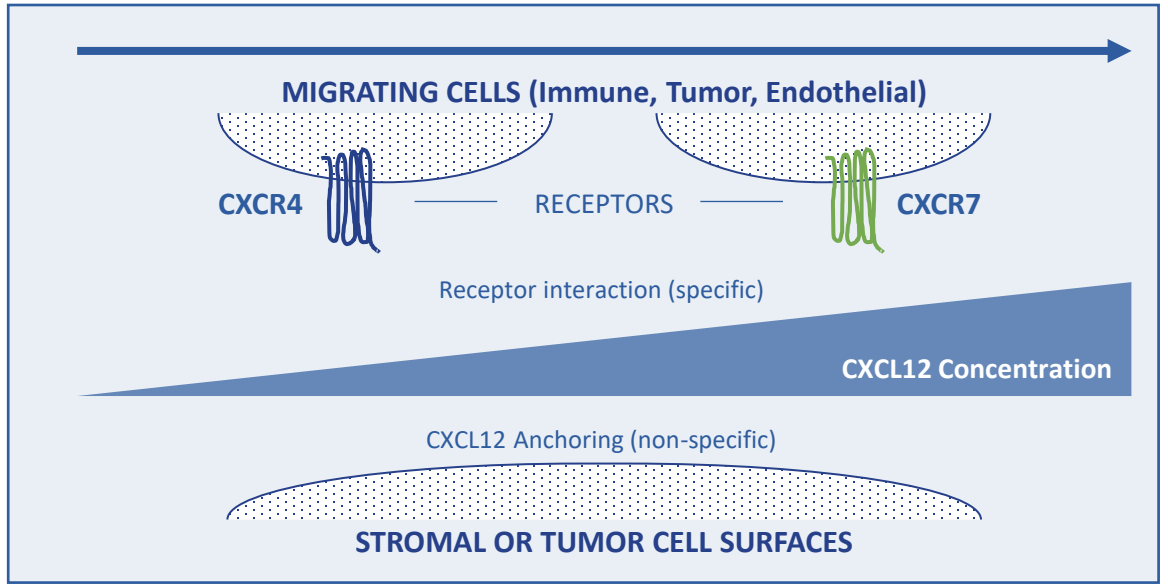
(c) Bartneck 2019, Cell Mol Gastroenterol Hepatol 7:371. Lazarus 2017, Poster PT165 Soc Surg Oncol 70th Annual Cancer Symposium.

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

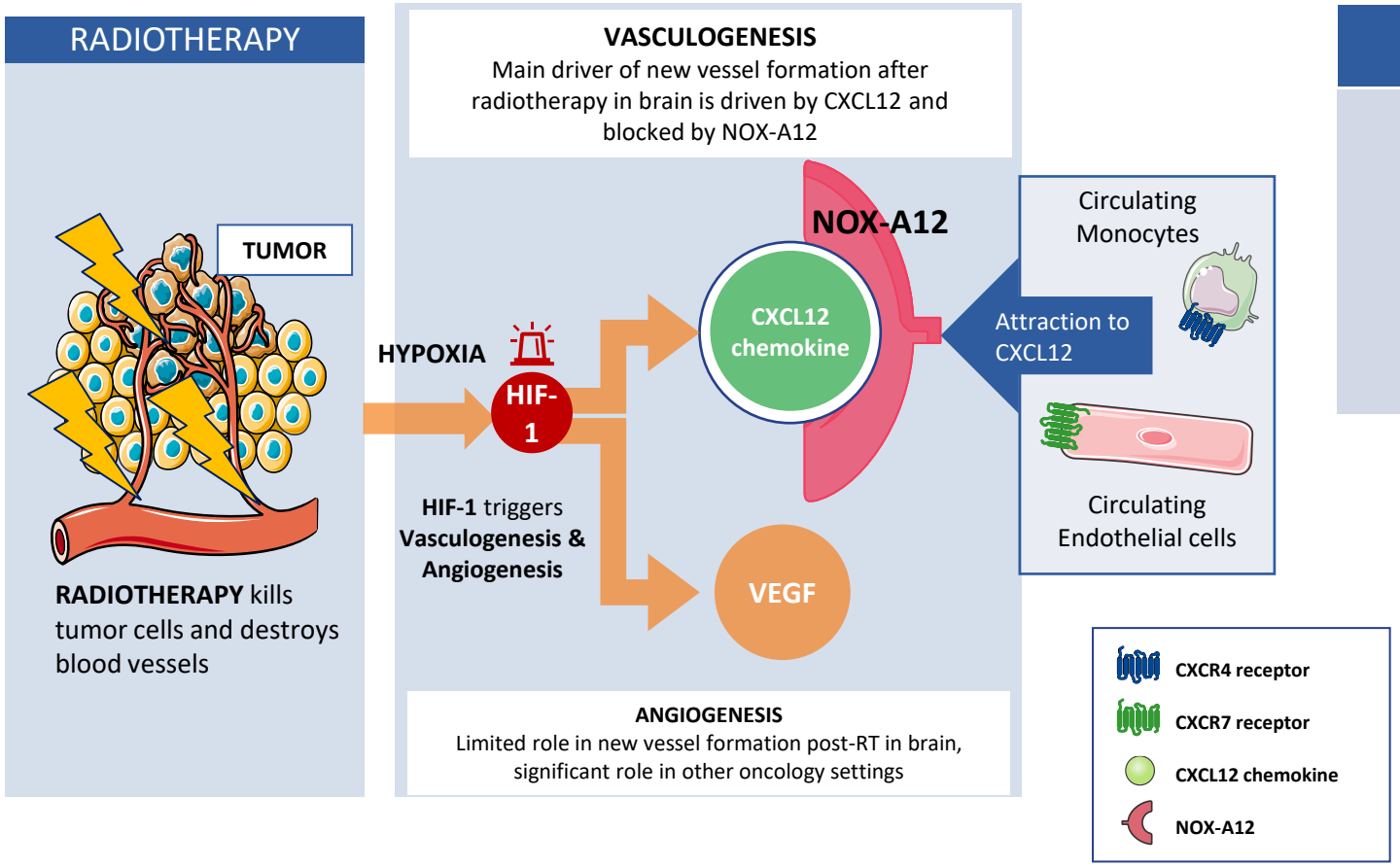
2) neutralizes anchor domain detaching chemokine & destroying the location information of the chemokine concentration gradient

Based on information from Guo et al., 2015, Walters, M.J. et al., Br J Cancer. 2014, Würth, R. et al., Front Cell Neurosci, 2014; Guo, J-Ch. et al., Oncotarget, Advance publications, 2016; Miao, Z. et al., PNAS, 2007; Yun, H-J. et al., Oncol Lett, 2015; C. Jiang (2020) Mol. Med. Reports; Biasci D. et al. PNAS 117 (46) 28960-28970, 2020; and Seo Y.D. et al., Clinical Cancer Research 2019 Vol. 25(13) 3934.

NOX-A12 – Dual Mechanism of Action

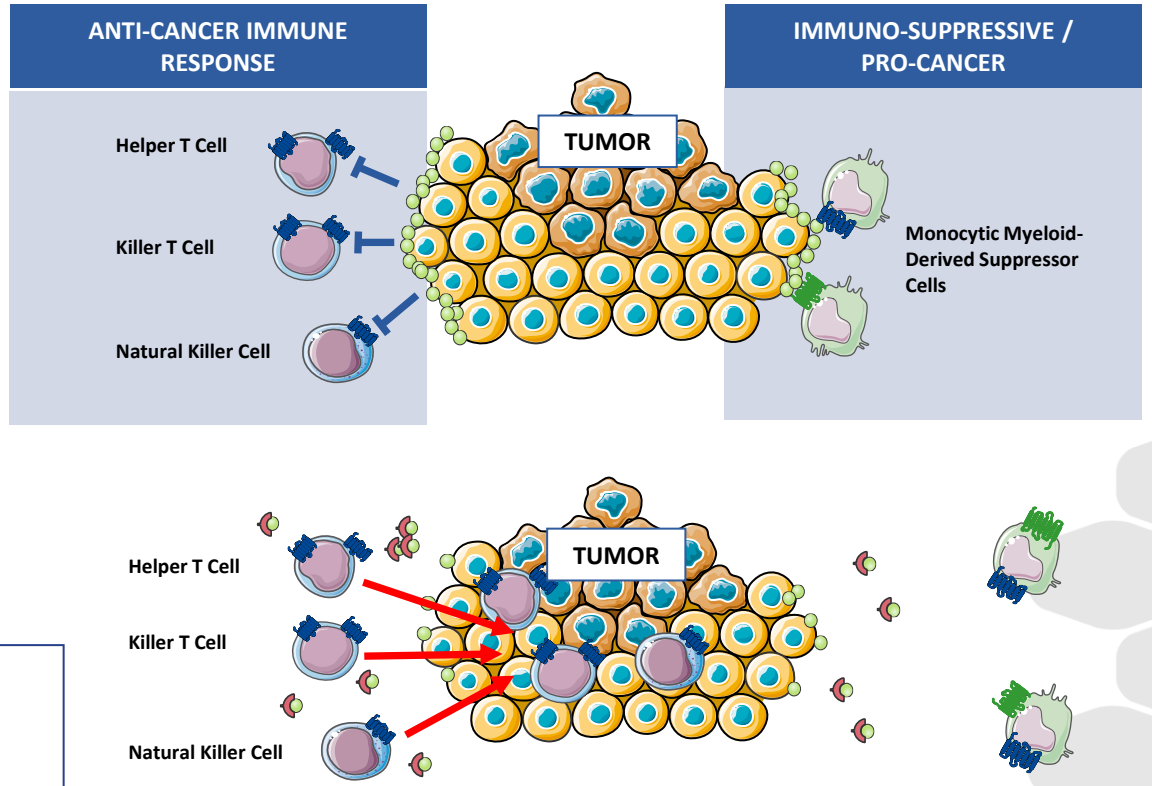
Blockage of Vasculogenesis:

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



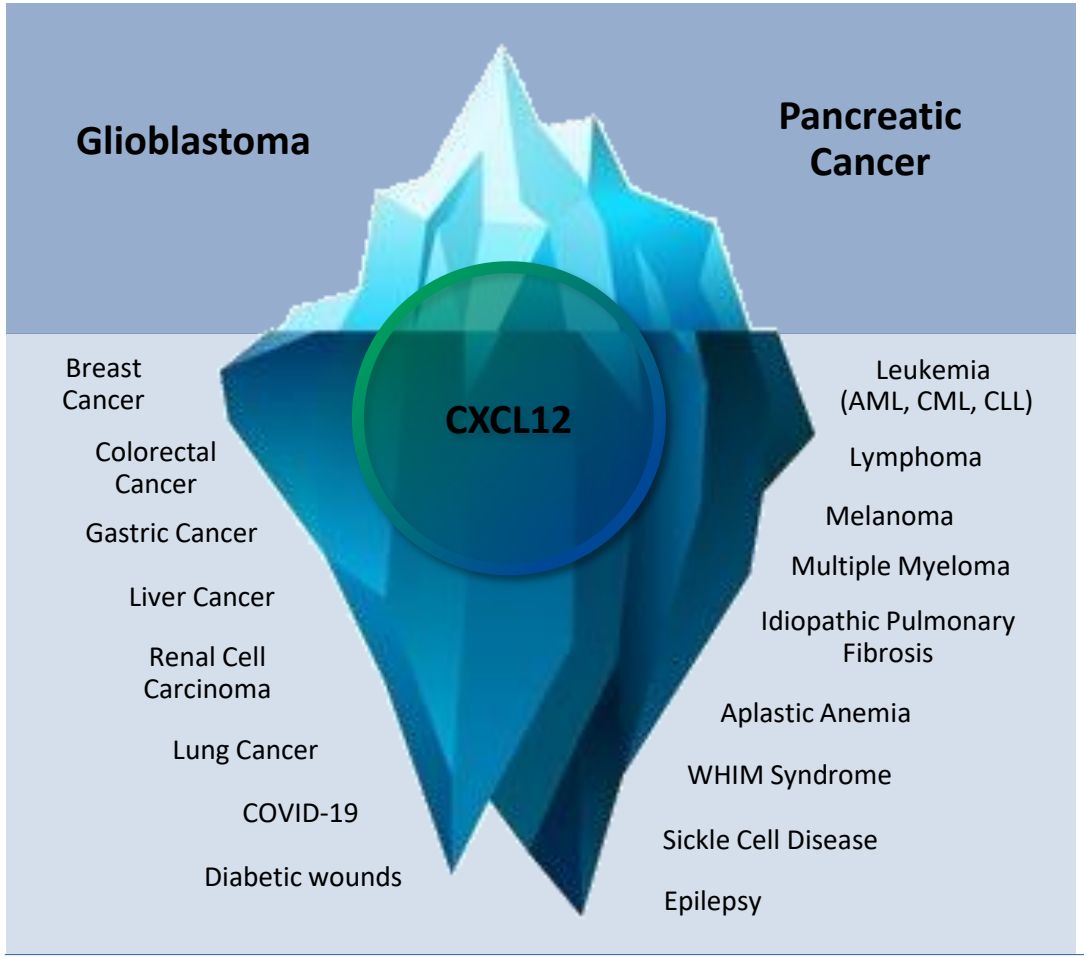
Overcome immune exclusion & prevent recruitment of immune-suppressive cells

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.

NOX-A12 + Radiotherapy ± Bevacizumab in Chemotherapy Refractory Glioblastoma

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

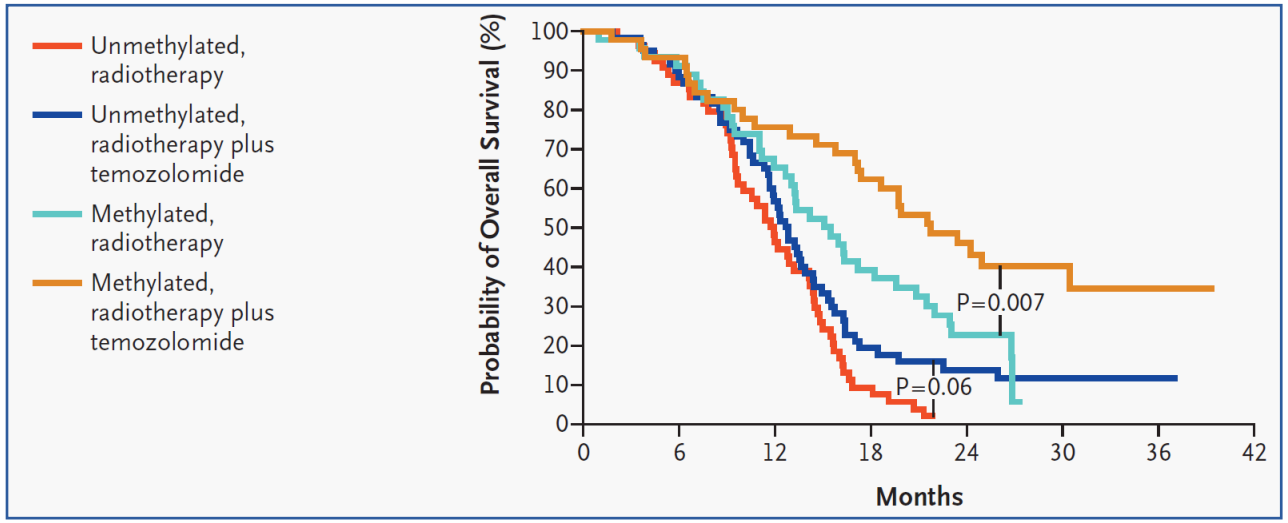
LACK OF EFFECTIVE THERAPIES & LOW OVERALL SURVIVAL

Orphan Status
29,000 New Cases per year US + Eur-5 [1]

5-year Survival
6,9%[2]

mOS
8 months[2]

~ 315 active clinical trials in US & Europe[3]



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

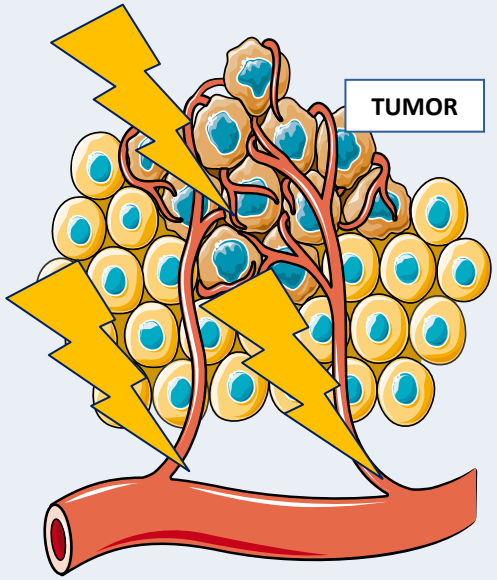
- Patients with measurable **tumor remaining** after maximal safe surgical removal of cancer have worse prognosis vs. patients with complete tumor resection

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.

Sources: 1) In the US, UK, FR, ES, DE & IT, Global Data April 2022, 2) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2016—2020.
3) Citeline Clinical Intelligence Phases 1 – IV trials in glioblastoma in North America or Europe analyzed 22 Feb 2024. Graph from Hegi ME et al. N Engl J Med 2005;352:997-1003

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

RADIOTHERAPY



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

Vessel destruction triggers **HYPOXIA**

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

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

HIF-1

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

CXCL12 chemokine

NOX-A12

Attraction to CXCL12

Monocytes

Endothelial cells

CXCR4 receptor

CXCR7 receptor

VEGF

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

Although anti-VEGF has shown to improve PFS it had no impact on survival benefit in GBM[1]

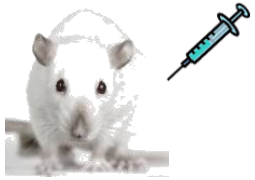
Inhibition of the CXCL12/CXCR4/CXCR7 axis can block tumor vasculogenesis

Source: Figure Adapted from Liu 2014, Neuro-Oncology 16:21 and Kioi 2010 J. Clin. Invest, 120:694
1. Gilbert 2014, NEJM 370:699 & Chinot 2014, NEJM 370:709

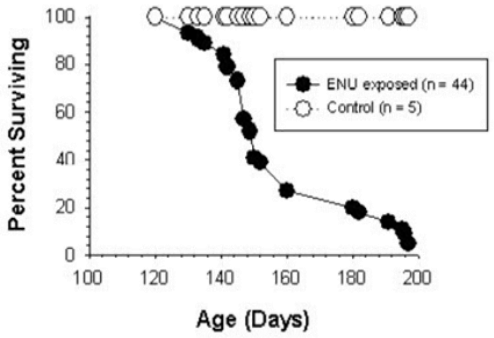
NOX-A12 + Radiotherapy Increases Survival and Demonstrates Complete Regression of Brain Tumors

Autochthonous brain tumor model in rats

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

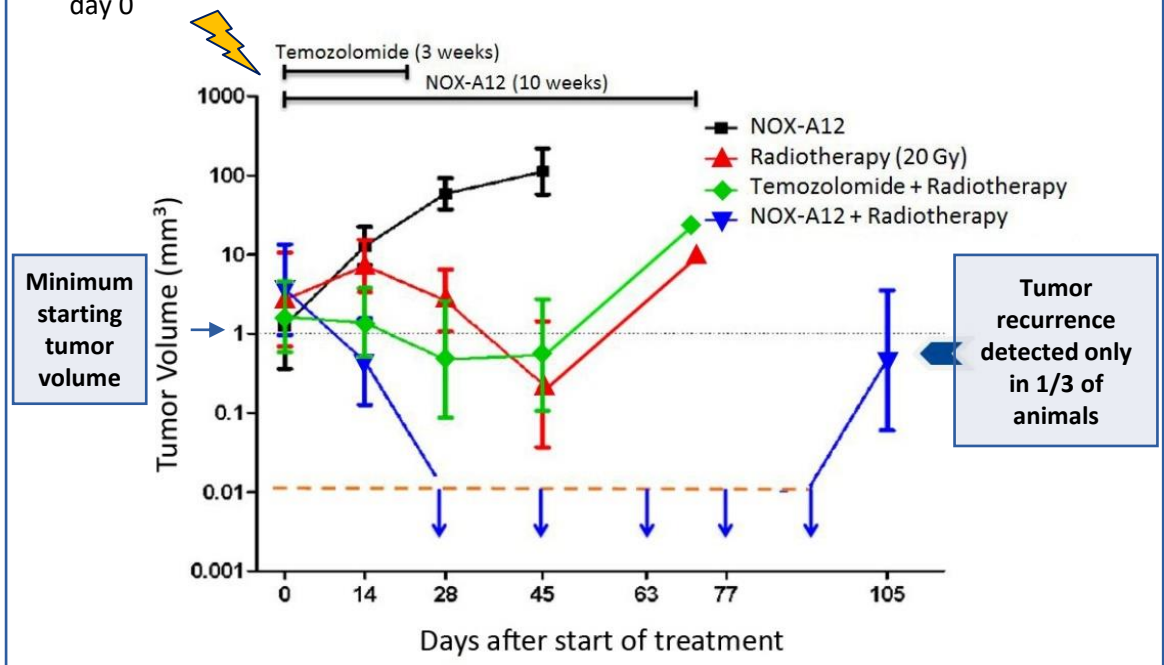


Pregnant rats:
ENU (carcinogen) on gestational age day 17 - 18



EFFECTS OF TREATMENTS

Radiotherapy at day 0



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

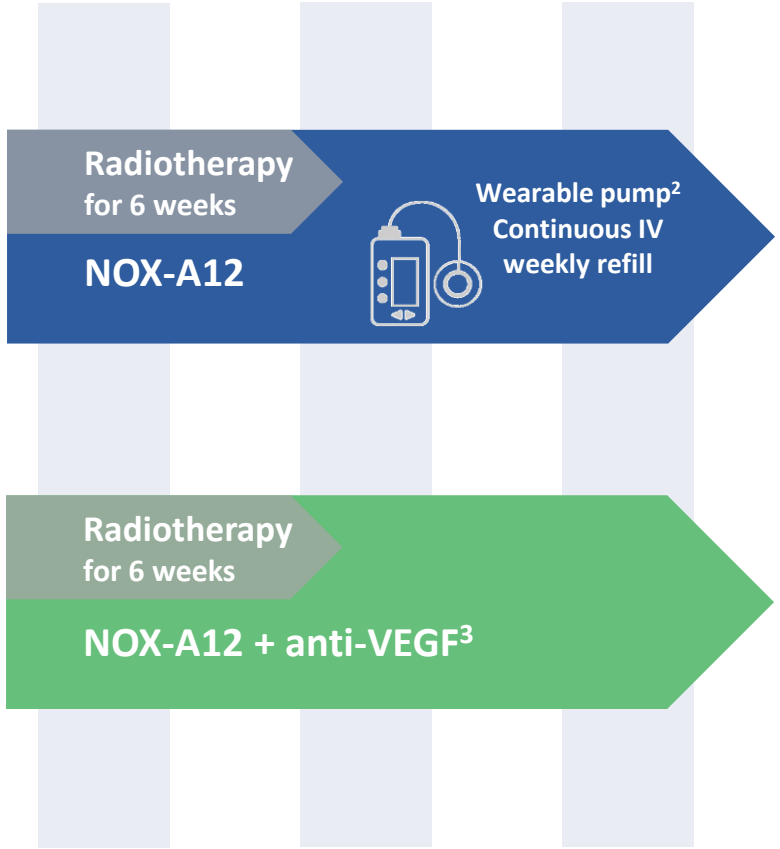
Source: Liu 2014, Neuro-Oncology 16:21

GLORIA Phase 1/2 Dose Escalation Study & Expansion 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 months[1]



Dose Escalation Cohort NOX-A12 + RT

NOX-A12 Doses tested:

200, 400 & 600 mg/week

Expansion Arms

NOX-A12 at 600 mg/week +

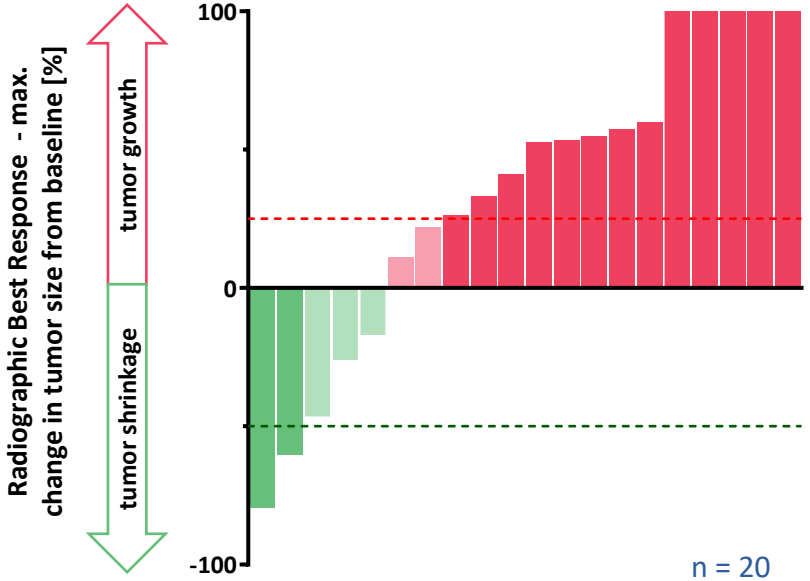
Radiotherapy + anti-VEGF

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

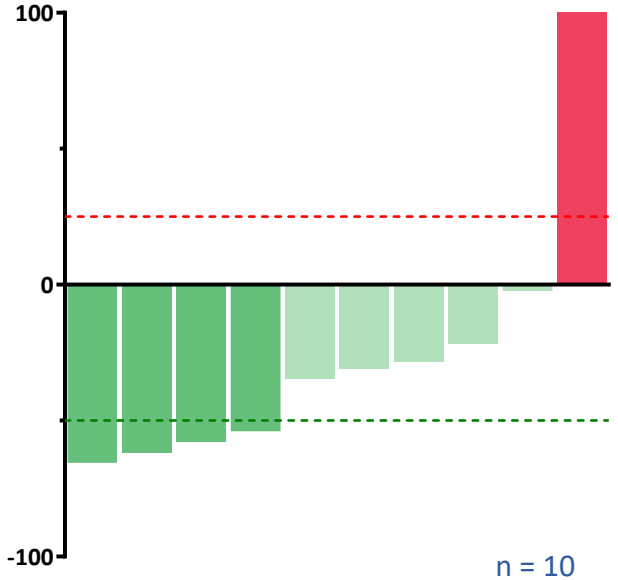
(Matched reference cohort from center participating in trial: MGMT Unmethylated & incomplete surgical resection or biopsy only)



Median Overall Survival (mOS)

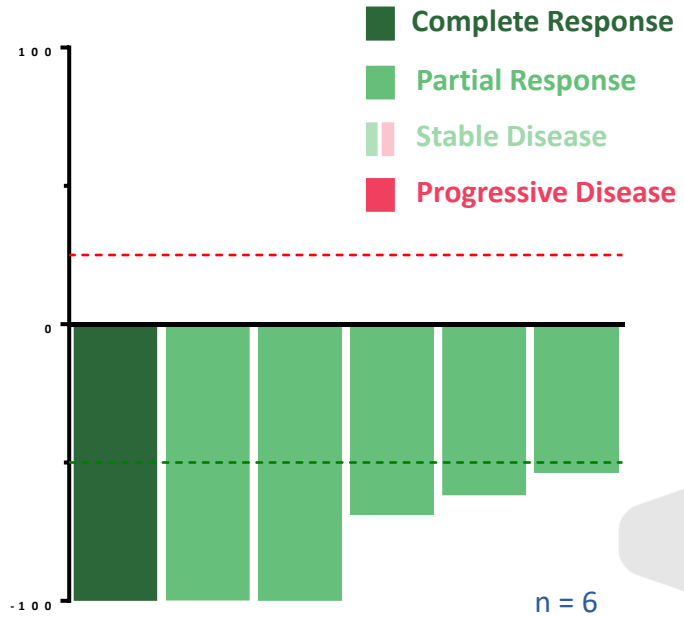
10.5 months

Radiotherapy + NOX-A12



12.7 months
15.8 months biomarker high

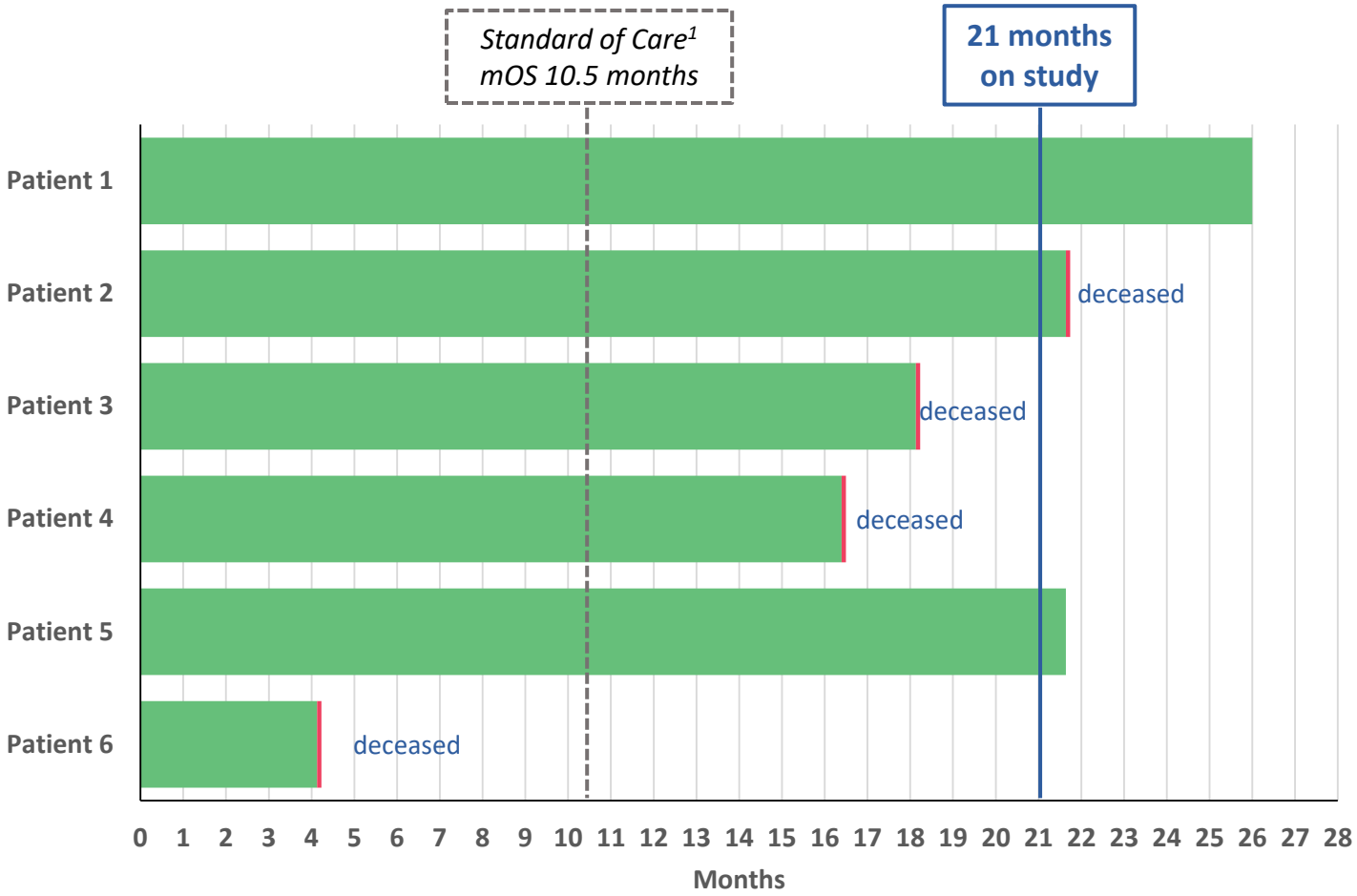
Radiotherapy + NOX-A12 + anti-VEGF



19.9 months

Sources: Giordano (2022) ASCO Annual Meeting Presentation #2050; Giordano (2022) SNO Annual Meeting Poster Presentation #CTNI-67, Giordano (2023) ASCO Annual Meeting Poster Presentation #405 & *TME Pharma* Press Release from 19 November 2022, 26 May 2023, 13 July 2023, 2 February 2024

NOX-A12 + RT + Bevacizumab: Final Survival Data median Overall Survival of 19.9 months



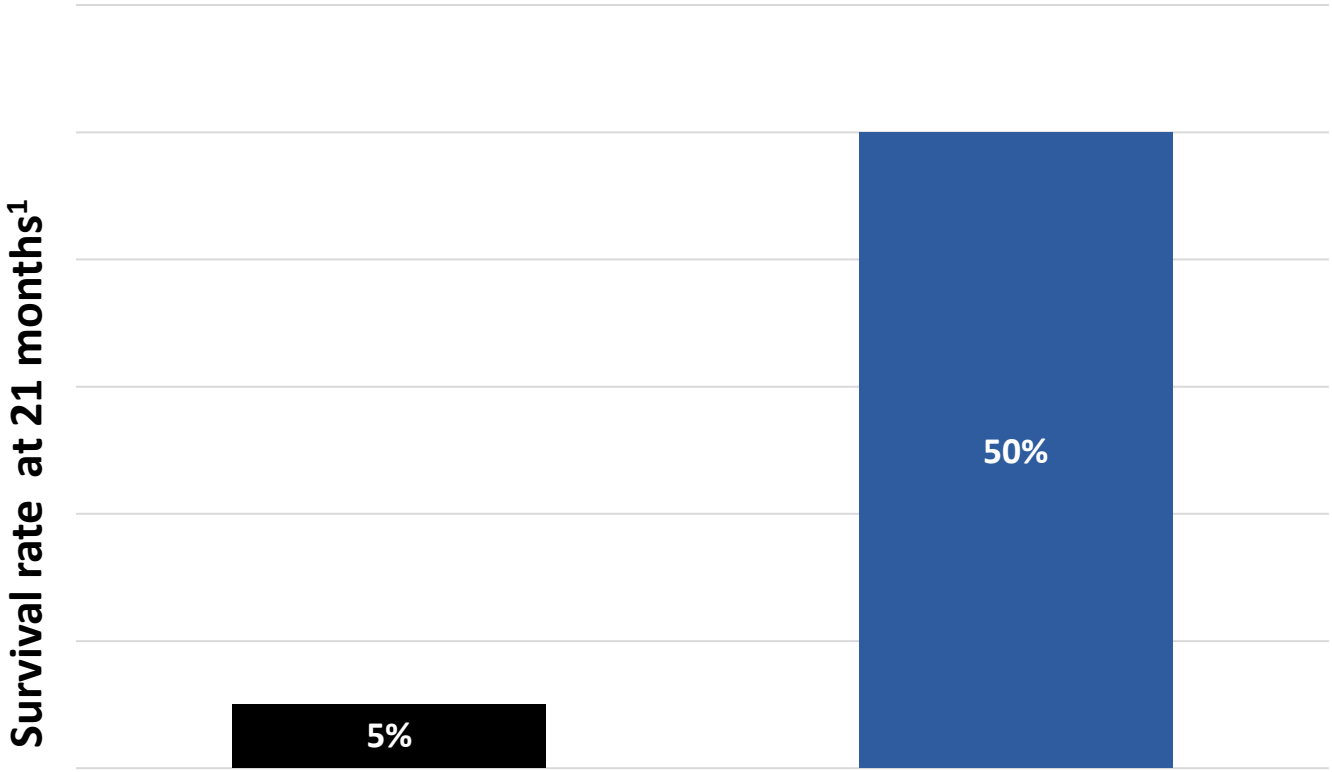
- **Median overall survival (mOS): 19.9 months**
- **2 out of 6 patients remain alive**
- **50% overall survival at 21 months**
- **5 out of 6 patients achieved durable mRANO responses >6 months**

Source: *TME Pharma* Press Release from 2 February 2024

1. Standard of care data from 20-patient matched reference cohort of newly diagnosed glioblastoma with MGMT unmethylated, incompletely resected or biopsy-only tumors

Cut off date 31-Jan-2024

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 [2], 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

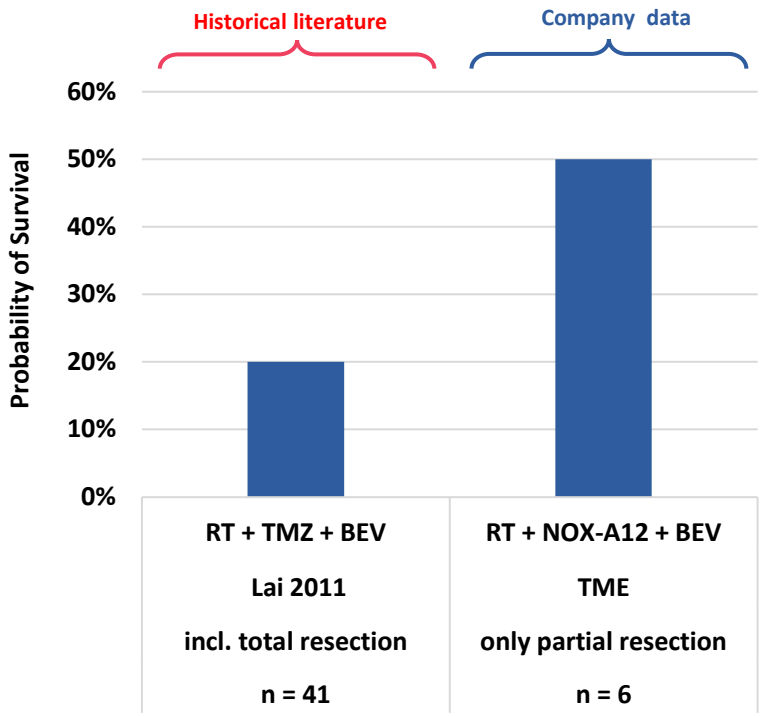
Relevant Benchmark Studies in Chemotherapy Resistant Glioblastoma from US and EU

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
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

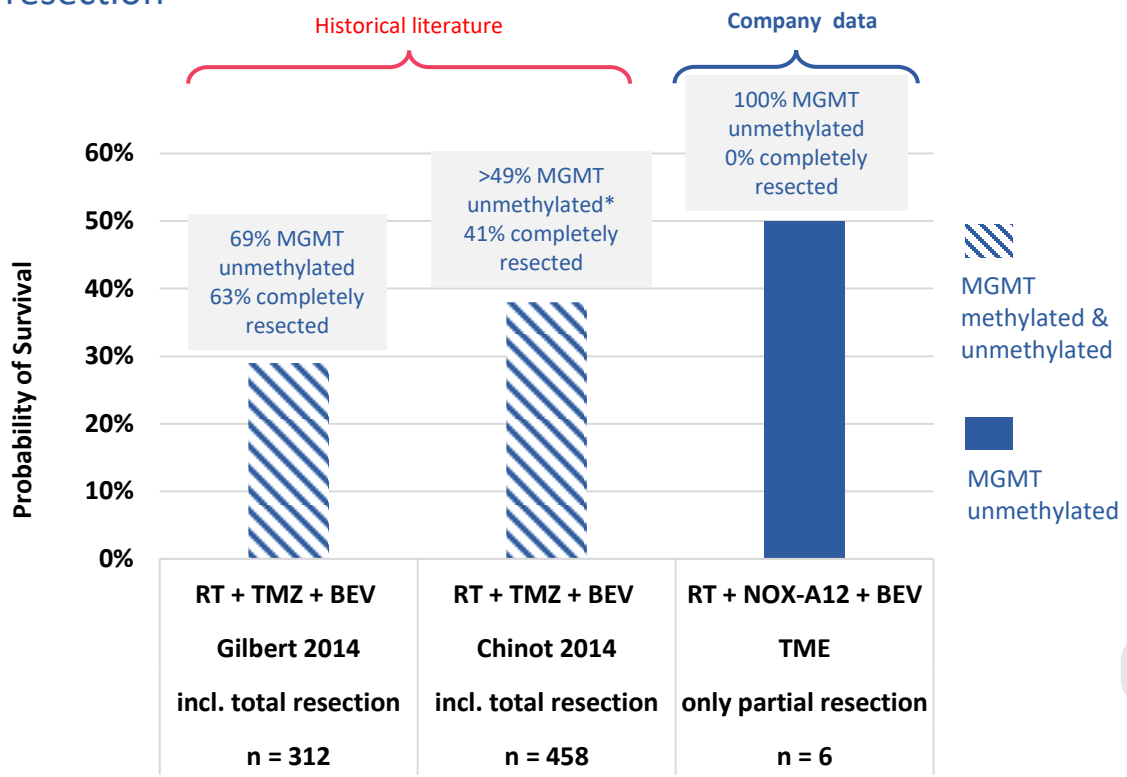
Source: *TME Pharma* Press Releases from 13 September 2023 and 2 February 2024, 2 April 2024

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

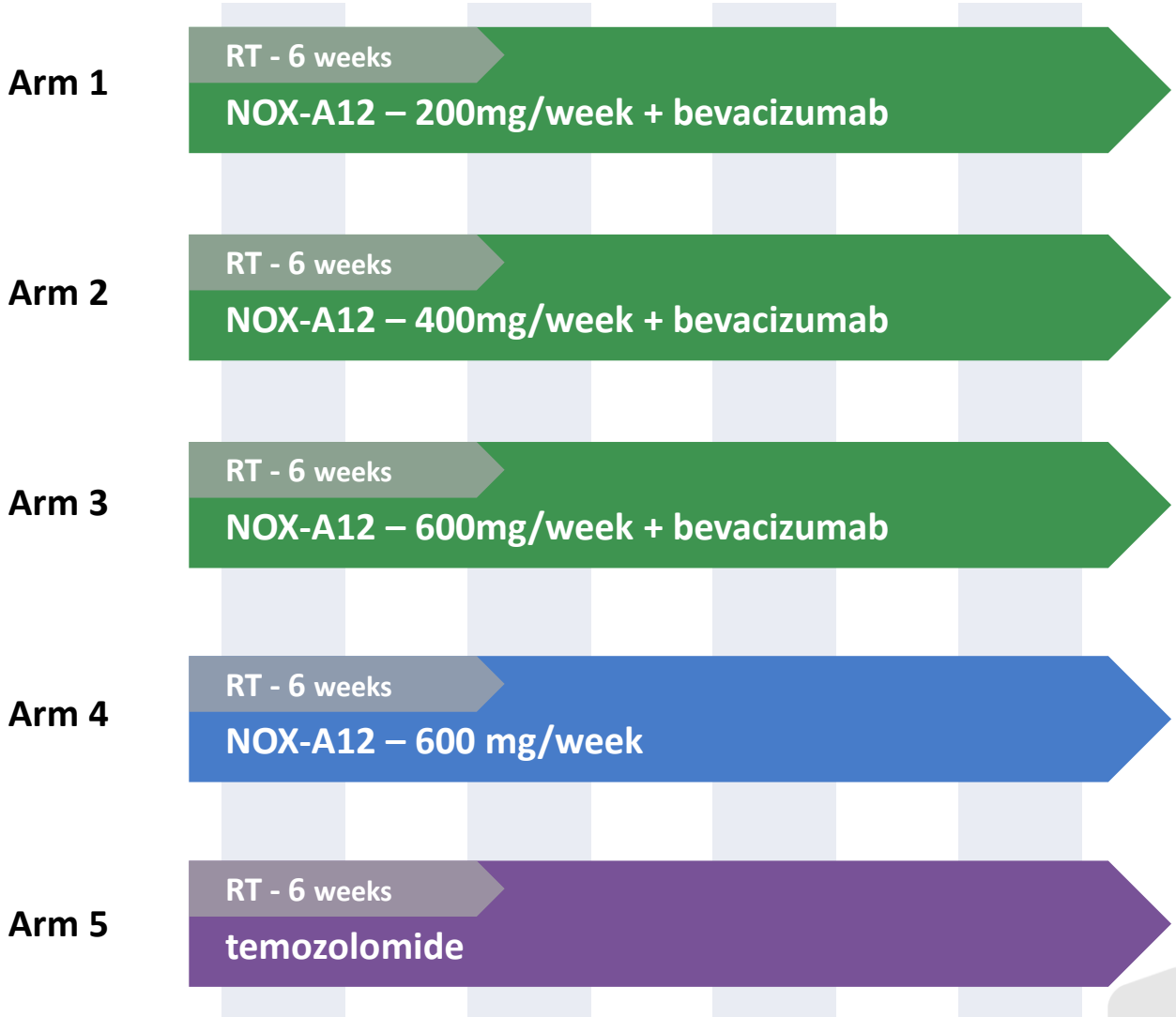
Sources: Lai 2011, J Clin Oncol 29:142; Gilbert 2014, NEJM 370:699; Chinot 2014, NEJM 370:709
* MGMT status not available for 25% of patients; actual percentage of unmethylated patients thus expected to be higher

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[1]:
- mOS of approx. 10 months

Orphan Drug and Fast Track Designations awarded by FDA

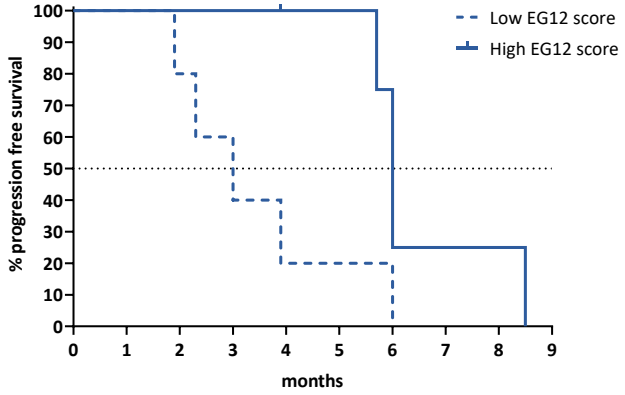


1. Standard of care data from 20-patient matched reference cohort of newly diagnosed glioblastoma with MGMT unmethylated, incompletely resected or biopsy-only tumors; Giordano (2022) ASCO Annual Meeting Pres. #2050

The EG12 Score:
A Potential Predictive Biomarker for Clinical Outcome

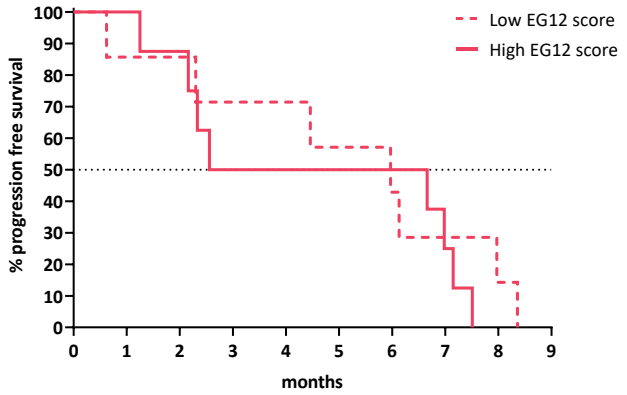
- A predictive biomarker is a measurable biological characteristic that provides information about the **likelihood of an individual patient to respond to a specific treatment**
- Analysis of tumor tissue revealed that the EG12 score **strongly and significantly correlated with PFS** in GLORIA patients 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)

NOX-A12 + Radiotherapy



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

Standard of Care



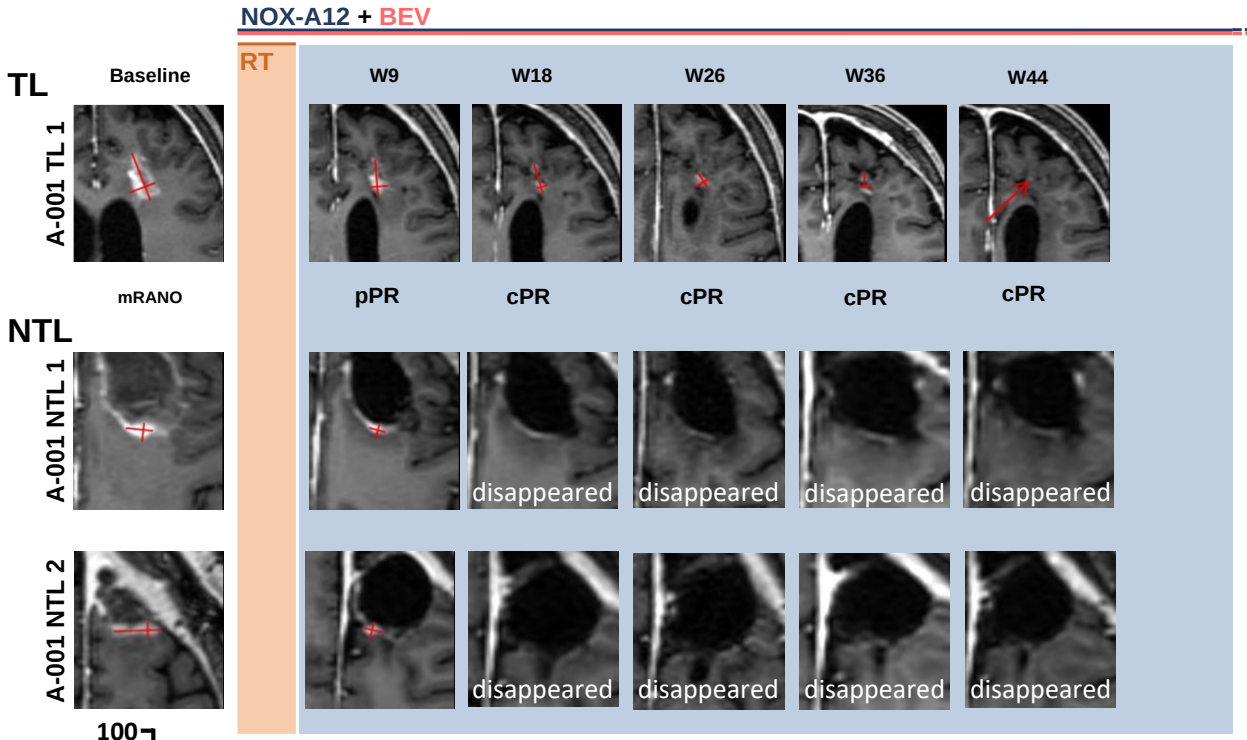
No significant difference in PFS (p=0.502; mPFS 4.6 vs. 6.0 months for EG12^{high} vs EG12^{low})

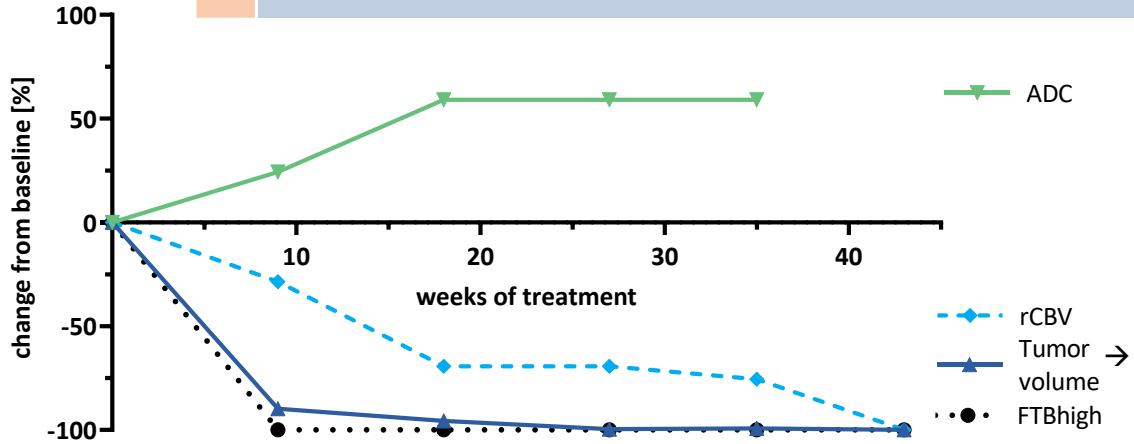
- There is also a **strong trend for the EG12 score to predict OS for NOX-A12 treated patients** (p=0.075)

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

Source: Giordano (2023) ASCO Annual Meeting Poster Presentation #405

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





→ **>99% reduction**

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

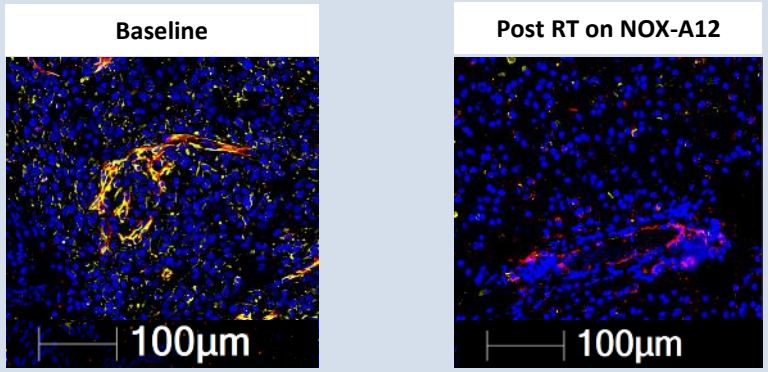
Changes from baseline
ADC: increase in change represents improvement
rCBV, Volume, FTBhigh: decrease in change represents improvement

cut off date: 01-Nov-2022

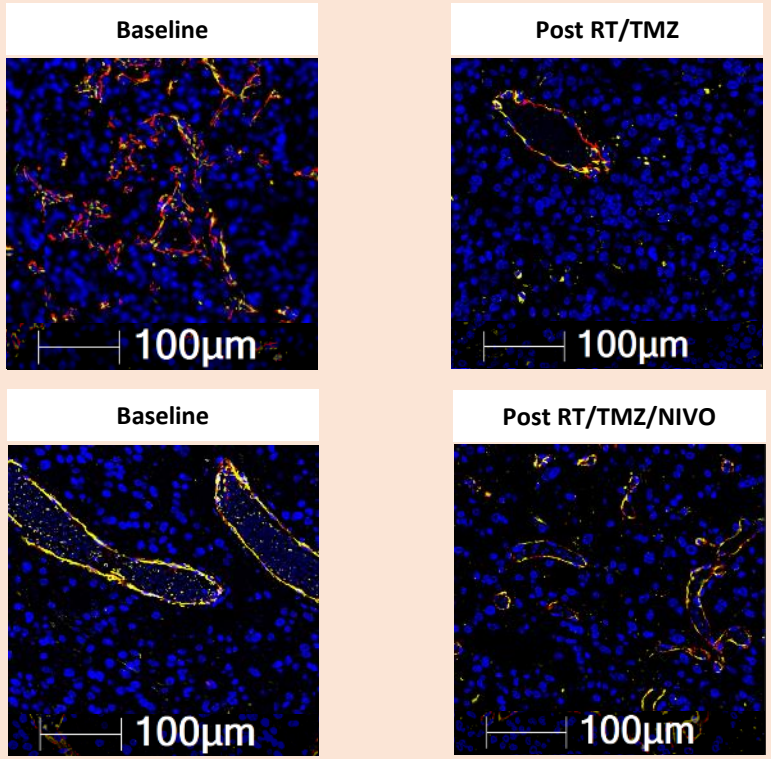
Sources: Giordano (2022) SNO Annual Meeting Poster Presentation #CTNI-67 & *TME Pharma* Press Release from 19 November 2022

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

GLORIA
C1-001

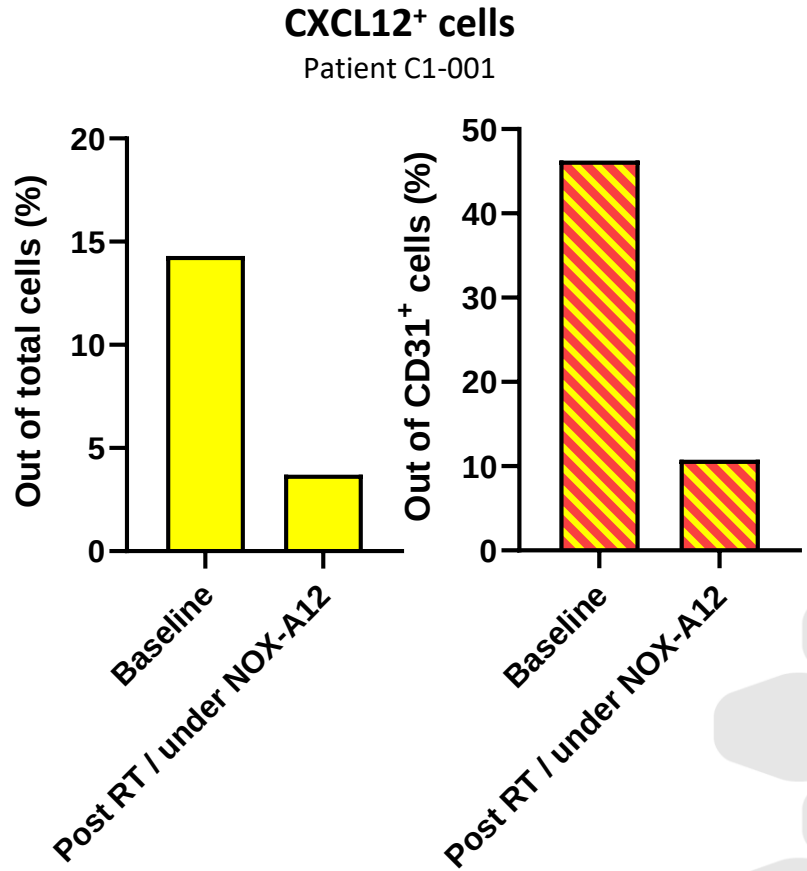


Reference patients



DAPI
CD31
CXCL12

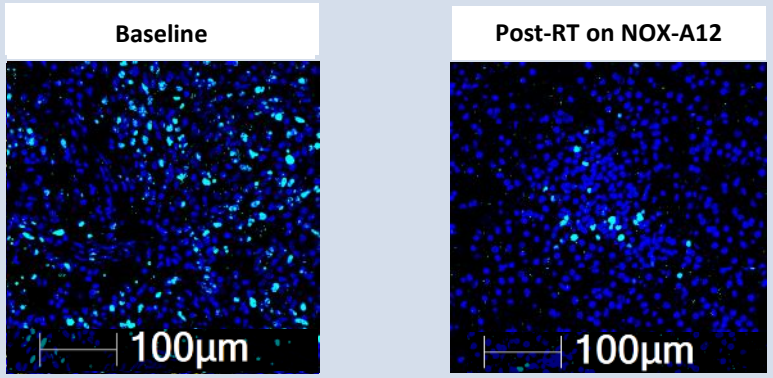
Images show areas of pathologist-confirmed tumor tissue



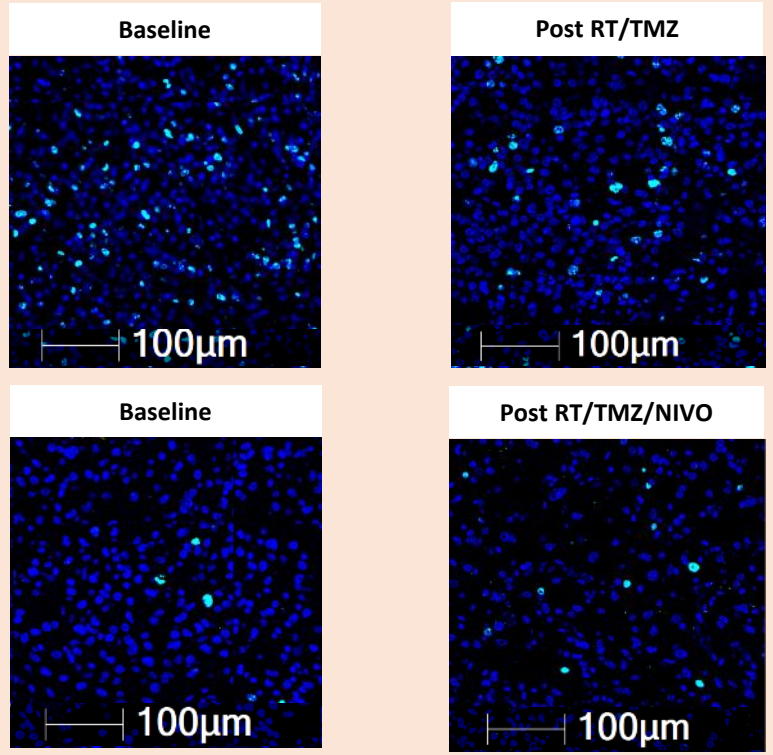
Source: Giordano (2021) Society for Neuro-Oncology 2021 Annual Meeting Presentation CTNI-43 – of phase I/II GLORIA trial (NCT04121455)

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

GLORIA
C1-001

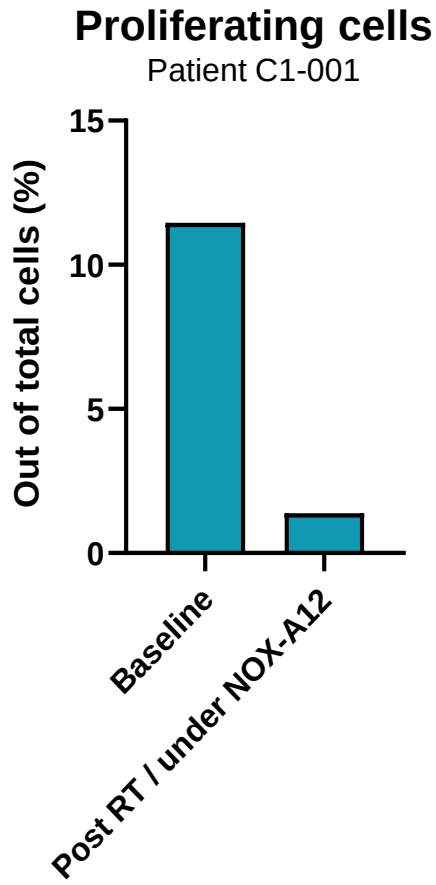


Reference patients



DAPI
Ki67

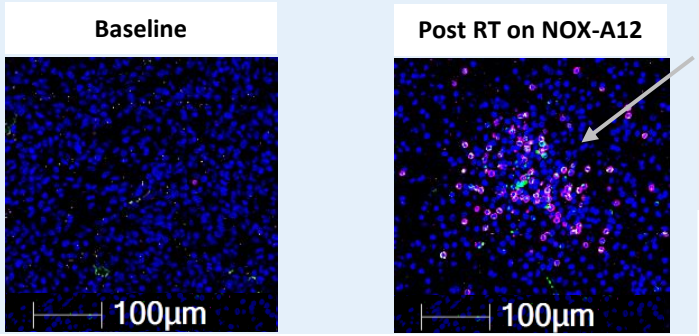
Images show areas of pathologist-confirmed tumor tissue



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

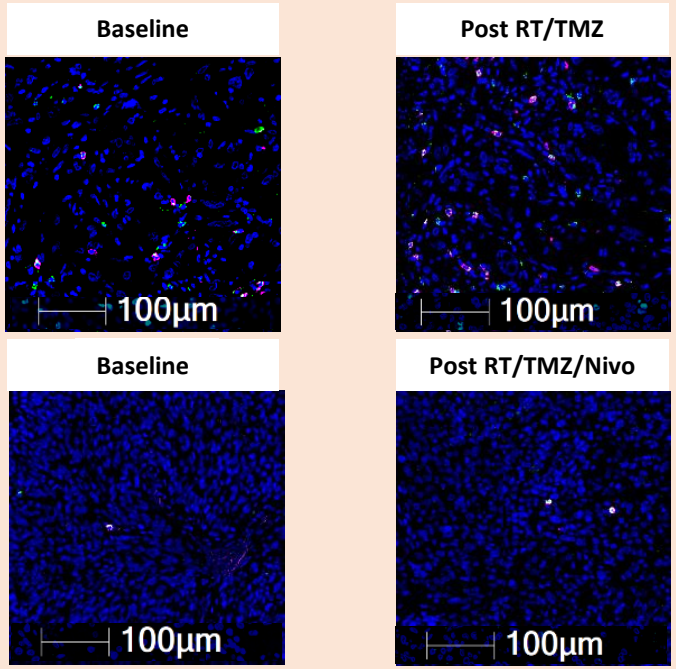
NOX-A12 + RT Lead to Extensive Penetration of Immune System (Cytotoxic T Cells) in the Tumor of GBM Patient

GLORIA
C1-001

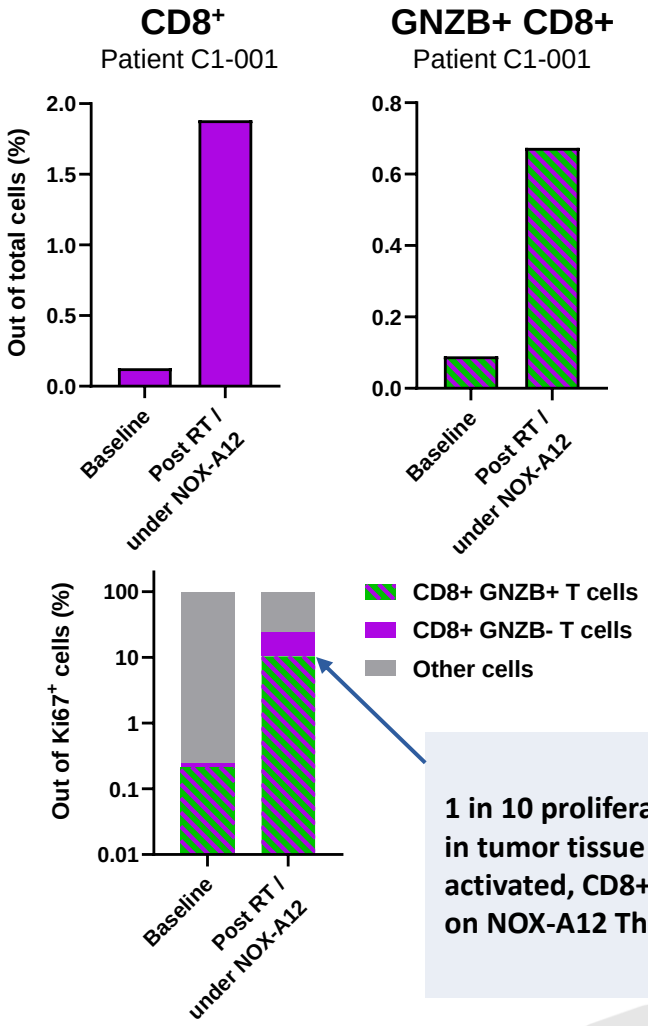


Clusters of Granzyme B positive, cytotoxic T cells consistent with coordinated immune response

Reference patients



DAPI
CD8
GNZB



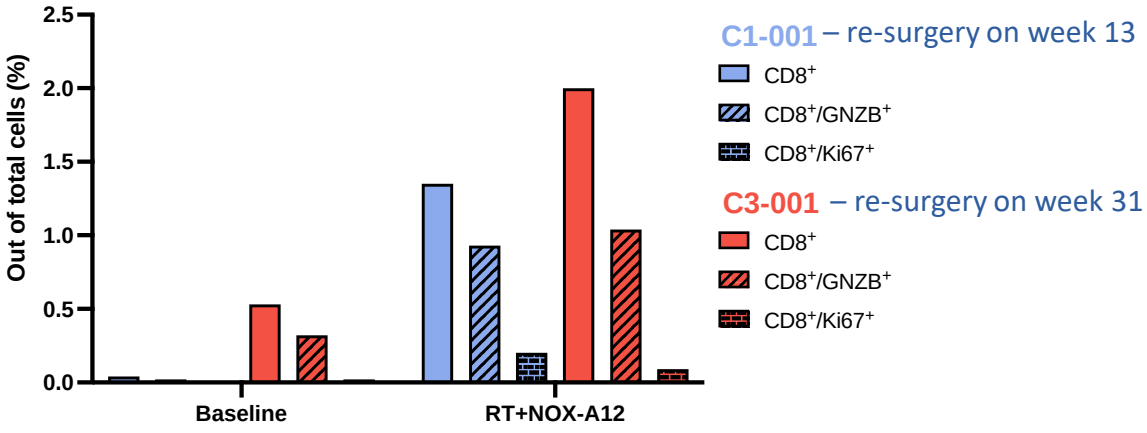
1 in 10 proliferating cells in tumor tissue are activated, CD8+ T-cells on NOX-A12 Therapy

Images show areas of pathologist-confirmed tumor tissue

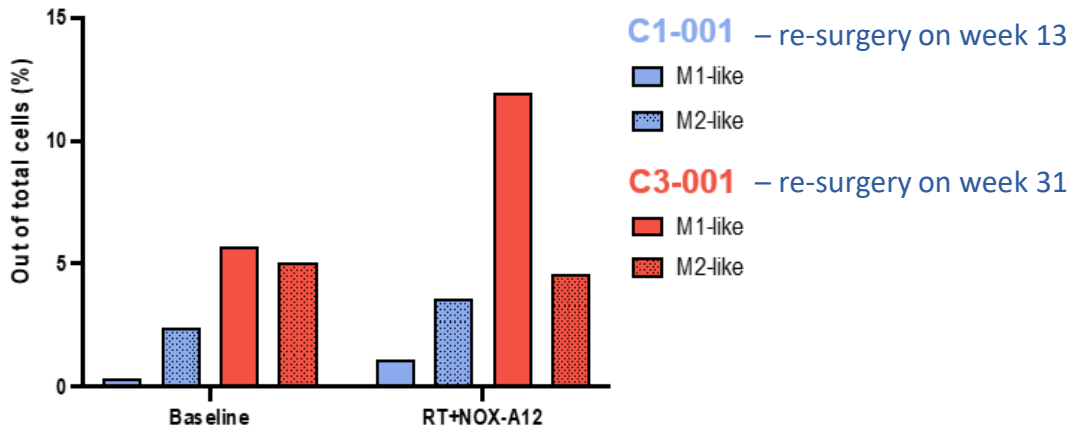
Source: Giordano (2021) Society for Neuro-Oncology 2021 Annual Meeting Presentation CTNI-43 – of phase I/II GLORIA trial (NCT04121455)

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)

Source: Giordano (2022) ASCO Annual Meeting Presentation #2050

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

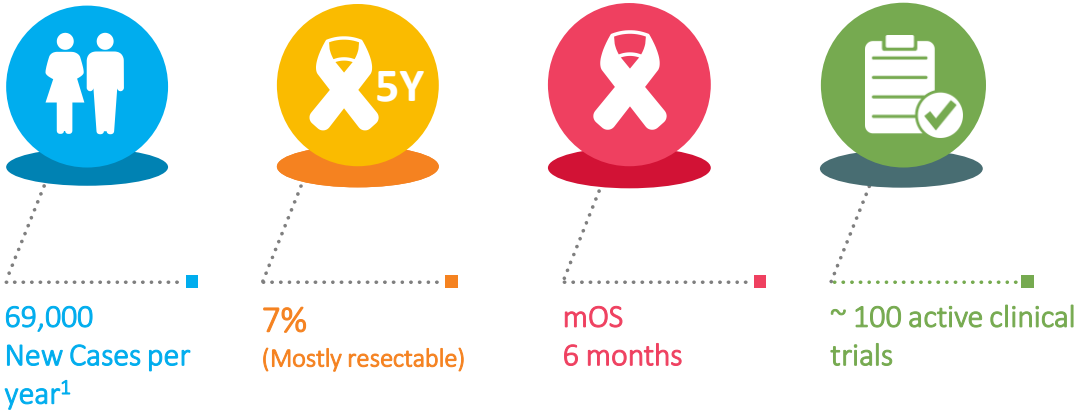
- **Good safety and tolerability** profile of all combinations
- Tissue analysis **confirms mode(s) of action**[2,3]
- **Potential biomarker identified** which is **predictive for PFS** in patients treated with NOX-A12 + RT[7]
- **Promising response rates** for the combination of NOX-A12 + RT and for NOX-A12 + RT + BEV[3,5]
- **Clinical outcome beyond expectation for the study population**[8]
- NOX-A12 + RT + BEV:
    - **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:**
    - **Open IND** for upcoming Phase 2 in newly diagnosed, chemotherapy-resistant glioblastoma with 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)

Sources: 1) Radiographic partial response; 2) Giordano (2021) Society for Neuro-Oncology 2021 Annual Meeting Presentation CTNI-43; 3) Giordano (2022) ASCO Annual Meeting Presentation #2050; 4) Wick, W. (2013) J. Clin. Oncol. Vol 31, 15 suppl 2002; 5) Giordano (2022) SNO Annual Meeting Poster Presentation #CTNI-67 & TME Pharma Press Release from 19 Nov 2022; 6) Disease control rate which also includes patients that had an increase of tumor size up to 25%; 7) Giordano (2023) ASCO Annual Meeting Presentation #405; 8) TME Pharma Press Releases 10 October 2023 and 20 October 2023, 2 February 2024, 2 April 2024

NOX-A12 + Immunotherapy in Pancreatic Cancer

Pancreatic Cancer – Extremely Low Overall Survival and Limited Treatment Options

LACK OF EFFECTIVE THERAPIES & LOW OVERALL SURVIVAL

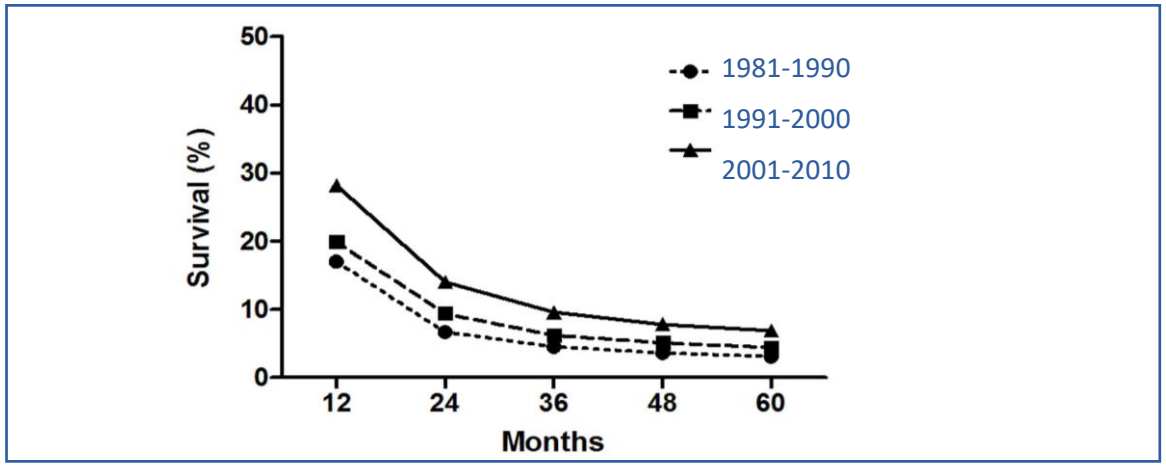


69,000
New Cases per year[1]

7%
(Mostly resectable)

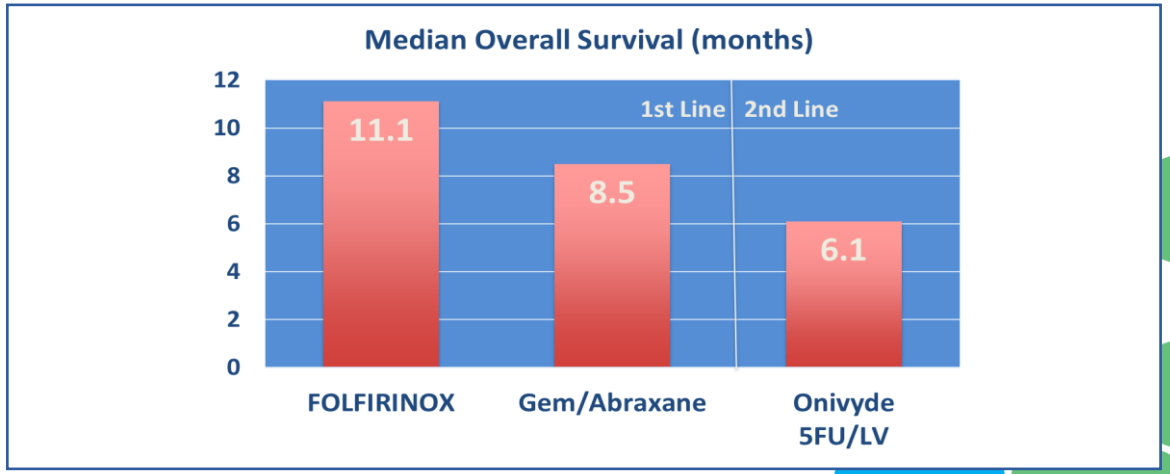
mOS
6 months

~ 100 active clinical trials



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



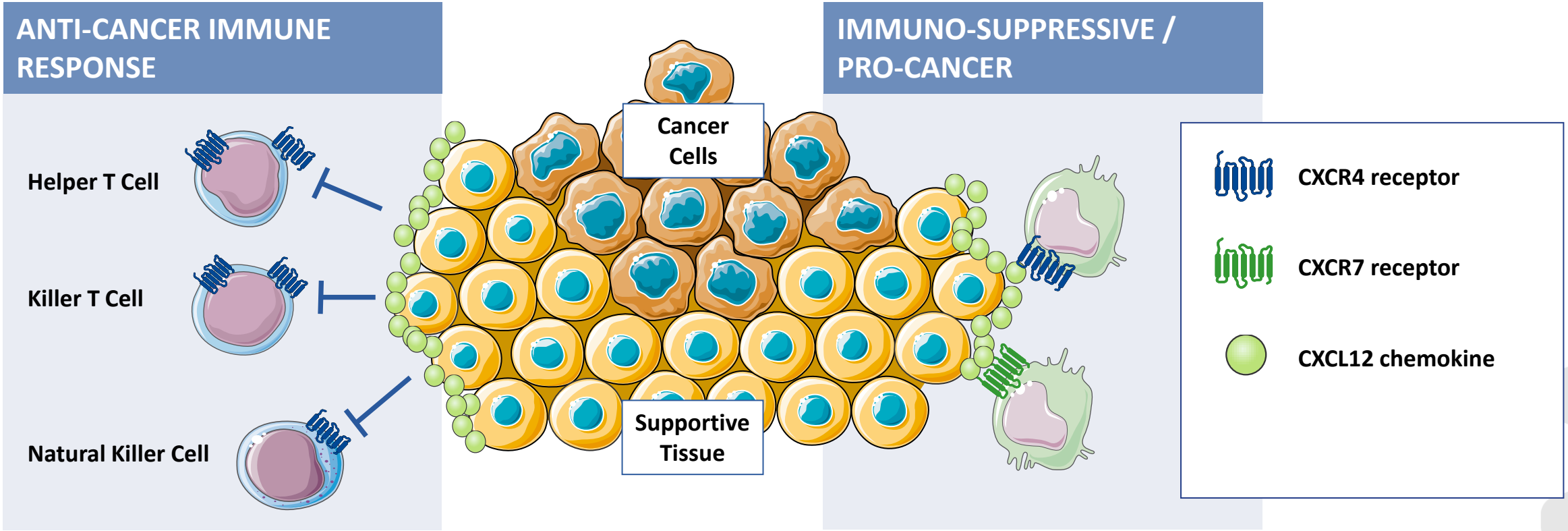
1. Second-line In the US, UK, FR, ES, DE & IT, 107k first-line. Global Data April 2022

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

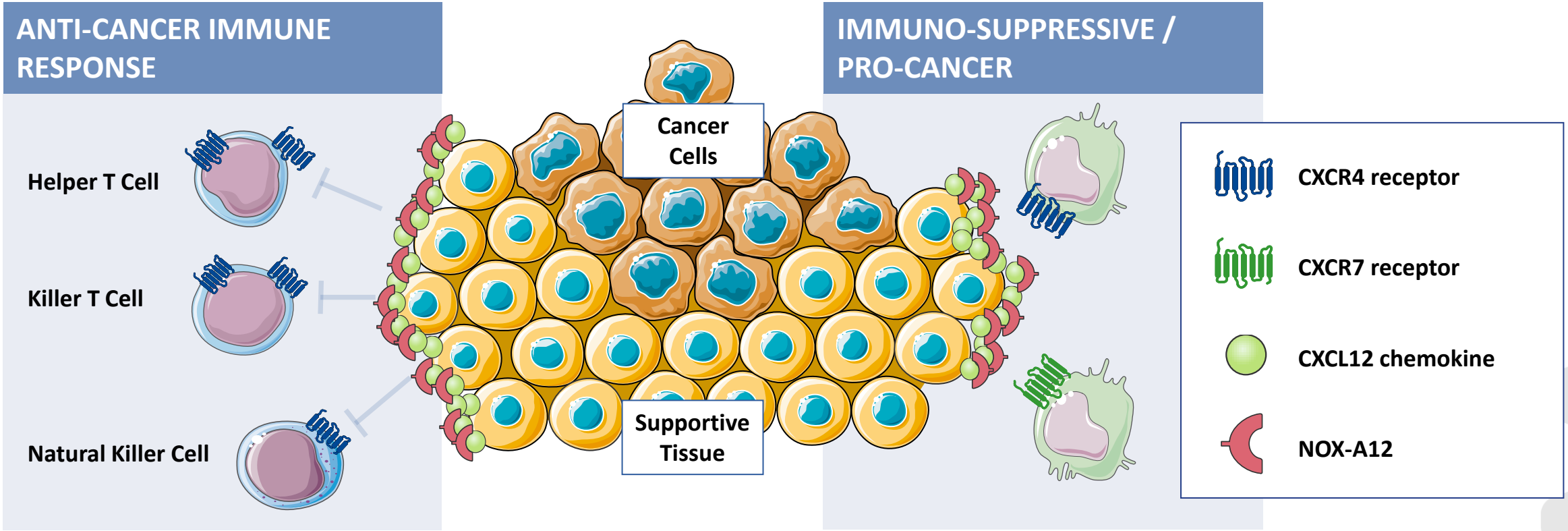


Sources: Feig 2013, PNAS 110:20212; Fearon 2014, Cancer Immunol Res 2:187; Liu 2014, Neuro-Oncology 16:21; *TME Pharma* data

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[1]



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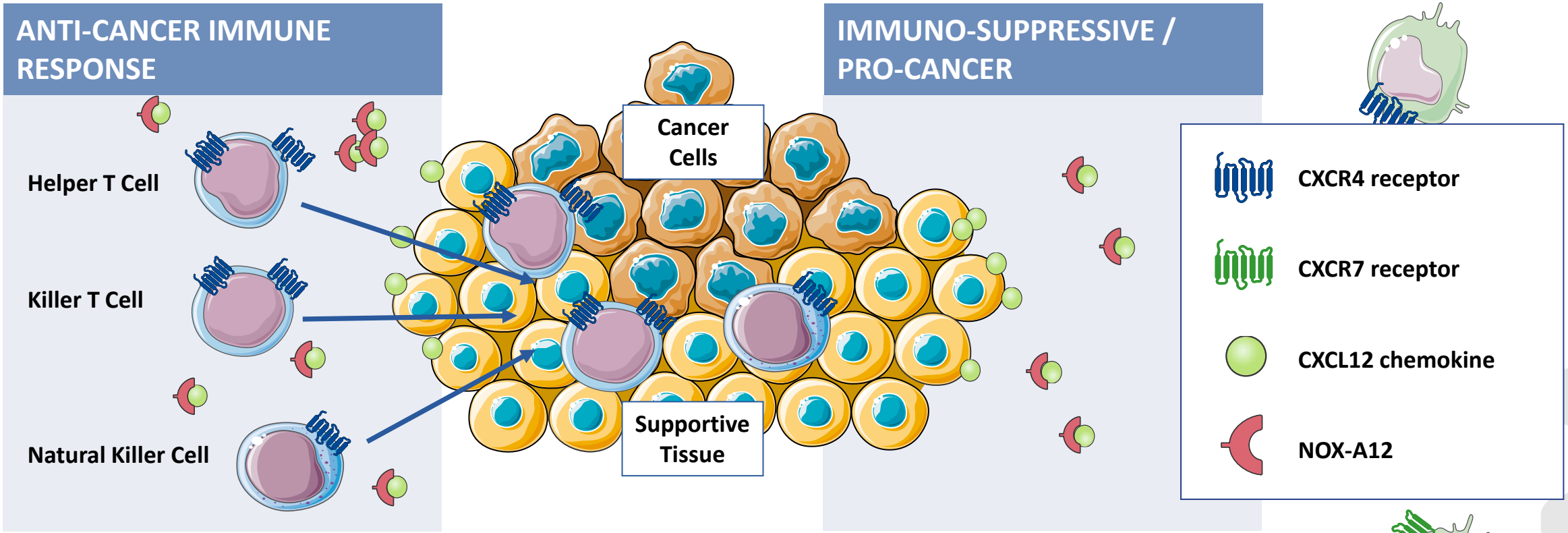


Sources: Feig 2013, PNAS 110:20212; Fearon 2014, Cancer Immunol Res 2:187; Liu 2014, Neuro-Oncology 16:21; *TME Pharma* data

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

Baseline tumor biopsy

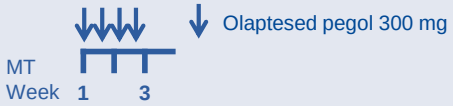
2nd tumor biopsy

NOX-A12

1 NOX-A12 **monotherapy** for 2 weeks

PRIMARY ENDPOINT:

Changes in the tumor microenvironment induced by NOX-A12: immune cells & cytokine/chemokine profile



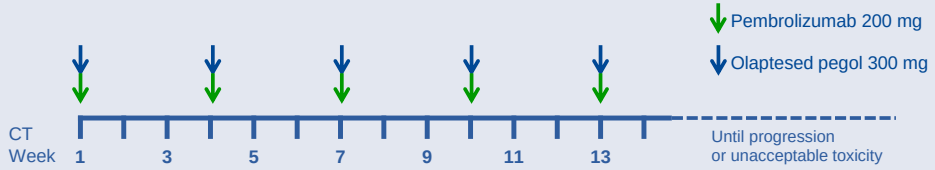
CXCL12 axis fully inhibited

NOX-A12 + Keytruda®

2 Patients from Part 1 then transitioned to **combination treatment** of NOX-A12 with checkpoint inhibitor until progression

ENDPOINT:

Assess safety and efficacy of combination



CXCL12 axis incompletely inhibited for at least 2 weeks per cycle

Clinical Trial a Scientific Collaboration with:

MERCK Be well

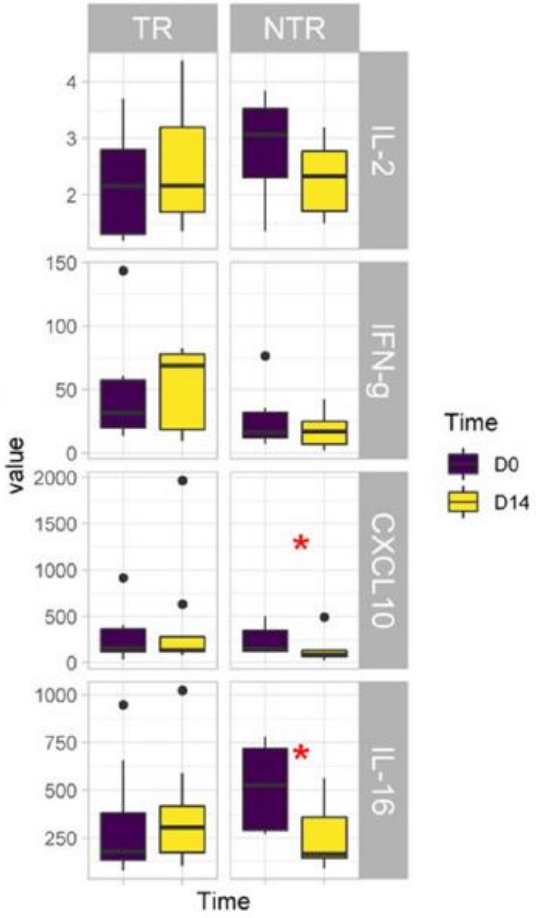
MSD

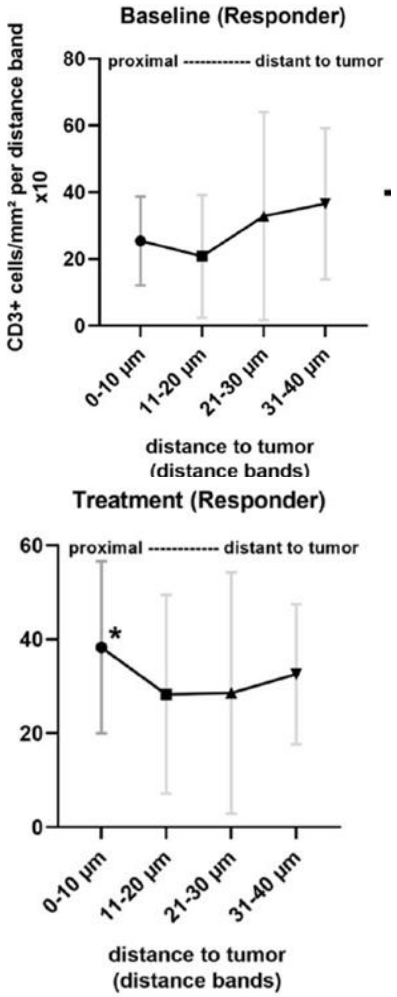
NCT

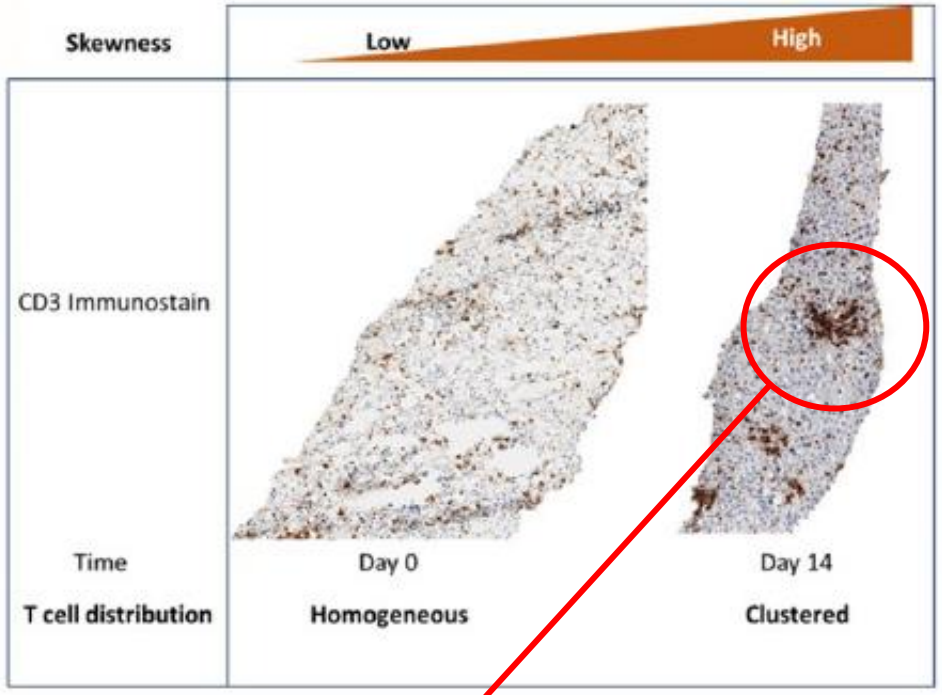
In PDAC / CRC Patients NOX-A12 Monotherapy Induces Integrated Immune Response and T Cell Clustering

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).





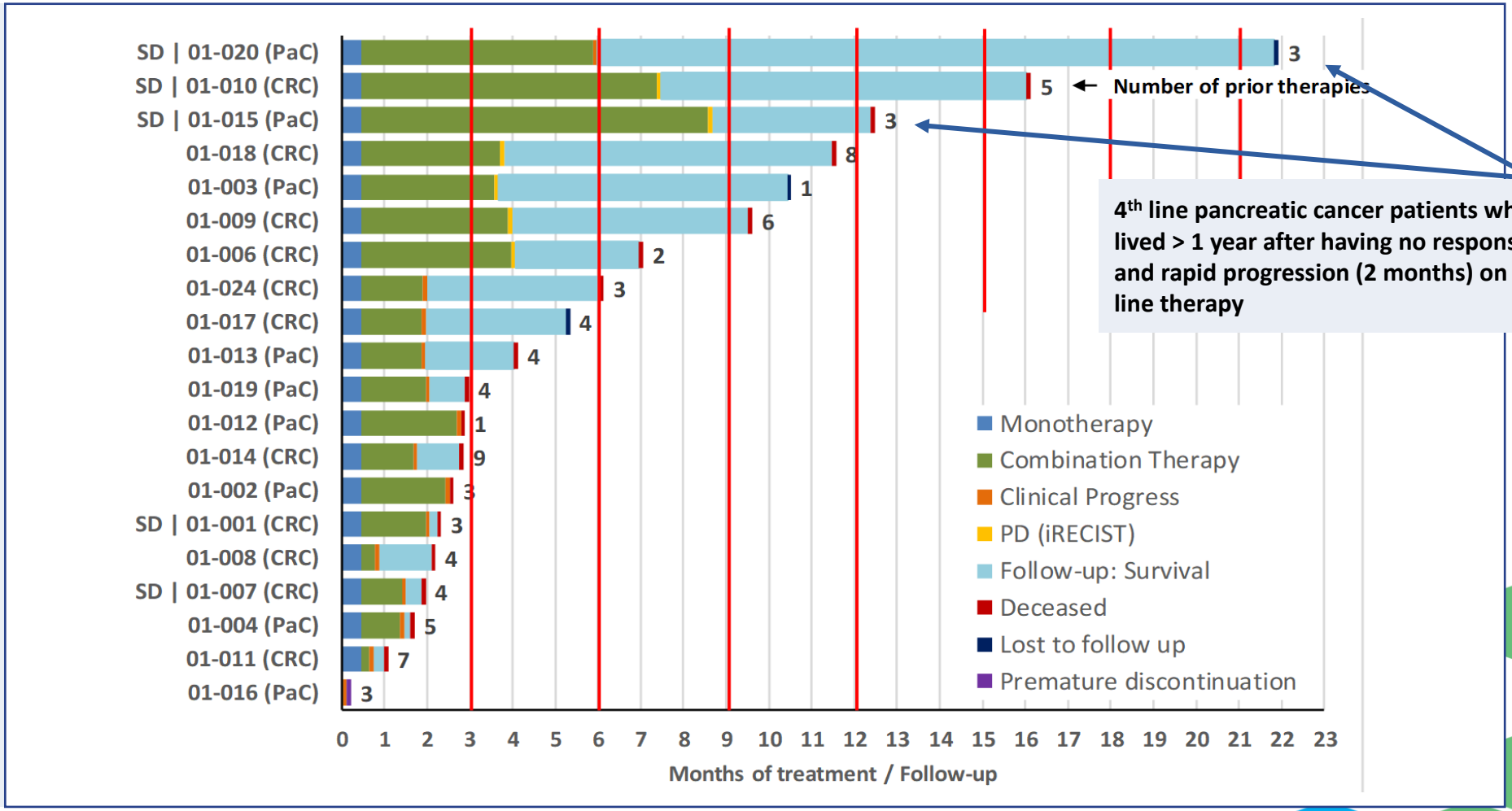


T-cell clustering in PaC/CRC patients on NOX-A12 monotherapy similar to that seen in glioblastoma patients while on NOX-A12 therapy post-RT with infiltration of proliferating GNZB+/CD8+ cells

Source: Suarez-Carmona 2021, J Immunother Cancer 9:e002505

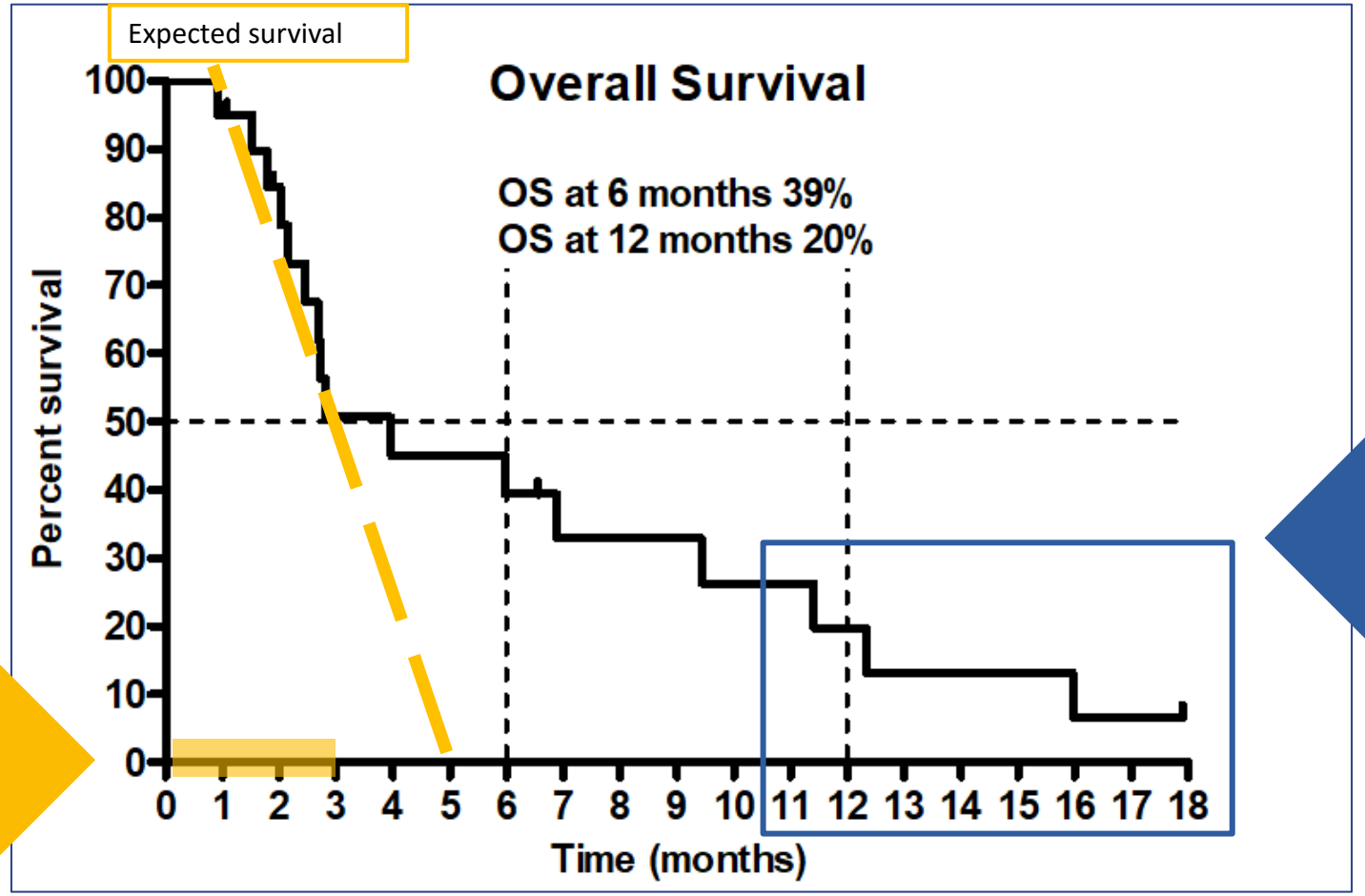
Impressive Survival in Heavily Pre-Treated Patients

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



Source: Suarez-Carmona M, et al. J Immunother Cancer 2021

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**

Source: Halama et al, Final Top-Line Data: CXCL12 inhibitor NOX-A12 and pembrolizumab in microsatellite-stable, metastatic colorectal or pancreatic cancer, ESMO Virtual Conference Poster 4103 Sept 2020

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

Source: *TME Pharma* Press Releases 23 June 2022 & 15 June 2023

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

	NOX-A12 Brain Cancer Fast Track & Orphan Drug Status Granted	NOX-A12 Pancreas Cancer
Target population US & EU – New cases per year	29,000	69,000 (2nd line) 107,000 (1st line)
Expected duration of treatment based on median OS	>12 months	>12 months
Total Addressable Market[1]	$2.5 bn (1st line)	$6bn (2nd line) $9.3bn (1st line)
Next inflection points	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.

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