NOXXON PHARMA

What's next in treatment of brain cancer patients? Testing NOX-A12 + Radiotherapy in a Phase 1/2 Clinical Trial

23 September 2019

ALNOX
EURONEXT GROWTH

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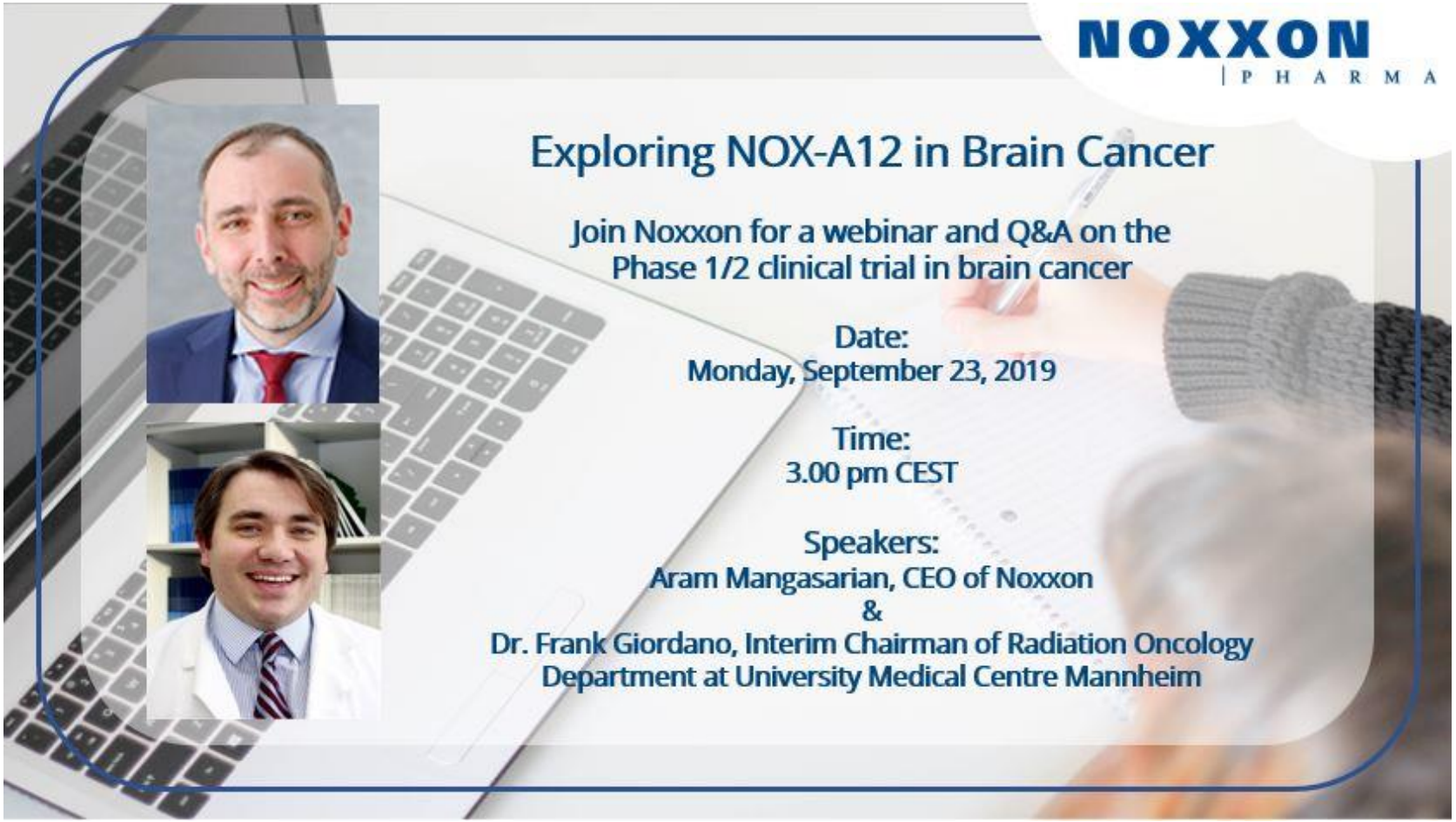
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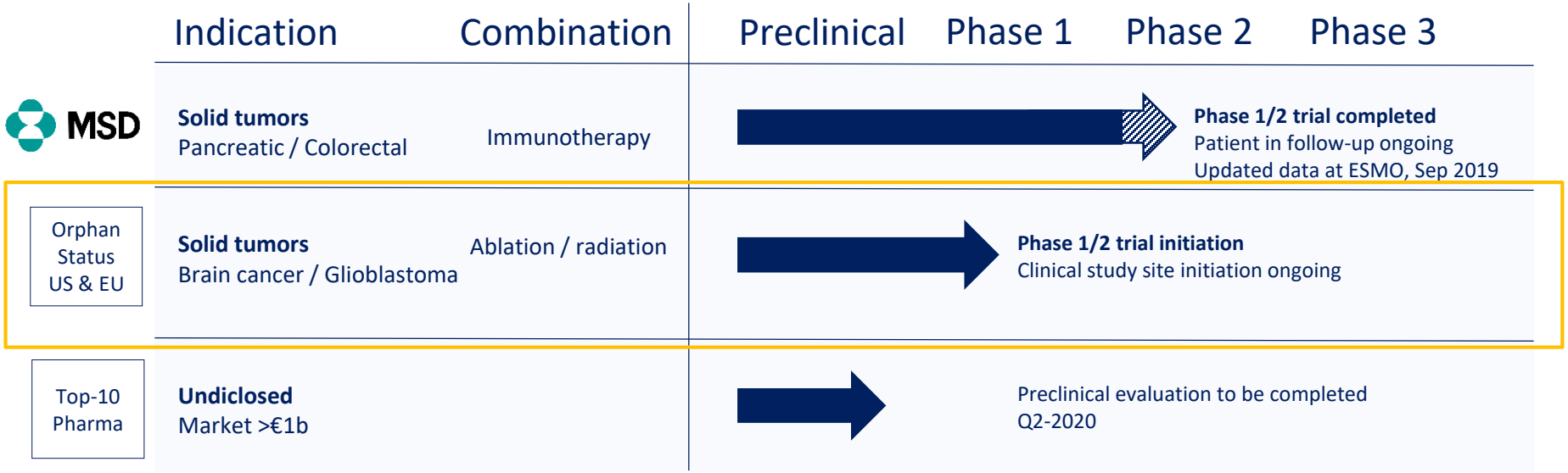
Exploring NOX-A12 in Brain Cancer
Join Noxxon for a webinar and Q&A on the
Phase 1/2 clinical trial in brain cancer
Date:
Monday, September 23, 2019
Time:
3.00 pm CEST
Speakers:
Aram Mangasarian, CEO of Noxxon
&
Dr. Frank Giordano, Interim Chairman of Radiation Oncology
Department at University Medical Centre Mannheim

Overview

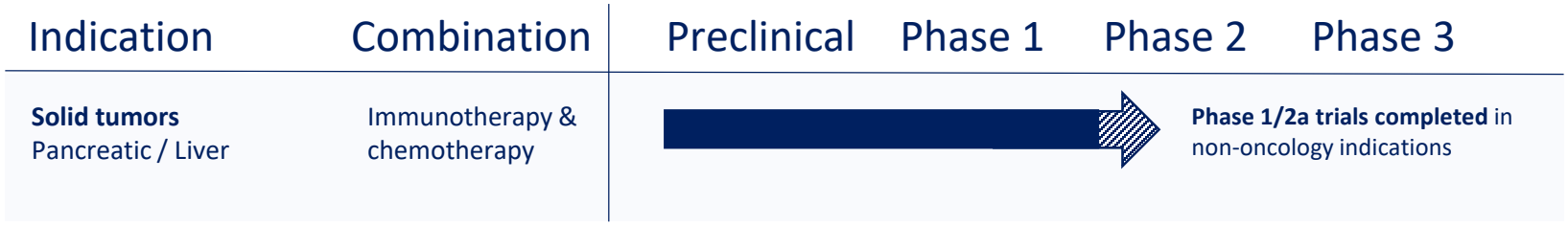
- **Glioblastoma**
  - Description
  - Standard of care
  - Medical need
- **Overview of recent clinical trials in Glioblastoma**
- **Glioblastoma tumor microenvironment**
- **NOX-A12 mechanism of Action**
- **Clinical trial testing NOX-A12 + radiotherapy**
  - Patient population
  - Trial design
  - Timelines

Pipeline Assets Leverage Existing Anti-Cancer Therapies to Optimize their Therapeutic Efficacy

NOX-A12



NOX-E36



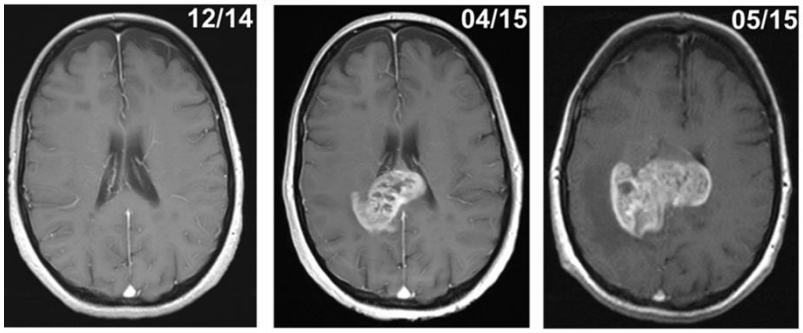
Trial to be completed by Noxxon

Trial to be completed with partner

All time-lines subject to financing

Background - Glioblastoma

- Glioblastoma (GB, WHO Grade IV astrocytoma) is the most malignant and aggressive of all brain tumors
- Despite surgery, radiotherapy and chemo-therapy, the survival rate of these patients has not been shown to increase significantly
- Etiology of the disease unknown
- Median age at diagnosis is 64 years, occurrence increases with age
- Age-adjusted incidence in the US is 3.19 per 100,000 persons
  → approx. 10,000 new cases per year



Effects of Patient Profile on Overall Survival and Progression-Free Survival

Surgical tumor removal	MGMT Methylation Status Methylated = benefit from chemotherapy Unmethlyated = no/little benefit from chemotherapy	Progression Free Surivial (PFS) Months	Overall Surivival (OS) Months
Incomplete	Unmethlyated	**6.1**	**9.7**
Total	Unmethlyated	**6.4**	**13.9**
Incomplete	Methylated	**7.6**	**17.9**
Total	Methylated	**10.2**	**25.2**

NOX-A12 + radiotherapy trial population

Source: Kreth (2013) Annals of Oncology 24: 3117–3123

Glioblastoma (GBM) Medical Need & Market

- Very poor prognosis
- Temozolomide (TMZ) sole approved option for 1st line therapy
- GBM with MGMT unmethylated promoter, i.e. more than half of all cases, is highly resistant to TMZ (no benefit from TMZ treatment)
- Malignant cells frequently migrate into adjacent brain tissue, making complete surgical resection difficult
- Current treatments often cause neurotoxicity

- GBM as entry route to blockbuster pharma development
- Worldwide sales of Temozolomide reached >1 billion USD
- Short prognosis of patients allows quick estimation of clinical efficacy
- Domino effect: efficacy in GBM results in evaluation in other cancers

Current Developments - Chemotherapy

Chemotherapy:

- Temozolomide chemotherapy during and after radiotherapy is standard of care
- A DNA repair protein called MGMT renders TMZ largely ineffective

What's new?

- "Classical" chemotherapy: German CeTeG trial showed that the addition of lomustine (CCNU) is beneficial in terms of OS in MGMT methylated patients
  → only positive chemo trial in GB for >13 years
- Targeted therapy: all trials failed since pathways are redundantly activated (EGFR, FGFR, MET, PDGFR, PI3K/AKT/mTOR and MAPK signaling pathways).
- Immunotherapy: showed weak single-agent efficacy but overall had no significant effects in patients with primary or recurrent GB.
  But the problems are known:
  - No trafficking of T cells into tumors
  - Ratio of immune suppressor cells to T cells is 1,000 : 1

Current Developments - Radiotherapy

External-beam radiotherapy (EBRT):

- Standard of care for all patients with GB, alone or in combination with chemotherapy
- Hypofractionated irradiation schemes for elderly patients

What's new?

- Radiotherapy can be focused to the tumor by improved on-board imaging (image-guided radiotherapy) and highly precise beam modulation (intensity-modulated radiotherapy, IMRT)
  → considerably lower toxicity if treated with IMRT
- Stereotactic radiosurgery has no role in GB treatment (no localized disease).
- Radiotherapy can elicit immune effects that were undetected until immune checkpoint inhibitors became available (abscopal effects)
  → a variety of trials are set up that combine RT with immune checkpoint inhibitors
- Intraoperative radiotherapy (IORT): alternative currently tested in Phase 3. Rationale: to deliver high single doses without the need to irradiate through healthy tissue.
- Proton or heavy ions: no data - all trials published so far were negative (one proton beam trial had even worse outcomes)

Current Developments - Immunotherapy

- **Vaccination Therapy:** One of the most promising approaches in GBM, although negative results from several phase II and III trials challenge the current concept of vaccination as a single modality immunotherapy

- **Checkpoint Inhibitors:** Promising therapeutic activity in preclinical models, but results from clinical trials in recurrent GB are disappointing; larger studies underway in newly diagnosed disease (recent failure of CheckMate-498 trial evaluating Opdivo/nivolumab plus radiation May 2019)

- **Oncolytic Viral Therapy:** This approach might exert pro-inflammatory responses that could potentially be exploited in future combined modality immunotherapy studies

- **CAR-T Cell Therapy:** The future of chimeric antigen receptor (CAR) T cell therapy for GBM depends on the identification of stably expressed and sufficiently expressed tumor-specific antigens

➢ ***Future immune-based strategies are focused on combinations of different immune checkpoint inhibitors with diverse treatment modalities that reverse local immunosuppression in the microenvironment, converting a 'cold' tumor into a 'hot' tumor[1]***

1- Lim 2018, Nat Rev Clin Oncol 15:422

The Glioblastoma Tumor Microenvironment
A major hurdle for current therapies

- **Glioblastoma is perceived as a poorly immunogenic[1], "cold" tumor with**
  - Only few tumor-infiltrating lymphocytes (TILs) that, moreover, express markers of exhaustion[2,3]
  - High numbers of myeloid cells, such as microglia and macrophages which probably have predominantly immunosuppressive activities[4]
  - Physical aspects that attenuate antitumor immune responses, e.g. necrosis which leads to hypoxic areas in which the resulting increase in extracellular K^+ concentrations can inactivate TILs[5]

BUT:

  - It has been known for decades that the CNS is subject to active immunosurveillance and vigorous immune responses[6]
  - Lymphatic vessels connect the brain with deep cervical lymph nodes where antigen presenting cells exiting the brain can prime T and B cells[7]

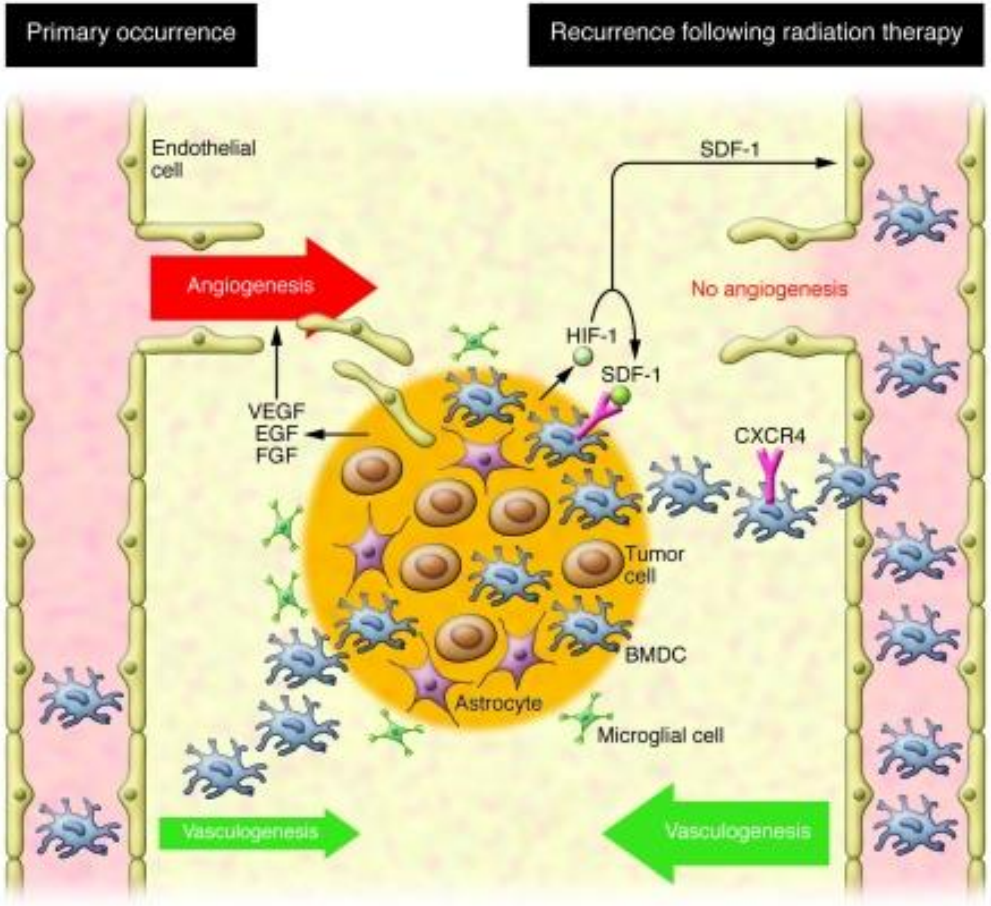
- **→ Although the CNS is an immunologically distinct site, its immune microenvironment offers opportunities to implement immunotherapy for treatment of brain tumors[8]**

1-Patel 2015, J Neurooncol 123:323; 2-Hao 2002, Acta Neuropathol 103:171; 3-Wherry 2011, Nat Immunol 12:492; 4-Li 2016, Genome Biol 17:174; 5-Eil 2016, Nature 537:539; 6-Waksman 1955, J Exp Med 102:213; 7-Louveau 2015, Nature 523:337; 8-Lim 2018, Nat Rev Clin Oncol 15:422

Attacking Glioblastoma by Blocking Key Tumor Micro-Environment (TME) Survival Mechanisms

Chain of events:

- *Irradiation induces SDF-1 (=CXCL12) expression in tumors*
- *SDF-1 is a chemoattractant that recruits myeloid cells into the tumor*
- *Myeloid cells then form new vessels that re-nourish the tumor*



Greenfield et al. 2010, J Clin Invest 120:663

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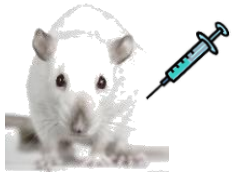
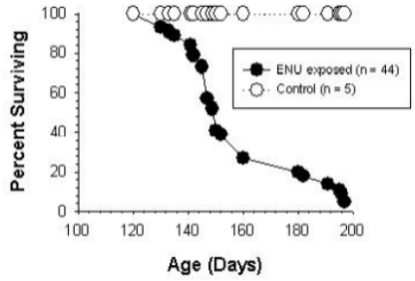
NOX-A12 + Radiotherapy Significantly Increases Survival and Demonstrates Complete Regression of Brain Tumors

Autochthonous brain tumor model in rats

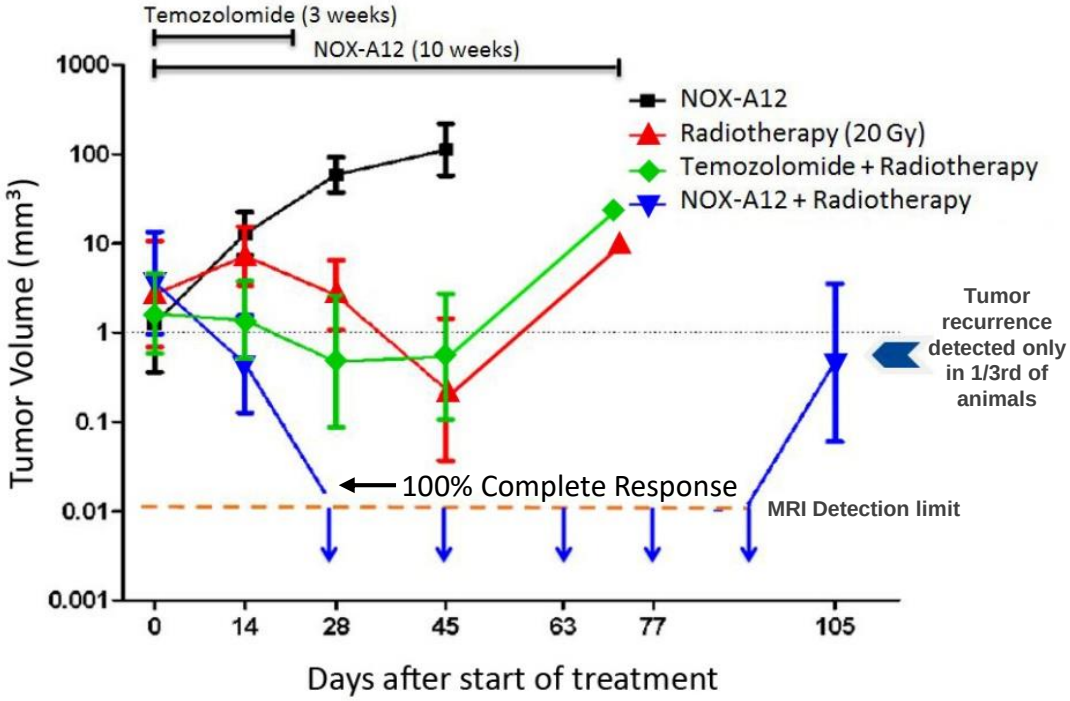


Pregnant rats: ENU on gestational age day 17 - 18



Key features:

- Spontaneous tumor development in immuno-competent host
- Diversity of tumor cell sensitivity comparable to human situation
- Refractory to standard therapies
- In the 2nd study, MRI was used and only rats with identifiable tumors were sorted into the groups



➢ **Combining NOX-A12 with irradiation shows treatment-duration driven efficacy and resulted in 100% complete response (66% durable)**

Source: Liu S-C et al., Neuro Oncol. 2014 Jan;16(1):21-8

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External Clinical Validation for CXCL12 Axis Interference in Glioblastoma: Reported at ASCO 2018

- **Phase I/II study assessing the impact of CXCR4 blockade**
  (PI: Lawrence D. Recht, Stanford, CA)

- **Population: newly diagnosed adult GBM patients**

- **Initial results (presented at ASCO 2018):**
  - 29 patients enrolled
  - It is safe to block the CXCL12-CXCR4 axis in GBM patients
  - Improved response to radiation therapy
  - Promising survival data (estimated median overall survival was 20.7 months)
  - **Out of field first recurrence rate of 58.8% compared to 10% in control group**

- **Study showed proof-of-concept of blocking the CXCL12-CXCR4 communication**

1. GBM: Glioblastoma
2. Reference: http://abstracts.asco.org/214/AbstView_214_230151.html

NOX-A12: Recruiting Phase 1/2 Trial 1st Line, Chemotherapy Resistant, Unresectable Brain Cancer with Radiotherapy

Overview Study population

- Newly diagnosed brain cancer (glioblastoma, recruit in cohorts of 3, wait for safety/efficacy signals after each triplet, then increase dose)
- Include only patients where standard of care chemotherapy temozolomide will not be active, and is thus not given
- Only patients with tumor remaining after surgery which allows imaging to assess efficacy
- For this population Progression-Free Survival (PFS) is 6 months and Overall Survival 10 months[1]

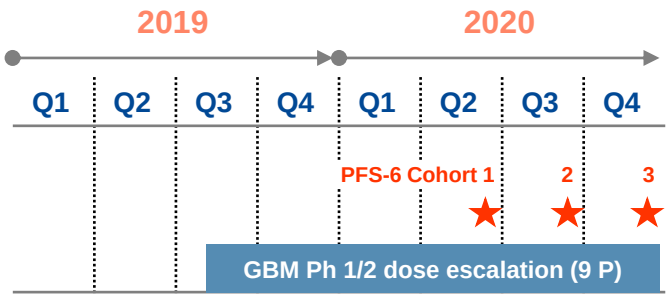
Primary objective and efficacy endpoints

- Safety of NOX-A12 in combination with radiation therapy (RT), definition of recommended Phase 2 dose

Secondary objectives and endpoints

- Efficacy of NOX-A12 in combination with radiation therapy: tumor vascularization, PFS-6, mPFS, mOS
- Pharmacokinetics and pharmacodynamics of NOX-A12 during and after administration

Planned Timeline



Timeline subject to financing recruitment rate

Regulatory Status

- Orphan drug status obtained for NOX-A12 + radiotherapy in US & EU
- Trial approved by competent regulatory authority in Germany

1. Kreth (2013) Annals of Oncology 24: 3117–3123

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Questions ?

Thank you.

For more information do not hesitate to contact us at

BrainCancerEvent@noxxon.com

Available Models of Glioma/ Glioblastoma and Their Strengths and Weaknesses

Model type	(Epi)genetic make up	Heterogeneity	Immuno-competent	Brain micro-environment	Blood brain barrier	Stable/ reproducible
ENU-induced murine tumors	**Partly relevant**	**Genetically heterogeneous, different neural cells may be initiator cells**	**Yes**	**Relevant**	**Yes**	**No – but diversity of fast-growing tumor types enhances translational relevance (Doblas, 2010 J. Mag. Reson. Imag.)**
GEMMs[1]	Partly relevant	Genetically homogeneous, initiator cell type dependent on promoter driving Cre expression	Yes	Relevant when Cre expression induced in CNS	Yes	Yes
PDX[2] (subcutaneous)	Partly relevant	Genetically homogeneous, but intratumoral heterogeneity (lack of pre-existent vasculature, hypoxia, angiogenesis dependence)	No	Non-relevant	No	Yes
PDX[2] (orthotopic)	Relevant	Partly heterogeneous, not known to which extent PDX models represent most aggressive parts of the originating tumor	No	Only relevant for PDXs that retained capacity to grow via diffuse infiltration	Yes	Yes
Cell lines (adherent)	Less relevant	No	No	Non-relevant	No	Yes
Cell lines (spheroids)	Possibly relevant	No	No	Non-relevant	No	Yes
Zebrafish	Non-relevant	No	No	Probably non-relevant	No	Yes
Canine	Possibly relevant	Yes	Yes	Relevant	Yes	No
Fruit fly	Non-relevant	No	No	Relevant	No	No

[1]GEMMS: enetically engineered mouse models with conditional expression of oncogenes/loss of tumor suppressor genes; [2]patient-derived xenografts

Adapted from Lenting 2017, Acta Neuropathol 133:263

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