Innovative Clinical Programs Targeting the Tumor Microenvironment to Improve Outcomes in Underserved Cancers

April 2019
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NOXXON: High-value Clinical Assets from de-risked RNA Platform

- NOXXON has translated a validated RNA-based platform into two clinical-stage drug candidates addressing critical molecular pathways to treat solid tumors

- **NOX-A12**: Targeting the adaptive immune system through the chemokine CXCL12, key player in the tumor microenvironment
  - Compelling activity and safety data from Phase 1/2 anti-PD-1 (pembrolizumab) combo trial in metastatic, microsatellite-stable colorectal and pancreatic cancer, collaboration with Merck & Co./MSD
  - Company primed to start 1st line brain cancer trial combining NOX-A12 and radiotherapy in Q2-2019

- **NOX-E36**: Complementary MoA targeting the innate immune system through the chemokine CCL2 involved in recruitment of immuno-suppressive tumor associated macrophages
  - Established safety and on-target activity in multiple non-oncology clinical trials
  - Preclinical data showing monotherapy activity in solid tumors

- Committed team with clinical, regulatory and business development experience

- Strong IP position: Key patent families cover composition of matter on NOX-A12 and NOX-E36

- Focused on demonstrating clinical impact in indications with high need and commercial potential
Recent News

- **21 November 2018** - Noxxon to launch NOX-A12 with radiotherapy clinical trial in patients with brain cancer [Press Release]

- **1st February 2019** - New data published supporting monotherapy activity of CCL2 inhibitor NOX-E36 in an additional solid tumor type: liver cancer [Press Release] [Article]

- **1st April 2019** - NOXXON presents updated results from Phase 1/2 NOX-A12 / Keytruda combination trial at AACR 2019 [Press Release] [Article]
Team with Strong Commitment

Dr. Aram Mangasarian  
CEO

- 18 years biotech experience in EU, moved NOXXON to a lean oncology focused profile with listing on Euronext Growth
- Headed Business Development at Novexel - €150m licensing deal with Forest Labs on avibactam; company bought by AstraZeneca for $505m
- Ran Business Development at ExonHit Therapeutics; closed $30m discovery and development alliance with Allergan

Dr. Jarl Ulf Jungnelius  
CMO

- Oncologist with more than 25 years clinical and research experience in large pharma and academic organizations
- Leadership positions at Celgene, Pfizer, Takeda and Eli Lilly & Company
- Significant role in the approval of multiple successful oncology drugs including Abraxane®, Gemzar®, Alimta® and Revlimid®

Dr. Mauizio PetitBon  
Chairman

- General Partner and co-founder of Kreos Capital
- Leadership positions at PMA Europe, SRI International, Emerson Electric Digital Equipment and Xerox
- Over 30 years of experience in tech sector
- Doctor’s degree in mechanical engineering from the University of Rome and MBA from INSEAD in Fontainebleau, France.

Supervisory Board

- Dr. Hubert Birner
  TVM Capital
- Dr. Don deBethizy, Independent, Chairman of Albumedix & Board member arGEN-X NV, Newron Pharma SPA, Proterris
- Bertram Köhler
  DEWB
- Dr. Walter Wenninger, Independent, former management board member Bayer
NOXXON’s proprietary compounds target core chemokines modulating the **tumor microenvironment** (TME) which has been confirmed as a key contributor to tumor growth and survival (“address the soil not just the weed”)

- Altering the TME is a core approach to break tumor survival mechanisms and improve therapeutic impact from standard of care and address treatment-resistant patient sub-populations

- The modified RNA approach creates stable, injectable oligonucleotides, resistant to nuclease degradation that directly bind and neutralize protein targets

- Potential of RNA-based cancer therapy approaches is now accepted: the science and medical practice has caught up to the vision of NOXXON

*Although chemokines and their receptors were originally identified as mediators of inflammatory diseases, it is being increasingly recognized that they serve as critical communication bridges between tumor cells and stromal cells to create a permissive microenvironment for tumor growth and metastasis.*

F. Guo et al. Oncogene 2016
Pipeline Assets Leverage Existing Anti-Cancer Therapies to Optimize their Therapeutic Efficacy

<table>
<thead>
<tr>
<th>NOX-A12</th>
<th>Indication</th>
<th>Combination</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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<td>Solid tumors</td>
<td>Pancreatic / Colorectal</td>
<td>Immunotherapy</td>
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<td>Phase 1/2 trial completed</td>
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<td>Orphan Status</td>
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<td>Ablation / radiation</td>
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<td>Targeted for Q2 2019</td>
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<th>NOX-E36</th>
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<th>Phase 3</th>
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<td>Solid tumors</td>
<td>Pancreatic</td>
<td>Immunotherapy &amp; chemotherapy</td>
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<td>Phase 1/2a trials completed in non-oncology indications</td>
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<td>Trial to be completed by Noxxon</td>
<td>Trial to be completed with partner</td>
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NOX-A12 Overview

- **NOX-A12 neutralizes the chemokine CXCL12, a key player in the TME**
  - NOX-A12 blocks binding of CXCL12 to both receptors CXCR4 and CXCR7 and neutralizes anchor domain
  - CXCL12 plays an important role in tumor vasculogenesis & angiogenesis, proliferation and chemo-resistance
  - Levels of CXCL12 correlate with poor prognosis in many tumor types

- **NOX-A12 has a strong safety & tolerability profile & clear PK/PD profile**
  - Tested in >135 subjects in Phase 1/2 development
  - Dose-dependent mobilization of tumor cells in 56 hematological cancer patients (CLL & MM)

- **Two core programs to solidify scientific rationale with ability to expand**
  - Combination trial with anti-PD-1 (Keytruda®) in pancreatic and colorectal cancer
  - Combination with radiotherapy in brain cancer

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2. Liu 2014, Neuro-Oncology 16:21
Prior clinical experience in hematological cancers: dose dependent mobilization & improved responses
NOX-A12 – Completed Phase 2a in Relapsed MM
Clear PKPD & Improved Rate and Quality of Responses vs. Competitors

**Study design: Phase 2a trial in MM**

- Single-arm study in 28 patients with relapsed MM
- Treatment regimen: NOX-A12 + Velcade® (bortezomib) (V) and dexamethasone (D)
- Primary endpoint: overall response rate (ORR) after 6 months
- Results:
  - ORR of 68% with 25% CR + vgPR
  - ORR of 60% in bortezomib pre-treated patients
  - Combination regimen well tolerated
  - NOX-A12 did not add any significant tolerability or safety burden to underlying regimen

**NOX-A12 improved ORR as a combination therapy compared to other studies**

<table>
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<tr>
<th>Treatment</th>
<th>ORR</th>
<th>CR</th>
<th>vgPR</th>
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<tbody>
<tr>
<td>V +/- D</td>
<td>40%</td>
<td>1%</td>
<td>1%</td>
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<tr>
<td>VD + Mozobil</td>
<td>40%</td>
<td>40%</td>
<td>40%</td>
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<td>VD + UPM</td>
<td>51%</td>
<td>35%</td>
<td>40%</td>
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<tr>
<td>VD + NOX-A12</td>
<td>68%</td>
<td>18%</td>
<td>43%</td>
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**Dose-dependent myeloma cell mobilization**

- Rapid dose-dependent mobilization of plasma/myeloma cells at 1 hour post-NOX-A12
- Mobilization lasting for up to 72 hours post-NOX-A12

**NOX-A12 had an overall response rate of 68% compared to 40-51% for similar studies in multiple myeloma**

NOX-A12 – Completed Phase 2a in Relapsed CLL Compares Favorably with BTK and PI3-K Inhibitors

Trial design

- Open-label, single arm Phase 2a study with 28 relapsed CLL patients with background therapy of Bendamustine and Rituximab (BR)
- Treatment:
  - During 4 to 6 cycles NOX-A12 was dosed at the highest individually titrated dose
  - BR administered IV at 375 mg/m² on day 1 of 1st 28-day cycle and 500 mg/m² on day 1 of subsequent cycles
  - Bendamustine (70 - 100 mg/m²) given IV on days 2-3 (cycle 1) or days 1-2 (cycles 2-6) of each 28-day cycle following BR
- Safety & tolerability:
  - Combination regimen well tolerated
  - NOX-A12 did not add any significant tolerability or safety burden to underlying regimen

Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>N = 28</th>
<th>12 female (43%)</th>
<th>16 male (57%)</th>
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<tr>
<td>Age</td>
<td>41 – 79</td>
<td>Mean = 66</td>
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<td>Binet stage</td>
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<td>A:</td>
<td>6 (21%)</td>
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<tr>
<td>B:</td>
<td>11 (39%)</td>
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<td></td>
</tr>
<tr>
<td>C:</td>
<td>11 (39%)</td>
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<tr>
<td>Prior treatment</td>
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</tr>
<tr>
<td>1 line</td>
<td>17 (61%)</td>
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<tr>
<td>2 lines</td>
<td>10 (36%)</td>
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<tr>
<td>3 lines</td>
<td>1 (4%)</td>
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<tr>
<td>Fludarabine / Bendamustine</td>
<td>Naïve</td>
<td>5 (18%)</td>
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<tr>
<td>Risk Status^5</td>
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<tr>
<td>High risk</td>
<td>10 (36%)</td>
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</table>

Response rate compares favourably to BR alone and to novel BR combinations

<table>
<thead>
<tr>
<th>Source</th>
<th>ORR:</th>
<th>Company Data</th>
<th>Historical Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>86%</td>
<td>BR + NOX-A12</td>
<td>59%</td>
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<tr>
<td>2</td>
<td>75%</td>
<td>BR alone</td>
<td>68%</td>
</tr>
<tr>
<td>3</td>
<td>72%</td>
<td>BR + ibrutinib</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>65%</td>
<td>BR alone</td>
<td>68%</td>
</tr>
</tbody>
</table>

BR = Bendamustine and Rituximab
NOX-A12 + Keytruda® in metastatic MSS Pancreatic & Colorectal Cancer
Completed Phase 1/2 Trial in MSS Colorectal & Pancreatic Tumors

**Overview**

- **Phase 1/2 proof-of mechanism/concept trial in 2 indications:**
  - Colorectal cancer (MSS)*
    - 11 patients
  - Pancreatic cancer (MSS)*
    - 9 patients
- **Response rate in targeted patient population to anti-PD-1 alone ~0%**
- **Regulatory scientific advice will be planned when data available**

* MSS = microsatellite stable

**Patient Profile**

- Patients with progressive disease (PD) after multiple prior lines of therapy.
- Best response to previous treatment was progressive disease in 95% of cases
- Micro-satellite stable disease where checkpoint inhibitors (CPI) are not efficacious

**Scientific Collaboration with**

1. Clinicaltrials.gov trial NCT03168139
2. Topalian 2012 NEJM Jun 28;366(26):2443-54

**Trial Design**

**Part 1**

NOX-A12 Induction

1. Tumor biopsy before and after NOX-A12 treatment for 2 weeks

**Part 2**

NOX-A12 + Keytruda®

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

**Primary endpoint:**

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

**Endpoint:**

Assess safety and efficacy of combination

**Top-Line Data**

- In MSS metastatic pancreatic and colorectal cancer patients with impaired immune systems and a high tumor load that have failed multiple prior lines of therapy, NOX-A12 plus Keytruda® shows induction of immune response (Th1) and clinical benefit, manifesting as stable disease (SD) and prolonged time on treatment vs. prior therapy

- **Link to Poster**
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Colorectal Cancer (CRC)</th>
<th>Pancreatic Cancer (PaC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7 / 4</td>
<td>8 / 1</td>
</tr>
<tr>
<td>Age: mean (range)</td>
<td>63 (55 – 73)</td>
<td>67 (48 – 82)</td>
</tr>
<tr>
<td>Stage at study entry</td>
<td>100% stage IV (metastatic) w/ liver mets</td>
<td></td>
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<tr>
<td>Microsatellite status at study entry¹</td>
<td>All patients MSS</td>
<td></td>
</tr>
<tr>
<td>Prior lines of systemic treatment: mean (range)*</td>
<td>5 (2 – 9)</td>
<td>3 (1 – 5)</td>
</tr>
<tr>
<td>Patients with prior surgery (# of surgeries)</td>
<td>7 (1 – 4)</td>
<td>3 (1 – 2)</td>
</tr>
<tr>
<td>Best response last treatment²</td>
<td>PD (10), SD (1)</td>
<td>PD (9)</td>
</tr>
<tr>
<td>Time since last systemic prior treatment (mean)</td>
<td>2.0 months</td>
<td>1.5 months</td>
</tr>
</tbody>
</table>

¹ MSS = Microsatellite Stable; ² PD: progressive disease; SD: stable disease

* excluding surgery

Source: Halama et al 2018 ESMO IO Poster 463 Presentation 84P
NOX-A12/Keytruda® Patients presented with low T cell density in tumors which has been shown to be predictive of poor patient outcome

- CD3+ T cell counts at baseline should be 600 /mm² or more at the invasive margin of the tumor for a strong immune response¹

- Only one patient in the NOX-A12/Keytruda® study – CRC patient 010 who had stable disease – presented above this threshold with 603 CD3+ T cells / mm²

- Mean CD3+ T cell number in patients at invasive margin 327/mm² at baseline²

- Mean CD11b+ myeloid cell number in patients at invasive margin 145/mm² at baseline²

- Impaired immune responses in these heavily pretreated patients combined with heavy tumor burden make this an exceptionally difficult population for immunotherapy modalities

NOX-A12 Target, CXCL12, Abundantly Expressed in All Pancreatic and Colorectal Tumor Tissues Tested

- Immunohistochemical staining shows abundant presence of CXCL12 (brown stain) in tumors of all patients

- CXCL12 positive cell types are tumor cells, monocytic-macrophage-like cells, and stromal cells (i.e. fibroblasts)
Increased Neutralization of CXCL12 in Tumor Tissue Correlates with a Favorable Cytokine Profile and Disease Stabilization

- Increased CXCL12 levels in all post-treatment tumor biopsies indicate penetration of NOX-A12 into the tumor
- Higher changes of CXCL12 levels in tissue observed upon monotherapy – indicating more complete CXCL12 neutralization – correlated with a favorable cytokine profile (Th1 response) and clinical benefit
- It is warranted to optimize the dosing regimen in subsequent trials; the NOX-A12 regimen in this study leaves ample room to explore greater exposures

**Box Plot**
- Colorectal cancer
- Pancreatic cancer

**Increased CXCL12 levels = increased binding and neutralization of CXCL12 by NOX-A12 which prolongs half-life**

**Source:** Halama et al 2018 ESMO IO Poster 463 Presentation 84P
NOX-A12 monotherapy leads to beneficial changes in the tumor microenvironment after 14 days of treatment:
- Increase in concentrations of key cytokines (IL-2 / IFN-γ / IL-16) is indicative of Th1 response
- Th1 response, activation of cytotoxic CD8+ T cells and also of CD4+ T helper cells was found for approx. half of the patients

Decrease in concentrations of IL-1α/β and IL-6 indicative of reduced presence or activity of myeloid-derived immunosuppressive cells

Decrease in Th1 signature cytokines and CXCL10 indicates a decrease of T cell attraction to and activation in the tumor

Source: Halama et al 2018 ESMO IO Poster 463 Presentation 84P
Unexpectedly High Number of Patients with Long Time on Study

- Overall survival (OS) 48% at 6 months and 33% at 12 months

Source: Halama et al., AACR 2019, Poster CT092 / 16, Session PO.CT03
Disease Stabilization Following NOX-A12 + Keytruda® Therapy Seen in Highly Pretreated and Rapidly Progressing Patients

Regardless of the number of prior lines of therapy or outcome of prior therapy, patients can still derive benefit extending expected progression-free survival time.

Duration Prior Treatment and OPERA Treatment

*Patients with stable disease only*

| Source: Halama et al 2018 ESMO IO Poster 463 Presentation 84P |
|-------------------------|-----------------|-----------------|-----------------|
| **Ratio**               | **Prior lines of treatment** | **Best response last treatment** | **Best response OPERA study** |
| 4.6                    | 3                | PD              | SD              |
| 3.1                    | 3                | PD              | SD              |
| 2.1                    | 3                | PD              | SD              |
| 0.2                    | 4                | SD              | SD              |
| 2.5                    | 5                | PD              | SD              |

SD, Stable disease; PD, Progressive disease
Comparison Time-on-Treatment: NOX-A12 + Keytruda® vs. Prior Therapy Shows Extensions up to 10-fold

- Potential benefit from NOX-A12/pembrolizumab treatment is not limited to early lines or successful previous treatment\(^1\)
- Ratios of > 1.3 are remarkable early findings for immunotherapy in microsatellite stable patients where no clinical benefit is expected\(^2\)

1. Halama 2011, Cancer Res 71:5670
2. Halama et al 2018 ESMO IO Poster 463 Presentation 84P
NOX-A12/Keytruda Shows Favorable Overall Survival in Pancreatic and Colorectal Cancer Patients

- NOX-A12/Keytruda® overall survival compares favorably with approved drugs tested in earlier lines of therapy in metastatic pancreatic and colorectal cancer\(^1\)

1. Onivyde (2nd line pancreas cancer agent): overall survival (OS) at 12 months ~22%; Lonsurf (3rd line CRC agent): OS-12 months ~27%; Stivarga (3rd line CRC agent): OS-12 months ~25%. Source: US FDA approved product labels.
NOX-A12 does not add to pembrolizumab safety profile

Ample Room to Optimize NOX-A12 Dosing

- All adverse events (AEs) are listed which were reported by at least two patients
- All reported serious adverse events (SAEs) are listed
- Six AEs are potentially related to NOX-A12, thereof one SAE (diarrhea)
- No Grade 4 adverse events were reported
- One death / Grade 5 adverse event due to tumor progression (General physical health deterioration)
- Preferred terms including SAEs are indicated by an asterisk (*)
- Percentages are based on the total number of patients

### System Organ Class

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
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<tbody>
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<td>Nausea</td>
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<td>General physical health deterioration</td>
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<td>Cholestasis</td>
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<td>Hyperbilirubinaemia</td>
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<td>Dyspnoea*</td>
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<td>Pruritus</td>
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<td>Myalgia</td>
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<td>Leukocytosis</td>
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<td>Hypothyroidism</td>
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<td>Wound dehiscence*</td>
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<td>Hypertension*</td>
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AEs: adverse events ; SAEs: serious adverse events
Source: Halama et al., AACR 2019, Poster CT092 / 16, Session PO.CT03
NOX-A12 plus Keytruda® Shows Induction of Immune Response and Clinical Benefit

- NOX-A12 target CXLC12 is abundantly present in tumor lesions, and NOX-A12 penetrates into the tumor and neutralizes the chemokine
- Level of CXCL12 neutralization correlates with immune response and disease control
- NOX-A12 monotherapy triggers cytokine signatures consistent with Th1 type response making the tumor ‘hotter’
- Unexpectedly high number of patients with long time on study for the high number of prior therapies and low T cell density at invasive margin at baseline
- Comparison of time-on-treatment: NOX-A12 + Keytruda® vs. prior therapy shows extensions up to 10-fold
- Disease stabilization following NOX-A12 + Keytruda® therapy seen in highly pretreated and rapidly progressing patients (27% CRC, 22% PaC)
- NOX-A12 does not appear to add to the AE profile of Keytruda® in advanced cancer patients

In MSS metastatic PaC and CRC patients with impaired immune systems and a high tumor load that have failed multiple prior lines of therapy, NOX-A12 plus Keytruda® shows induction of immune response and clinical benefit, manifesting as stable disease and prolonged time on treatment

Further studies are warranted with optimized NOX-A12 dosing and potentially additional targeting of myeloid-derived immunosuppressive cells with NOX-E36

Abbreviations: MSS: Microsatellite Stable; PaC: Pancreatic cancer; CRC: Colorectal cancer; AE: adverse events
Source: Halama et al 2018 ESMO IO Poster 463 Presentation 84P & accompanying NOXXON Pharma Press Release 14 Dec 2018
NOX-A12 + Radiotherapy in Brain Cancer
Recently, we have learned that glioblastomas recover efficiently after radiotherapy through recruiting mononuclear cells from the bone marrow, which then induce new vessels and hogtie immune cells that could fight the tumor. Through inhibiting the CXCL12 axis, the main communication signal of the tumor to these cells, NOX-A12 could make a significant impact in this most aggressive form of cancer, breaking its survival mechanisms.”

Frank A. Giordano
Vice Chair & Associate Professor, Radiation Oncology, University Medical Center Mannheim
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
Combining NOX-A12 with irradiation significantly reduced the influx of monocytes/macrophages into breast cancer-derived brain metastases and delayed tumor progression which translated into prolongation of survival.
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
Strong Support for NOXXON Approach at KOL event
On 4 Sept 2018 in Frankfurt

Key Opinion Leader Event

Novel Concepts to Tackle the Most Aggressive Form of Brain Cancer

Frank A. Giordano, MD
Vice Chair & Associate Professor, Dept. of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg

Martin Glas, MD
Professor and Head, Division of Clinical Neurooncology, Dept. of Neurology and Neurooncology Centre at the West German Cancer Centre, University Hospital Essen

Ulrich Herrlinger, MD
Professor of Clinical Neurooncology and Head, Division of Clinical Neurooncology, Department of Neurology and Center for Integrated Oncology, University of Bonn

Frederik Wenz, MD
CEO and CMO, University Medical Center Mannheim, Professor and Chairman, Dept. of Radiation Oncology, University Medical Center Mannheim, University of Heidelberg

Link to slides
NOX-A12: Planned Phase 1/2 Trial 1st Line, MGMT Unmethylated, Unresectable GBM with Radiotherapy

Overview Study population

- 9 patients with newly diagnosed glioblastoma multiforme (recruit in cohorts of 3, wait for safety/efficacy signals after each triplet)
- Include only patients with unmethylated MGMT promoter (no activity of temozolomide – therefore not given)
- Biopsy-only or partial tumor resection (to have an imaging correlate to assess for efficacy)

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

Planned Timeline

- 2018
  - Q1
  - Q2
  - Q3
  - Q4
- 2019
  - Q1
  - Q2
  - Q3
  - Q4
- 2020
  - Q1
  - Q2
  - Q3
  - Q4

GBM Ph 1/2 dose escalation (9 P)

PFS-6 Cohort 1 2 3

Regulatory Status

- Orphan drug status obtained for NOX-A12 + radiotherapy in US & EU

Timeline subject to financing and regulatory approvals
NOX-E36 in Solid Tumors
NOX-E36 – A Phase 2-ready Monotherapy Oncology Drug Candidate

- **Targeting a core tumor survival mechanism, preventing Tumor Associated Macrophage (TAM) recruitment**
  - NOX-E36 binds and neutralizes CCL2 (MCP-1) and three other related chemokines\(^1\) implicated in creating immune privilege of tumors via recruitment of tumor associated macrophages (TAMs)
  - TAMs have been recognized to play a crucial role in tumor survival strategies by repressing other immune cell activity, encouraging blood and lymph vessel development to support growing tumors, and help cancer cells metastasize to new sites in the body

- **De-risked program with good clinical safety profile and strong scientific rational**
  - NOX-E36 has demonstrated its safety, tolerability and activity on CCR2+ monocytes in Phase 1 and a non-oncology Phase 2\(^2\) in 175 subjects/patients
  - Data from Pfizer’s CCR2 antagonist in pancreatic cancer patients suggests that even partial inhibition this axis translates into improved efficacy\(^3\)
  - A rodent version of NOX-E36 prevents recruitment of TAMs, enhances cytotoxic T cell infiltration and reduces tumor burden in pancreatic and liver cancer models\(^4\)

- Providing potentially best in class pharmacology on monocyte/macrophage chemokines in the Innate PD-1 Resistance Signature (IPRES)\(^5\) through activity on CCL2, CCL8 and CCL13

- Ready to move into proof-of-concept studies in cancer patients

---

NOX-E36 Prevents Recruitment of TAMs, Enhances Cytotoxic T cell Infiltration and Reduces Tumor Burden in a Pancreatic Cancer Model

Statistically significant decrease in TAM infiltration in mNOX-E36 group

Model: Syngeneic PDAC in immunocompetent mice

Trend towards higher CD8 T cell infiltration in mNOX-E36 group

Trend towards smaller tumor size in established tumor group

Reduced tumor volume in mice treated after tumor establishment

Source: J. Lazarus et al. (2017) Poster PT165 A Novel CCL2 Inhibitor Reduces Tumor Associated Macrophage Infiltration in a Murine Model of Pancreatic Cancer. Society of Surgical Oncology 70th Annual Cancer Symposium
mNOX-E36 Shows Monotherapy Activity in Hepatocellular Cancer Model

Objective of Research
- Exploration of the effect of CCL2 inhibition on angiogenesis in a model for hepatocellular cancer (HCC)

Methods
- Two-hit fibrosis-HCC model, induced with diethylnitrosamine exposure after birth and repetitive CCl4 injections.
- Mice were treated with mNOX-E36 or inactive control Spiegelmer revmNOX-E36 from week 8-16

Results
- Treatment with mNOX-E36 inhibited the infiltration of CCR2+ tumor-associated macrophages
- Treatment with mNOX-E36 reduced pathogenic vascularization, hepatic blood volume and subsequently tumor volume, as measured by contrast-enhanced micro-computed tomography

Conclusions
- Angiogenesis-promoting inflammatory macrophages are responsible for progression from fibrosis to HCC
- Blocking their recruitment by CCL2 inhibition might be beneficial in HCC prevention/treatment

mNOX-E36 reduces pathogenic vascularization

Hepatic vascular microstructure Ex vivo µCT imaging

mNOX-E36 reduces tumor volume
### Phase I Clinical Trials Overview

<table>
<thead>
<tr>
<th>Trial No. /Status</th>
<th>Type</th>
<th>Design</th>
<th>Treatment groups</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SNOXE36C001</strong></td>
<td><strong>Phase I</strong></td>
<td>Single center, double blind, placebo-controlled</td>
<td>Single dose, i.v.: 0.03-2.0 mg/kg</td>
<td>Safe and well tolerated</td>
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<tr>
<td><strong>Completed</strong></td>
<td><strong>First in human</strong></td>
<td>Single ascending doses</td>
<td>Single dose, s.c.: 0.25, 0.5 mg/kg</td>
<td>MTD not reached</td>
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<td><strong>n=72 (56+16)</strong></td>
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<td>Healthy volunteers</td>
<td>Placebo</td>
<td>Dose-linear PK</td>
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<td></td>
<td>Safety, PK &amp; PD</td>
<td>All healthy subjects</td>
<td>PD effect on CD14+ /CCR2+ monocytes</td>
</tr>
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</table>

| **SNOXE36C101**         | **Phase Ib**    | Multi center, double blind, placebo-controlled | Multiple dose, i.v.: Healthy subjects: 0.25 mg/kg, q2d, over 15 days | Safe and well tolerated                          |
| **Completed**           | **Multiple dose** | Multiple ascending doses                | Patients: 0.0625-0.25 mg/kg, q2d, over 27 days | MTD not reached                                  |
| **n=48 (36+12)**        |                 | Healthy volunteers & T2DM patients      | 12 healthy subjects, 36 diabetics | Dose-linear PK                                    |
|                         |                 | Safety, PK & PD                        |                           | PD effects on CD14+ /CCR2+ monocytes              |

| **SNOXE36C201**         | **Phase I**     | Multi center, open label                | Single dose, s.c.: 0.25 mg/kg | Safe and well tolerated                          |
| **Completed**           | **Renal impairment** | Single dose                           | Patients with normal, mildly, moderately & severely impaired renal function | No relevant impact of renal function on PK       |
| **n=33**                |                 | Healthy & renally impaired patients    | 8 per renal function group   | → no dose adjustment required                     |
|                         |                 | PK, safety                             |                           |                                                  |
Phase 2 Data: Strong Activity of NOX-E36 on CCL2 Chemokine Axis and CCR2+ Monocytes Which Become TAMs

UPON TREATMENT WITH NOX-E36:

- The presence of the CCL2 receptor, CCR2, on the monocytes is reduced 4 to 5-fold
- The number of monocytes in peripheral blood decreases by 15-20%

NOX-E36 – Key Messages

- Generally Safe and well tolerated following i.v. and s.c. administration with 175 subjects having received NOX-E36
- Clear pharmacodynamic effect of on circulating monocyte populations including those thought to become TAMs
- No competitor with comparable pharmacology on monocyte/macrophage relevant chemokines in Innate PD-1 Resistance Signature (IPRES) in industry pipeline
- Compound ready to move into proof-of-concept studies in cancer patients
NOXXON: Corporate Profile & Financials

- **NOXXON Pharma NV** is a Dutch management holding company listed on Euronext Growth Paris (ALNOX) and located in Berlin, Germany
- **NOXXON Pharma AG** is the operational subsidiary from which all clinical development is carried out and where all intellectual property is held
- ~10 employees, headquarters in Berlin, Germany

### Financials and Shareholding structure

- Market capitalization: **~€8 million** (at 22 March 2019)
- Cash: **~€4.3 million** as of 31 December 2018\(^1\)
- Projected cash burn: **~€525K/month\(^1\)** (including the NOX-A12/Keytruda\(^\circ\) clinical trial and NOX-A12 + radiotherapy brain tumor trial)
- Most important remaining dilutive instruments are the warrants in hands of Acuitas, Yorkville and Kreos as well as the ESOP

![Shareholding structure chart]

* Rounded to one decimal place, based on information received for 2019 EGM and taking into account shares issued in Dec. 2018

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\(^1\) NOXXON Pharma NV Annual Financial Report, published 12 April 2019
NOXXON Opportunity

- Validated and de-risked anti-cancer approach targeting the **tumor microenvironment** through potent activity on the adaptive (NOX-A12) and innate (NOX-E36) immune system

- **Lead program NOX-A12 + radiotherapy in brain cancer** trial initiation places NOX-A12 on fast-track in high-value indication with minimal investment needed

- **Next NOX-A12 trial in pancreatic / colorectal cancer** has potential for breakthrough designation and market authorization, ideal opportunity for partner

- **NOX-E36 monotherapy potential**: Targeting the chemokine CCL2 involved in recruitment of immuno-suppressive tumor associated macrophages, **clear rationale for solid tumor clinical trials**

- **Lean and focused organization**, management and Supervisory Board committed to translating these assets into value for investors
Contact

Aram Mangasarian, CEO
E-mail: amangasarian@noxxon.com