Targeting the Tumor Microenvironment to Enhance the Effectiveness of Cancer Therapies

Oct 2017
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### Who Are We?

**Aram Mangasarian, PhD - Chief Executive Officer**
- Formerly Chief Business Officer at NOXXON
- Headed Business Development at Novexel - €75m upfront licensing deal with Forest Labs in 2008 on avibactam; company bought by AstraZeneca for $505m in 2010
- 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®
Novel anti-cancer approach that targets the **tumor micro-environment (TME)** through potent, clinically validated activity on key TME chemokines

**Ongoing**: Phase 1/2 as combo of lead program NOX-A12 with Merck & Co.’s KEYTRUDA® to test efficacy in strategic solid tumor indications

**Established combination therapy safety and efficacy data** for NOX-A12 in two hematological cancers: CLL & MM

Company primed to deliver top-line results on Phase 1/2 trial in 2018

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**Market**: EuroNext Growth Paris – ALNOX

**Market capitalization**: ~ €27 million - Key shareholders include: TVM, Sofinnova, Edmond de Rothschild Investment Partners, NGN & Seventure Capital

**Cash**: ~ €1.4 million as of 31-May-2017¹, subsequent financing of €1.5 million via convertible debt² / an additional €2m may be pulled by the company³, venture debt remaining not-yet-converted to equity reduced to €841K⁴

**Projected cash burn**: ~€350K/month (including the NOX-A12/KEYTRUDA® clinical trial)

~ 10 employees, headquarters in Berlin, Germany

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¹ Management Accounts, Pharma NV Prospectus, approved 10 July 2017
² NOXXON Press releases 18 July 2017, 19 Sept 2017
³ NOXXON Press release 2 May 2017
⁴ NOXXON Press release 2 May 2017, 18 July 2017
Recent Business Highlights

Dec - **Collaboration with Merck & Co./MSD** on NOX-A12 and Keytruda® (pembrolizumab), combination trial

Jan - **Preclinical Spiegelmer® programs assigned and licensed** to Aptarion in exchange for cash, royalties and equity stake in Aptarion

Feb - Experienced industry cancer clinician **Dr. Jarl Ulf Jungnelius recruited as CMO: Celgene, Pfizer, Lilly** with significant involvement in approved drugs: Abraxane®, Gemzar®, Alimta® and Revlimid®

May - **Private placement & convertible debt financing vehicle** designed to secure financing of clinical trial combining NOX-A12 and Keytruda® (pembrolizumab)

May - **German National Tumor Center** collaboration announced for NOX-A12 & Keytruda trial in pancreatic and colorectal cancer

July – **First patients treated in NOX-A12 and Keytruda® combination study**, transfer of ALNOX shares to public offering segment of EuroNext Growth & 1st tranche convertible debt

Sept – Patients recruitment reaches half-way mark in NOX-A12 and Keytruda® combination study, safety of NOX-A12 as expected from established studies and confirmation of activity on target in tumor tissue

Sept - Don deBethizy, US & EU biotech industry veteran elected chairman
The Problem: Key Tumor Types With High Unmet Needs that are Non-Responsive to Checkpoint Inhibition – T-cells Excluded

- **Metastatic COLORECTAL cancer**
  > Median survival: 6 months - 2 years\(^1\)
  > 5 year survival rate: **13.5 %**\(^2\)

- **Metastatic PANCREATIC cancer**
  > Median survival: 6 months – 1 year\(^3\),
  > 5 year survival rate: **2.6 %**\(^4\)

- Both tumor types are **non-responsive to checkpoint inhibitors** (e.g. Merck’s KEYTRUDA® or BMS’ Opdivo®) alone when microsatellite stable (the vast majority of patients)\(^5\)

- Both tumors **exclude killer T-cells via the chemo-repulsive action of high CXCL12 concentrations**, creating a chemokine “wall”\(^6\)

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

**NOX-A12** - anti-CXCL12/SDF-1

**COMBINE WITH**

1. **BREAK TUMOR PROTECTION**
2. **EXPOSE HIDDEN TUMOR CELLS**
3. **BLOCK TUMOR REPAIR**

**IMMUNOTHERAPY**

**SOLID TUMORS**
- **PANCREATIC/COLORECTAL CANCERS**
  - Status: Ongoing Phase 1/2 in combination with Keytruda® (anti-PD-1)
- **BLOOD CANCERS** MM & CLL
  - Status: Phase 2a studies completed in MM & CLL

**TARGETED THERAPIES**

The combination of NOX-A12 + standard of care (SoC) resulted in an increased rate and quality of response relative to comparable trials with SoC or SoC + competitor molecules

**ABLATION/RADIATION**

**SOLID TUMORS** GLIOBLASTOMA (orphan drug status)
- Status: Phase 1/2 planned 1st line, Temodar resistant inoperable patients

**BLOOD CANCERS**

**Targeted Therapies**

**Combination with Immunotherapy**

**NOX-E36** - anti-CCL2/MCP-1 and related chemokines

**COMBINE WITH**

1. **BREAK TUMOR PROTECTION**

**IMMUNOTHERAPY**

**SOLID TUMORS**
- Status: Phase 1 & 2a completed in non-oncology indications, plan to shift into solid tumors with the goal of blocking tumor resistance to immuno-oncology agents

Spiegelmer Platform: Next-Generation L-stereoisomer RNA Aptamers with Activity on an Important Family of TME Targets, Chemokines

- Spiegelmers use Mirror-image (L-stereoisomer) chemistry to build injectable oligonucleotide (RNA or DNA) therapeutics

- Spiegelmers are aptamers that directly bind and neutralize protein targets in the extracellular space

- Mirror image stereochemistry provides resistance to nuclease degradation and prevents reaction of the innate immune system via toll-like receptors (TLRs)

- Confirmed clinical activity on two chemokines known to be key players in the tumor microenvironment (TME) and difficult to effectively target with other platforms

Novel Approach: Targeting the Tumor Microenvironment to Overcome Therapeutic Resistance

- The tumor microenvironment plays a critical role in all aspects of cancer biology including growth, angiogenesis, metastasis, progression and immune evasion

- Target the tumor microenvironment (TME) to:
  - weaken tumors
  - allow the immune system to reach tumor cells
  - strengthen efficacy of best-in-class cancer therapies

- Lead product candidate NOX-A12:
  potential combination partner for a wide variety of cancer treatment regimens including:
  - immune checkpoint inhibitors
  - T-cell based (CAR-T) and NK cell based approaches, and
  - ablation/radiation and targeted therapies

NOX-A12 Neutralizes a Key Player in the TME: The Chemokine CXCL12

**NOX-A12 binding**
neutralizes anchor domain detaching chemokine / destroying the chemokine concentration gradient

**NOX-A12 binding**
the ligand CXCL12 blocks receptor interaction with BOTH receptors and down-stream signaling

**CXCL12 CHEMOKINE**
Normal function: attraction of cells
High concentration: T-cell chemo-repulsion

**Receptor interaction domain**

**TUMOR CELL OR IMMUNE SYSTEM CELL**

**CXCR4**

**CXCR7**

**STROMAL CELL** (connective tissue cell)

Anchor domain to form gradient
NOXXON Clinical-stage Compounds Address Essential Steps in the Cancer Immunity Cycle

- **Trafficking** of T-cells and myeloid cells to tumors
- NOX-A12 & NOX-E36
- **Infiltration** of T-cells and myeloid cells into tumors
- **Enable immune cell infiltration & recognition of cancer cells**
- **Boost anti-tumor immunity**

A unique mechanism to enable TME infiltration of anti-cancer immune cells

Adapted from Chen & Mellman 2013 Immunity.
NOX-A12 Full Blockade of CXCL12 Axis Superior to CXCR4 Antagonists

Select companies active on the CXCL12 / CXCR4 / CXCR7 axis in cancer:\(^1,2\):

- All clinical-stage competitors target only CXCR4 and do not block the CXCL12/CXCR7 interaction
- Clear differentiation vs. mAbs and small molecules in development

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1. Clinicaltrials.gov and company websites (accessed October 2015)
NOX-A12 activity blocking CXCL12-CXCR7 interaction provides strong differentiation in solid tumors

**CXCR7 (ACKR3) is an atypical chemokine receptor**
- Binds CXCL12 with 10-fold higher affinity than CXCR4\(^1,2\)
- Expressed on wide variety of tumor cells and tumor-associated vasculature\(^1,4\)
- Acts as CXCL12 scavenger\(^2\), potentially modulating CXCL12 gradients
- Triggers intracellular signaling pathways via Akt, MAPK, JAK/STAT3\(^2\), mTOR\(^3\)

**CXCR7 has key functions for tumor development and contributes to an invasive phenotype\(^3,7\)**
- Growth
- Migration & chemotaxis
- Adhesion
- Angiogenesis
- Chemotherapy resistance
- Spreading / metastasis

**CXCR7 expression correlates with advanced tumor stage and poor prognosis\(^13-15\)**

**CXCR7 is a target for tumor therapy independent from CXCR4 in**
- Glioblastoma\(^1,10\)
- Pancreatic Cancer\(^3\)
- Breast Cancer\(^4\)
- Lung Cancer\(^4\)
- Head and Neck Cancer\(^8\)
- Hepatocellular Carcinoma\(^11\)
- Colon Cancer\(^12\)
- Gastric Cancer\(^9\)
- Multiple Myeloma\(^5\)

1: Walters, M.J. et al., Br J Cancer, 2014
3: Guo, J-Ch. et al., Oncotarget, Advance publications, 2016
4: Miao, Z. et al., PNAS, 2007
7: Yun, H-J. et al., Oncol Lett, 2015
8: Maussang, D. et al., J Biol Chem, 2013
10: Liu, Y. et al., Anticancer Res, 2015
11: Xue, T-C. et al., Exp Ther Med; 2012
12: Guillemot, E. et al., Br J Cancer, 2012
Solid Tumors are Protected by a “Biochemical CXCL12 Wall”

- **T-cells are excluded from “cancer cell nests”**
- Intratumoral CXCL12 is produced by carcinoma-associated fibroblasts (CAFs) and is associated with cancer cell nests\(^1\)
- CXCL12 expression and T-cell exclusion is associated with human pancreatic, colorectal, ovarian and lung cancer\(^2\)
- Mechanism for T-cell exclusion might be apoptosis and/or chemorepulsion by CXCL12\(^2,3\)
- CXCL12 appears to coat tumor cells and serve as a repulsion factor for certain cells types, including killer T cells keeping them out of tumors even in presence of checkpoint inhibitors
- Both metastatic pancreatic and colorectal cancers are non-responsive to checkpoint inhibitors (e.g. Merck’s KEYTRUDA\(^®\) or BMS’s Opdivo\(^®\)) alone when microsatellite stable (the vast majority of patients)\(^4\)

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1. Feig, C. et al. PNAS 110.50 (2013): 20212-20217
NOX-A12 Enhances Infiltration of Primary Human T-cells and NK Cells into Tumor Stroma Spheroids and Synergizes with Checkpoint Inhibitors to Boost Their Anti-Cancer Activity \textit{in vivo}

\textbf{In Vitro, NOX-A12 shows}\textsuperscript{1}
- Increased T and NK cell infiltration in tumor spheroids
- Synergy with checkpoint inhibition on T-cell activity
- Synergy with NK cells on ADCC

\textbf{In Vivo NOX-A12 study shows}\textsuperscript{2}
- Significant reductions in tumor growth in a model poorly responsive to PD-1 inhibition
- A majority of animals with stable or reduced tumor volumes

\textsuperscript{1} Spheroid data: Zboralski, D., et al., (2016) ESMO Congress 2016, Copenhagen, Denmark, October 2016 Session Immunotherapy of cancer: Abstract #1083P

\textsuperscript{2} Syngeneic colon cancer mouse model CT26 tumor: Unpublished Company data
Collaboration with Merck & Co. / MSD\textsuperscript{1}
Potential Route to Early Approval in Solid Tumors

• Collaboration on Phase 1/2 clinical trial of NOXXON’s anti-CXCL12 agent, NOX-A12, and MSD’s anti-PD-1 inhibitor, Keytruda\textsuperscript{®} (pembrolizumab)

• Indication - patients with metastatic solid tumors where response to checkpoint inhibition has been dismal

• Clinical trial design - collaborative effort between NOXXON and Merck

• Merck to provide Keytruda\textsuperscript{®} free of charge to NOXXON for trial

• Multiple paths for further development of the combination in pivotal clinical trials are envisioned as part of agreement

• Agreement grants no commercial rights to either party for other party’s compound

• With the potential for breakthrough designation in these indications NOXXON believes these indications may be a potential route to early approval in solid tumors\textsuperscript{2}

1. NOXXON Pharma Press release 15 Dec 2016
2. NOXXON Pharma NV Prospectus of 10 July 2017
NOX-A12; Ongoing Phase 2a Trial in Colorectal & Pancreatic Tumors

**Next development steps**

- Phase 1/2 proof-of mechanism/concept trial in 2 indications:
  1. Colorectal cancer (MSS) 10 patients
  2. Pancreatic cancer (MSS) 10 patients

- Response rate in targeted patient population to anti-PD-1 alone ~0%

- Regulatory scientific advice will be planned when data available

**Trial Design**

<table>
<thead>
<tr>
<th>Part 1</th>
<th>Part 2</th>
</tr>
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<tbody>
<tr>
<td>NOX-A12 Induction</td>
<td>NOX-A12 + Keytruda®</td>
</tr>
</tbody>
</table>

1. Patients with available tumor for assessment before and after NOX-A12 treatment for 2 weeks

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

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

   **Endpoint:**
   Assess safety and efficacy of combination

**Timeline**

- **Q2-2018** - Top-line data from Part 1 for all patients
- **Q4-2018** - Response rate of NOX-A12 + Keytruda in all patients

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1. Clinicaltrials.gov trial NCT03168139
2. NOXXON Pharma NV Prospectus of 10 July 2017

*MSS = microsatellite stable*
NOX-A12: Strong Synergy with Ablative Therapy in Glioblastoma

ORPHAN DRUG STATUS for glioblastoma in combination with radiotherapy in the US and for glioma in the EU

NOX-A12 + radiotherapy:
- Tumor regression with complete response in all animals;
- Complete response maintained after stop of treatment in two-thirds of animals
NOX-A12: Planned Phase 2a Trial
Temodar Resistant Brain Tumors in Combination with Radiotherapy

Next development steps¹

- Phase 1/2 proof-of-concept trial in

- Anticipated trial design:
  - Open-label, single arm in patients with inoperable glioblastoma who are resistant to standard of care temozolomide
  - Primary endpoint: progression-free survival (PFS) after 6 months
  - Standard radiotherapy + NOX-A12
  - ~18 patients with inoperable brain tumors, may be extended up to ~35 patients
  - Positive study will be basis for regulatory interaction on pivotal trial design
NOX-A12: High Potential as Combination Partner for Broad Range of Cancer Therapies

- Antibodies
- Cytotoxics
- Targeted therapies
- Ablation *including* radiation
- Immunotherapies
  - checkpoint inhibitors
  - co-stimulators
  - CAR-T
  - other

NOX-A12: TME targeting yields combination potential with broad range of cancer therapies
NOX-E36: Phase 2-ready Oncology Drug Candidate

- **CCL2/MCP-1 is implicated in cancer spread and immune privilege of tumors**, data from Pfizer’s antagonist of CCR2 (receptor for CCL2) in pancreatic cancer patients suggests this translates into improved efficacy¹

- **NOX-E36 binds and neutralizes CCL2 (MCP-1) and three other highly related chemokines**²

- **NOX-36 neutralizes 3 of 4 monocyte/macrophage relevant chemokines of the Innate PD-1 Resistance (IPRES) Signature³ while competing receptor antagonists will only fully block 1 of these 4 chemokines**

- **NOX-E36 is ready to enter Phase 2 in oncology: safety & tolerability, activity on relevant cell types established in Phase 1 and a non-oncology Phase 2⁴**

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1. Nywening Lancet Oncol 2016 http://dx.doi.org/10.1016/S1470-2045(16)00078-4
NOX-E36 Inhibits Activity of Chemokines Important in PD-1 Resistance

- NOX-E36 binds and neutralizes CCL2 (MCP-1), CCL8 (MCP-2), CCL13 (MCP-4) and CCL11 (Eotaxin) chemokines

- CCL2, CCL7, CCL8 and CCL13 are the monocyte/macrophage relevant components of the Innate PD-1 Resistance (IPRES) Signature\(^1\) – NOX-E36 neutralizes 3 of 4\(^2\)

- CCR2 or CCR2/CCR5 specific receptor antagonists will not fully block any of the chemokines other than CCL2: potential for best in class
Phase 2a Pharmacodynamics of NOX-E36 (Monocyte Shift)

Upon treatment with NOX-E36,
- The number of monocytes in peripheral blood decreases by 15-20% on treatment
- The presence of the CCL2 receptor CCR2 on the monocytes is reduced 4 to 5-fold

NOX-E36– Key Messages

- Generally safe and well tolerated following i.v. and s.c. administration
- Clear pharmacodynamic effect on monocyte-relevant chemokines on circulating monocyte populations…
- …and reduced urinary ACR and HbA1c levels in treated patients
- 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 Highlights

- Novel anti-cancer approach using proprietary Phase 2 agents targeting the tumor microenvironment to weaken tumors and strengthen efficacy of best-in-class cancer therapies including immuno-oncology (IO) agents

- Lead product candidate NOX-A12 positioned as a potential combination partner for a wide variety of cancer treatment regimens, including immune checkpoint inhibitors, T-cell based (CAR-T) and NK cell based approaches

- NOX-E36 provides additional upside potential in TME space

- Significant progress planned in 2018 with potential to achieve additional clinical data-points rapidly with additional financing
  - NOX-A12 Go/No-Go for pivotal studies
    - In combination with Keytruda in MSS disease mCRC and/or Pancreatic cancer
    - In combination with radiotherapy in Glioblastoma (additional financing required)
  - NOX-E36 clinical proof of concept in advanced solid tumors (additional financing required)
Appendix
Supervisory Board

Dr. Don deBethizy (Chairman)
- CEO of Santaris Pharma, Denmark and USA until sale to Roche
- Chairman of Rigontec GmbH until sale to Merck & Co./MSD
- Formerly Chairman Contera Pharma ApS, Serendex A/S
- Co-founder and former CEO of Targacept
- Current Board member arGEN-X NV, Newron Pharma SPA, Proterra and Alumedix
- 30 years of experience in the biotechnology and consumer products industry

Dr. Hubert Birner
- Managing Partner TVM Capital Munich and Montreal
- Chairman of the Board of AL-S Pharma (Zurich), Argos Therapeutics (Durham, NC), leon-nanodrugs (Munich), Spepharm Holdings (Amsterdam)
- Board member of Proteon Therapeutics (Boston)
- Previously at McKinsey and Zenea

Dr. Maurizio Petitbon
- General partner and co-founder of Kreos Capital
- Former managing partner of PMA Europe
- SRI International, in Menlo Park, California and London
- Managerial positions at Emerson Electric, Digital Equipment and Xerox.

Dr. Walter Wenniger
- Held several international executive management positions at Bayer Pharma life sciences including as member of the management board of Bayer AG
- Board member of several European pharma companies
- >30 years of pharma industry experience

Bertam Köhler
- CEO and board member of DEWB
- Board member of of Nanotron Technologies Ltd. and LemnaTec GmbH
- Previously risk management consultant Commerzbank
- Former management consultant KPMG
## NOXXON’s Key Patent Families Related to NOX-A12 and NOX-E36

### NOXXON’s key patent families related to NOX-A12 (olaptesed pegol)

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<tr>
<th>Family</th>
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### NOXXON’s key patent families related to NOX-E36 (emapticap pegol)

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