Targeting the Tumor Microenvironment to Enhance the Effectiveness of Cancer Therapies

ASCO
1 June 2018, Chicago, IL
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**NOXXON Overview/Story on a Page**

- **Important unmet need in solid tumors:** metastatic, microsatellite stable colorectal cancer and metastatic pancreatic cancer (non-responsive to checkpoint inhibitors, NSCLC progressing on anti-PD-1 therapy, brain tumors)

- **NOX-A12 unique MoA:** Targeting the chemokine CXCL12, a key player in the tumor micro-environment (TME) active in T-cell exclusion, macrophage and endothelial progenitor cell infiltration into damaged tumors and blood cancer homing to protective niches
  - Established safety and efficacy data for NOX-A12 in more than 116 subjects including two Phase 2a trials in CLL & MM
  - Merck collaborating with NOXXON on lead program NOX-A12 in ongoing Phase 1/2 KEYTRUDA® combo to test efficacy in solid tumor indications that are non-responsive to anti-PD-1/PD-L1
  - Company primed to deliver top-line results on Phase 1/2 trial in 2018
  - Rapid start to brain tumor trial and additional upside potential in anti-PD-1 failures in NSCLC where patient samples show strong potential

- **NOX-E36 provides a complementary innate immune system MoA:** Targeting the chemokine CCL2 as well as highly related CCL7, 8, and 13 involved in recruitment of immuno-suppressive tumor associated macrophages (TAMs) into tumors and resistance to anti-PD-1/PD-L1 therapy
  - Established safety and activity data in >150 subjects
  - Monotherapy therapeutic potential in solid tumors to be tested alongside multiple combination approaches

- **Significant commercial opportunity**:  
  - Metastatic Pancreatic Cancer: $1.7 billion in 2015 - projected to reach $4.2 billion in 2025
  - Metastatic Colorectal Cancer: $8.15 billion 2016 - projected reach $11 billion by 2025
  - Glioblastoma: $0.7 billion in 2014 – projected to reach $3.3 billion by 2024

- **Strong IP position:** two key patent families related to NOX-A12 and NOX-E36

- **Financials:** ~€10-15 million market cap (ALNOX on Euronext Growth Paris Stock Exchange), cash balance of €622 K (as of 31 Dec 2017)
Experienced Management and Supervisory Board

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®

Supervisory Board

Dr. Don deBethizy, Chairman

- Chairman of Albumedix, Board member arGEN-X NV, Newron Pharma SPA, Proterris
- Formerly CEO of Santaris Pharma (sale to Roche), chairman of Rigontec (sale to Merck & Co./MSD), Chairman Contera Pharma ApS, Serendex A/S
- Co-founder and former CEO of Targacept

- Dr. Hubert Birner, TVM
- Bertam Köhler, DEWB
- Dr. Maurizio Petitbon, Kreos
- Dr. Walter Wenniger, Independent
Pipeline Assets Leverage Existing Anti-Cancer Therapies to Optimize their Therapeutic Efficacy

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

**COMBINE WITH**

**BREAK TUMOR PROTECTION**

**IMMUNOTHERAPY**

**SOLID TUMORS: PANCREATIC/COLORECTAL CANCERS**
- **Status:** Ongoing Phase 1/2 in combination with Keytruda® (anti-PD-1)
- Additional Potential in NSCLC PD-1 failures

**BREAK TUMOR REPAIR**

**ABLATION/ RADIATION**

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

**EXPOSE HIDDEN TUMOR CELLS**

**TARGETED THERAPIES**

**SOLID TUMORS:**
- **Pancreatic**
  - **Status:** Phase 1 & 2a completed in non-oncology indications
  - Planned study in pancreatic cancer patients as monotherapy and in multiple combinations

**Near-term Milestones**
- Topline (mono): Q2’18
- Topline (combo): Q4’18

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

**BREAK TUMOR PROTECTION**

**IMMUNOTHERAPY & CHEMOTHERAPY**

**SOLID TUMORS:**
- **Pancreatic**
  - **Status:** Phase 1 & 2a completed in non-oncology indications
  - Planned study in pancreatic cancer patients as monotherapy and in multiple combinations

Inhibition of the CXCL12/CXCR4/CXCR7 axis as a Targeted Therapy

Key characteristics of CXCL12

- CXCL12 is expressed by immune cells, endothelial cells, cancer cells, stromal fibroblasts and stem cells
- CXCL12 binds and activates two receptors, CXCR4 and CXCR7
- CXCL12 and its receptors are key factors linking cancer cells with their microenvironment

CXCL12’s role in cancer

- Reduction of tumor cell death (apoptosis)
- Promotion of tumor proliferation
- Promotion of new blood vessel formation
- Promotion of metastasis

Inhibition of the CXCL12/CXCR4/CXCR7 axis to

1. Break tumor protection
2. Block tumor repair
3. Expose hidden tumor cells

Indication: Solid Tumors (e.g. pancreatic, colorectal cancer, NSCLC)

Indication: Solid Tumors (e.g. glioblastoma)

Indication: Blood Cancers (e.g. multiple myeloma, T-ALL)

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
  - Rituximab 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

**Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>N = 28</th>
<th>12 w, 16 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41 – 79</td>
<td>Median = 67</td>
</tr>
<tr>
<td>Binet stage</td>
<td>A: 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B: 11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C: 11</td>
<td></td>
</tr>
<tr>
<td>Prior treatment</td>
<td>1 line 17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 lines 10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 lines 1</td>
<td></td>
</tr>
<tr>
<td>Fludarabine / Bendamustine</td>
<td>Naïve 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pre-treated 23</td>
<td></td>
</tr>
</tbody>
</table>

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

- Combination regimen generally well tolerated
- NOX-A12 did not seem to add any significant tolerability or safety burden to underlying BR regimen
The Problem: Key Tumor Types 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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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

- CXCL12 expression and T-cell exclusion is associated with human pancreatic, colorectal, ovarian and lung cancer

- Mechanism for T-cell exclusion might be apoptosis and/or chemorepulsion by CXCL12

- 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)

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1. Feig, C. et al. PNAS 110.50 (2013): 20212-20217
NOX-A12 - Ongoing Phase 2a Trial in MSS Colorectal & Pancreatic Tumors

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%³
Regulatory scientific advice will be planned when data available

Patient Profile
- Patients with PD after multiple prior lines of therapy.
- Best response to previous treatment generally PD
- Micro-satellite stable disease where checkpoint inhibitors (CPI) aren’t efficacious³

Part 1 NOX-A12 Induction
- 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

Part 2 NOX-A12 + Keytruda®
- Patients from Part 1 then transitioned to combination treatment of NOX-A12 with checkpoint inhibitor
- Endpoint: Assess safety and efficacy of combination

Timeline²
- 15 May 2018 – Patient recruitment at 90%
- Q2-2018 - Top-line data from Part 1 for all patients
- Q4-2018 - Response rate of NOX-A12 + Keytruda in all patients

Collaboration with: MERCK, MSD, NCT

¹ Trial Design
² Timeline
³ MSS = microsatellite stable
### NOX-A12 + Keytruda Trial Patient Demographics at Enrollment

<table>
<thead>
<tr>
<th>Status 7 May 2018</th>
<th>Colorectal Cancer</th>
<th>Pancreatic Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Male/Female</td>
<td>7 / 3</td>
<td>7 / 1</td>
</tr>
<tr>
<td>Age, mean (range)</td>
<td>64 (55 – 73)</td>
<td>66 (48 – 82)</td>
</tr>
<tr>
<td>Disease stage at diagnosis:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>III</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>IV</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Prior lines of systemic treatment (mean)*</td>
<td>5 (2 – 9)</td>
<td>3 (1 – 5)</td>
</tr>
<tr>
<td>Pts w/ prior surgery (# of surgeries)</td>
<td>7 (1 – 4)</td>
<td>3 (1 – 2)</td>
</tr>
<tr>
<td>Best response last treatment**</td>
<td>PD (6), SD (1), UNK (3)</td>
<td>PD (8)</td>
</tr>
<tr>
<td>Time since last prior systemic treatment (mean)</td>
<td>2.2 months</td>
<td>1.5 months</td>
</tr>
</tbody>
</table>

* excluding surgery; ** data not available for all patients

- **Heavily pretreated population with high tumor burden in both cancers**
- **Vast majority patients with progressive disease as best response to prior therapy**
Overview on the Treatment of Metastatic Colorectal Cancer

FDA approved regimes & drugs for mCRC

- 1\textsuperscript{st} and 2\textsuperscript{nd} line: FOLFOX, FOLFIRI, FOLFERNINOX regimens include cytotoxic drugs: 5-FU, oxaliplatin, irinotecan, capecitabine, and targeted agents; cetuximab, panitumumab, and bevacizumab

- 3rd line and beyond: FDA approvals include single agent: Ziv-aflibercept, regorafenib, ramucirumab, TAS-102, and bevacizumab beyond progression

- Immunotherapies for mCRC: pembrolizumab and nivolumab (only \textbf{MSI-High} and 2\textsuperscript{nd} line)

- Efficacy of treatment and line of therapy
  - ORR 1\textsuperscript{st} line ~40% (38-65%), 2\textsuperscript{nd} line 20% (5-35%), 3\textsuperscript{rd} line or greater 10% (1-17%)
  - PFS months 1\textsuperscript{st} line ~10 months, 2\textsuperscript{nd} line 5 months, 3\textsuperscript{rd} line or greater ~2 months
Overview on the Treatment of Metastatic Pancreatic Cancer

**PANCREAS CANCER**

<table>
<thead>
<tr>
<th>1ST LINE</th>
<th>ORR (%)</th>
<th>mPFS (months)</th>
<th>mOS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gem/+</td>
<td>Gem</td>
<td>Gem/+</td>
</tr>
<tr>
<td>Phase 3</td>
<td>Gem/Erlotinib vs Gem</td>
<td>8.6</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>n=569</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Gem/Irinotecan vs Gem</td>
<td>16.1</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>n=360</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Gem/Oxaliplatin vs Gem</td>
<td>26.8</td>
<td>17.3</td>
</tr>
<tr>
<td></td>
<td>n=326</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 3</td>
<td>Gem vs 5FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=126</td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>2ND LINE</th>
<th>SD(%)</th>
<th>PR(%)</th>
<th>mPFS (weeks)</th>
<th>mOS (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Oxaliplatin/5FU/Leukovorin</td>
<td>30</td>
<td>13.3</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>n=30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Oxaliplatin/Capecitabine</td>
<td>25.6</td>
<td>2.6</td>
<td>9.9</td>
</tr>
<tr>
<td></td>
<td>n=41</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Folfiri.3 vs Folfox</td>
<td>18.4/8.6</td>
<td>0/5.7</td>
<td>8.3/6.0</td>
</tr>
<tr>
<td></td>
<td>n=61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2</td>
<td>Abraxane</td>
<td>31.6</td>
<td>5.3</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>n=19</td>
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</tbody>
</table>

| 3RD LINE No Available Data |
Therapeutic Context for Metastatic CRC & PaC
anti-PD(L)1 monotherapy

First reports in CRC and PaC showed no objective responses (Brahmer 2012, Topalian 2012) to PD-1/L1 monotherapy, and no mention of stable disease in these populations.

Stable disease not seen with anti-PD-1/PD-L1 monotherapy in documented Micro-Satellite Stable (MSS) PaC and rarely in MSS CRC in less sick populations than tested in the NOX-A12 study (Le 2015, O’Neil 2017)

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage</th>
<th>ECOG</th>
<th>≥ 3 prior tmt</th>
<th>≥ 4 prior tmt</th>
<th>Median # prior tmt</th>
<th>Median age</th>
<th>Enrichment for efficacy</th>
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</thead>
<tbody>
<tr>
<td>NOX-A12 + Keytruda OPERA</td>
<td>Met.</td>
<td>0-1</td>
<td>90%</td>
<td>80%</td>
<td>5</td>
<td>64</td>
<td>-</td>
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<tr>
<td>Study in MSS N=10 PaC +10 CRC</td>
<td></td>
<td></td>
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<tr>
<td>Le 2015</td>
<td>Met.</td>
<td>0-1</td>
<td></td>
<td>57%</td>
<td></td>
<td>61</td>
<td>-</td>
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<tr>
<td>N= 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SD in 11% of MSS</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>O’Neil 2017</td>
<td>Loc. adv. or</td>
<td>0-1</td>
<td>65%</td>
<td></td>
<td>3</td>
<td>57</td>
<td>PD-L1+</td>
</tr>
<tr>
<td>Met.</td>
<td></td>
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<tr>
<td>N= 22</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(138 patients screened,</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>24% PD-L1+ eligible),</td>
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<td></td>
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<tr>
<td>SD in 18% of PD-L1+ enriched,</td>
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<td></td>
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<tr>
<td>MSS population</td>
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</tr>
</tbody>
</table>
NOX-A12 Penetrates Tumor Tissue and Neutralizes CXCL12 (interim data n=12)

- NOX-A12 binding and neutralization of CXCL12 results in increased CXCL12 half-life.
- Increased total CXCL12 levels signaling neutralization seen in all patients.
- Clear tissue immune response profiles seen in patients with largest increases.

![CXCL12 Graph](attachment:cxcl12_graph.png)
Multiplex Cytokine Analysis in Biopsies: PaC Patient 015

PaC patient 015

% change from baseline

-100 0 100 200 300

beta-NGF  CCL27  LIF  SCF  IFN-alpha 2  IL-1alpha  IL-1b  IL-6  IL-8  MIF  CCL2/MCP-1  CCL3/MIP-1a  CCL4/MIP-1b  TNF-a  FGF basic  G-CSF  GM-CSF  GROalpha  CCL7/MCP-3  PDGF bb  VEGF  IL-4  IL-5  IL-10  IL-13  IL-17  IL-18  IL-2 R-alpha  IL-12p70  IL-12p40  IL-15  IL-16  IL-18  M-CSF  IL-2  IL-9  IL-10  IL-12p70  IL-12p40  IL-15  IL-16  IL-18  CCL5/RANTES  CXCL9/MIG  CXCL10/IP-10  TRAIL  TNF-beta  HGF  IL-1ra  IL-3  IL-7  IL-9

Homeostasis/migration/differentiation  Inflammation  Myeloid signature  Th2 signature  Immune response / CD8 T cells/ NK cells  Pleiotropic
NOX-A12 Monotherapy Can Trigger Signatures Consistent with Immuno-Stimulatory, Cytotoxic / Th1 type Response

Preliminary interim data

n = 17 patients of which 12 with matched biopsies available for analysis
Immunohistochemistry Analysis of Tumor Biopsies

CD3+ T cells in liver metastases

![Graph showing CD3+ T cell counts over time](image1)

CD11b+ myeloid cells in liver metastases

![Graph showing CD11b+ myeloid cell counts over time](image2)

Ratio CD3/CD11b+ cells in liver metastases

![Graph showing ratio of CD3 to CD11b+ cells over time](image3)

Data consistent with clearing of suppressive cells of both T and myeloid lineages from tumor where tissue TME response seen

Preliminary interim data
10 SAEs in 8 patients reported so far under treatment:

- **Abdominal pain** and **bleeding in the abdominal cavity**: the event is linked to the event exacerbation of pain; both events are assessed as **not related** to study medication
- **Diarrhea**: the event is assessed as **related** to treatment with olaptesed pegol (SUSAR)
- **Exacerbation of pain**: the event, reported after liver puncture, is assessed as **not related** to study medication olaptesed pegol
- **Hyperbilirubinaemia**: the event is assessed as **not related** to study medication olaptesed pegol
- **Pain exacerbation**: the event is assessed as **not related** to study medication olaptesed pegol
- **Perforation ileal**: the event is assessed as **not related** to study medication olaptesed pegol
- **Pneumonia**: the event is assessed as **not related** to study medication olaptesed pegol
- **Vomiting**: the event is assessed as **not related** to study medication olaptesed pegol; newly diagnosed cerebral metastases were identified as the cause of vomiting
- **Wound dehiscence**: the event is linked to the event perforation ileal and is assessed as **not related** to study medication olaptesed pegol lizumab

→ **In all cases the criterion for seriousness was hospitalization**
Ten NSCLC tumors were stained for CXCL12, FOXP3 and CD3 to provide insight into the validity hypothesis that CXCL12 presence excludes T-cell infiltration in tumor tissue¹.

The results strongly suggest that CXCL12 excludes T-cell infiltration in NSCLC patients¹.

Clinical trial design in 1st line anti-PD-1 failures/non-responders with an enrichment biomarker for potential responders is currently being refined with experts. Goal is to significantly boost ~25% response rate of anti-PD1 monotherapy.
NOX-E36: Phase 2-ready Oncology Drug Candidate

- **CCL2/MCP-1** is implicated immune privilege of tumors via recruitment of tumor associated macrophages (TAMs), data from Pfizer’s CCR2 antagonist in pancreatic cancer patients suggests that even partial inhibition this axis translates into improved efficacy\(^1\)

- **NOX-E36** binds and neutralizes CCL2 (MCP-1) and three other highly related chemokines\(^2\) providing potentially best in class pharmacology on monocyte/macrophage chemokines in the Innate PD-1 Resistance Signature (IPRES)\(^3\)

- A rodent version of **NOX-E36 prevents recruitment of TAMs**, enhances cytotoxic T cell infiltration and reduces tumor burden

- **NOX-E36** has demonstrated its **safety, tolerability and activity on CCR2+ monocytes** in Phase 1 and a non-oncology Phase 2\(^4\)

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1. Nywening Lancet Oncol 2016 http://dx.doi.org/10.1016/S1470-2045(16)00078-4
Tumor Associated Macrophages (TAMs) derived from circulating monocytes promote tumor growth and are linked to poor survival

- Tumor associated macrophages (TAM) are derived from circulating monocytes and are recruited to tumors by the CCL2/CCR2 pathway\(^1\), \(^2\)

- Multiple studies have identified accumulation of TAMs in various tumors including melanoma, prostate cancer, breast cancer and colon cancer\(^1\), \(^4\) Recent data have identified a prominent role for TAMs in pancreas cancer progression and have linked high levels in the systemic circulation and tumor microenvironment to poor survival\(^2\), \(^5\)

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

Model: syngeneic PDAC in immunocompetent mice

A. Trend towards smaller tumor size in established tumor group
B,C. Statistically significant decrease in TAM infiltration in mNOX-E36 group

D,E. Trend towards higher CD8 T cell infiltration in mNOX-E36 group

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
**NOX-E36– Key Messages**

- **Generally Safe and well tolerated** following i.v. and s.c. administration with >150 subjects having received NOX-E36

- **Clear pharmacodynamic effect on circulating monocytes** including the CCR2+ population 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:**
  - Phase 1/2 single agent trial to confirm dosing schedule and safety profile
  - Phase 1/2 multi-arm combination trial in metastatic pancreatic cancer combining NOX-E36 with 1) anti-PD-1, or 2) approved chemotherapy, or 3) NOX-A12
  - Randomized Phase 2 proof of efficacy trial
NOXXON Highlights

- Novel anti-cancer approach that targets the **tumor micro-environment (TME)** through potent, clinically validated activity on the **adaptive** (NOX-A12) as well as **innate** (NOX-E36) immune system

- **Lead program NOX-A12 in ongoing Phase 1/2 as combo with Merck & Co.’s KEYTRUDA®** to test efficacy in strategic solid tumor indications non-responsive to anti-PD-1/PD-L1

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

- Data in **indications with potential for accelerated / provisional** approval rapidly available with additional funding and cooperation with industry or government/foundation financed consortia
  - NOX-A12 - NSCLC – anti-PD-1 monotherapy failures, enriched for potential responders
  - NOX-A12 - Glioblastoma 1st line, MGMT unmethylated (adult and/or pediatric)
  - NOX-E36 – metastatic pancreatic cancer – monotherapy & multiple combinations
  - NOX-A12 – solid tumors in combination with anti-angiogenics

- **Revitalized organization**, management and Supervisory Board