Who we are

**iOnctura: an integrated drug development engine**

- Experienced executive management team with solid track records in drug development and commercialisation
- Rich pipeline of best in class molecules with first in class potential and free clinical supply of avelumab
- High profile SAB and access to Cancer Research UK’s broad KOL network
- Collaboration with established R&D infrastructure at Cancer Research UK’s Therapeutic Discovery Laboratories & Netherlands Cancer Institute.
- Strong connection with leading CROs, eg Crown Bioscience

17 March 2021
## iOnctura’s portfolio

### Complementary modes of actions

<table>
<thead>
<tr>
<th>Modes of Action</th>
<th>Discovery</th>
<th>Candidate Identification</th>
<th>Preclinical Development</th>
<th>Phase 1 Start</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOA-244</td>
<td></td>
<td>PI3Kδ inhibitor</td>
<td></td>
<td>2019</td>
</tr>
<tr>
<td>Selective inhibition of Tregs &amp; MDSCs &amp; Inhibition of tumour cell proliferation and survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOA-289</td>
<td></td>
<td>ATX inhibitor</td>
<td></td>
<td>2020</td>
</tr>
<tr>
<td>Increase T cell infiltration &amp; Inhibition of tumour cell proliferation, metastasis and angiogenesis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOA-290</td>
<td></td>
<td>ATX inhibitor</td>
<td></td>
<td>2020</td>
</tr>
<tr>
<td>Inhibition of LPA mediated fibrosis and inflammation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOA-237</td>
<td></td>
<td>Anti-CD73</td>
<td></td>
<td>TBD*</td>
</tr>
<tr>
<td>Relieve effector T cell suppression in TME</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Potential outlicensing/partnering program*
PI3Kδ: A new era in immuno-oncology

Class I phosphoinositide 3-kinases

Targeting PI3K in cancer

This provides a strong rationale for developing PI3Kδ inhibitors in solid cancers

Okkenhaug & Vanhaesebroeck Nat Rev Imm 2013

Okkenhaug et al. Cancer Discovery 2016
**iOnctura focus on precision targeting of PI3Kδ in solid tumour indications**

**Haematological malignancies**
- Extreme burden of B cells
- Dose setting at MTD

**Solid tumour indications**
- Precision targeting to redress the balance of immune cells in the tumour microenvironment
  - Oral checkpoint inhibition
  - Targeted therapy in PI3Kδ expressing tumours

Adapted from “Targeting regulatory T cells in tumour immunotherapy”, 2014, Smyth et al
**PI3Kδ: Why are we different?**

*IOA-244 is a Phase I-ready molecule with unique properties and a differentiated development strategy*

IOA-244 is a best in class PI3Kδ inhibitor

- iOnctura will be the first company to evaluate single agent immuno-modulatory effects of a specific PI3Kδ inhibitor in patients with solid tumours

- iOnctura will be the first company to explore the hypothesis that a PI3Kδ inhibitor can inhibit intrinsic cancer cell survival pathways in solid tumours

- iOnctura has selected indications with a high burden of Tregs and MDSCs and over expression of PI3Kδ to demonstrate this dual mechanism in first in human trials

- IOA-244’s best in class properties include a unique chemical structure, exquisite selectivity, non-ATP competitive activity, superior DMPK properties and favourable safety profile
Thus, IOA-244 can shift the balance from immune tolerance towards effective anti-tumour immunity!

### PI3Kδ as an Immuno-Oncology target

#### Internal and external target validation

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Role in the TME</th>
<th>Effect of PI3Kδ inhibition / inactivation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regulatory T cell</td>
<td>Highly immune suppressive</td>
<td>▼ Number of suppressive Treg in TME</td>
<td>Ali <em>et al</em> 2014, <em>in house data</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ahmad <em>et al</em> 2017, <em>in house data</em></td>
</tr>
<tr>
<td>Myeloid Derived Suppressors</td>
<td>Highly immune suppressive</td>
<td>▼ Number and function Tumour eradication in combination with PDX ▼ Function ▼ Number of infiltrating MDSCs</td>
<td>Ali <em>et al</em> 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Kim <em>et al</em> 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Davis <em>et al</em> 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>In house data</em></td>
</tr>
<tr>
<td>Cytotoxic CD8+ T cells</td>
<td>Kill cancer cells</td>
<td>Maintain anti-tumour immunity ▲ Inherent anti-tumour immunity ▲ Responses in combination with anti-PD-L1</td>
<td>Ali <em>et al</em> 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bowers <em>et al</em> 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Davis <em>et al</em> 2017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><em>Ahmad et al</em> 2017, <em>in house data</em></td>
</tr>
<tr>
<td>Natural Killer cells</td>
<td>Kill cancer cells</td>
<td>Not cytotoxic, but may inhibit cytokine release ▲ Number of infiltrating NK cells</td>
<td>Herman <em>et al</em> 2010</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Produce growth factors, chemokines and ECM</td>
<td>▼ Proliferation</td>
<td><em>In house data</em></td>
</tr>
<tr>
<td>Tumour Associated Macrophages</td>
<td>Produce immune suppressive, metastatic and angiogenic factors</td>
<td>▼ Macrophage recruitment</td>
<td>Mouchemore <em>et al</em> 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Goulielmaki <em>et al</em> 2018</td>
</tr>
</tbody>
</table>
Unlike idelalisib and duvelisib IOA-244 will preserve CD8\(^+\) & CD4\(^+\) T cell responses at therapeutic exposure levels.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IOA-244</th>
<th>idelalisib</th>
<th>duvelisib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>20 mg (QD)</td>
<td>150 mg (BID)</td>
<td>25 mg (BID)</td>
</tr>
<tr>
<td>Exposure</td>
<td>0.5 – 2 (\mu)M</td>
<td>0.3 – 7.5 (\mu)M</td>
<td>1.2 – 3.6 (\mu)M</td>
</tr>
</tbody>
</table>

- **Treg**
- **CD4\(^+\) T cells**
- **CD8\(^+\) T cells**
IOA-244 demonstrates dose dependent combination efficacy in mouse syngeneic CT26 model
IOA-244 modifies the TME in the CT26 model

- IOA-244 increases the total infiltrating leukocytes
- IOA-244 increases the CD8+ cytotoxic T cells
  - Increases the capacity of the immune system to fight the tumour

- IOA-244 reduces the Tregs and MDSCs
  - Creates a less hostile TME allowing the immune system to fight the tumour
A20 syngeneic model

**IOA-244 significantly enhances anti-PD-1 activity**

5/10 animals TV < 600 mm$^3$ in anti-PD-1 treated group
9/10 animals TV < 600 mm$^3$ in IOA-244 + anti-PD-1 treated group
**PAN-02 syngeneic model**

**IOA-244 significantly enhances anti-PD-1 activity**

- **Graphs**:
  - **Tumour volume (mm^3)** over **Day post start of treatment**
  - **Vehicle**, **anti-PD-1**, and **anti-PD-1 and IOA-244**
  - **AUC** comparisons:
    - **Vehicle**, **anti-PD-1**, and **IOA-244 + anti-PD-1**
    - Improved response to anti-PD-1 tumour regression
Preliminary data from Incyte (AACR 2018) confirms that selective PI3Kδ inhibition in combination with inhibition of PD-1 significantly increases the intratumoral CD8+ : Treg ratio and reduces the number of intratumoral Tregs in patients with advanced solid tumours.

Additionally, the combination of INCB050465 plus pembrolizumab results in peripheral CD8+ T-cell activation.

Encouraging response rates are observed including a CR in an anti-PD-1 refractory melanoma patient.

Based on IOA-244’s differentiated chemotype and binding mode, and by focusing directly on monotherapy in solid tumours, iOnctura expects to rapidly advance its program and confirm a best in class profile.
Besides haematology indications, PI3Kδ is also highly expressed in certain solid tumour indications.
### PI3Kδ as an oncology target

**PI3Kδ as an intrinsic driver of cancer in solid tumours**

<table>
<thead>
<tr>
<th>Indication</th>
<th>Observation</th>
<th>Effect of PI3Kδ inhibition / inactivation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuroblastoma</td>
<td>Overexpression of PI3Kδ in primary samples and cell lines</td>
<td>Impaired cell growth and survival</td>
<td>Boller et al 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apoptosis of SH-SY5Y cells</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Elevated PI3Kδ activity dampens the activity tumour suppressor PTEN</td>
<td>Inhibition of <em>in vitro</em> proliferation</td>
<td>Tzenaki et al 2012</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>PI3Kδ expression increases during cancer progression</td>
<td>Inhibition of <em>in vitro</em> proliferation and abrogation of tumour growth <em>in vivo</em></td>
<td>Tzenaki et al 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Goulielmaki et al 2018</td>
<td></td>
</tr>
<tr>
<td>Liver cancer</td>
<td>PI3Kδ expression increases during cancer progression</td>
<td>Inhibition of <em>in vitro</em> proliferation and abrogation of tumour growth <em>in vivo</em></td>
<td>Yue and Sun 2018</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ko et al 2018</td>
<td></td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>PI3Kδ expression significantly correlates with poor prognostic factors and shorter patient survival</td>
<td>-</td>
<td>Ji et al 2016</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>PI3Kδ expression is an independent predictor of overall survival</td>
<td>Inhibition of CRC cell growth, migration and invasion <em>in vitro</em>, abrogation of tumour growth <em>in vivo</em></td>
<td>Chen et al 2019</td>
</tr>
<tr>
<td>Merkel cell cancer</td>
<td>High expression of PI3Kδ in isolated patient sample</td>
<td>Complete clinical response induced by idelalisib in a patient with stage IV Merkel-cell carcinoma</td>
<td>Shiver et al 2015</td>
</tr>
</tbody>
</table>

**iOnctura will be the first to explore PI3Kδ expression as a patient enrichment strategy in clinical development**
PI3Kδ as an oncology target

Initial preclinical evidence of IOA-244 intrinsic anti-cancer activity

- **Effect on breast cell line**
  - inhibition of P-AKT in MDA-MB-231 cell lines
  - Next steps: *in vitro* proliferation assay and *in vivo* xenograft model

- **Effect on liver cell lines**
  - inhibition of proliferation of liver cell lines *in vitro* in line with published data from Ko *et al* and Yue *et al*
  - Next steps: *in vivo* xenograft models with PIK3Cd high expressing PDX cells and a liver cancer cell line
PI3Kδ as an oncology target

**PI3Kδ as an intrinsic driver of cancer**

**Immune effects only**
4T1 / Balb/C

**Combination immune + intrinsic**
MDA-MB-231 / Nude

**Intrinsic effects only**
MDA-MB-231 / NSG

Gouielamki (2018)
Priority indications for monotherapy and immunotherapy combinations

**Improve on SoC**

- Focus on indications wherein (i) where poor prognosis is correlated with MDSCs and Tregs and/or low CTL/Treg ratios and (ii) the oncogenic transformation may be related to activation of the PI3Kδ pathway

**Combine with immunotherapy**

- Explore indications where it is possible to enhance or break resistance to IO based therapies
- Immunotherapy has greatly improved outcomes in certain indications, but there are still around two-thirds of patients who don’t respond
- IOA-244 is expected to enhance the response to IO by recalibrating the immune response & mediating a direct anti-cancer effect

**Lymphoma (fast to registration path)**

- PI3Kδ inhibitor idelalisib is approved for the treatment NHL but has a black box warning
- Opportunity for a safer targeted therapy with fast route to registration
First in human clinical trial

**Phase I design: bringing together the dual MOA of IOA-244**

- Study design (CTA submission April 2019):
  - 28 day cycle, once daily dosing, **two indications selected (high Pi3Kδ expression and Treg/MDSC burden)**
  - Dose escalation to generate PK/PD readouts in blood
  - Mechanism of action to be demonstrated in tumour biopsies at Biologically Effective Dose (BED)

### Part A

- **Cohort 1 (10 mg)**: No DLT, PK/PD, BED
- **Cohort 2 (20 mg)**: No DLT, PK/PD, BED
- **Cohort 3 (40 mg)**: No DLT, PK/PD, BED
- **Cohort 4 (80 mg)**: No DLT

### Part B

- Expansion cohorts at BED
- MTD
First in human clinical trial

**Study design: Part B expansion phase in dedicated cohorts**

**Part B**

**Group 1:** Indication A
Monotherapy arm at BED

**Group 2:** Indication B
Monotherapy arm at BED

**Group 3:** Indication C
Monotherapy arm at BED

**Group 4:** Indication A
Combination arm at BED-1
SOC chemotherapy

**ADDITIONAL GROUP**

**Group 5:** Indication B
Combination arm at BED-1
PD (L)-1

---

**Part A**

Dose IOA-244

BED

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**Treatment period**

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**Post-treatment period**

- Safety follow up
- Survival follow up
Clinical biomarker strategy
Confirmation of immune modulation

Circulating biomarkers
• ↓ Treg counts
• ↑ IFNγ response factors (CXCL9, CXCL10)
• ↑ NK cell activity (e.g. granzyme B)
• ↓ MDSC counts

Tumour biopsy (pre- v post-treatment) IHC
• CD8+ T cell: Treg ratio
• PI3Kδ protein levels
• Macrophages, MDSCs, NK cells

Idelalisib: circulating Treg changes

INCB-50465:IFNγ and NK cell activity

Data: Ysebaert L.

Kirkwood et al. 2018

INCB050465:CD8+:Treg changes

PI3Kδ expression: breast cancer

Kirkwood et al. 2018

Goulielmaki et al. 2018
**PI3Kδ competitive landscape**

**First generation inhibitors have major deficiencies**

*IOA-244 has the potential to be first-in-class in solid tumours*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IOA-244</th>
<th>idelalisib</th>
<th>duvelisib</th>
<th>umbralisib (TG-1202)</th>
<th>HMPL-689</th>
<th>parsaclisib (INCB-465)</th>
<th>ME-401</th>
<th>nemiralisib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotype</td>
<td>Unique</td>
<td>Idelalisib</td>
<td>Idelalisib-like</td>
<td>Idelalisib-like</td>
<td>Idelalisib-like</td>
<td>Idelalisib-like</td>
<td>Unique</td>
<td>Unique</td>
</tr>
<tr>
<td>Selectivity</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>ATP competitive</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>PK</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Tolerability</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Combination potential</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No (COPD)</td>
</tr>
<tr>
<td>Haematology development</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Inhaled

IOA-244 has a unique and ideal profile for development in solid tumours as immuno-oncology drug
IOA-244

- **is a best in class PI3Kδ inhibitor** with a unique chemical structure, exquisite selectivity and DMPK properties and superior safety profile
- **is developed as a novel targeted therapy** for solid tumours that
  - are burdened by an immune-suppressive TME
  - over-express PI3Kδ
- **will start first-in-human studies in patients** in 2019

IOA-289

- **is a novel first in class autotaxin inhibitor** with superior potency and *in vitro* safety profile
- **is being developed as a first-in-class targeted therapy** for solid tumours
  - that over express ATX
  - are subject to lipid mediated immune suppression
- **has demonstrated preclinical proof-of-concept** in oncology and fibrosis

Adapted from Hanahan and Weinberg Cell 2011, 144, 646–674
How will iOnctura compete?

• The current clinical landscape of IO is exciting and also crowded
  – We will target selected indications with strong rationale
• Many IO agents concentrate on a few targets such as PD-1; anti-PD-1/L1 combination
  – We will investigate novel combinations beyond the PD-1 axis
• Many trials are small, and single-center that may fail to recruit enough patients
  – We will use our extensive network and sites with high patient engagement in the indications we are targeting

From: Comprehensive analysis of the clinical immuno-oncology landscape
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