PI3Kδ: A New Era in Immuno-Oncology

Zoë Johnson
Who we are

**iOncitura: 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
### 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><strong>IOA-244</strong></td>
<td></td>
<td></td>
<td>PI3Kδ inhibitor</td>
<td>Q1 2019</td>
</tr>
<tr>
<td>• Selective inhibition of Tregs &amp; MDSCs</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>• Inhibition of tumour cell proliferation and survival</td>
<td></td>
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<tr>
<td><strong>IOA-289</strong></td>
<td></td>
<td></td>
<td>ATX inhibitor</td>
<td>Q1 2020</td>
</tr>
<tr>
<td>• Increase T cell infiltration</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Inhibition of tumour cell proliferation, metastasis and angiogenesis</td>
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<tr>
<td><strong>IOA-290</strong></td>
<td></td>
<td></td>
<td>ATX inhibitor</td>
<td>Q1 2020</td>
</tr>
<tr>
<td>• Inhibition of LPA mediated fibrosis and inflammation</td>
<td></td>
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<tr>
<td><strong>IOA-237</strong></td>
<td></td>
<td></td>
<td>Anti-CD73</td>
<td>TBD*</td>
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<tr>
<td>• Relieve effector T cell suppression in TME</td>
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</tbody>
</table>

*Potential outlicensing/partnering program*
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 is the first company to evaluate single agent immuno-modulatory effects of a specific PI3Kδ inhibitor in patients with solid tumours

• iOnctura is the first company to explore the emerging 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
IOA-244 is a non-competitive inhibitor of ATP

- Cancer cells and immune cells turnover large amounts of ATP
- An ATP competitive inhibitor will be less potent in highly metabolic cells, whereas a non-ATP competitive inhibitor will not be influenced
  - Increasing the ATP concentration from 20 to 2000 µM increases the IC50 ofidelalisib on PI3Kδ from 7 to 122 nM
  - Competition studies indicate that IOA-244 potency is unchanged in increasing conditions of ATP
- This confers a potential advantage for IOA-244 in a reduced dose level and/or frequency in patients
First generation inhibitors lack selectivity

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

<table>
<thead>
<tr>
<th>Company</th>
<th>Product</th>
<th>Status</th>
<th>Selectivity (vs PI3Kγ)</th>
<th>Chemotype</th>
<th>Indications pursued</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilead Sciences</td>
<td>Idelalisib</td>
<td>Launched</td>
<td>20 fold</td>
<td>Idelalisib</td>
<td>Approved for CLL, FL and SLL</td>
</tr>
<tr>
<td>Incyte</td>
<td>INCB-465</td>
<td>Phase I/II</td>
<td>&gt; 1,000 fold*</td>
<td>Idelalisib like</td>
<td>Solid tumours +/- pembrolizumab, NHL</td>
</tr>
<tr>
<td>iOnctura</td>
<td>IOA-244</td>
<td>IND Ready</td>
<td>&gt; 1,000 fold</td>
<td>Unique</td>
<td>Solid tumours +/- avelumab</td>
</tr>
<tr>
<td>MEI Pharma</td>
<td>ME-401</td>
<td>Phase III</td>
<td>~400 fold</td>
<td>Unique</td>
<td>CLL, NHL, haematological</td>
</tr>
<tr>
<td>Chi-Med</td>
<td>HMPL-689</td>
<td>Phase I</td>
<td>~100 fold</td>
<td>Idelalisib like</td>
<td>Cancer, haematological</td>
</tr>
<tr>
<td>TG Therapeutics</td>
<td>TGR-1202</td>
<td>Phase III</td>
<td>~50 fold</td>
<td>Idelalisib like</td>
<td>NHL, CLL</td>
</tr>
<tr>
<td>Amgen / CRUK</td>
<td>AMG-319</td>
<td>Phase I</td>
<td>~50 fold</td>
<td>Idelalisib like</td>
<td>HNSCC (trial discont. for safety concerns)</td>
</tr>
<tr>
<td>Verastem</td>
<td>Duvelisib</td>
<td>Launched</td>
<td>~10 fold</td>
<td>Idelalisib like</td>
<td>Approved for CLL, FL and SLL</td>
</tr>
</tbody>
</table>

- Development of PI3Kδ inhibitors in haematological indications has been hampered by poor tolerability
- Selectivity and tolerability will be the key drivers for successful development in solid tumours especially in combination with checkpoint inhibitors*

*In-house studies underway to confirm selectivity

*Despite FDA alert about clinical trials with Zydelig (idelalisib) in combination with other cancer medicines (FDA press release 14 March 2016), an investigator sponsored study started in September 2017 to evaluate Idelalisib in combination with pembrolizumab in lung cancer
This provides a strong rationale for developing PI3Kδ inhibitors in solid cancers

Okkenhaug & Vanhaesebroeck Nat Rev Imm 2013

Targeting PI3K in cancer

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 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>Impaired maintenance and functionality&lt;br&gt;Number of suppressive Treg in TME</td>
<td>Ali et al 2014, in house data&lt;br&gt;Ahmad et al 2017, in house data</td>
</tr>
<tr>
<td>Myeloid Derived Suppressors Cells</td>
<td>Highly immune suppressive</td>
<td>Number and function&lt;br&gt;Tumour eradication in combination with PDX&lt;br&gt;Function&lt;br&gt;Number of infiltrating MDSCs</td>
<td>Ali et al 2014&lt;br&gt;Kim et al 2014&lt;br&gt;Davis et al 2017&lt;br&gt;In house data</td>
</tr>
<tr>
<td>Cytotoxic CD8+ T cells</td>
<td>Kill cancer cells</td>
<td>Maintain anti-tumour immunity&lt;br&gt;Inherent anti-tumour immunity&lt;br&gt;Responses in combination with anti-PD-L1&lt;br&gt;Tumour infiltrating CD8+ T cells</td>
<td>Ali et al 2014&lt;br&gt;Bowers et al 2017&lt;br&gt;Davis et al 2017&lt;br&gt;Ahmad et al 2017, in house data</td>
</tr>
<tr>
<td>Natural Killer cells</td>
<td>Kill cancer cells</td>
<td>Not cytotoxic, but may inhibit cytokine release&lt;br&gt;Number of infiltrating NK cells</td>
<td>Herman et al 2010&lt;br&gt;In house data</td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>Produce growth factors, chemokines and ECM</td>
<td>Proliferation</td>
<td>In house data</td>
</tr>
<tr>
<td>Tumour Associated Macrophages</td>
<td>Produce immune suppressive, metastatic and angiogenic factors</td>
<td>Macrophage recruitment</td>
<td>Mouchemore et al 2013&lt;br&gt;Goulielmaki et al 2018</td>
</tr>
</tbody>
</table>

Thus IOA-244 can shift the balance from immune tolerance towards effective anti-tumour immunity!
PI3Kδ as a clinical target in Immuno-Oncology

**PI3Kδ clinically confirmed as immune checkpoint in solid tumours**

- 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.
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
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 µM</td>
<td>0.3 – 7.5 µM</td>
<td>1.2 – 3.6 µM</td>
</tr>
</tbody>
</table>

- **Treg**
  - IOA-244: [Data Graph]
  - Idelalisib: [Data Graph]
  - Duvelisib: [Data Graph]

- **CD4+ T cells**
  - IOA-244: [Data Graph]
  - Idelalisib: [Data Graph]
  - Duvelisib: [Data Graph]

- **CD8+ T cells**
  - IOA-244: [Data Graph]
  - Idelalisib: [Data Graph]
  - Duvelisib: [Data Graph]
Besides haematology indications, PI3Kδ is also highly expressed in certain solid tumour indications.

**PI3Kδ as an oncology target**

**mRNA expression levels in selected tumour types**

![Graph showing mRNA expression levels in various cancer types including DBCL, SCCHN, RCC, Mesothelioma, Sarcoma, Melanoma.](Image)
PI3Kδ protein expression in GC and OS

IHC staining for p110δ: neg (A) and pos (B)

Survival curves for gastric cancer according to p110δ expression: OS (A) and RFS (B)

Ji et al Int J Clin Exp Pathol 2016, 9, 9415-9421

PI3Kδ expression in gastric cancer is associated with poor OS
PI3Kδ protein expression in HCC and OS

Survival analysis of HCC patients related to p110δ protein expression


PI3Kδ expression in hepatocellular cancer is associated with poor OS
**PI3Kδ as an intrinsic driver of cancer: liver**

**In vitro cell viability**

Yue and Sun, Cell death & Disease 2018

**In vivo anti-tumour effects: Hep-G2/nude**

IHC of p110-isoforms in human liver tumor samples and non-tumor samples

**In vitro cell proliferation**

Ko, Hepatology, 2018

**In vivo anti-tumour effects: Hep3B/NSG**

Ko, Hepatology, 2018
PI3Kδ as an oncology target

**PI3Kδ as an intrinsic driver of cancer: new literature**

- iOnctura’s strategy is to inhibit tumour immune evasion and target intrinsic cancer drivers
- Emerging data strengthen the hypothesis that PI3Kδ is upregulated in selected solid tumour indications

**PI3Kδ expression: breast cancer & macrophages**

**Human tissue**

- p110δ staining positivity, quantified as the percentage of p110 δ-stained cancer cells was much higher in grade II and III carcinomas compared with grade I carcinomas

**Tumour intrinsic (+ macrophage) effects**

- Nude mice have normal B cells, macrophages, NK cells and APCs and can be “leaky”
- However the strong inhibition suggests that intrinsic cancer cell PI3Kδ plays a role in tumour control

**Immune effects (no cancer intrinsic expression)**

- 4T1 is a mouse breast cancer cell line which does not express PI3Kδ
- These cells can be successfully implanted into T cell competent mice
- The effects of PI3Kδ inhibition in this model are therefore driven by the immune response
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
Priority indications for monotherapy and immunotherapy combinations

**Mesothelioma**

*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
- MPM has a high burden of Tregs and a high expression of PI3Kδ

**Melanoma**

*Combine with Immunotherapies*

- Explore indications where it is possible to enhance or break resistance to IO based therapies
- Immunotherapy has greatly improved outcomes in melanoma 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/Leukaemia**

*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
Phase I solid tumour trial design

- Study design:
  - 28 day cycle, once daily dosing
  - Dose escalation to generate PK/PD readouts in blood
  - Mechanism of action to be demonstrated in tumour biopsies at Biologically Effective Dose (BED)
  - Initial indications: melanoma and mesothelioma
  - Establish MTD

### Cohort Design

- **Cohort 1** (10 mg)
  - No DLT
  - Screening biopsy

- **Cohort 2** (20 mg)
  - No DLT
  - PK/PD

- **Cohort 3** (40 mg)
  - No DLT
  - PK/PD

- **Cohort 4** (60 mg)
  - No DLT
  - PK/PD

### Human Exposure

- NOAEL rat
- HNSTD dog

- Dose predicted to show full target inhibition
- Dose predicted to be safe and to show partial target inhibition

**Expansion cohorts at BED**
Clinical biomarker strategy

Confirmation of on-target efficacy

- IOA-244 induces concentration dependent inhibition of PD markers on human basophils (CD63) \textit{in vitro} and on human B cells (p-Akt and CD69) \textit{in vitro} and on mouse B cells \textit{ex vivo}
- EC$_{50}$ are in a similar range across read-outs and species \textit{in vitro}
- EC$_{50}$ in a mouse \textit{ex vivo} assay after oral administration is in line with \textit{in vitro} EC50

<table>
<thead>
<tr>
<th>Biomarker read-out</th>
<th>In vitro WB HD (nM)</th>
<th>In vitro WB rodent (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basophil αIgE-induced CD63 up-regulation*</td>
<td>1380 ± 400</td>
<td>not applicable</td>
</tr>
<tr>
<td>B cell αIgM / αIgD-induced p-Akt</td>
<td>1390 ± 400</td>
<td>507 ± 12 (r) 361 ± 201 (m)</td>
</tr>
<tr>
<td>B cell αIgM / αIgD-induced CD69</td>
<td>688 ± 323</td>
<td>412 ± 90 (m)</td>
</tr>
</tbody>
</table>

*Used in Phlb for Idelalisib development

Inhibition of p-Akt 1h after oral administration (\textit{ex vivo}, mouse)

![Graph showing inhibition of p-Akt 1h after oral administration](image)

- Vehicle
- 10 mg/kg
- IOA-244 (mg/kg)

Control

Vehicle

10 mg/kg

10

3

1

[C] μM 0.88 2.3 0.56 0.25

% of inhibition

Vehicle 42% 81% 52% 37%

10 mg/kg 42% 81% 52% 37%

10 42% 81% 52% 37%

3 42% 81% 52% 37%

1 42% 81% 52% 37%
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

INCB-50465:CD8+:Treg changes

PI3Kδ expression: breast cancer
Kirkwood et al 2018 Goulielmaki et al. 2018
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 Q1 2019
- is explored as novel treatment for fibrotic indications

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 with fibrosis studies ongoing
- is in preclinical development

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
Acknowledgements

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