Preclinical development of a novel, highly selective PI3Kδ inhibitor, IOA-244, for the treatment of solid malignancies

Zoë Johnson
Our PI3Kδi has reached CTA ready status thanks to....

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Characterization of novel PI3Kδ inhibitors as potential therapeutics for SLE and lupus nephritis in pre-clinical studies

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17 March 2021
**IOA-244 is a unique PI3Kδ inhibitor**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IOA-244</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC$_{50}$ PI3Kδ</td>
<td>142 nM</td>
</tr>
<tr>
<td>ATP competitive</td>
<td>no</td>
</tr>
<tr>
<td>IC$_{50}$ PI3Kα (ratio)</td>
<td>130</td>
</tr>
<tr>
<td>IC$_{50}$ PI3Kβ (ratio)</td>
<td>20</td>
</tr>
<tr>
<td>IC$_{50}$ PI3Kγ (ratio)</td>
<td>&gt;1,000</td>
</tr>
<tr>
<td>IC$_{50}$ CD63 (hWB)</td>
<td>~ 1 µM</td>
</tr>
</tbody>
</table>
# PI3Kδ: an Immuno-Oncology target

<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>
</table>
| Regulatory T cell                  | Highly immune suppressive                    | Impaired maintenance and functionality  
↓ Number of suppressive Treg in TME                                                                  | Ali et al 2014, iOnctura              |
|                                    |                                              |                                                                                                           | Ahmad et al 2017, iOnctura            |
| Myeloid Derived Suppressor Cells   | Highly immune suppressive                    | ↓ Number and function  
↓ Tumor eradication in combination with PDX  
↓ Function  
↓ Number of infiltrating MDSCs                                                               | Ali et al 2014                           |
|                                    |                                              |                                                                                                           | Kim et al 2014                           |
|                                    |                                              |                                                                                                           | Davis et al 2017                           |
|                                    |                                              |                                                                                                           | iOnctura                               |
| Tumor Associated Macrophages       | Produce immune suppressive, metastatic and angiogenic factors | ↓ Macrophage recruitment                                                                   | Mouchemore et al 2013                 |
|                                    |                                              |                                                                                                           | Goulielmaki et al 2018                 |
|                                    |                                              |                                                                                                           | iOnctura                               |
| Fibroblasts                        | Produce growth factors, chemokines and ECM   | ↓ Proliferation                                                                                           | iOnctura                               |
| Cytotoxic CD8+ T cells             | Kill cancer cells                            | Maintain anti-tumor immunity  
↑ Inherent anti-tumor immunity  
↑ Responses in combination with anti-PD-L1  
↑ Tumor infiltrating CD8+ T cells                                                      | Ali et al 2014                           |
|                                    |                                              |                                                                                                           | Bowers et al 2017                           |
|                                    |                                              |                                                                                                           | Davis et al 2017                           |
|                                    |                                              |                                                                                                           | Ahmad et al 2017, iOnctura              |
| Natural Killer cells               | Kill cancer cells                            | ↑ Number of infiltrating NK cells                                                                        | iOnctura                               |

**PI3Kδ inhibition can shift the balance from immune tolerance towards effective anti-tumour immunity**
IOA-244 inhibits human Treg proliferation & function whilst sparing CD8\(^+\) and CD4\(^+\) T cells

- Tregs are more sensitive to PI3K\(\delta\) inhibition than CD4\(^+\) T cells, CD8\(^+\) T cells are resistant
- Dual PI3K\(\delta\)/PI3K\(\gamma\) inhibition inhibits CD4\(^+\) and CD8\(^+\) T cell proliferation to a greater extent than selective PI3K\(\delta\) inhibition
- IOA-244 significantly inhibits IL-10, a surrogate for Treg function (3 different donors)
IOA-244 significantly enhances anti-PD-1 activity

A20 syngeneic mouse model
IOA-244: 30 mg/kg BID
Anti-PD-1 10 mg/kg BIW
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
PI3Kδ drives intrinsic growth / proliferation in certain solid tumors

<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 ↑ Apoptosis of SH-SY5Y cells</td>
<td>Boller et al 2008</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>Elevated PI3Kδ activity dampens the activity tumour suppressor PTEN</td>
<td>Inhibition of in vitro 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 in vitro proliferation Abrogation of tumour growth in vivo</td>
<td>Tzenaki et al 2012 Goulielmaki et al 2018</td>
</tr>
<tr>
<td>Liver cancer</td>
<td>PI3Kδ expression increases during cancer progression</td>
<td>Inhibition of in vitro proliferation and abrogation of tumour growth in vivo</td>
<td>Yue and Sun 2018 Ko et al 2018</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 in vitro, abrogation of tumour growth in vivo</td>
<td>Yang et al 2017 Chen et al 2019</td>
</tr>
<tr>
<td>Merkel cell carcinoma</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>
IOA-244 can reverse tumour growth in PI3Kδ high tumours

The expression levels of p110δ protein increase during MDA-MB-231 tumour growth in mice which is in accordance with human breast cancer samples. The expression levels of p110α were unaffected Goulielmaki et al 2018
PI3K expression levels in selected tumour types

PIK3CD is more highly expressed than PIK3CA in uveal and cutaneous melanoma based on FGM profiling

Moek et al Annals of Oncology 2017
IOA-244 inhibits tumour growth in a melanoma PDX

We are developing an IHC test for clinical use to:
- Test the prevalence of PI3Kδ expression in solid tumour indications
- Examine any correlation between PI3Kδ expression and outcome in our phase I trial
- Eventually support a companion diagnostic test

<table>
<thead>
<tr>
<th>PDX</th>
<th>PIK3CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>8.7</td>
</tr>
<tr>
<td>MEXF2104</td>
<td>8.91</td>
</tr>
</tbody>
</table>
Clinical PK/PD biomarker strategy

- IOA-244 induces concentration dependent inhibition of PD markers on human basophils (CD63) in vitro and on human B cells (p-Akt and CD69) in vitro and on mouse B cells ex vivo.

- EC_{50} are in a similar range across read-outs and species in vitro.

- EC_{50} in a mouse ex vivo assay after oral administration is in line with in vitro EC_{50}.

<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>-</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>

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

[C] μM 0.88 2.3 0.56 0.25

% of inhibition

Vehicle 10 mg/kg 10 3 1
Control IOA-244 (mg/kg)

42% 81% 52% 37%
IOA-244 has received regulatory approval from MHRA

Study design

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

- Screening biopsy
  - Cohort 1
  - No DLT
  - PK/PD
  - BED

- Cohort 2
  - No DLT
  - PK/PD
  - BED

- Cohort 3
  - No DLT
  - PK/PD
  - BED

- Cohort 4
  - PK/PD
  - BED

Part B: Expansion cohorts

Dose predicted to show full target inhibition

Dose predicted to be safe & show partial target inhibition

IOA-244

NOAEL rat
HNSTD dog
Part B: Expansion phase in selected patient cohorts

- **Group 1:** Melanoma
  Monotherapy arm at BED

- **Group 2:** Uveal melanoma
  Monotherapy arm at BED

- **Group 3:** Mesothelioma
  Monotherapy arm at BED

- **Group 4:** Mesothelioma
  Combination arm at BED-1
  Pemetrexed/platinum chemotherapy

- **Group 5:** Melanoma
  Combination arm at BED-1
  Avelumab 800mg
Development of an IHC test to support clinical testing

- We have developed an accurate, precise IHC test for PI3Kδ expression in tumour tissue
- Test will initially be used to evaluate PI3Kδ protein levels in patient biopsies

PI3Kδ - mesothelioma

PI3Kδ expression
Summary

• IOA-244 is a highly selective and novel PI3Kδ inhibitor with a unique chemotype

• We will clinically test the hypothesis that IOA-244
  • can modulate the immune response in the tumor microenvironment (TME)
  • can modulate cellular and soluble biomarkers in the circulation, predicting the changes in the TME
  • can directly affect tumour progression as a monotherapy

• IOA-244 may represent a novel, orally bioavailable therapeutic strategy for treatment of solid tumor indications which
  • have a high burden of Treg and / or MDSCs or a high Treg:CD8+ T cell ratio
  • have a high expression of PI3Kδ

• Phase Ib cohort expansion indications, combinations and further readouts under investigation
iOnctura open for collaborations...

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