Conclusions of the Paediatric Strategy Forum on checkpoint inhibitors in combination
Paediatric Strategy Forum on checkpoint inhibitors in combination

- Paediatric Strategy Forums
- Format of Forum on checkpoint inhibitors in combination
- Overview of monotherapy trials of checkpoint inhibitors
- The Way Forward - Checkpoint inhibitors in lymphomas and hypermutant malignancies
- Checkpoint inhibitors in combination
- Conclusions
• **Specific issue**

• **Goal** - To *share* information between all stakeholders, in a pre-competitive setting, to *inform* paediatric drug development strategies and *subsequent* decisions

• **This will be achieved by** providing a unique opportunity to facilitate *dialogue* and enable constructive interactions between *all* stakeholders on *topics requiring discussion in drug development* in children and adolescents with malignancy
ACCELERATE-EMA-FDA
Paediatric Strategy Forums

- **First Forum** for ALK Inhibition in Paediatric Malignancies - EMA - January 2017 - 6 products; 5 companies
- **Second Forum** - Medicinal Product Development for Mature B cell Malignancies in Children - EMA - November 2017 - 20 products; 14 companies
  
- **Third Forum** - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies - EMA - September 2018 - 20 products; 16 companies (32 EOI)

- **Fourth Forum** - Medicinal Product Development for Acute Myeloid Leukaemia in Children - Rotterdam - 11-12 April 2019 28 products; 18 companies

  **Target or disease focussed**

  **Continually developing and adapting to needs**
• Immune checkpoint inhibitors have shown impressive success in some adult malignancies
• Results of early phase trials in children of single agent checkpoint inhibitors are now available
• Some combination studies are in progress and others are planned

Opportune to review early results of early phase trials in children and consider opportunities for paediatric studies of check-point inhibitors in combination
Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

EMA
September 2018

73 Participants at the EMA and 25 by remote access

- 20 Medicinal products discussed
- 16 Pharmaceutical companies (29 EOI)
- European and North American experts in paediatric immunotherapy and drug development
- Patient representatives from Unite2Cure (Europe) and Children’s Cause for Cancer Advocacy (US)
- Regulators from EU national competent authorities, EMA & US FDA
- NCI
### Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

#### Companies - Participated in the Forum
- AstraZeneca
- Autolus Ltd
- BeiGene Inc.
- Boehringer Ingelheim
- BMS
- Celgene
- Immunicum AB
- Merck KgaA
- Merck, Sharp & Dohme (MSD)
- Novartis
- Pfizer inc
- Regeneron Ireland U.C
- Roche
- Sanofi
- Syndax Pharmaceuticals
- Tesaro Bio GmbH

#### Companies - Expressed an interest but did not participate
- Bayer AG
- CATS Ergomed
- Faron Pharmaceuticals Ltd.
- GlaxoSmithKline R&D
- Incyte Biosciences
- IPSEN
- Janssen Research & Development, LLC
- Kinesys
- Les Laboratoires Servier
- MedImmune
- MSD
- PPD
- PsiOxus Therapeutics Limited
Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Programme

• Immunological environment and immunotherapeutic challenge of paediatric malignancy

• Rational design of clinical immunotherapy combination trials for maximum benefit and information

• Review of Paediatric Investigation Plans of Checkpoint inhibitors

• Results of Checkpoint inhibitors in early phase clinical studies

• The Way Forward - Checkpoint inhibitors in lymphomas and hypermutant malignancies

• Presentation by pharma of Checkpoint inhibitor combinations
Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Medicinal Products Presented at the Forum

- Pembrolizumab
- Atezolizumab
- Nivolumab
- Ipilimumab
- Pembrolizumab and chemotherapy
- Nivolumab and brentuximab
- Avelumab and standard of care and axitinib
- Cemiplimab and radiotherapy
- Niraparib
- Tislelizumab
- Entinostat
- CTLA- 4
- Nivolumab and ipilimumab

- Tremelimumab and durvalumab
- Anti - LAG 3
- Anti-LAG-3 mAb - Boehringer Ingelheim
- TSR-033
- NKTR
- Bispecific CD20xCD3 antibody
- Isatuximab
- M7824
- TSR 022
- Anti TGF beta – Sanofi
- Ilixadence
- ATMP
- ATIMP
Paediatric Strategy Forum on checkpoint inhibitors in combination

- Paediatric Strategy Forums
- Format of Forum on checkpoint inhibitors in combination
  - Overview of monotherapy trials of checkpoint inhibitors
  - The Way Forward - Checkpoint inhibitors in lymphomas and hypermutant malignancies
  - Checkpoint inhibitors in combination
  - Conclusions
Overview of monotherapy trials of checkpoint inhibitors

317 Patients recruited into early phase studies of three checkpoint inhibitors

- RP2D and safety profile essentially the same as adults
- Low toxicity
- No major untoward effects on the developing immune system
- Limited informative tumour material
### Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>Enrolled</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>33</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>Adrenocortical carcinoma</td>
<td>5</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>5</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Non-rhabdomyosarcoma soft tissue</td>
<td>13</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Malignant ganglioglioma</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Lymphoepithelial carcinoma</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ORR - All - 14% (20/317); Hodgkin’s 36% (12/33); Excluding Hodgkin’s 2.8% (8/284)**
Lack of clarity of the mechanism of action of checkpoint inhibitors in children

- Lack of biomarkers
- Majority of paediatric tumours – cold(ignored tumours)
- Hodgkin's Disease - different mechanism infiltrate of T4 cells - histological subtype specific

van der Woude LL, et al.
Trends Cancer
2017;3:797-808
Conclusions

- Priority - to understand the immune microenvironment of paediatric cancers at the different stages of treatment by standardised, harmonised and integrated studies across histologies.
- Tumour biopsy at the time of enrolment, should be considered as a prerequisite of entering early clinical trials of checkpoint inhibitors; however the results of the biopsy should potentially benefit the patient.
- High priority should be given to considering combining biological data of 3 early phase studies of checkpoint inhibitors.
Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Activity of checkpoint Inhibitors as monotherapy in children

Conclusions

No benefit to children with malignancy to have more trials of other checkpoint inhibitors with the same mechanism of action until there is more scientific knowledge.

*In the EU a product specific waiver could be submitted supported by academia based on scientific evidence of lack of therapeutic benefit for other checkpoint inhibitors*

*Similar a modification of an existing Paediatric Investigational Plan could be submitted*
Paediatric Strategy Forum on checkpoint inhibitors in combination

- Paediatric Strategy Forums
- Format of Forum on checkpoint inhibitors in combination
- Overview of monotherapy trials of checkpoint inhibitors
  - The Way Forward - Checkpoint inhibitors in lymphomas and hypermutant malignancies
    - Checkpoint inhibitors in combination
    - Conclusions
The way forward for checkpoint Inhibitors in lymphomas
Hodgkin's Disease

- ORR -36%
- Await the results of ongoing studies which evaluate the role of checkpoint inhibitors in Hodgkin's Disease
- Randomised studies are very valuable scientifically and should be always considered
- As the response to monotherapy with checkpoint inhibitors should be improved, combinations should be developed
- Checkpoint inhibitors might allow other components of therapy to be replaced
<table>
<thead>
<tr>
<th><strong>Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The way forward for checkpoint inhibitors in lymphomas</strong></td>
</tr>
<tr>
<td><strong>Primary Mediastinal B Lymphoma</strong></td>
</tr>
<tr>
<td>• ORR of checkpoint inhibitors 41%</td>
</tr>
<tr>
<td>• Need for randomized trials with international and adult collaboration evaluating anti-PD1 combination with standard backbones</td>
</tr>
<tr>
<td>• Consider enrolling children on adult studies - separate cohort</td>
</tr>
<tr>
<td><strong>Anaplastic Large Cell Lymphoma</strong></td>
</tr>
<tr>
<td>• Limited clinical experiences but strong biological background</td>
</tr>
<tr>
<td>• Phase II trial of nivolumab for paediatric and adult relapsing/refractory ALK+ ALCL</td>
</tr>
</tbody>
</table>
The way forward for checkpoint inhibitors in hypermutated tumours

Original Article

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

The way forward for checkpoint inhibitors in hypermutated tumours

- Response rate **ORR 69%** in hypermutated tumours (International Biallelic Mismatch Repair Deficiency Consortium trial)

- Definition - hypermutated tumours >10/mb and ultrahypermutation as >100/MB (Campbell et al, Cell (2017), https://doi.org/ 10.1016/j.cell.2017.09.048)

**Conclusions**

- Consolidate data through global entry on International Biallelic Mismatch Repair Deficiency Consortium trial
- Evaluate combinations
- Evaluate hypermutation at relapse – however lack of activity in paediatric phase II trials of checkpoint inhibitors to date suggests that “clinically relevant” hypermutation is uncommon
Paediatric Strategy Forum on checkpoint inhibitors in combination

- Paediatric Strategy Forums
- Format of Forum on checkpoint inhibitors in combination
- Overview of monotherapy trials of checkpoint inhibitors
- The Way Forward - Checkpoint inhibitors in lymphomas and hypermutant malignancies

- Checkpoint inhibitors in combination
- Conclusions
Paediatric Strategy Forum - Immune Checkpoint Inhibitor Combinations in Paediatric Malignancies

Combinations presented at the Forum

In the region of 20 very recently opened or soon to open studies of checkpoint inhibitors in combination

- Chemotherapy/anti angiogenics
- Radiotherapy
  - Concept of addition of checkpoint inhibitor to established therapy
- PARP Inhibitors
  - Design – enrichment based on “BRCA” signature
- HDAC inhibitors
- Other checkpoint Inhibitors
  - Anti-CTLA-4
  - Anti-LAG-3

Other immunoncology products

- Monoclonal antibodies directly targeting tumour antigens.
- Combined checkpoint inhibitor and anti-TGF-beta
- Anti-TIM-3
- Anti-TGF-beta
- Cell therapy
Combinations

How to identify the best choices of combinations for the treatment of children with cancer?

• **Combinations need to be based on strong scientific rationale in paediatrics**

• **Combinations being studied in adults to boost anti-PD-1/PD-L1 response to tumour neoantigens have limited paediatric applicability - absent additional scientific rationale**
Combinations

• Strategies should be **based on immunological landscape**
  • Intra-tumoural reactive T cell cells
  • Excluded reactive T cell cells
  • No tumour reactive lymphocytes

• Development in paediatrics should be **considered EARLY**
• Immune checkpoint inhibitor combinations should be evaluated in hypermutated tumours and lymphomas to improve response rates
• Combinations in which checkpoint inhibitors are “added” to established therapy - very difficult to interpret without randomised studies and “controls”
Combinations

- Global industry supported, academic sponsored studies with compounds from different pharmaceutical companies using a master protocol in rare populations have considerable merit
- These protocols should be designed with “intent to file”
Conclusions

• Monotherapy with checkpoint Inhibitors in children - very limited activity in children except for lymphomas, hypermutant tumours and rare paediatric tumours
• Except for hypermutation there are no clearly defined biomarkers
• The immune microenvironment of paediatric cancers needs to investigated
• Immune Checkpoint Inhibitor Combinations should be evaluated in lymphomas and hypermutated tumours
• Combinations of checkpoint inhibitors should be explored in paediatrics based on hypotheses and scientific data and not only because these combinations are being evaluated in adults
• Need for international inter-company registry of early and late adverse effects