Mind the Gap: Challenges in First-in-Man Evaluation of Immuno-Oncology Drugs

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Oncology First-in Man Principles

Key ethical/scientific principle:

• Expose a minimal number of subjects to an unknown risk and at the same time to obtain information for a safe development in later phases with a larger number of subjects.
  – An adequate risk/benefit evaluation is the key

...but also

• Avoid exposing FIM participants to doses unlikely to have any biological effect

• Main scientific outcome: Dose and schedule(s) as single agent based on objective parameters (safety, PK, PD, activity...)

When Benefit Enters to Play...

• The main concern during drug development is the risk. Benefit evaluation remained as minor and somewhat pessimistic.

• There were “fixed benefit categories”:
  • Metastatic solid tumors progressing to all approved therapies: Phase 1 as a “compassionate trial”
  • Metastatic tumor for which there is an approved treatment (but greater benefit is expected from the intervention): “hope to prolong survival”

• For cytotoxics and most targeted agents there was not real hope that treatment could do other than prolonging life and benefiting quality of life.

• This changed with checkpoint inhibitors
Principles of Non-Clinical Evaluation

• Main goals of non-clinical evaluation:
  – identify the pharmacologic properties of a pharmaceutical;
  – establish a safe initial dose level for the first human exposure; and
  – understand the toxicological profile of a pharmaceutical (e.g., identification of target organs, exposure-response relationships, and reversibility)

• This Goals and the derived Guidelines (Safety ICHs) haven used with few modifications for cytotoxics, targeted agents, and now, immunotherapy
Cytotoxic FIM Paradigm

- Cytotoxics are chemicals normally without a very definite target, with a narrow therapeutic window.
- 2-3 week cycles.
- Finite number of cycles (6-cycles paradigm)
- Dose based on BSA
- IV route in many cases because the narrow therapeutic window
- Treatment interruptions needed to allow for toxicity recovery
- More is better: doses pushed up to MTD
- MTD based mostly in DLTs
- Well characterized toxicity with adequate CTCAE grading
- Histology driven without biomarker
- The non-clinical evaluation system was developed for them ➔ preclinical toxicology together with preclinical efficacy to calculate a safe initial dose and the margin of safety
Targeted Agents

- Small molecules or biotechnology-derived products created with some biological rationale
- Wider therapeutic index allowed for:
  - Oral formulation of fixed doses
  - Continuous dosing until progressive disease
  - Dosing at home under patient’s responsibility
  - Variability in oral absorption
- Co-development with biomarkers
- Non-clinical safety and efficacy models started to fail
  - Off-target effects → multikinase inhibition
  - Different target affinity across species
- Dose estimate based on DLTs resulted more and more difficult
  - In 201 Ph1 trials with 119 cytotoxics vs. 82 non-cytotoxics, DLTs were identified in 89% vs 52%*
  - Exposure-based PK/PD models started to be the rule

Targeted Agents Phase 1 development

- Initial clinical development started to change
  - Phase 0 trials (microdosing)
  - Healthy volunteers studies
  - Bayesian designs to estimate MTD
  - Dosed selection based in biological effective dose (BED)
  - Multiple biopsies to assess target engagement in tumor and surrogate tissues
  - Phase 1 trials included several dose/schedule evaluations and/or cohort expansions → Ph1 trials with Ph2 size.

- Things that did not change:
  - CTCAE used for AE evaluation
  - DLT evaluation window stayed set at 3-4 weeks for pragmatic reasons
  - Increasing doses tend to increased activity but also toxicity
New Issues with Targeted agents

• New toxicities appeared:
  – Skin, muscle, liver, immunosupression...
  – ...and other disappeared or changed: bone marrow, alopecia
• Compliance and cost are new players to consider
• Lack of overlapping toxicity with cytotoxics, allowed for successful combinations though without a clear biological rationale
• Despite biological rationale, combinations of targeted agents resulted difficult with some exceptions
  – BRAF+MEK inhibitors, pertuzumab+trastuzumab...
  – Cytotoxic-free treatment has been more the exception than the rule
• Overall targeted agents did not cure metastatic cancer but incrementally improved OS with better tolerability and less intensive supportive care
  – Few of them made a big impact like imatinib, trastuzumab, rituximab...
  – In most occasions chemotherapy remained as treatment cornerstone
Is Immunotherapy (IT) Anything New?

What it is not new:
- Previous IT drug were not “targeted”
- Drugs like IL-2, BCG, interferons are natural products with many functions
- Allogenic BMT has a graft vs. tumor effect
- Small impact in survival with lots of toxicity
- Rituximab, daratumumab, alemtuzumab can elicit ADCC (NK activation) and complement activation by binding to tumor-specific surface antigens
- Also, it is not new our limited understanding of the MoA

What it is new:
- Checkpoint inhibitors stimulate T-cell response against tumors as a primary mechanism of action
- Against surface molecules (lymphocytes and tumors) that are directly involved in antitumor immune-surveillance
- They work across indications and in tumors not considered susceptible to immunotherapy
- Produce adverse events related with the activation of the immune system
- For the first time in a long time the word “cure” can be used for patients with metastatic solid tumors.
Checkpoint inhibitors have a Novel Adverse Event Profile

Target Organs

- Hypophysitis
- Thyroiditis
- Adrenal insufficiency
- Enterocolitis
- Dermatitis
- Pneumonitis
- Hepatitis
- Pancreatitis
- Motor and sensory neuropathies
- Arthritis

- Less common: hematologic, cardiovascular, ocular, renal

Time Course

![Graph showing the time course of toxicity grades over weeks](image)
Other irAEs Characteristics

• Not clear dose/toxicity relationship. Important idiosyncratic component
• Human safety profile not predicted by non-clinical toxicology
• No safety biomarkers available: we never cared about this before...
• Lack of specific supportive treatment: discontinuation → steroids → anti-TNFs
• Conflicting usage of immunosuppressants in a context of enhanced immune system activation against tumor
• Difficult balance between treatment discontinuation due to SAEs vs. potentially life-saving therapy
• irAEs might be correlated with antitumor effect
Changes in Response Pattern

• Different efficacy patterns
  – Slower response
  – Longer time to CR
  – Pseudoprogression

• Predictive BM are still unclear:
  – Unspecific BM: Age, PS, LDH,
  – Specific: PD-L1, mutation load, immune infiltrates

• Limited value of preclinical models for safety and efficacy
  – How can dose be estimated?
The potential for cure or long term benefit is already a possibility even for patients participating in FIM trial.
IT FIM Uncertainties

• Are irAEs dose-related?
  – Are they idiosyncratic?
  – No safety BM has been evaluated so far

• There is no clear dose-exposure/effect relationship
  – Are PK/PD models useful?
  – There are responders who have received single doses
  – Some BM like PD-L1 expression have good positive predictive value but BM negative patients also respond
  – Final dose was selected during Phase 2 and 3
Ipilimumab Dose Selection

- Monkey NOAEL 10mg/kg
- Three doses of ipilimumab were compared in a double-blind phase II trial, in patients with advanced melanoma: 0.3 mg/kg, 3 mg/kg, and 10 mg/kg
- ORR and survival increased progressively with dose but also the toxicity. Therefore the 3 mg/kg dose was selected
- 10 mg/kg has been tested in adjuvant melanoma with positive results but greater toxicity
  - Only 13.4% of the patients 3 year treatment period and 40% had stopped ipilimumab after 4 doses
- Toxicity is clearly limiting treatment duration
Nivolumab Dose Selection

• Monkey NOAEL 50 mg/kg
• Human dose was selected based on anti-tumor activity and safety from a large Phase Ib study (N=306) with advanced cancer (melanoma, NSCLC and kidney) treated at doses from 0.1 to 10 mg/kg every 2 weeks.
• An integrated quantitative analysis was performed to estimate the relationships of dose-exposure response to biomarkers: receptor occupancy, AEs leading to discontinuation, objective response rate (ORR), progression free survival, and tumor growth dynamics.
• No DLT was observed at 10 mg/kg.
• Safety was similar across doses and tumor types.
• ORRs were similar between 1 and 10 mg/kg in melanoma and RCC, however higher ORRs were observed in NSCLC at 3 and 10 mg/kg
• 3 mg/kg every 2 weeks schedule was selected for registration trials.
Pembrolizumab Dose Selection

- Monkey NOAEL 200 mg/kg
- Dose selection strategy was driven by understanding of Biological Effective Dose (BED)
  - PK/PD relationship by measuring serum IL2 response between 0.005 and 10 mg/kg
  - BED was estimated at 2 mg/kg
  - In clinical studies BED and MAD of 10 mg/kg were explored from safety/efficacy standpoint and were shown to be equivalent
    - In NSCLC Keynote 001 trial was a mix of 10/3w, 10/2w and 2/3w doses. FDA accepted the uncertainties over the dose based on exposure-response relationship for safety and efficacy, melanoma dose was already 2mg/kg, supportive information from other trials.
    - Pembro is now used in the clinical at 2 mg/kg every 3 weeks in both melanoma and NSCLC indications.
Combinations

• Combination is an obvious path forward to increase efficacy
• Combinations are being developed under the same paradigm as cytotoxics or targeted agents.
• The combination ipilimumab+nivolumab is approved
• There are novel/novel combinations in development
• Combination groups:
  – 2 immunotherapies,
  – Checkpoint inhibitors with targeted agents (BRAF, ALK, VEGFR, EGFR or MEK inhibitors)
  – Checkpoint inhibitors and cytotoxics
IT Combinations: the Next Epidemic

<table>
<thead>
<tr>
<th>Immunotherapy + Immunotherapy</th>
<th>Mechanisms of action</th>
<th>Phase</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab + ipilimumab</td>
<td>Anti-PD1 + anti-CTLA-4</td>
<td>I/II</td>
<td>Gastric, TNBC, PA, SCLC, Bladder, Ovarian</td>
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<tr>
<td>Nivolumab + BMS-986016</td>
<td>Anti-PD1 + anti-LAG3</td>
<td>II/III</td>
<td>Melanoma, RCC</td>
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<tr>
<td>Nivolumab + viagenpumatucel-L</td>
<td>Anti-PD1 + vaccine</td>
<td>III</td>
<td>SCLC, GBM, NSCLC</td>
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<tr>
<td>Nivolumab + urelumab</td>
<td>Anti-PD1 + anti-4-1BB</td>
<td>I</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Atezolizumab + MOXR0916</td>
<td>Anti-PD1 + anti-CTLA-4</td>
<td>I</td>
<td>NSCLC</td>
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<tr>
<td>Atezolizumab + varilumab</td>
<td>Anti-PD1 + anti-LAG3</td>
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<td>Solid tumors, B-cell NHL</td>
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<tr>
<td>Atezolizumab + GDC-0919</td>
<td>Anti-PD1 + anti-CD27</td>
<td>II</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Epacadostat + atezolizumab, durvalumab, or pembrolizumab</td>
<td>IDO inhibitor + anti-PDL1 or anti-PD1</td>
<td>I/II</td>
<td>Solid tumors</td>
</tr>
<tr>
<td>Pembrolizumab + T-Vec</td>
<td>Anti-PD1 + vaccine</td>
<td>III</td>
<td>Melanoma</td>
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<tr>
<td>Durvalumab + tremelimumab</td>
<td>Anti-PD1 + anti-CTLA-4</td>
<td>I/II</td>
<td>Melanoma</td>
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<tr>
<td>Pidilizumab + dendritic cell/RCC fusion cell vaccine</td>
<td>Anti-PD1 + vaccine</td>
<td>II</td>
<td>RCC</td>
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<tr>
<td>Atezolizumab + bevacizumab</td>
<td>Anti-PD1 + anti-VEGF</td>
<td>II/III</td>
<td>RCC</td>
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<tr>
<td>Atezolizumab + cobimetinib</td>
<td>Anti-PD1 + MEK inhibitor</td>
<td>I</td>
<td>Solid tumors</td>
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<tr>
<td>Atezolizumab + vemurafenib</td>
<td>Anti-PD1 + BRAF inhibitor</td>
<td>I</td>
<td>Melanoma</td>
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<tr>
<td>Atezolizumab + erlotinib or alectinib</td>
<td>Anti-PD1 + EGFR or ALK inhibitor</td>
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<td>Nivolumab + bevacizumab</td>
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<td>RCC</td>
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<td>Pembrolizumab + pazopanib</td>
<td>Anti-PD1 + tyrosine kinase inhibitor</td>
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<td>RCC</td>
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<tr>
<td>Pembrolizumab + dabrafenib + trametinib</td>
<td>Anti-PD1 + BRAF inhibitor + MEK inhibitor</td>
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<tr>
<td>Durvalumab + dabrafenib + trametinib</td>
<td>Anti-PD1 + BRAF inhibitor + MEK inhibitor</td>
<td>II</td>
<td>Melanoma</td>
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<tr>
<td>Nivolumab + sunitinib, pazopanib, or ipilimumab</td>
<td>Anti-PD1 + RTK inhibitor, RTK inhibitor,</td>
<td>I</td>
<td>RCC</td>
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Non-Clinical Nivolumab plus Ipilimumab

- Preclinical rationale for complementation
- Activity assessed in syngeneic mouse models
  - Limited translatability to humans: cell of origin, sequencing...
- Synergistic PD changes with the combination in tumor microenvironment and TILs
- In vitro cytokine release: IFN-\(\gamma\), TNF-\(\alpha\)
- Cynomolgus toxicology: diarrhea in up to 40% and inflammatory changes in lymph nodes and spleen

Selby et al. PLOS ONE, 2016
FIM Nivolumab plus Ipilimumab

• G3/4 related SAEs
  – Liver: 15%
  – gastrointestinal in 9%
  – Renal in 6%
  – Isolated cases of pneumonitis and uveitis

• MTD DL2: G3 uveitis and G3 AST/ALT elevation

• DLT at DL3 was persistent G3/4 lipase elevation (!)
Current Challenges for FIM in IT

- In theory minimal anticipated dose level effect (MABEL) should be used rather than NOAEL to estimate the initial dose.
- However reliable PK/PD models are challenging
  - Lack of validated efficacy models
  - Lack of relevant toxicology species
- For combinations the situation is even more complicated
  - Synergistic efficacy should be the driver
  - Already some combinations were too toxic
- Obvious possibility also to boost autoimmunity
  - Cytokine release syndrome observed with CAR-T
- Not every toxicity is the same: Grade 5, sequels...
- The hope of long-term benefit is out there
- In many cases the only experiment possible is a clinical trial (!)
FIM Research Principles are Still Important Safeguards

• General Phase 1 built-in safety breaks still work well:
  – Enrolling patients no with other standard treatment availability
  – Expose a minimal number of patients
  – Transparent informed consent process
  – Staggered enrollment
  – Explicit stopping rules
  – Very low dose starting dose
  – Specialized Phase 1 units/oncologists/nurses
  – Cautious monitoring of known irAEs
  – Improved management of cytokine release syndrome

• Overall these unspecific safeguards are the first defense line to maintain the risk benefit within ethically acceptable boundaries
Conclusions

- Risk/benefit of IT drugs is evaluated basically under the same premises as cytotoxics or targeted agents
- There is greater uncertainty about starting dose, safety monitoring, dose escalation, etc
- Long-term survival benefit (cures) increases pressure on risk/benefit side
- No major “safety” crises happened so far during clinical development of ITs in oncology
- Combinations of ITs offer the greatest risk as they can trigger unknowns immune reactions
- All non-clinical information available needs to be integrated in the decision-making process to reduce the uncertainty
- Built-in general safety safeguards in FIM trial are still helpful to ensure an adequate risk/benefit to the trial participants