CDDF 9TH ALPINE CONFERENCE

CURRENT AND FUTURE CHALLENGES OF INNOVATIVE ONCOLOGY DRUG DEVELOPMENT

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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

* Penel et al. 2010. J New Anticancer Agents

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:

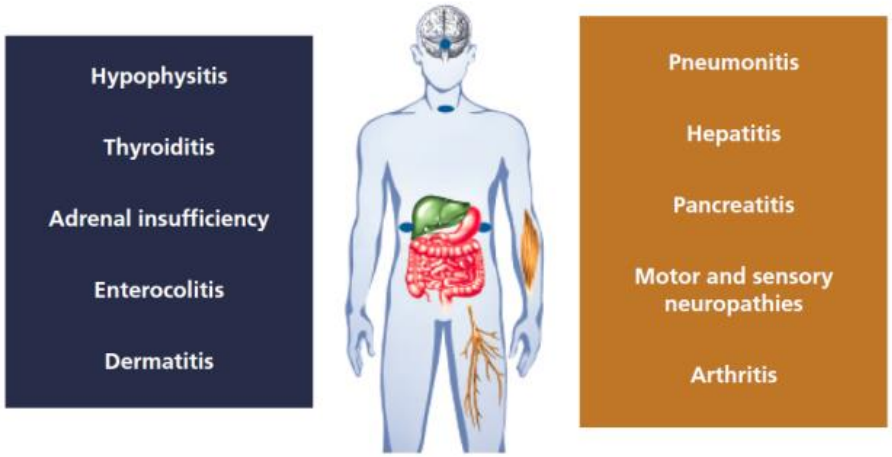
- Previous IT drug were not “targeted”
- Drugs like IL-2, BCG, interferons are natural products with many functions
- Allogenic BMT has a graft vs. tumor effect
- Small impact in survival with lots of toxicity
- Rituximab, daratumumab, alemtuzumab can elicit ADCC (NK activation) and complement activation 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.

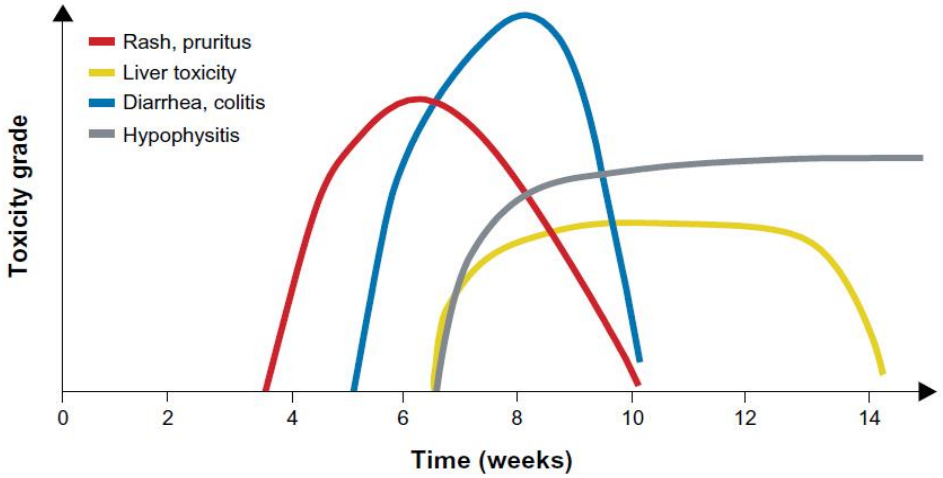
Checkpoint inhibitors have a Novel Adverse Event Profile

Target Organs



- Less common: hematologic, cardiovascular, ocular, renal

Time Course

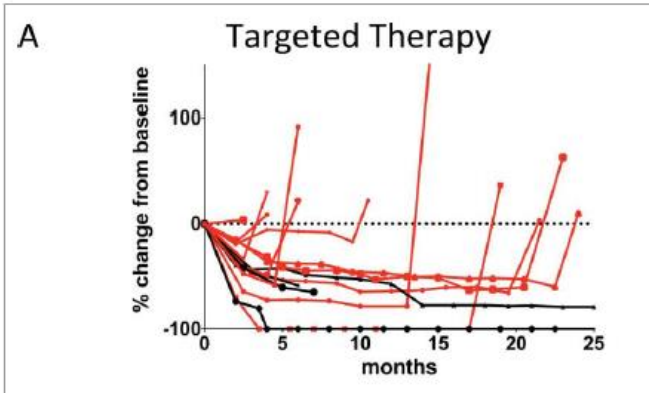


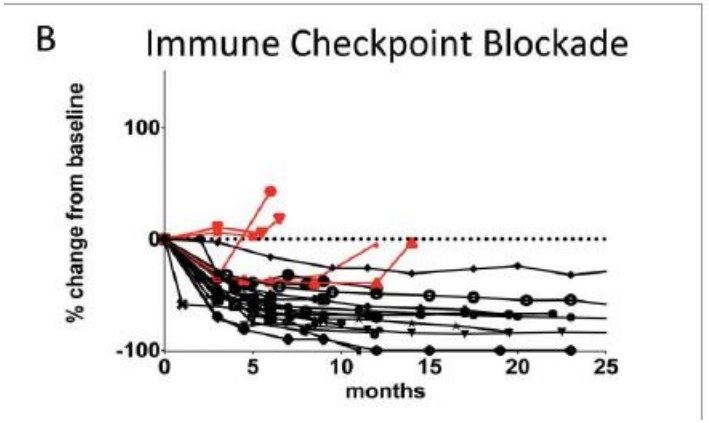
Other irAEs Characteristics

- 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

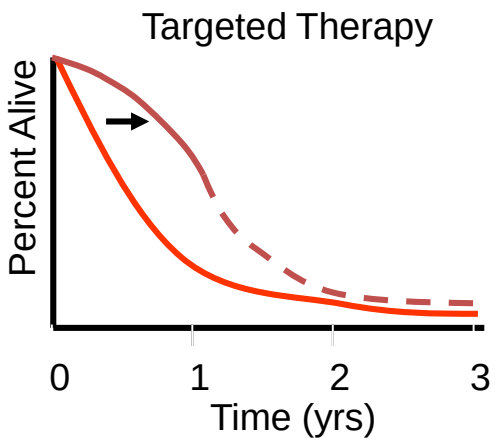
Changes in Response Pattern

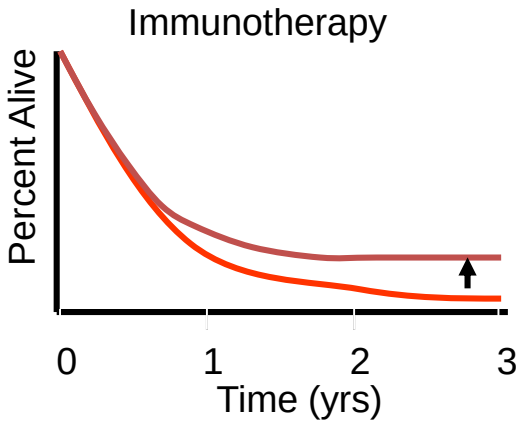
- Different efficacy patterns
  - Slower response
  - Longer time to CR
  - Pseudoprogression
- Predictive BM are still unclear:
  - Unspecific BM: Age, PS, LDH,
  - Specific: PD-L1, mutation load, immune infiltrates
- Limited value of preclinical models for safety and efficacy
  - How can dose be estimated?

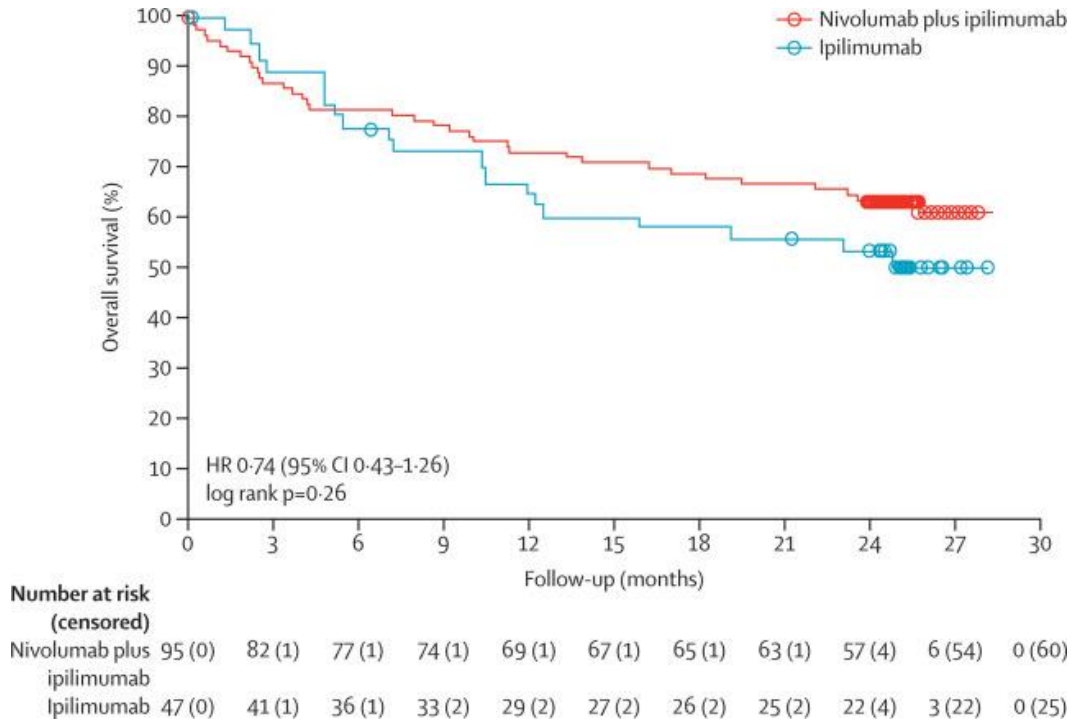




The Elephant in the Room: the Hope of Cure







Number at risk (censored)											
Nivolumab plus ipilimumab	95 (0)	82 (1)	77 (1)	74 (1)	69 (1)	67 (1)	65 (1)	63 (1)	57 (4)	6 (54)	0 (60)
Ipilimumab	47 (0)	41 (1)	36 (1)	33 (2)	29 (2)	27 (2)	26 (2)	25 (2)	22 (4)	3 (22)	0 (25)

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

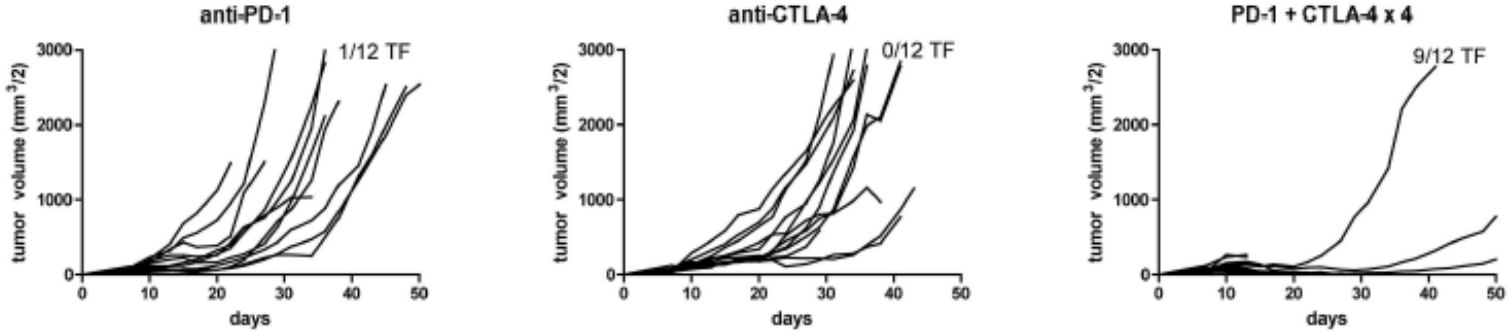
Table 3 Selected list of combination immunotherapies in clinical development

Immunotherapy + Immunotherapy			
Combination therapy	***Mechanisms of action***	***Phase***	***Indication***
Nivolumab + ipilimumab	Anti-PD1 + anti-CTLA-4	I/II	Gastric, TNBC, PA, SCLC, Bladder, Ovarian
		II/III	Melanoma, RCC
		III	SCLC, GBM, NSCLC
Nivolumab + BMS-986016	Anti-PD1 + anti-LAG3	I	Solid tumors
Nivolumab + viagenpumatucel-L	Anti-PD1 + vaccine	I	NSCLC
Nivolumab + urelumab	Anti-PD1 + anti-4-1BB	I/II	Solid tumors, B-cell NHL
Atezolizumab + MOXR0916	Anti-PDL1 + anti-OX40	I	Solid tumors
Atezolizumab + varlilumab	Anti-PDL1 + anti-CD27	II	RCC
Atezolizumab + GDC-0919	Anti-PDL1 + IDO inhibitor	I	Solid tumors
Epacadostat + atezolizumab, durvalumab, or pembrolizumab	IDO inhibitor + anti-PDL1 or anti-PD1	I/II	Solid tumors
Pembrolizumab + T-Vec	Anti-PD1 + vaccine	III	Melanoma
Durvalumab + tremelimumab	Anti-PDL1 + anti-CTLA-4	I/II	Melanoma
		I/II/III	SCCHN
		II	Mesothelioma, UBC, TNBC, PA
		III	NSCLC, Bladder
Pidilizumab + dendritic cell/RCC fusion cell vaccine	Anti-PD1 + vaccine	II	RCC
Immunotherapy + Targeted Therapy			
Combination therapy	***Mechanisms of action***	***Phase***	***Indication***
Atezolizumab + bevacizumab	Anti-PDL1 + anti-VEGF	II/III	RCC
Atezolizumab + cobimetinib	Anti-PDL1 + MEK inhibitor	I	Solid tumors
Atezolizumab + vemurafenib	Anti-PDL1 + BRAF inhibitor	I	Melanoma
Atezolizumab + erlotinib or alectinib	Anti-PDL1 + EGFR or ALK inhibitor	I	NSCLC
Nivolumab + bevacizumab	Anti-PD1 + anti-VEGF	II	RCC
Pembrolizumab + pazopanib	Anti-PD1 + tyrosine kinase inhibitor	I	RCC
Pembrolizumab + dabrafenib + trametinib	Anti-PD1 + BRAF inhibitor + MEK inhibitor	I/II	Melanoma
Durvalumab + dabrafenib + trametinib	Anti-PDL1 + BRAF inhibitor + MEK inhibitor	I/II	Melanoma
Nivolumab + sunitinib, pazopanib, or ipilimumab	Anti-PD1 + RTK inhibitor, RTK inhibitor,	I	RCC

Morrissey, et al. Clin Transl Sci (2016) 9, 89–104

Non-Clinical Nivolumab plus Ipilimumab

- Preclinical rationale for complementation
- Activity assessed in syngeneic mouse models
  - Limited translatability to humans: cell of origin, sequencing…

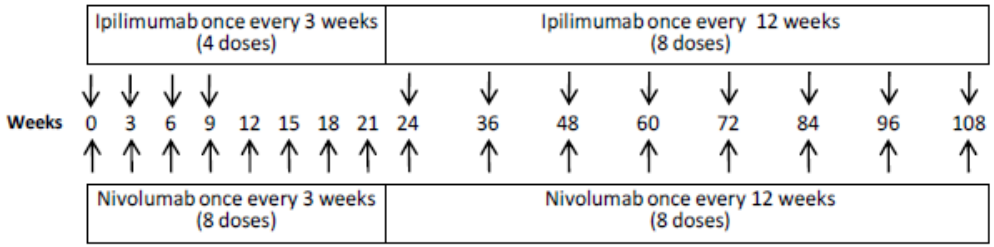


- Synergistic PD changes with the combination in tumor microenvironment and TILs
- In vitro cytokine release: IFN-γ, TNF-α
- Cynomolgus toxicology: diarrhea in up to 40% and inflammatory changes in lymph nodes and spleen

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 (!)



Cohort	Nivolumab (mg/kg)	Ipilimumab (mg/kg)
Concurrent regimen		
1	0.3	3
2	1	3
2a	3	1
3	3	3
4	10	3
5	10	10

Wolchok et al 2013 NEJM

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 toxics
- 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