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IMMUNO-ONCOLOGY INSIGHTS

SPOTLIGHT ON:

Addressing lingering safety issues for I-O product candidates in development

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ADDRESSING LINGERING SAFETY ISSUES FOR I-O PRODUCT CANDIDATES IN DEVELOPMENT

SPOTLIGHT

COMMENTARY

The rise of next-generation T-cell engagers with better safety and efficacy

Omid Vafa

The last decade has witnessed a gradual increase in the number of T-cell engagers (TCEs) entering the clinic for various oncology indications. The culmination of learnings from intensive research and development spanning the last thirty-five years in this space has yielded two TCE approvals: 1) catamuxamab (anti-EPCAMxCD3, Fresenius Biotech, Germany), a mouse-rat hybrid bispecific for malignant ascites that was approved by the EMA in 2009 and voluntarily withdrawn in 2017, and 2) blinatumomab (Micromet, Inc., Germany and Amgen, CA) comprising a mouse anti-CD19xCD3 dual single-chain variable fragment (scFv) that is administered intravenously (IV) for acute lymphoblastic leukemia (ALL, FDA approval in 2014). Blinatumomab remains the single approved and marketed TCE to date. Other first-generation TCEs have since suffered attrition in early development due to their toxicity or safety profiles as well as manufacturing complications. This review highlights key impediments to the clinical advance and the design limitations of first generation TCEs and discusses new approaches to overcome these hurdles. By addressing these fundamental shortcomings, next-generation TCEs have the potential to transform cancer treatment.

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TCE BENEFIT–RISK PROFILES

TCEs are bi- or multi-specific engineered antibodies that can circumvent the T-cell receptor (TCR) and peptide-major histocompatibility (pMHC) complex recognition by bridging CD3 of the TCR with a

tumor-associated antigen (TAA) [1,2]. By doing so, TCEs form an immunological synapse between T-cells and cancer cells to elicit tumor cytotoxicity through the secretion of granzymes, perforins and pro-inflammatory cytokines, including TNFα, IL-6, IL-2 and IFNγ [3,4]. There are currently more than 75 such TCEs in clinical development (Paulina Szymanska, Beacon Target Therapies). Most recently, TCEs in early development have demonstrated clinical successes in hematological malignancies by targeting common plasma or B-cell antigens (e.g. CD19, BCMA, and CD20). There is also a growing trend towards targeting solid tumor antigens (e.g. HER2, PSMA, and CEA) to further address the 10x greater cancer patient population in need [4]. Several TCEs have shown promising overall response rates (ORRs) and complete responses (CRs) in early clinical trials and will soon enter Phase 2 and/or pivotal studies (e.g. glofitamab, epocritamab, REGN1979, REGN5458, CC-93269, JNJ-64007957, plamotamab; www.clinicaltrials.gov).

Earlier this year, Kampershroer *et al.* (2020) shared a summary of the "Preclinical safety and Translational Safety Assessment of CD3-based Bispecifics", a workshop that was sponsored and organized by the Health and Environmental Sciences Institute (HESI) Immuno-safety Technical Committee and the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) [5]. The article highlighted that the "key safety concerns with CD3 bispecifics are excessive release of cytokines, which translate to potentially life threatening cytokine release syndrome (CRS), target organ toxicity due to redirection of T-cells to normal tissues expressing the tumor-associated antigen (TAA) (off tumor/on-target toxicity) and in some cases neurotoxicity" [5]. To address these safety concerns related to CRS for blinatumomab, the only currently marketed CD3 bispecific to date, it was noted that step-up dosing (intra-patient dose escalation) and corticosteroid pre-treatment are standard protocol. This approach has since been commonly used for the numerous TCEs currently in clinical development. An important additional variable when considering dose escalation regimens is the level of tumor burden that can contribute to the onset of CRS [6]. Dose-reduced re-administration of blinatumomab after a grade 4 CRS adverse event was shown to be safe in a patient with relapsed acute lymphoblast leukemia [7]. Along with corticosteroids, tociluzimab (anti-IL-6 receptor) has also been used to manage grade 3 and 4 adverse events in the clinic [8]. While patient monitoring and management have improved for T-cell redirecting therapeutics, the safety concerns persist, and reports of adverse events from TCEs are well-documented in the public sector and in recent press releases.

With respect to blinatumomab, neurotoxicity is also considered a dose-limiting adverse event and can occur independently of systemic CRS [6]. As such, Dr Hermann Einsele (University of Wurzburg, Germany) has purported that blinatumomab increases T-cell adhesiveness to vascular endothelium, thereby enhancing extravasation into the central nervous system (CNS). This results in targeting B-cells, causing localized cytokine release and subsequent migration of monocytes into the CNS that increases local inflammation and neurotoxicity [9]. Thus, beyond step-up dosing and dexamethasone use, Einsele has used a P-lectin antagonist, pentosan polysulfate to reduce T-cell adhesion to the endothelium and subsequent local cytokine release in the CNS. Most recently, Parker *et al.* identified CD19 expression in brain mural cells using single cell RNA sequencing data and confirmed protein expression by perivascular staining [10]. Hence, on target activity may also contribute to CAR T-cell and BiTE neurotoxicity, though this has not been formally demonstrated clinically. Together, the Einsele and Parker *et al.* data suggest that both extravasation and on target toxicity on mural cells may contribute to neurotoxicity with anti-CD19 T-cell redirection [11]. Curiously, a number of anti-CD20 TCEs that are currently in development and targeting the same B-cell population have not reported significant neurotoxicity in the clinic (e.g.

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mosenutuzmab and glofitumab, Roche; epocritamab, Genmab; odronextamab, Regeneron; plamotamab, Xencor). Whether these discrepancies in neurotoxicity are related to the specific target (CD19 versus CD20) or TCE format and whether subsequent inflammation in the CNS can be avoided with next-generation TCEs targeting CD19 are currently unknown. Recent pre-clinical studies of TNB-486 (Teneobio, CA), an anti-CD19 TCE that targets a novel conformational epitope on CD3 and possesses an extended half-life, show that it exhibits tumor cytotoxicity with minimal cytokine release [11]. This feature of the TCE may increase the benefit–risk ratio of targeting CD19 with the advantage of an extended half-life. The pending Phase 1 studies of TNB-486 in ALL and DLBCL will reveal the physiological relevance and potential increase in the therapeutic index, given its preclinical cytokine release profile. Moreover, epocritamab (anti-CD20x-CD3, Genmab), a subcutaneously administered bispecific DuoBody®, has demonstrated efficacy without severe neurotoxicity and is now undergoing further assessment in a dose expansion cohort (Genmab presentations at ASCO, 2020 and EHA 2020). Subcutaneously administered TCEs have reduced C_{max} and this may dampen cytokine release (Genmab presentation at EHA, 2019; [12]). Nevertheless, the general longer-term impact of this delivery route on anti-drug antibody responses (ADA), efficacy and toxicity remain to be established.

The FDA's recent retrospective study of 17 TCEs of different formats and related INDs involving Minimum Anticipated Biological Effect Level (MABEL) approaches in determining starting dose selection for First-in-Human (FIH) studies revealed that animal models are not ideal in predicting safe starting doses for FIH studies [13]. In general, non-human primates used for toxicological assessment of TCEs with conserved binding to TAA and CD3 better tolerate toxicities than patients. CRS and inflammatory responses were the most common adverse events along with neuro-, hepato- and gastrointestinal-toxicity and decreased lymphocytes [13]. Consistent with prior observations, lymphopenia was attributed to either direct depletion by the product or redistribution of B- and T-cells through endothelial attachment [14]. Moreover, neither receptor occupancy nor a non-severe toxic dose in animals were deemed appropriate for dose selection. Rather, a recommendation based on 30% or lower *in vitro* pharmacological activity (PA) was considered a better indicator of safe starting dose for FIH [13].

Beyond safety concerns associated with drug potency, additional variables may limit and negatively impact TCE efficacy. Highly potent TCEs may induce T-cell exhaustion or anergy through overstimulation and possibly induce cell death. Moreover, in some patients the native T-cell population maybe insufficient or too low for significant efficacy. Hence, the biological design of the next generation of TCEs should consider a number of structural and quality attributes to elicit the desired patient biology that may not be captured by the first generation of CD3 bispecific formats that were optimized for *in vitro* potency and not for long-term efficacy. Important to this end, it would be beneficial to have continuous exposure and durable response of an active but non-toxic dose where T-cell exhaustion or anergy will not occur. Chronic T-cell stimulation from greater TCE exposure and target antigen engagement can extend the effector phase of T-cell activation and elicit T-cell exhaustion and the loss of memory T-cells [15]. Moreover, it was established that PD-1 upregulation is one of the mechanisms of resistance to blinatumomab, and combination treatment with pembrolizumab enhanced T-cell function and induced an anti-leukemic response [16]. Hence, many are now considering combinations (e.g. with checkpoint inhibitors) and multispecific platforms that can engage T-cell co-stimulatory molecules (e.g. CD28) to overcome such T-cell exhaustion and maximize effector activity. Nevertheless, these approaches would need to be carefully balanced in consideration of potential risks for adverse events, including

CRS. TCE-induced CRS detected in the clinic generally occurs after the initial dose, and subsequent doses are less problematic. Thus, it will be important to assess the upregulation of T-cell exhaustion markers with greater exposures that can reduce efficacy in subsequent dosing during continuous or periodic IV infusions. Blinatumomab, in light of its short half-life and toxicity profile, requires both step dosing and continuous IV delivery by infusion pump at microgram quantities over 4–8 weeks (e.g. 9 mcg/day for the first week, followed by 28 mcg/day for the remaining 3 weeks) [17]. Arguably, while blinatumomab's short half-life poses a delivery inconvenience, it also enables controlled administration to quickly stop infusion at signs of toxicity (e.g. pro-inflammatory cytokine increase associated with CRS or neurotoxicity). Hence, the increase in half-life of any TCE should be weighed against the potential increases in toxicities or T-cell exhaustion and anergy posed by improved pharmacokinetic and pharmacodynamic (PK/PD) profiles.

Unlike blinatumomab, next-generation TCEs possessing "silent" Fc (muted effector function) or other half-life extending moieties (e.g. anti-albumin or albumin fusion constructs) will enable a more convenient intermittent dosing schedule on a weekly or biweekly basis [4]. Several strategies have been developed to maximize therapeutic indices while mitigating toxicity profiles of highly potent TCEs, including:

i. Using an infusion pump to continuously deliver TCEs in a tight range below dose limiting toxicity;

ii. Introducing metalloprotease cleavage sites in pro-drug forms of TCEs that are activated site-specifically at the tumor site;

iii. Localized viral delivery of TCEs to tumors;

iv. Subcutaneous delivery of TCEs to minimize C_{max} and enable gradual systemic exposure;

v. Step-up dosing regimens and vi) next-generation TCEs that can decouple tumor cytotoxicity from cytokine release. Additionally;

vi. The measure of safety and efficacy through relevant biomarkers that monitor T-cell activation, proinflammatory cytokines, CRS and tumor cell killing can inform better dosing regimens and reduce the CRS without compromising efficacy.

Predictive modeling that integrates such measures has been applied to assess dosing regimens in the clinic for mosunetuzumab (anti-CD20xCD3, Roche) using mechanistic quantitative systems pharmacology (QSP) modeling [18]. Such modeling, combined with preclinical *in vivo* non-human primate and human clinical studies have further demonstrated that step fractionated dosing regimens can mitigate the risk of high systemic cytokine (e.g. IL-6) peaks in non-Hodgkin's lymphoma (NHL) patients without compromising anti-tumor efficacy [18]. Cytokine levels were shown to be highest after the first dose of mosunetuzumab when B-cells were present in peripheral blood and lymphoid-tissue compartments. For the subsequent doses, IL-6 secretion from peripheral blood was negligible after initial depletion of circulating B-cells, and the bulk of the IL-6 was secreted within tissues [18]. Undoubtedly, systems modeling approaches will be extended to other B-cell malignancies to identify better protocols for improved therapeutic indices in the future. Still, these approaches are of afterthoughts to address and optimize regimens for already existing potent molecules. What about designing the next generation of molecules for better therapeutics windows?

The clinical safety and toxicity of TCEs are also determined by their humanicity (relative level of human peptide sequences) developability and manufacturability profiles. The first two are the most critical, given that a) an ADA response to non-human peptides can potentially cross-link the TCE and b) physiologically unstable CD3 bispecifics can aggregate. Both can negatively impact TCE pharmacokinetics (PK) and potentially trigger CRS by prematurely activating T-cells in the absence

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of tumor target engagement. Such liabilities could also significantly impact the distribution and exposure of the TCE in circulation, restricting it to lymphatic tissues, increasing the likelihood of immunogenicity or an ADA response that may compromise safety and efficacy. Attention to these potential liabilities will be most critical for the scientists and physicians who are focused on discovering and developing novel bi- or multi-valent antibody formats, including asymmetric, symmetric and scFv- and variable heavy chain-based or alternative scaffold fusion constructs (reviewed by [1,4,19]). The clinical successes or failures of these various formats will inform future structure and function-related design considerations for optimal PK/PD, including the appropriate TCE affinities, valencies, epitopes on the TAA and CD3 as well as understanding optimal half-life.

NEXT-GENERATION TCES FOR BETTER SAFETY & EFFICACY

Moving forward with next-generation TCEs, a holistic approach to design and format warrants careful consideration. The complexity and interdependency of the various binding domains can impact the overall safety-efficacy profile of the therapeutic. To this end, a number of newly engineered TCE formats comprise the next generation of CD3 bispecifics that are entering the clinic. Some of these efforts involve the fine-tuning of TAA binding domains and CD3 affinity and epitopes to minimize CRS while retaining efficacy with half-life, culminating in a better therapeutic index. For example, companies like Macrogenics and Xencor have sought to engineer CD3 affinity for reduced cytokine release [1,2]. Others, like Teneobio, have identified novel anti-CD3 binders to a novel conformational CD3 epitope that capture a "sweet spot" of activity, where TCEs can elicit tumor cytotoxicity with minimal cytokine release [20]. These approaches, and the biology enabling this window of engagement within such a "sweet spot" were reviewed recently [4]. There are ongoing efforts [Teneobio unpublished data] to further elucidate the signal transduction pathways that differentiate these novel TCEs from the previous generation of high-affinity potent bispecifics engaging the epsilon chain of CD3.

Teneobio's CD3-bispecific platform was discovered and characterized in light of observations of dual threshold activation that triggers cytotoxicity versus cytokine release. This dual threshold was previously characterized for TCR-pMHC interactions and immune synapse formation [21,22]. Of import, beyond the characteristic decoupling of cytotoxicity from cytokine release, Teneobio's TCEs have demonstrated an increased therapeutic index in animal models, with reduced upregulation of inhibitory checkpoints associated with T-cell exhaustion (e.g. PD1 and CTLA-4) and preferential activation of cytotoxic T-cells over regulatory T-cells (Tregs) [4,20]. The clinical benefit-risk ratio of such novel TCEs will be revealed in the near future, as many of these assets are now in the clinic (e.g. TNB-383B, anti-BCMAxCD3) or soon entering the clinic (TNB-486, anti-CD19xCD3; TNB-585, anti-PSMAxCD3, IND filings Q3/Q4 2020).

Other drug developers have engineered proteolytic sites in CD3-bispecific pro-drugs that are activated in the tumor microenvironment by local proteases [23]. In doing so, T-cell activation and tumor targeting is relatively restricted in space and time, potentially minimizing systemic exposure and cytokine release for a better therapeutic index. These approaches are in preclinical stages and will soon enter the clinic (Cytomx, Maverick, Harpoon, Amunix). Still others have explored site specific tumor delivery of TCEs as payloads using vaccinia, oncolytic adenovirus, and in oncolytic measles viruses [24–26]. Efficacy with such viral payloads was shown in both xenograft and syngeneic models without toxicity [26]. In the near future, the outcomes of these more complex engineered formats and viral delivery approaches will be determined by their clinical validation for localized tumor persistence, their immunogenicity and ease of manufacturing and their stability. Additional efforts to target solid tumors involve format plays, where

preferential dual-antigen targeting of tumors is favored by multivalency and avidity relative to single-target antigens on normal tissues [27]. Alternatively, low-affinity bivalency against specific TAAs has been shown to enable improved targeting of antigens that are expressed at higher levels on tumors than on normal tissues and may reduce off-tumor, on-target toxicities in the clinic [28]. Importantly, these advantages will need to be carefully weighed for each TAA considered, given that some TAAs when cross-linked by bivalent TCEs can rapidly internalize and reduce surface copy number required for robust and redirected T-cell mediated tumor toxicity.

Increasing the therapeutic index through the various aforementioned approaches will likely provide opportunities to further assess synergistic benefits of combination therapies. A major impediment to addressing solid tumors has been the immunosuppressive tumor microenvironment (TME) and the physical barrier to penetration known as the stroma [29]. Various strategies are being explored to turn the immune deprived "cold tumors" into inflamed "hot tumors" that comprise T-cell infiltrating lymphocytes [30]. These strategies include targeted depletion of immune suppressive cells, including macrophages, Tregs, myeloid-derived suppressor cells (MDSCs) by using checkpoint inhibitors, introducing proinflammatory cytokines, and localizing costimulatory molecules to the tumor among other approaches. Additional approaches focus on disrupting the extracellular matrix/basement membrane, and fibroblasts [31,32]. Undoubtedly, future combination studies with these many disruptive approaches will further enhance anti-tumor access and boost the anti-tumor immune response of TCEs with better safety and efficacy profiles.

CONCLUSION

Looking to the future, there is much optimism that next-generation TCEs will transform the treatment of liquid and solid tumors. As the operations researcher, Russell L Ackoff, once famously said, "A problem never exists in isolation; it is surrounded by other problems in space and time. The more of the context of a problem that a scientist can comprehend, the greater are his chances of finding a truly adequate solution." To that end, iterative learnings from the clinical outcomes of the next wave of multispecific therapeutics will further inform the creation of TCEs with better benefit–risk profiles. With innovative dosing regimens (e.g. step-up dosing), alternative delivery routes (e.g. localized or subcutaneously), and novel drug combinations, next-generation TCEs are on the trajectory to providing meaningful solutions to unmet cancer patient needs.

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SPOTLIGHT

COMMENTARY/ OPINION

Model-based dose escalation designs used in early-phase 1 trials to assess safety and tolerability of immuno-oncology therapies

Céline Adessi & Francesca Michielin

The drug development process in oncology has significantly evolved in the last decade with the clinical investigation and approval of immuno-oncology therapies, providing new treatment modalities in various cancer types to patients. These efficient and promising treatments have in parallel benefited from the new regulatory accelerated approval paths, giving patients access to these cancer drugs in a relatively short period of time. While progress is made to understand and manage the side effects of these therapies, the unique safety profile and variable time to onset of the adverse effects lead to a re-think of how dose escalation designs could be adapted for these new molecular entities. Model-based designs seem to be particularly suitable to include specific features that could help assess the safety and tolerability of immuno-oncology agents. These models aim to provide a better estimate of tolerable doses for long-term treatment with immuno-oncology therapy and some, such as the mDA-CRM and the TITE-CRM, have the potential to even reduce the time taken by the clinical investigation process.

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CHALLENGES OF THE SAFETY ASSESSMENT OF IMMUNO-ONCOLOGY THERAPIES AT FIRST IN HUMAN STUDY

Safety profile of immuno-oncology therapies

New cancer treatment modalities, grouped under the term immuno-oncology (I-O) therapies, have profoundly changed the drug development process and landscape in cancer in the last decade. It required more than one century to sufficiently understand and master the underlying immune escape process that tumor cells develop to proliferate and disseminate. The new generation of I-O therapies offer multiple options to reactivate the immune response against the tumor and overcome this escape, providing convincing evidences of clinical benefit in various types of cancer [1,2,3]. Examples of those agents are listed in Box 1.

While these I-O therapies may target different immune-biological pathways, all aim to activate and redirect the immune cells of the patient surrounding the tumor to the cancer; ultimately killing cancer cells resulting in a confirmed clinical benefit. Because those agents such as CPIs and immunomodulatory cytokines compromise the self-tolerance of individuals, a broad spectrum of side effects associated with the inflammatory response of the treatment is observed, and these are less predictable than those for cytotoxic agents. These side effects, namely immune-mediated or –related adverse events, can potentially affect the entire body, all types of organs and organ function via an inflammation manifestation in the skin (e.g. rash, pruritus, vitiligo), the gastro-intestinal tract (e.g. diarrhea, colitis), the liver (e.g. hepatitis), the endocrine system (e.g. hypothyroidism, adrenal insufficiency), the musculoskeletal system (e.g. arthralgia myalgia), and less frequently, observed in the kidney (e.g. nephritis), the eyes (e.g. uveitis), the respiratory system (e.g. pneumonitis), and the cardiovascular system (e.g. pericarditis vasculitis). Additionally, patients may experience abnormalities of vital signs (hypotension, bradycardia) and of hematological parameters (classically neutropenia, anemia and lymphopenia) [4,5,6].

With potent adoptive cell immunotherapies, such as IEC and CAR T-cell, patients may also suffer from supra-physiologic response causing activation or engagement of endogenous or tissue-infused T cells. These result in a wide spectrum of signs and symptoms, each of varying severity, which are grouped under the term syndrome, e.g. cytokine release syndrome (CRS). The main clinical manifestations include at the onset pyrexia, and vital signs abnormalities such as hypotension and hypoxia, and may result in severe/life-threatening organ dysfunctions [7]. As part of the risk mitigation approach to overcome these toxicities and reduce their severity, variations in the classical flat dosing given at regular intervals of time, classically every 3 weeks for biologicals, might need to be explored. Possible strategies include intra-patient dose increment study design, for example: 1) the "step-up dosing" approach where the dose is increased at regular interval of time following the proposed schedule, or 2) "fractionated dosing" approach where the targeted maximum dose is divided into fractions given in a relatively short period of time during the first cycle of treatment (e.g. cycle 1 day 1, day 8, day 15) [8].

If, as frequently happens, treated patients present their first severe (≥ grade 3) toxicity at the very first administration, the time to

BOX 1

Examples of immuno-oncology therapies

- **Check point inhibitor (CPI)**, e.g. anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and anti-programmed cell death protein 1 (PD-1) and the ligand (anti-PD-L1)
- **Adoptive cell immunotherapy** (e.g. CART-cell) and immune effector cell (IEC) therapies
- **Immunomodulatory cytokine group**, including IFN-α and IL-2
- **Cancer vaccine** including the Dentritic Cell vaccine Sipuleucel-T

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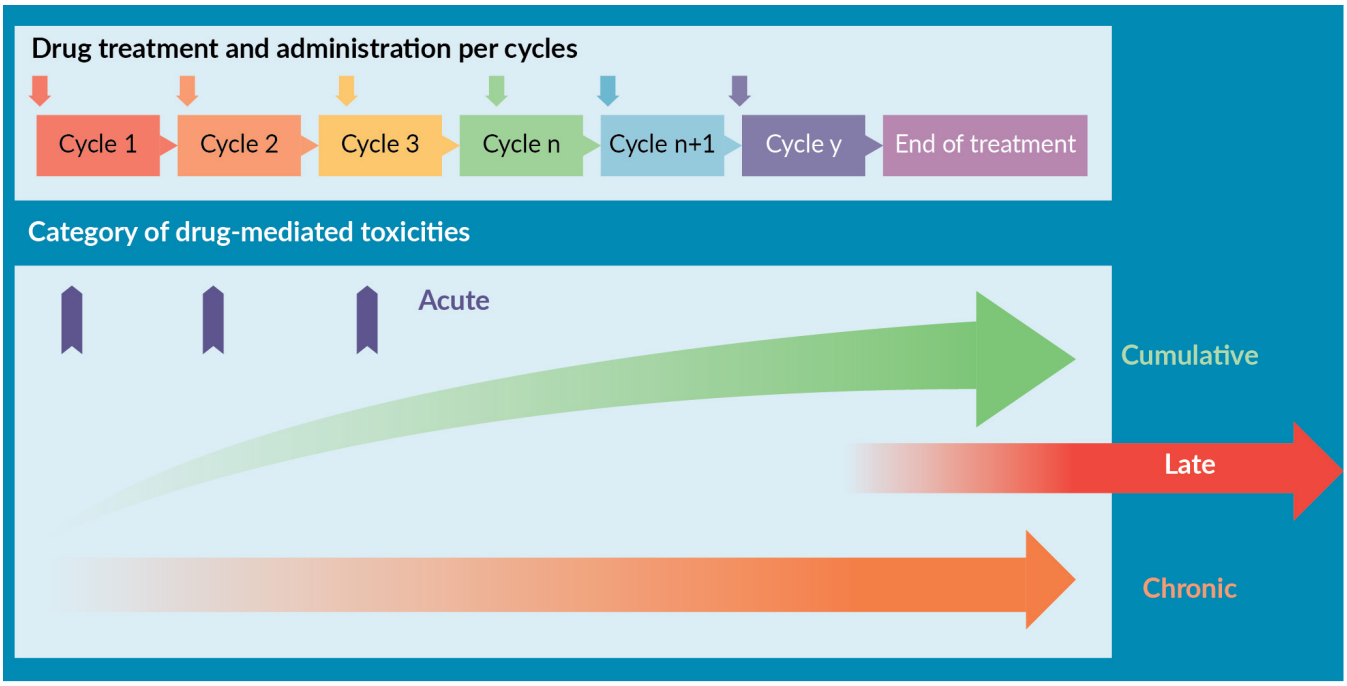
onset of toxicities of I-O therapies differs depending on the type of agent, mode of action, cancer type and tumor location, individual heterogeneity, dose and schedule of the therapy. In patients treated with nivolumab, a CPI antibody that blocks PD-1, early manifestations commonly include gastro-intestinal and skin toxicity, but vitiligo, for example, typically does not appear until months after the initiation of checkpoint blockade. Severe (≥ grade 3) enterocolitis onset varies from day 1 to >30 months after the initiation of treatment. Late manifestations after the third and fourth dose are generally autoimmune manifestations such as hepatitis, pneumonitis and endocrinopathies [9]. A representation of time-to-event toxicities profile of I-O, grouped schematically into four categories, is presented in Figure 1 [10].

The acute effects, which develop shortly after the initiation of administration, are transient and can reoccur at each administration. These may include liver function test elevation (hepatic transaminases and eventually bilirubin levels), hematologic toxicity (e.g. thrombocytopenia, neutropenia, anemia), vital signs abnormalities (e.g. pyrexia, tachycardia, hypotension), and syndromes (e.g. CRS). The syndromes secondary to IEC therapies rarely present beyond 14 days after initiation of therapy [11]. CRS is considered an acute and early-onset phenomenon, even if late-onset or less predictable syndromes have also been reported with cellular therapies (e.g. CAR T cell) [7]. These toxicities are unlikely to evolve into severe organ failures if their clinical management and intervention are promptly implemented, and usually resolve prior to the next cycle of drug administration. CRS requires body fluid and vasopressor treatment in particular [12]. Chronic effects developed over time such as skin or gastro-intestinal toxicities are persistent or recurrent by a series of events, even without any re-challenge with the drug (e.g. drug administration delay). Cumulative effects such as the endocrine toxicities may develop and increase in incidence and severity over time with repeated exposures to the drug (progressive over time). A late-onset effect of thyroid dysfunction may also be observed in subclinical or asymptomatic physiological conditions

FIGURE 1

Schematic view of the longitudinal or time-to-event toxicities of I-O.



over an extended timeframe, even after cessation of treatment.

While the traditional approach with cytotoxic agents (e.g. chemotherapy), is to reach a maximum tolerated dose when the target-mediated biologic pathway is optimally altered, toxicities with I-O agents have different features and challenges requiring identification of a tolerated dose able to provide an optimal pharmacodynamic effect and acceptable benefit-risk balance [13].

Acceleration of drug development of immuno-oncology therapy

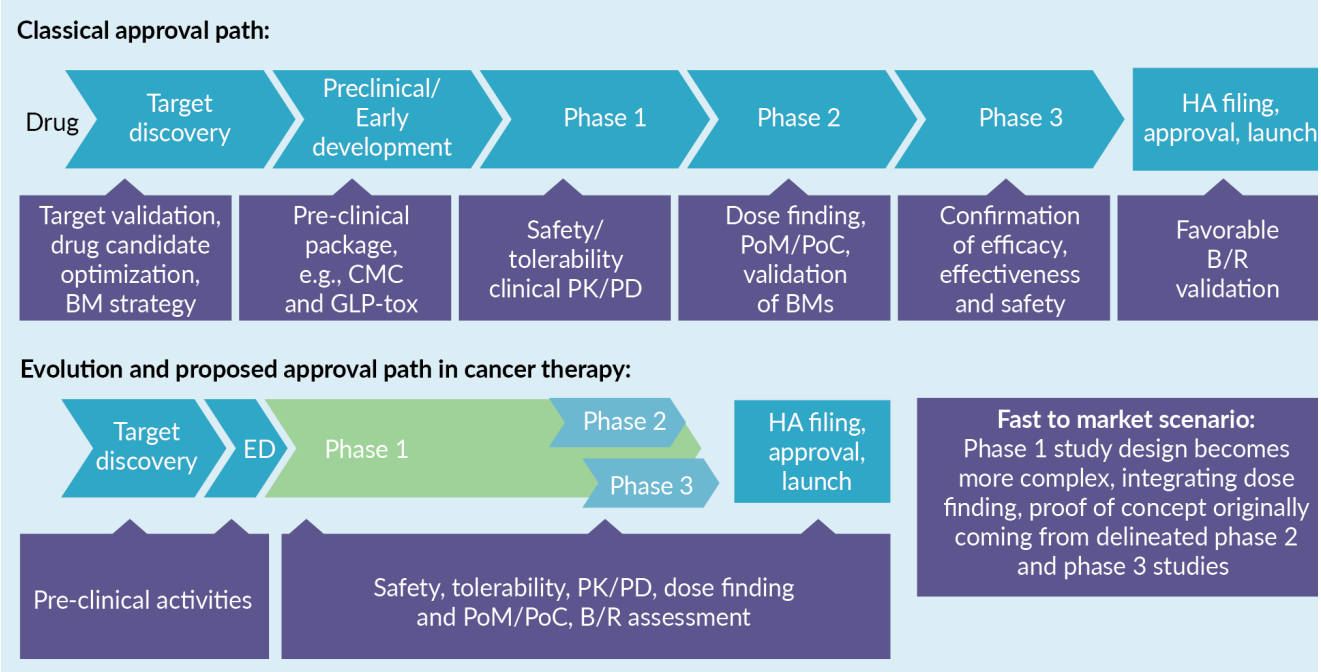
Accelerated regulatory approval paths provide an opportunity for patients to gain quick access to new treatment modalities [14]. The classical and stricter delineation between first-in-human (FIH) p hase 1 s tudy, p hase 2 and the confirmatory p hase 3 h as e volved into a more condensed format, where the early-phase clinical studies become a platform for the health authority approval pathway (Figure 2), particularly in the I-O therapeutic field.

Pembrolizumab, a CPI drug, was certainly one of the first I-O therapies to benefit from an unprecedented regulatory outcomes approval arising from a single entry into human protocol with a unique design. The innovative and groundbreaking study led in 5 years to multiple regulatory achievements, including orphan drug designation, breakthrough therapy designations, accelerated approvals for the treatment of melanoma and NSCLC, and approval for a companion diagnostic for PD-L1 tumor expression in NSCLC [15].

In this context, the FDA and EMA health authorities published in 2017 and 2018, respectively, two guidance documents. These documents provide advice to sponsors regarding the design and conduct of FIH clinical trials, ultimately intended to efficiently expedite the clinical development of cancer drugs, whilst in parallel, ensuring more in-depth analysis and information on efficacy and tolerability to assess benefit-risk [13,16].

FIGURE 2

Evolution of the drug development to fast to market strategy.



CMC: chemistry, manufacturing and controls; GLP: good laboratory practices; Tox: toxicology studies; PK: pharmacokinetics; PD: pharmacodynamics, BM: biomarker; PoM: proof of mechanism; PoC: proof of concept; B/R: benefit and risk ratio.

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Phase 1 trials now cover multiple aims such as characterizing the safety profile, conducting dose finding and exploring different schedules, establishing proof of concept, and validating the clinical benefit. FIH studies have therefore also increased their complexity, combining dose escalations with several dose extension cohorts, some of which involve combinations of the new molecular entity (NME) with established products or even additional NME(s).

MODEL-BASED DOSE ESCALATION DESIGNS FOR FIRST IN HUMAN IMMUNO-ONCOLOGY STUDIES

During the early phase of clinical development, the safety and tolerability of the new drug is the primary focus, with the aim to characterize as much as possible the safety profile of the drug and eventually, to identify a maximum tolerated dose. In recent years, model-based dose escalation designs have established themselves as a valuable alternative to rule-based designs. A retrospective analysis of more than 1,500 phase 1 oncology dose escalation studies indeed shows that model-based designs have become more popular in recent years, despite their use being still rather limited compared to rule-based designs [17].

Model-based versus rule-based designs

In both types of design, the primary outcome is usually binary, defined as the presence or absence of a dose limiting toxicity (DLT) in the first cycle(s) of treatment. However, while with rule-based designs (e.g. the 3+3) there is no prior assumption of the dose–toxicity curve, and the patients are assigned to pre-defined dose levels according to pre-specified rules based on number of observed DLTs on last cohort (Figure 3A), the model-based design instead assumes a dose–toxicity relationship. Data from similar compounds, therapeutic target, and preclinical data package are used to build a prior, which is then updated at each clinical dose decision stage using all available information from all treated patients (i.e. not limited to information from the last cohort only) [Figure 3B]. A further difference is that rule-based designs require a fixed size of cohort in each case, whilst model-based designs can deal with any cohort size.

In the literature, many different types of model-based designs have been presented [18,19], of which the most famous is the continuous reassessment method (CRM) and its modifications, such as the escalation with overdose control (EWOC). In the latter design, a target toxicity interval for the probability of DLT is defined and via Bayesian statistics, dose recommendations which maximize the probability of being in the target toxicity interval are made. This model incorporates the clinical data from all enrolled and ongoing patients to estimate more precisely the dose–toxicity relationship. In other words, all available information continuously feeds an a priori model of dose response toxicity [20]. As such, the model recommendation for the next dose cohort could be higher, lower, or the same as the one just tested. Notably, in contrast to the classical 3+3 design, these models provide the flexibility to propose a

BOX 2

Example of target toxicity range

- [0–10%] Under dosing
- [10–25%] Targeted toxicity
- [25–100%] Overdosing

Example of overdose probability curve

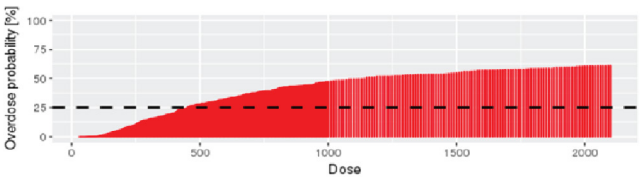
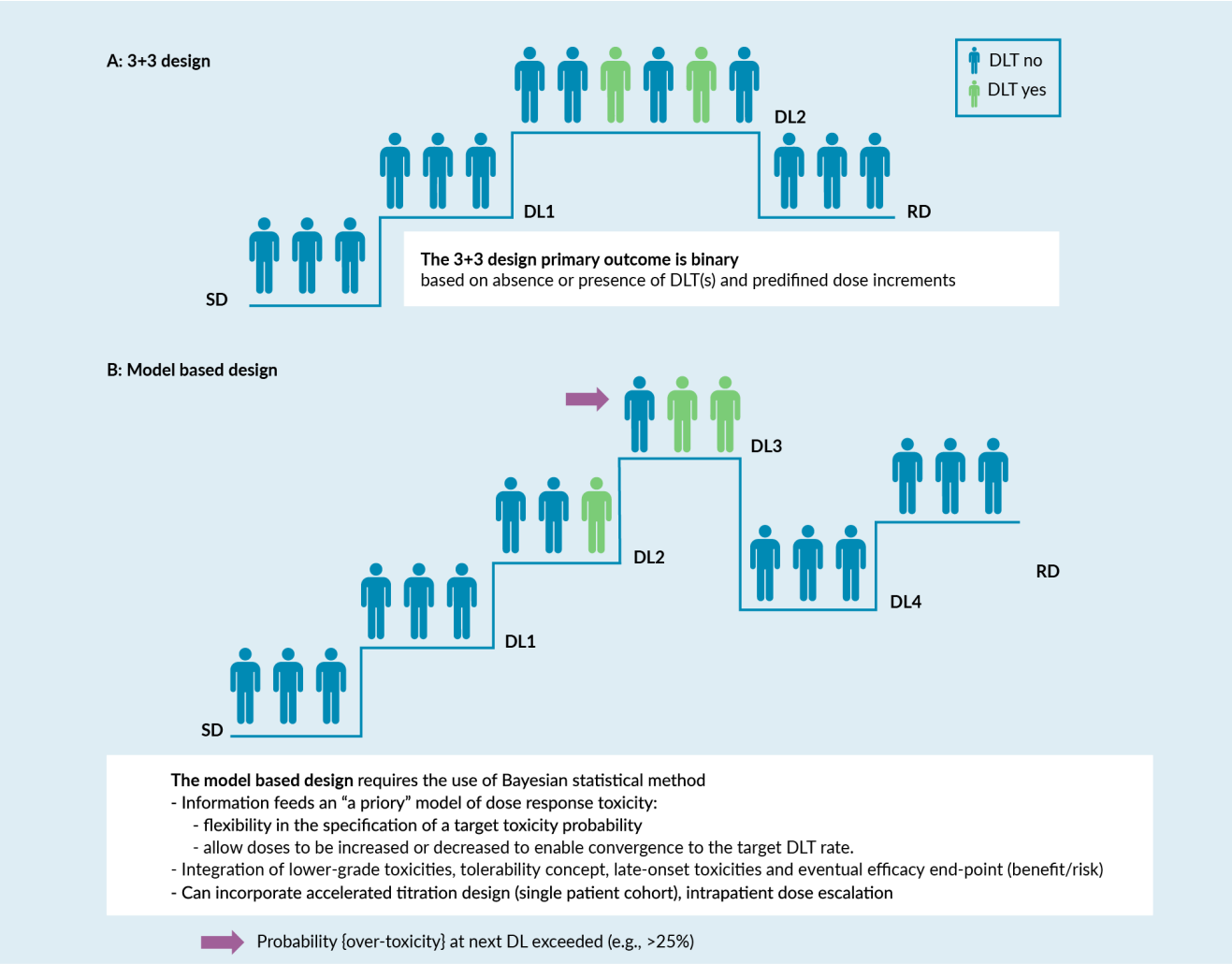


FIGURE 3

Dose escalation and dose levels examples, A) a rule-based (3+3) and B) model based design.



SD: starting dose; RD: recommended dose; DL: dose level; DLT: dose limiting toxicity or non-tolerable dose.

reduced dose that has not been already tested, and to re-escalate again to a higher dose at next dose cohorts if the tolerability is further confirmed in more treated patients [21,22]. In addition, rules to avoid exposing patients to undue harm are included to ensure patients' safety. For instance, it is common to impose maximum dose increments (as 3-fold) and in the EWOC, doses which are considered too toxic (usually with a probability of overtoxicity >25%) cannot be tested. The initial model recommendation is therefore further limited by those rules and a final proposal is then made (Box 2). Last but not least, stopping rules deciding whether the dose escalation can be ended are also an integral part of the design. For instance, this could occur if sufficient information to characterize the MTD was already achieved, the maximum feasible dose was proven to be safe, or a maximum sample size was reached.

As described above, model-based designs have an adaptive component in the sense that the choice of the dose to be tested in the following cohort is not pre-determined, but rather depends on all accumulated data. As with other adaptive designs, there is an increased flexibility compared to a fixed design but through pre-planning, the validity and integrity of the trial is not undermined.

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Adaptivity does not mean that all is allowed, nor that it fits all purposes [23].

MODEL-BASED DESIGNS IN SUPPORT OF THE SAFETY ASSESSMENT OF IMMUNO-ONCOLOGY THERAPIES AT FIRST IN HUMAN STUDY

Beyond the general characteristics of model-based designs, which make them appealing in the early stage of drug development irrespective of the drug class, novel methods that deal with e.g. late-onset toxicities, chronic and cumulative toxicities, and occurrence of syndromes might also be more adapted to I-O drugs [22,23]. The flexibility that characterizes model-based designs could be used to address the challenges associated with other safety features of I-O agents, requiring adapted dosing approaches to overcome complex toxicities such as syndromes (e.g. CRS).

Advantages of model-based designs are also clear in the presence of an accelerated regulatory approval pathway, since the already-accumulated information can be leveraged to speed up development even in early-phase, e.g. the investigation of different schedules, or the assessment of the toxicity for combination drugs [24].

One possible strategy to deal with late-onset toxicities is to extend the DLT/safety observation periods beyond initial cycles, in order to include cycle 1 acute toxicity as well as prolonged and late toxicity, thus impacting overall tolerability. However, this would prolong trial durations prohibitively with standard designs (both rule- and model-based) since the entire observation of the full DLT period is required before being able to take a decision on the dose for the following cohort. With this in mind, adaptations to the previously discussed CRM have been proposed, all of which have in common the idea of additionally using information from partially observed subjects throughout the trial, allowing for some gain in enrollment timelines. Different variations of this type of model exist, such as the mDA-CRM and the TITE-CRM [25–27].

Another feature of immuno-oncology drugs is the potential emergence of syndromes such as CRS, which could compromise further dosing of the patients particularly during the first and high dose administration of IEC [8]. In this case, model-based designs can be applied. For instance, one might decide to maintain a fixed proportion between the first and second dose and only have one statistical model, which would then define increments of both the first and second dose. In addition, the model might also be adapted to be able to guide not only the dose escalation in general, but also the fraction between the different doses. In this area, further methodological development is required since to date, no model-based methods specifically focused on step-up dosing or dose fractionations have been published. However, this situation is likely to change in the near future.

Finally, the flexibility of model-based designs offers the possibility to simultaneously incorporate both toxicities and a measure of potential efficacy to select the optimal biological dose and optimum benefit-risk [28–30]. However, application of those models in early phase 1 studies is hampered by the lack of a strong and confirmed dose-efficacy relationship, which is hard to observe particularly in the absence of a defined biomarker reflective of clinical activity.

Advantages of model-based design in an accelerated approval pathway

The general idea of a model-based design is that dose-toxicity relationship is present and accumulated data are used to better characterize this curve. In cases where hypotheses can be made to an analogous setting (e.g. exploring a different schedule, or a combination therapy) the accumulated information can still be informative.

For instance, contrary to what happens with a 3+3, gathering information on the dose-toxicity relationship of a specific schedule can

also help when a different schedule is subsequently explored. In this case, understanding the PK profile of the drug is key: once there is a clear idea of which PK parameter is the main driver for toxicity, this information can be used to adjust the prior for the new model.

Analogously, the data accumulated in the monotherapy dose escalation could be used to inform the combination dose escalation of the NME with an established drug (e.g. chemotherapy) which is usually given at a fixed dose. The monotherapy information has to be opportunely discounted and further hypotheses on how the safety profile of the individual drugs influence each other will contribute to defining the prior for the combination dose escalation.

CONCLUDING REMARKS

Immuno-oncology therapies present unique toxicity profiles which are distinct from cytotoxic drugs. The safety profile assessment of these immune-compromising agents requires broadening of the dose-limiting toxicities definitions combined with longer safety observation periods. Adaptive designs using Bayesian statistical models are new avenues to assess the safety profile of I-O therapies as early as the dose escalation FIH phase 1 stage and allow for rapid integration of the concept of tolerability.

The adaptive nature of model-based designs presents clear advantages, and the implementation of such studies involves the collaboration of expert biostatisticians, clinicians, and safety scientists to develop a robust, statistics-based model defined prior to study commencement. The need for specialized expertise in setting the model up and the computational complexities are often singled out for criticism. However, to overcome these complexities, model-assisted designs have been described in the literature [31–34] which simplify the design set-up and dose decisions. Additionally, the computational complexities are more limited today than they were in the past, due to the many tools available for building a model-based design and the greater flexibility of model-based designs compared to model-assisted designs. These factors contribute to our opinion that model-based designs are preferable.

Close and early interaction with regulatory agencies provides crucial support to sponsors in order to guide and assess the feasibility of the proposed statistical models. During the conduct of the study, frequent interim/cohort analysis to adapt the target-toxicity probability model implies an agile operational and clinical environment to ensure the safety of patients and compliance with the regulatory requirements (i.e. Good Clinical Practice and Good Pharmacovigilance Practices).

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IMMUNO-ONCOLOGY INSIGHTS

ADDRESSING LINGERING SAFETY ISSUES FOR I-O PRODUCT CANDIDATES IN DEVELOPMENT

SPOTLIGHT

COMMENTARY/OPINION

Necessity for next-generation quality assessment of CAR T cell manufacturing and advanced therapy guidance

Barbara Seliger, Kristin Reiche, Chiara Massa, Stephan Fricke, Gerno Schmiedeknecht, Friedemann Horn, Conny Blumert, Miriam Alb, Michael Hudecek & Ulrike Koehl

Despite encouraging clinical results in B-cell malignancies, redirected chimeric antigen receptor (CAR) T cells bear several medical and economic challenges. On the one hand, increasing numbers of patients require reproducible and automatic manufacturing of high quality, clinical-grade CAR T cells retaining the expression of the CAR gene and their catalytic function as well as respective biomarkers to predict processing failure, which is lacking so far. On the other hand, there is an increasing interest in advanced biomarkers for therapy guidance and especially, for preclinical testing to assess side effects such as CRS and CRES.

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NEED FOR AUTOMATED CAR T CELL MANUFACTURING

The adoptive transfer of CAR T cells and the successful remissions in B cell leukemia and lymphoma is attracting growing interest for the treatment of various malignant diseases. Despite the clinical efficacy and their approval by the FDA and EMA, these patient-specific therapies must be improved regarding their robustness, reproducibility, and cost. Thus, with further applications and increasing numbers of patients, the reproducible manufacture

of high-quality clinical-grade CAR T cells in a shortened time of production is becoming an even greater challenge [1,2]. Continuous improvement has been described on the evolution of CAR design regarding increased safety, better efficacy, prolonged persistence, and effective trafficking to the cancer side [3–5]. In addition, new processing techniques, quality control mechanisms and logistic developments are required to meet both medical needs and regulatory restrictions. Still, manufacturing of autologous cells for personalized medicine is time consuming and expensive. Preliminary results with automated manufacturing gives rise to improvement in both centralized and decentralized manufacturing units [6]. However, a modular, open, and transferable system with AI-mediated robotics and digital control as well as the respective automated documentation of all in process parameters is still missing. Thus, a new concept, which addresses a 100-fold increase in number of patients if tumors can successfully be targeted is urgently needed (Figure 1).

ADVANCED CELL QUALITY ASSESSMENT TO PREDICT MANUFACTURING FAILURE

Currently, there are no harmonized rules for patient selection regarding the leukapheresis starting material and most importantly, surrogate markers are completely missing to predict production failure and functional activities of engineered T cells. In several cases, failure in manufacturing occurs because the patients are heavily pre-treated, which leads to limited bone marrow function, less functional, more exhausted T cells, and finally, a median production failure rate of approximately 7% (with a range between 1% and 17%, respectively) [7–9]. So far, it is known that steroids, the duration of pre-treatment with immune checkpoint inhibitors, ibrutinib, and immune suppressive therapies impair the quality of the leukapheresis products. This can influence the fitness of the cells substantially with a change in the senescence during the manufacturing process [10]. In addition, Marco Ruella reported on a single observation that the relapse of the disease belongs to a contaminating transduced leukemic clone with a final cis/trans formation during the manufacturing process [11]. In summary, there is an urgent need for advanced strategies to improve prediction of manufacturing failure as well as to enhance the assessment of the product after manufacturing and prior to infusion. Continuous cost reduction of genome- and transcriptome-wide methods and their unbiased assessment of cellular states facilitate identification of precise biomarkers for cell quality assessment pre- and post-CAR T cell manufacturing (Figure 1B). Next-generation sequencing (NGS) allows comprehensive characterization of genomic and transcriptomic footprints of cells, thus revealing genetic mutations or changes in pathway activities of genetically engineered T cells. Initial studies used single-cell RNA sequencing to correlate single-cell transcriptomes of CAR T cell infusion products regarding efficacy and safety [12,13]. With further studies to come, including longitudinal assessment of transcriptional variation, effects of T cell clonal diversity prior to manufacturing, or effects of the manufacturing process itself on e.g. T cell exhaustion, CAR gene transduction efficacy and cellular fitness of CAR T cells will be much better understood. The application of advanced methods (single-cell, where needed) such as NGS or Nanostring analysis will therefore be critical for the identification of novel biomarkers. These biomarkers will in turn improve pre-manufacturing cell quality assessment and thus, prediction of manufacturing failure based on investigation of the starting material, as well as improved assessment of the cell quality of the product itself.

NEED FOR ADVANCED BIOMARKER IDENTIFICATION FOR IMPROVED THERAPY GUIDANCE

Despite promising results of CAR T cell therapy, patients often relapse. This is mediated

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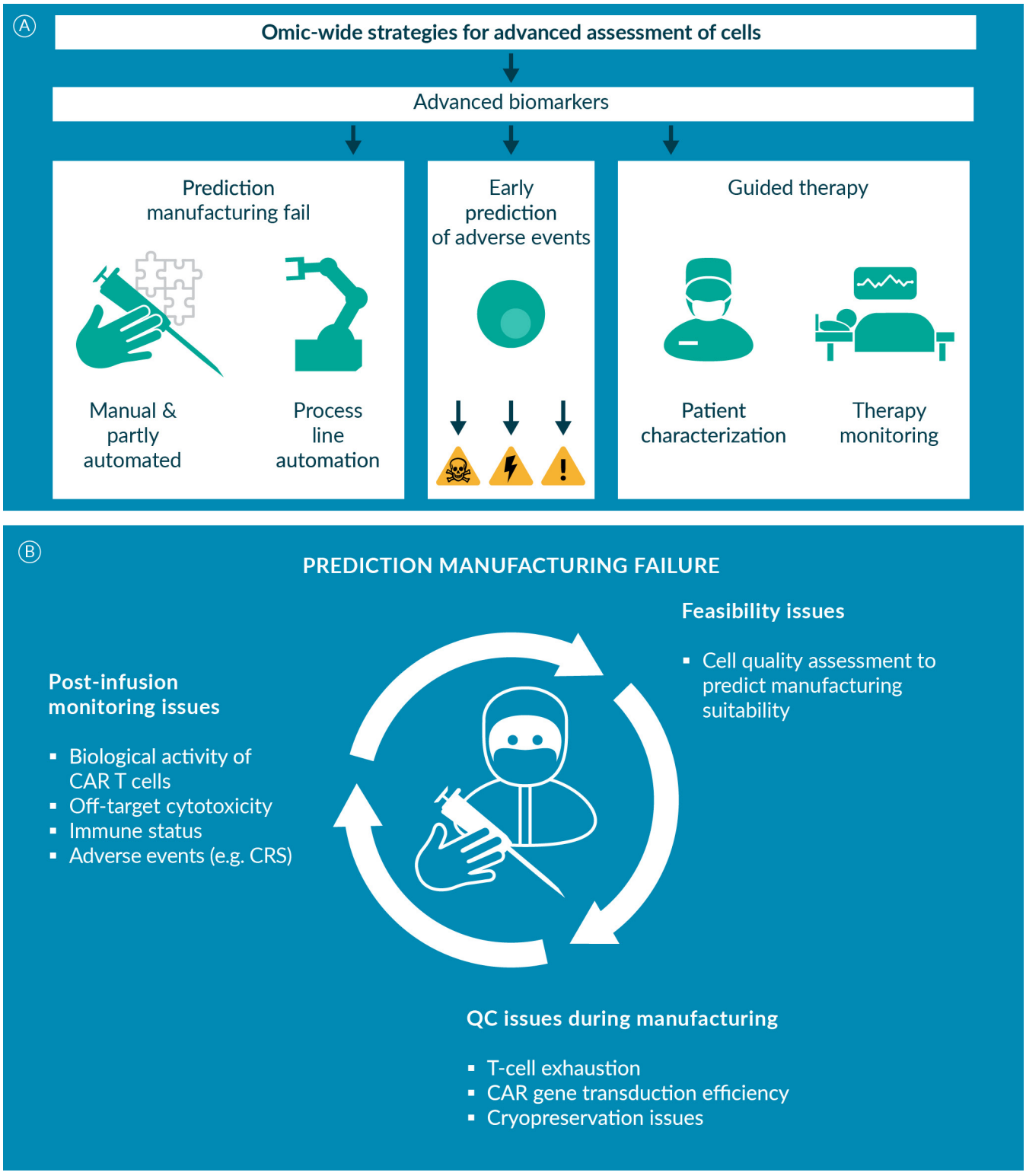
FIGURE 1

(A) Schematic overview of utilizing omic-wide strategies, such as NGS, to identify novel biomarkers, which are decisive for improvements in predicting manufacturing failure, adverse events, and therapy response of CAR T cells. (B) Representation of critical issues of CAR T cell manufacturing processes that require assessment by advanced biomarkers.



by the loss of the target structure due to selective pressure or insufficient CAR T cell persistence *in vivo* and has recently been shown to occur in an immune privileged organ, which might represent an early sign of relapse [14]. The lack of robust biomarkers predicting toxicity and/or efficacy are currently limiting the management of CAR T cells. Factors influencing the efficacy of CAR T cell therapy are highly variable and depend on the individual patients' and disease characteristics, and on the manufacturing of CAR T cell cultures (Figure 1A). Therefore, the identification of novel biomarkers predicting efficacy and toxicity, as well as early detection of relapse, are of high importance and should be implemented into the clinical routine in order to optimize CAR T cell products and the clinical benefit of this therapy. One should divide biomarkers into those predicting efficacy and those predicting toxicity, such as CRS and CRES. These are mediated by inflammatory responses and inflammation-associated tissue damages. Next to inflammatory factors, immune cells and tumor cells play vital roles in both processes.

STRATEGIES FOR ADVANCED BIOMARKER IDENTIFICATION & IMPROVED THERAPY GUIDANCE

Harmonization regarding the management of adults and children undergoing CAR T cell therapy has begun, and best practice recommendations are published from the European Society for Blood and Marrow Transplantation (EBMT) in cooperation with the Joint Accreditation Committee of International Society of Cell and Gene Therapy (ISCT) and the American Society for Transplantation and Cellular Therapy [15–17]. In contrast, less is established for guidance of CAR T cell therapy based on regular immune monitoring of patients by in depth flow cytometric characterization and advanced biomarker screening in longitudinal studies (Figure 1A). Again, genome- and transcriptome-wide strategies but also functional studies are key methods to reveal novel biomarkers to assess the individual therapy response [18]. These include T cell receptor (TCR) gene sequencing and transcriptome-wide NGS (single-cell, where needed) to analyze the CAR T cell and immune status in circulating cells (liquid biopsies) and in the case of addressing solid tumors, the tumor microenvironment. Next to NGS technologies, biomarker identification could be achieved by analysis of growth factors, cytokines, and/or chemokines in the supernatant of CAR T cells pre- and post-stimulation, and at various time points using multiplex ELISA.

In addition, CRS and CRES are key mediators of toxicities related to CAR T cell therapy. CRS results from the activation of myeloid cells by highly activated T cells and is of high interest for improved research activities. Although antibodies to the interleukin (IL)-6 receptor (e.g. tocilizumab) can ameliorate CRS, it is so far not possible to prevent CRS. In addition, factors associated with tissue damage have to be taken into account for monitoring. This gives rise to investigation and development of new biomarkers for early detection of CRS in patients' peripheral blood, as well as new models for screening mode of action (e.g. organ-on-a-chip models).

The majority of currently known biomarkers used to predict severe CRS were not detected by unbiased studies, but rather by assessing a preselected list of marker candidates [19–21]. However, utilizing unbiased approaches (e.g. NGS) for future biomarker discovery has the potential to reveal still unknown immunological characteristics leading to severe CRS and thus, to development of more precise biomarkers [13]. Currently, the EU project imSAVAR (immune safety avatar: non-clinical mimicking of the immune system effects of immunomodulatory therapies) is aiming to create a platform of novel tools, models and resources for early preclinical prediction of possible adverse events of immunomodulatory therapies. In the future, this platform should guide early preclinical safety assessment of novel immunotherapeutics, thereby reducing the cost of their development.

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CONCLUSIONS

It is noteworthy that responses to CAR T cell therapies vary considerably, which is due to the patients' and disease characteristics and procedures of the CAR T cell culture process. This might be characterized by a distinct composition of immune cell subpopulations and their function. On the one hand, this can be explored in detail by immunology-based technologies (e.g. multicolour flow cytometry or CyTOF) or by molecular biological methods (in particular, high throughput screening using NGS and/or Nanostring analysis). On the other hand, comprehensive and integrative bioinformatics analyses of the retrieved datasets linking biomarker candidates to (longitudinal) clinical outcomes in cohorts of representative sample size will be decisive for improvements in quality assessment of CAR T cell manufacturing and therapy guidance. The availability of novel biomarkers will be the key to providing critical information for the therapeutic success and failure of CAR T cell therapy, which could then be used to improve and optimize the efficacy and safety of this approach.

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IMMUNO-ONCOLOGY INSIGHTS

ADDRESSING LINGERING SAFETY ISSUES FOR I-O PRODUCT CANDIDATES IN DEVELOPMENT

SPOTLIGHT

SHORT COMMUNICATION

Early use of tocilizumab and lead-in dose to mitigate flotetuzumab associated infusion-related reaction/cytokine release reaction in patients with relapsed or refractory acute myeloid leukemia

Kenneth Jacobs, Ouiam Bakkacha, Priyanka Patel & Jan Davidson-Moncada

Flotetuzumab, an investigational CD123 x CD3 DART protein, is designed to target acute myeloid leukemia (AML) cells by co-engagement of a CD123 and CD3 expressing T cells as effector cells. The dose-dependent T-cell activation and concomitant cytokine release, including interleukin 6 (IL-6), is associated with antileukemic activity and cytokine release syndrome (CRS), significant treatment-related toxicity. CRS manifests as chills/rigors, fever, dyspnea, hypotension, hypoxia, and tachycardia. During the clinical development of flotetuzumab, notable strategies adopted to mitigate the incidence and severity of CRS events include early use of tocilizumab (8 mg/kg IV), IL-6 receptor antagonist, and "priming" with MS LID dosing regimen, resulting in decreased incidence and severity of IRR/CRS events leading to greater tolerability of the target dose of 500 ng/kg/day with fewer dose interruptions or discontinuation of flotetuzumab infusion.

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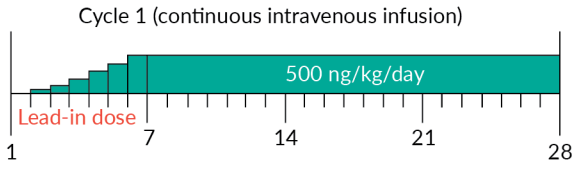
FIGURE 1

Lead-in-dose (LID) and use of tocilizumab decrease cytokine release syndrome (CRS) incidence, severity and duration and lead to increase in total dose intensity.



A) Summary of dose and dosing schedule for flotetuzumab: multi-step lead-in-dose (MS-LID) of 30, 60, 100, 200, 300, 400, 500 ng/kg/day for 24 hours each for days 1 through 7 given via continuous intravenous (CIV) infusion, followed by 500 ng/kg/day CIV from days 8 to 28 during Cycle 1.

Flotetuzumab (MGD006), an investigational CD123 x CD3 DART® molecule, is currently under development in a Phase 1/2 clinical trial in patients with relapsed or refractory acute myeloid leukemia. The flotetuzumab-redirected T-cell killing of AML blasts is associated with dose-dependent activation of T cells and concomitant cytokine release, resulting in CRS. The clinical manifestations of CRS include chills/rigors, fever, dyspnea, hypotension, hypoxia, and tachycardia, which may be associated with T-cell activation and high cytokine levels, including interleukin 6 (IL-6). In the flotetuzumab clinical trial, cytokine release, a surrogate of T-cell activation, has been associated with the antileukemic activity [1]. Hence, blunting rather than eliminating CRS has been aggressively pursued.

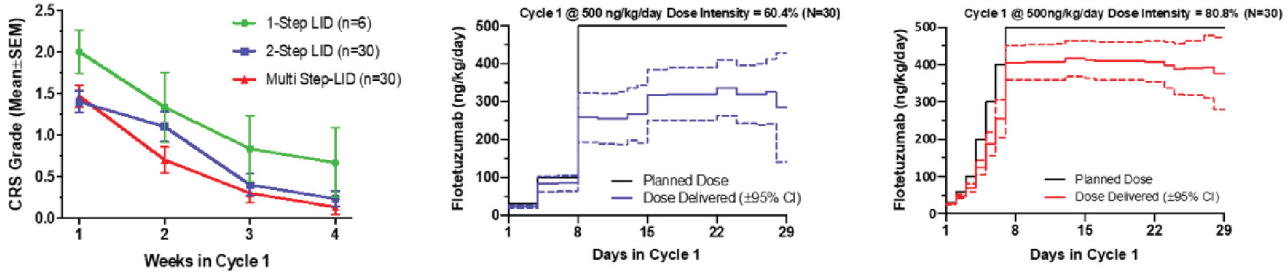
Several strategies have been implemented during the clinical development of flotetuzumab to mitigate the incidence and severity of CRS events. These include pre-medication with dexamethasone, "priming" with multi-step lead-in dose (MS LID) during Cycle 1 Week 1, early use of tocilizumab (Actemra®), an IL-6 receptor antagonist approved for the management of CAR T-induced severe or life-threatening CRS, and specific guidance on dose interruption and discontinuation as part of the supportive care regimen.

Flotetuzumab was administered in multiple small step-up doses (MS LID) for the first seven dosing days. MS LID comprised of step-up dosing every 24 hours (30, 60, 100, 200, 300, 400, 500 ng/kg/day; Figure 1). Flotetuzumab, when administered following MS LID, successfully decreased incidence and severity of CRS, leading to greater tolerability of the target dose of 500 ng/kg/day, compared to one-step or two-step LID (Figure 2). Early use of tocilizumab effectively modified IL6 activity (Figure 2A) and had a significant impact in reducing CRS duration by 33% with an average of 1.2 (range 1–3) versus 1.8 days (range 1–5; Figure 3).

As a result of these strategies, in the dose-expansion cohort (n = 50), the majority of CRS events have been mild to moderate in severity and overall of short duration. Only a single episode of Grade 3 IRR/CRS has been observed in each of 4 (8%) patients

FIGURE 2

Lead-in-dose mitigates CRS and consequently leads to improvement in dose intensity.



Panel A represent CRS grade (mean ± SEM) during each week of cycle 1. Panels B and C show dose intensity (%, mean ± 95% confidence interval [CI]) calculated as the amount of drug received during the time on study (actual drug delivered) relative to the intended dose during weeks 2–4 following respective LID during week 1–2-step (left) multi-step (right) LID.

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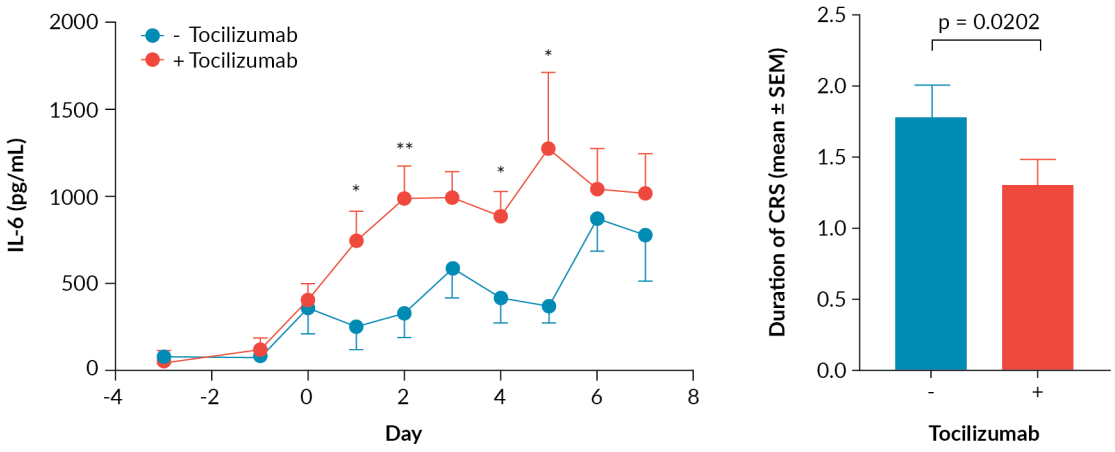
FIGURE 3

Tocilizumab effect on duration of IRR/CRS, irrespective of grade.



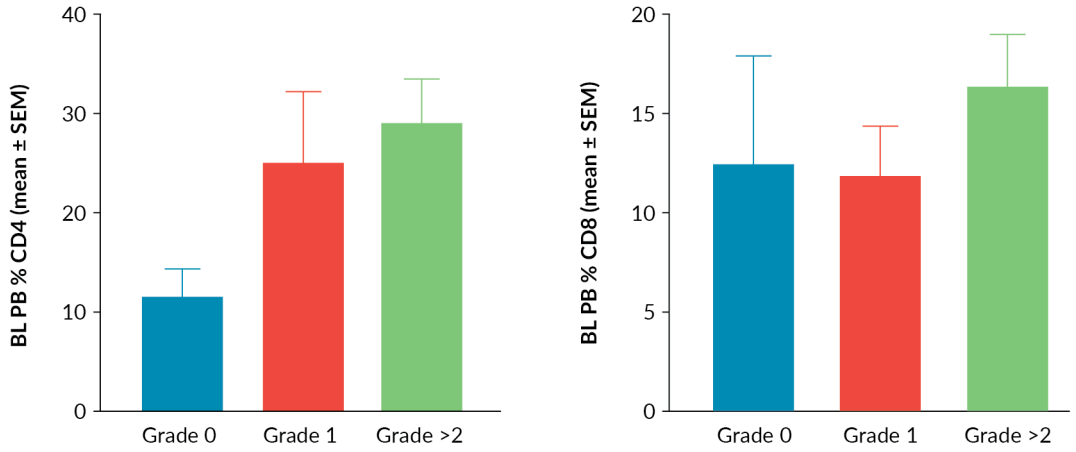
Only patients for whom the drug was not modified as a method of controlling IRR/CRS are included. Mean duration of CRS without tocilizumab 1.8 days (n = 42) and with tocilizumab 1.2 days (n = 13); P = 0.0202, Student t test.
SEM: Standard error of the mean.

treated at the RP2D, and no Grade 4/5 CRS per Lee criteria have been reported. Furthermore, due to these strategies, less aggressive treatment for the management of CRS has been required, i.e., with low ICU admissions and use of vasopressor or oxygen support. Notably, tolerability for the target dose of 500 ng/kg/day was increased, requiring fewer dose reductions and interruptions (Figure 2B & C), as noted by improvement in dose intensity. Additionally, the incidence of IRR/CRS decreased in Cycle 1 Week 2 and beyond.

Lastly, potential determinants of CRS, including immune cells [(T-cell subsets ($CD4^+$, $CD8^+$), monocytes] with tumor burden, percent $CD123^+$ AML blasts, and CD123 expression, were investigated. The aim is to select patients for more aggressive CRS prophylactic treatment. CRS severity was

FIGURE 4

CRS severity in days 1–15 showed a relationship with the baseline frequency of circulating $CD4^+$ cells (median 13.3% in G0 vs. 23% in G≥2; p= < 0.0001), while $CD8^+$ cell frequency did not associate with CRS.



associated with the baseline frequency of circulating $CD4^+$ cells. Other potential determinants of CRS, including $CD8^+$ cell, tumor burden, etc. did not correlate with CRS severity (Figure 4).

In summary, CRS was mitigated with early use of tocilizumab (8 mg/kg IV) and "priming" with MS LID dosing regimen, resulting in decreased incidence and severity of IRR/CRS events leading to greater tolerability of the target dose of 500 ng/kg/day with fewer dose interruptions or discontinuation of flotetuzumab infusion. While determining patients at high-risk for CRS has been preliminarily associated with circulating CD4 T-cells, more work need to be carried out.

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INTERVIEW

Future pathways towards improving clinical safety and efficacy of immunotherapy agents in melanoma

PROFESSOR PAOLO A ASCIERTO obtained his medical degree from the University of Naples, Italy, the institution where he subsequently earned his Board Certification in Oncology. He went on to serve consecutive positions at the National Tumour Institute "Fondazione G. Pascale", in Naples, as a postdoctoral fellow and then as Vice Director of the Department of Clinical Immunology. Professor Ascierto is currently Director of the Department of Melanoma, Cancer Immunotherapy and Innovative therapy at that same institution. He is an active Scientific Reviewer for several international journals, including, NEJM, JCO, Lancet Oncology, and Clinical Cancer Research, as well as being the Associate Editor for Onco-Immunology of Annals of Oncology, Chief Section Editor for Combination Strategies section of Journal of Translational Medicine, Associate Editor of Journal of ImmunoTherapy of Cancer, and member of the Editorial Board fro ESMO Open. As a result of Professor Ascierto's experience and expertise, he has been a valued invited speaker at more than 400 national and international meetings. Furthermore, he is an active member of the Italian Society of Medical Oncology (AIOM), American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Organization for Research and Treatment of Cancer (EORTC) and Society of Immuno Therapy of Cancer (SITC). Professor Ascierto has presided as Principal Investigator on over 120 clinical trials and he is author of more than 470 publications in peer-reviewed journals. Such journals include: The New England Journal of Medicine, The Lancet, Lancet Oncology, Journal of Clinical Oncology, Nature Medicine, JAMA Oncology, and Clinical Cancer Research, among others. Primarily, his major research interests are the genetics and proteomics of melanoma, the assessment of molecular markers for tumour progression in melanoma, management of targeted therapies for melanoma, vaccination treatments and immunotherapy of solid tumors, biochemical and immunological monitoring, and combination approaches for the cancer treatment.

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Q What are you working on right now?

PA: I am working on two different areas: translational research in the field of immunotherapy and melanoma, and clinical research.

In translational research, my main area of interest is mechanisms of resistance and predictive biomarkers for immunotherapies. I am also collaborating with companies on gene profiling, identifying other possible biomarkers in the field of immunotherapy, and working on some aspects of the microbiome.

On the clinical research side, I am working on clinical trials with different sequences of application of targeted therapies and immunotherapies in the melanoma field. This means looking at different sequences for administering the targeted therapy versus the immunotherapy, to try to verify if the order in which the therapies are given can result in a clinical benefit. We should be able to disclose the randomized phase II date from that study (SECOMBIT NCT02631447) shortly.

I am also focused on neoadjuvant trials, not only in melanoma but also in cutaneous squamous cell carcinoma (CSCC). We hope to begin clinical trials soon with targeted therapy and also the triple combination of vemurafenib, cobimetinib, and atezolizumab in the neoadjuvant setting, in order to see whether these treatment approaches will result in improvements in pathological complete response and long-term benefit.

Q Can you provide us with something of a 'gap analysis' of the safety of immuno-oncology therapeutics in the melanoma space, as you see it today?

PA: The safety profile is something that comes from the clinical trial, of course, but currently, I think we need more data from real-world experiments to properly define it. Any gap that exists between the desired and the actual safety profile will only become clear following more real-world experience and real-world analysis (although there are some toxicities we can see at the clinical trial stage, so that is data we need to study more).

"...the first question should be, do we always need to combine? ... we can often reach the same long-term benefit with single treatments."

This is something that we particularly need in the adjuvant setting. In metastatic cancer, we have patients who if they are not treated, will likely die. However, in the adjuvant setting, we have patients who could possibly be treated successfully solely through surgery. We must

understand the risks and the safety aspects as far as possible to inform our discussion of options with those patients - for example, a young person might be given adjuvant therapy and experience a permanent side effect. And while we do see fewer side effects with immunotherapies versus targeted therapies in terms of overall numbers, there are still permanent side effects.

"...those melanoma patients with a full-risk factor are likely to be the ones who gain increased benefit from a combination."

I believe that an international society or oncotherapy group should try to collect as much data as possible from real-world experience to give us a better view of the true safety profile of these therapies.

Q What are the key areas of focus in melanoma currently in terms of understanding mechanisms of adverse reactions to cancer immunotherapy and how to deal with them?

PA: There are some genetic evaluations underway that may prove to be important for discovering which patients might be predisposed to adverse reactions.

However, more research should be considered in this field – we don't need to know the mechanism of resistance only, we also need to know the mechanism of a side effect in order to try to prevent it, or treat it better. I personally believe that the key to some side effects lies in our genes, and of course, in the microbiota (thinking about GI toxicity – colitis, for instance).

Q As you've mentioned, understanding the optimal timing and sequence of administration for combinations involving one or more I-O therapeutic remains a challenge for the field - can you frame for us the current thinking in the melanoma area in this regard, relating to both safety and efficacy?

PA: This is a crucial question. We have some interesting data coming through now, with the triple combination of BRAF, MEK, and anti-PD-1, for instance. However, for me, the first question should be, do we always need to combine? In general, we can often reach the same long-term benefit with single treatments. I think the difference comes in subgroups of patients.

For example, the aforementioned triple combination, or other more aggressive combinations - ipilimumab/nivolumab, for instance - may be of benefit to full-risk patients who have brain metastasis, elevated LDH, and high tumor burden. And this is the approach we are taking in practice, considering that all other patients may be able to achieve the same benefit with a monotherapy. However, it does really depend on the individual patient's characteristics.

It is also important to consider that there are some melanomas different from cutaneous melanoma - uveal melanoma, for instance. Uveal melanoma patients don't tend to respond as

well to immunotherapy as cutaneous melanoma patients. While in general, I would prefer a monotherapy option if it looks likely the same clinical benefit can be achieved, there has been recent data to suggest that the combination of ipilimumab and nivolumab may result in a higher response rate and greater benefit for uveal melanoma patients.

Again, though, the key for me is that those melanoma patients with a full-risk factor are likely to be the ones who gain increased benefit from a combination.

Q Where in particular in your field have you seen recent advances in defining the mechanism of action of I-O therapeutics, and equally, where are the key remaining gaps in our knowledge?

PA: At the moment, we know that for at least 50% of metastatic melanoma patients, we can get long-term benefit – we can say that we can cure them. But for the others, there is still a lot of work to do.

Building on my earlier comments regarding the adjuvant setting, we see that if we treat patients with adjuvant therapy, at least 30% will see cancer recurrence in the first year, and an additional 20% will see recurrence later on. For those patients who fail treatment with anti-PD-1 during the first year, these are probably cancers refractory to immunotherapy. This is a different scenario to secondary resistance, which may possibly be addressed with the addition of another compound: refractory patients and patients that relapse after seeing an initial benefit present us with two different questions.

For the refractory cases, we need to know if this is due to an immune desert in the tumor microenvironment, or if there are other conditions – it is a question of identifying other markers for the generation of an immunosuppressive microenvironment. For instance, is expression of LAG-3 a potential biomarker?

In my view, we should focus more on the tumor microenvironment, and the most important approach is to try to make cold tumors hot - to make the tumor microenvironment responsive to immunotherapy.

There are some interesting combinations seeking to achieve this. For example, the addition of relatlimab (anti-LAG-3) to PD-1 can increase the efficacy of single agent. But this alone is insufficient, because if you look at data of patients who fail anti-PD-1 and are then treated with combination therapy, the response levels are not very high. For this reason, we need more and different combinations.

Q What emerging therapeutic approaches/modalities from across the broad cancer immunotherapy field particularly excite you in terms of their potential to improve clinical outcomes for melanoma patients?

PA: Currently, it is difficult to beat anti-PD-1 monotherapies in melanoma - with them, we can achieve long-term benefits in 40-45% of patients. For example, looking

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"...we should focus more on the tumor microenvironment, and the most important approach is to try to make cold tumors hot – to make the tumor microenvironment responsive to immunotherapy. There are some interesting combinations seeking to achieve this."

at pembrolizumab plus epacadostat (IDO inhibitor), this combination did not show an increase in benefits; the benefit is similar to monotherapy.

Having said that, we need to do more investigation of combinations. What is interesting from my point of view is the relationship with the expression of LAG-3 in the tumor microenvironment. This may be significant because I believe that in the future, with different combinations, we can better personalize our immunotherapy approach. And by better utilization of biomarkers, we can select the right combination for the right patient.

For instance, in the field of melanoma today, PD-L1 expression is not very significant - we don't use it in the clinic. But in the future, it may be that with anti-PD-L1 expression we can use a combination if we also see an increase in expression of LAG-3 or TIM-3. We could use an anti-PD-1 with anti-LAG-3 in the event that we have an increase in LAG-3 expression. Or we could use a combination of anti-PD-1 with pegylated IL2, which is another interesting recent study that has shown some promising phase I and II data.

Other interesting combinations include the combination of anti-PD-1 with toll-like receptor agonists. We have a current phase III trial with tilsotolimod in patients who failed anti-PD-1 in combination with ipilimumab, and we will have this data very soon. That is an interesting approach - as we saw from data reported last year at SITC, a toll-like receptor 9 agonist (CMP-001) in combination with pembrolizumab gave 70% of patients a major pathological response.

HDAC inhibitors, even in combination with anti-PD-1, is a further promising approach. We don't have a phase 3 trial underway in that area yet, but we have some data that looks promising from a study of entinostat in combination with pembrolizumab in patients who failed anti-PD-1.

Drug combinations that can target the adenosine pathway may have utility, although that will perhaps be more in the fields of lung, breast, or kidney cancer than melanoma.

I would also like to see an anti-TIGIT studied in melanoma, because we have already seen very encouraging data in lung cancer. The preclinical data suggests that a TIGIT/PD-1 combination in melanoma could potentially be effective.

Q Lastly, what are your chief priorities for your work over the short-, mid- and long-term future?

PA: My short-term goal is to identify predictive biomarkers of response that can be useful in selecting treatments for patients. In the mid-term, I hope to have identify some interesting combinations from current phase I/II trials that we can explore further in phase III.

And in the long-term it is about finding the right sequence and using that knowledge to increase the benefit to patients of drugs that are currently available.

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ADDRESSING LINGERING SAFETY ISSUES FOR I-O PRODUCT CANDIDATES IN DEVELOPMENT

SPOTLIGHT

INTERVIEW

T cell immunotherapy: addressing toxicity issues in a rapidly commercializing field

JOHN ROSSI joined Kite in 2015 after 13 years at Amgen. He is currently a Senior Director in the Department of Translational Medicine at Kite and leads pharmacology activities related to the clinical development of Kite's cell therapy pipeline. At Kite, he has built an effective translational team to support the clinical development of axicabtagene ciloleucel (Yescarta) and KTE-X19 (Tecartus). His team has contributed directly to the regulatory approval of these products through pharmacokinetic and pharmacodynamic evaluation. Among many achievements at Kite, he has represented the organization through external scientific presentations and collaborative manuscripts with leading academic researchers such as Steven Rosenberg and James Kochenderfer at the NCI. Accomplishments include the discovery of metrics to characterize CAR T based on functionality, novel biomarker knowledge of how CARs work in the clinic, mechanistic information on toxicities and insights into the biology of the TME, including immune checkpoints, and the role of IL-15 in the context of CAR T-cell function.

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Q What are you working on right now?

JR: I am a Senior Director and lead the Clinical Pharmacology group at Kite, A Gilead Company. The Clinical Pharmacology Group resides within the Department of

Translational Medicine and supports both development and discovery research. Of note are major contributions that have lead to the approval of T cell therapy products now, Yescarta® and Tecartus™.

We cover everything in terms of cell therapy development at Kite, from supporting preclinical work, through investigational new drug application (IND), to first-in-human (FIH), all the way to registration. This support involves performing all of the pharmacokinetic and pharmacodynamic assessments across our studies. We deep dive into product features that relate to clinical outcome. Additionally, we are now starting to look at starting manufacturing material for CAR T cell therapy, assessing what the influence of the fitness and function of those T cells is coming in, and how that relates to the product coming out. We also support immunogenicity and other safety measurements.

By and large, you can think of us a pharmacology group that also supports the development of novel biomarkers, in parallel with some of the core data deliverables for registration studies.

Q How would you define the current state of play in terms of our ability to understand and anticipate toxicities relating to T cell immunotherapy? Firstly, in hematologic malignancies: what have been the key recent advances/improvements there?

JR: Focusing in on CD19-targeted CAR therapies in CD19-expressing B-cell malignancies, almost across the board, whether it is a lymphoma or a leukemia, we see that cytokine release syndrome (CRS) and neurologic toxicity seem to be the predominant toxicities that are of concern. Secondary to that are cytopenias that are related to the therapy, the disease, or a combination thereof.

Over the last 5 years, from the Kite perspective, we have become much more adept at recognizing and managing CRS and neurologic toxicity. When we started the pivotal ZUMA-1 study in diffuse large B-cell lymphoma, there was a concern that giving corticosteroids would oblate the function of CAR T cells, and that while you might be able to dampen toxicity, those patients would have no hope of seeing a disease response.

To a certain extent, the use of anti-IL-6 agents was viewed in a similar light. What we learned over the course of the study was that by giving appropriately timed doses of either tocilizumab for CRS, or corticosteroids for neurologic toxicity – or sometimes a combination of both – we can more effectively manage toxicities. With this approach we could keep people hopefully out of the ICU entirely – or at least see ICU time decreased – and the number of fatalities minimized from those toxic events. A lot of this knowledge was obtained through physician learning on the management of toxicities.

We have also learned through biomarkers: a lot of the key cytokines, CAR T cell phenotypes, and other features of the patient that factor into toxicities. We are using this information to develop predictive algorithms that are going to enable us to identify high-, medium-, and low-risk patients, and that will hopefully influence how they are managed.

In parallel, through a lot of the translational work that has been done both at Kite and throughout the field, we now understand certain immunological pathways that we can dampen

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or interdict. This will lead to approaches with more targeted interventions, too, which we believe could manage toxicity effectively whilst maintaining robust anti-tumor response.

Through clinical identification of problems, and through translational science, we are starting to come together to see improvement in toxicity management with the current generation of cell therapies. At the other end of the spectrum, we can begin to think about using these learnings to design the next generation of cell therapies. These are going to be much safer than what we currently have, and hopefully will have equal, if not better, efficacy and durability of response.

Our ultimate goal is to put 100% of patients into remission long-term, and although we are not there yet, we are learning and working daily towards that.

Q It is still relatively early days in term of T cell immunotherapy's migration into the solid tumor area. How do you view the current status of our understanding of toxicities there?

JR: For solid tumor indications, you face several challenges. Target is one – chimeric antigen receptors require proteins expressed on the surface of non-essential cells. For example, if CD19 was expressed on the heart, we wouldn't have CD19 CAR T cells! Targets that are restricted to tumor cells represent a huge challenge for chimeric antigen receptors in their current configuration.

The features of the tumor microenvironment pose another hurdle; overcoming an immunologically hostile environment is a challenge both in the field of checkpoint inhibitors and for engineered cell therapies.

I think improved engineering of future cell therapy products will come into play here. Adopting approaches where two tumor antigens must be present to activate the CAR – Logic-gated CARs, or SynNotch, for example – is one strategy. On the other end, you have the engineered T-cell receptors that recognize private epitopes from the tumor cell, or shared epitopes that are presented in an HLA-dependent fashion, which you can target with T-cell receptor

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(TCR) expressing T-cells specific to those tumor antigens.

However, these cells lack co-stimulatory domains, and I think the jury is still out on potency. We have seen a lot of promise, but we need to overcome these barriers to start to see cell therapy gain a larger footprint and change how patients with solid tumor malignancies and epithelial cancers are managed. I believe we will get there, but there is a lot of work to do, both clinically and scientifically.

Q Tell us about the challenges presented by the rise of allogeneic T cell immunotherapy and how you are seeking to address these issues.

JR: First and foremost, at Kite we recognize the potential of allogeneic healthy donor CAR T cell products that can be used as a therapeutic, as well as long-term stem cell-based approaches to manufacture very uniform allogeneic T cell products. The hope is that having a product that is safe and highly efficacious will broaden patient access to cell therapy products, bring down the costs, and alleviate some of the supply chain and logistical challenges that one faces with autologous T-cell products. You have to make a new drug every time for thousands of patients, and obviously things can go wrong – not necessarily with the process, but with the health of the patient's T-cells, for example.

That is the promise, but I think the challenge is in getting there. We have a lot of great gene editing tools at our disposal now. Of course, CRISPR-Cas9 technology is at the forefront of gene editing, along with zinc finger nucleases and some other approaches. However, there is still a lot of work to do in engineering efficacious T-cells using those approaches, and finding ways to engineer healthy donor T-cells in such a way that you avoid host rejection. Graft-versus-host disease is always a concern but has been minimized through the use of targeted knock-in to the Treg loci.

There is a lot of work to do in getting good engraftment because of host rejection features. We believe that there are multiple potential mechanisms for graft rejection: it could be natural killer cell-, T cell-, or major histocompatibility complex (MHC) class II-mediated, or there could be complement antibody-based rejection. We have to look at all of these as Kite moves into the clinic.

These are major near-term challenges to advancing allogeneic approaches to the point where autologous cell therapy currently resides, in terms of what we see clinically for patients.

Q What are the major concerns around T cell immunotherapy in the combination setting currently, particularly regarding safety aspects - and again, what approaches is the field taking to alleviate them?

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JR: Most of the combinations we have seen to date have been fairly well tolerated. Kite ran the ZUMA-6 study, which was our CD19 CAR, axi-cel (Yescarta®), with atezolizumab, which is an anti-PD-L1 from Genentech. The toxicity profile of the CAR alone versus the combination was not much different. But then again, we didn't see much difference in efficacy, either. It is hard to move the needle when your overall response rate is pushing 90%, but we were hoping to see an increase in our complete response (CR) rate and durability of response. CR rate and durability of response were equivocal.

There are similar studies with checkpoint inhibitors – for example, pembrolizumab and nivolumab – that have shown some promise of efficacy without a lot of toxicity. However, they don't seem to be dramatically improving the situation.

We need to think about other potential combination therapies, whether they are potentially offer a safety or an efficacy benefit. Kite has two additional combination studies: the ZUMA-19 protocol is looking at GM-CSF access blockade for toxicity management, and ZUMA-11 is a combination study with Pfizer's utomilumab looking at 4-1BB agonism with the hope that we can increase efficacy. As these targeted intervention trials read out, we will see if we are moving the needle.

We initially hypothesized that the toxicity could potentially be exacerbated by combinations and in general, that hasn't been the case. It seems that most of the dominant toxicities are still CAR-related, without much exacerbation. More work needs to be done, but there are multiple opportunities to test different combinations with currently approved products, in order to try to achieve improvements in toxicity/efficacy profiles.

Q What are your plans and goals for the foreseeable future?

JR: Our major goals are to execute on our pivotal studies to either drive label expansion for indications, or to move into earlier lines of treatment – plus of course, continued optimization of our currently approved products for safety and efficacy. For example, ZUMA-7 is a pivotal randomized Phase 3 study in second line diffuse large B-cell lymphoma. We anticipate this will read out very soon, and we hope to file if the results are positive in order to bring this therapy to more patients at an earlier line.

In terms of indications we are striving towards, we are hoping for approval in indolent non-Hodgkin's lymphoma with Yescarta®. We filed on our ZUMA-5 study recently, which had fantastic results presented at the ASCO. We will be following up at ASH with the primary analysis results in December.

Our ZUMA-3 study in adult acute lymphoblastic leukemia (ALL) is reading out and

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with Tecartus™, we hope to be the first company to have a label for this indication – the only approved product is currently indicated for pediatric ALL.

One additional point of focus for us will be to continue providing translational data that allows us to look at running outpatient studies. This will allow us to test our hypotheses around patient prediction and selection of outpatient versus inpatient. Treating patients in the outpatient setting would ultimately be easier on both the patients and the hospitals, and would also decrease financial burden.

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