Design and Conduct of Early Clinical Studies of Immunotherapy

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Design and Conduct of Early Clinical Studies of Immunotherapy: Recommendations from the Task Force on Methodology for the Development of Innovative Cancer Therapies 2019 (MDICT)

Martin Smoragiewicz[1], Alex A. Adjei[2], Emiliano Calvo[3], Josep Tabernero[4], Aurélien Marabelle[5], Christophe Massard[5], Jun Tang[6], Elisabeth G.E. de Vries[7], Jean-Yves Douillard[8], and Lesley Seymour[1]; for the task force on Methodology for the Development of Innovative Cancer Therapies

ABSTRACT

Purpose: To review key aspects of the design and conduct of early clinical trials (ECT) of immunotherapy agents.

Experimental Design: The Methodology for the Development of Innovative Cancer Therapies Task Force 2019 included experts from academia, nonprofit organizations, industry, and regulatory agencies. The review focus was on methodology for ECTs testing immune-oncology therapies (IO) used in combination with other IO or chemotherapy.

Results: Although early successes have been seen, the landscape continues to be very dynamic, and there are ongoing concerns regarding the capacity to test all new drugs and combinations in clinical trials.

Conclusions: Optimization of drug development methodology is required, taking into account early, late, and lower grade intolerable toxicities, novel response patterns, as well as pharmacodynamic data.

Introduction

The Methodology for the Development of Innovative Cancer Therapies (MDICT) task force, established in 2006, is composed of experts from academia, nonprofit organizations, industry, and regulatory stakeholders, and provides guidance and recommendations on the development of novel anticancer agents (1–5). The focus for the 2019 meeting was methodology for early clinical trials (ECT) testing immune-oncology therapies (IO) used in combination with other IO or chemotherapy. These recommendations are timely, with over 3,000 IO targeting more than 400 targets in development (6). Moreover, there are more than 2,000 trials testing different anti-PD-L1 combinations. Critical evaluation of design, methodology, and efficiency is imperative, as well as development of sound strategies to minimize redundancy. MDICT feels that the principles of sound clinical trial design and conduct of ECT of combinations of anticancer therapies remain relevant (4), although updates for IO are required.

Materials and Methods

The 2019 meeting was held at the International Symposium on Targeted Anticancer Therapies (ESMO-TAT). Participants included experts from academia, nonprofit organizations, industry, and regulatory agencies. Topics were defined by the Steering Committee of ESMO-TAT, and refined by members of the MDICT. At the meeting, brief presentations summarized key developments and challenges, and a full discussion ensued. MDICT then formulated recommendations, which were reviewed by members and attendees.

Results

Preclinical assays and data required

Preclinical murine models may be unhelpful in identifying optimal dose/schedule. Nonetheless, optimal preclinical assays can help define receptor occupancy, pharmacokinetic/pharmacodynamic effect, and facilitate the design and conduct of ECT. Well-designed preclinical studies can explore some aspects of scheduling. The development of knockin and humanized models is critical, and the use of nonhuman primates should be expanded to their full potential to understand toxicity.

Selecting the optimal schedule and dose of IO–IO and IO–chemotherapy combinations

Challenges

The selection of optimal dose/schedule for any combination is challenging, but essential and must consider whether one agent is priming the other, or additive effect alone is anticipated. Unnecessarily high dosing may increase costs and toxicity, while suboptimal dosing increases the risk of false-negative outcomes.

Toxicity is not clearly dose dependent for IO, with grade 3–4 toxicities observed across the range of doses tested (7–9). Late toxicity (10) or chronic intolerable low-grade toxicity has often been described with IO agents, as well as molecularly targeted agents (11), and for most IO agents, MTD has not been defined (7–9) despite

[1]Canadian Cancer Trials Group, Queen's University, Kingston, Ontario, Canada. [2]Mayo Clinic, Rochester, Minnesota. [3]START Madrid-Centro Integral Oncológico Clara Campal Hospital, Madrid, Spain. [4]Vall d'Hebron University Hospital and Institute of Oncology (VHIO), UVic, IOB-Quiron, Barcelona, Spain. [5]Gustave Roussy, Université Paris-Saclay, Département d'Innovation Thérapeutique et d'Essais Précoces, INSERM U1015, Villejuif, France. [6]The Anna-Maria Kellen Clinical Accelerator, Cancer Research Institute, New York, New York. [7]Department of Medical Oncology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. [8]Medical and Scientific Affairs Division, ESMO, Lugano, Switzerland.

Corresponding Author: Lesley Seymour, Queen's University, 10 Stuart Street, Kingston, Ontario K7L 3N6, Canada. Phone: 613-533-6430; Fax: 613-533-2911; E-mail: lseymour@ctg.queensu.ca

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Translational Relevance

While new therapeutics targeting the immune environment are now the standard of care for a number of cancer types, there is ongoing concern that clinical trial methodology is empiric and based on that used for cytotoxic drugs. The Methodology for the Development of Innovative Cancer Therapies identified critical questions facing the field, and formulated recommendations, focusing on novel and promising biomarkers, pharmacokinetic/pharmacodynamic relationships, and clinical trial methodology.

testing 100 fold ranges in dose. Similarly, response rates do not seem dose dependent. Drug clearance can be variable, increasing in male and poor performance status patients but decreasing with response (12). Consideration of tumor micro- and macro environment is important, as it is complex, dynamic, and has considerable inter- and intrapatient variability (13).

The lack of precision in the definition of the best schedule and dose for many IO agents as a single agent is compounded when designing ECTs for IO/IO or IO/chemotherapy combinations. Many trials appear to have been designed empirically or are based on preclinical studies of single doses of chemotherapy prior to IO (14). Chemotherapies deplete lymphocytes and alter myeloid-derived suppressor cell and the immune environment. Effects may be unexpected; for example, in the Keynote-048 (head and neck cancer) study pembrolizumab + chemotherapy showed a shorter median duration of response compared with pembrolizumab alone, raising concerns that standard chemotherapy may impair long term IO-induced responses (15). Preclinical studies suggest a possible alternative would be to administer chemotherapy intratumorally to induce an immunogenic cell death, but spare the potentially adverse effects of systemic chemotherapy on lymphocyte populations (16).

Recommendations

Dose optimization is critical, but trials testing dose optimization could be conducted after initial marketing approval. While this provides earlier drug access for patients, if a suboptimal dose or schedule is taken forward, the drug/combination may fail in pivotal studies. Better precision in defining dose could be achieved by considering factors such as pharmacokinetic/pharmacodynamic relationships, which can be complex. As an example, ECTs of CD40 agonists identified a bell-shaped pharmacodynamic effect of antigen-presenting cell activation (17, 18), thus allowing selection of an intermediate dose.

Therapeutic drug monitoring and modeling might also be considered in later trials; Ratain and Goldstein recently argued for the evaluation of lower doses of nivolumab, citing the flat exposure-response and maximal receptor occupancy even at the lowest effective dose tested (0.1 mg/kg; ref. 12). Changes to both nivolumab and pembrolizumab dosing were supported by *in silico* modeling (12, 19, 20).

Schedule exploration, both preclinically and in ECT, is imperative and ECT exploring single-, lower-, or intratumoral doses of chemotherapy should be explored, rather than empirically adding IO to standard chemotherapy regimens (16). Larger and/or randomized trial designs may be required, including pharmacokinetic, pharmacodynamic, and clinical and imaging biomarkers described below to test specific hypotheses such as priming.

Investigators should consider the use of different terminology, for example "treatment-limiting toxicity" (TLT) including early, late, intolerable, prolonged, or recurrent toxicities. The recommended phase II dose should be based on TLTs while ensuring adequate dose intensity. TLTs should be refined and adjusted as experience with the new class of agents increase. Protocols should define an "immune-recommended dose" (IRD) for IO based on pharmacokinetic, serial pharmacodynamic, efficacy, and short and long-term toxicity, and include data from phase I and II studies.

Trial design and go/no-go decisions for drug development

Challenges

A series of positive IO trials in the last years does not mean that there has been rational drug development, as sometimes toxicities, dose intensity, and schedule have not been critically reviewed. A good example is the development of the antibody-drug conjugate rovalpituzumab Tesirine (Rova-T; refs. 21–23) that initially showed very encouraging response rates (38%) in a phase I trial in patients with small-cell lung cancer expressing high levels of the target DLL3 (23). A large, single arm phase II trial (TRINITY) was initiated, and shortly thereafter, but prior to the TRINITY results, a phase III trial (TAHOE) was launched. TRINITY reported disappointing results (21), and shortly afterwards the independent data monitoring committee halted enrollment to TAHOE (22). In retrospect, the response rate confidence intervals in the phase I trial were wide and included the results reported in TRINITY.

Recommendations

An understanding of pharmacokinetic/pharmacodynamic relationships and consideration of tumor micro and macro environment is important, but is complex and dynamic with considerable inter- and intrapatient variability. Given preclinical pharmacodynamic models are in general poorly developed, phase 0 or window of opportunity trials should also be considered to explore IO pharmacodynamic in humans.

Design of the phase I or II clinical trial will need to be optimized to address dose and schedule selection for IO combination trials given the complexity described above. Almost certainly, larger sample sizes will be required. Cohorts could be backfilled as dose escalation continues to increase data across a range of doses. Clearly, 3+3 designs are inadequate for this purpose, and adaptive Bayesian designs should be considered.

Seamless phase I–III designs may be appropriate in certain settings; while speed in development is desirable but not at the expense of good design and a full understanding of the data gleaned in phase I studies.

Randomized phase II studies have a clear role, especially in understanding toxicity profiles. Phase I studies need to be appropriately designed, and if expansion cohorts are included, clear statistical rules must be in place (24, 25). Furthermore, especially when there are numerous similar agents in development, decisions to proceed from phase I should not generally be taken unless a high bar for activity has been met (including real clinical benefit, or treatment failure at 4 months which includes efficacy and tolerability), unless the agent is not expected to have single-agent activity.

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Core clinical and imaging biomarkers

Challenges

Typically, biomarkers are not validated when ECT start, and technology changes rapidly, making it challenging to collect the right samples for later analysis. The collection of serial tumor samples is important to evaluate pharmacokinetic/pharmacodynamic effects but is very challenging.

Several reports have shown gut microbial composition differs between responders and nonresponders to IO (26, 27). Commensal microbiota influence systemic immunity, including the induction of IFNγ-producing CD8 cells that depends on $CD103^+$ dendritic cells and MHC class I (28). Numerous external and host factors that modulate the microbiome remain to be fully characterized, including geography, medication, diet, psychologic factors, sex, age, and host genomics (27, 29, 30). The recent FDA safety alert regarding possible transmission of multi-drug–resistant organism from fecal microbiota for transplantation highlights the need for adequate safety considerations (31).

The heterogeneity of biomarker expression is an important limitation for tumor sampling, and this has led to the development of imaging/biomarker approaches. Recent studies have demonstrated the feasibility of imaging markers such as PD-L1 and PD-1 using radiolabeled tracers (32, 33). Clinical responses were better correlated with baseline zirconium-89–labeled atezolizumab PET signal than with IHC PD-L1 expression. The identification of "hot and cold" tumors is largely related to T-cell infiltration within the tumor microenvironment, which can be heterogeneous. Imaging with radiolabeled anti-CD8 minibody has recently been reported and may serve to distinguish hot from cold tumors (33). A radiomics approach, the high-throughput extraction of large amounts of image features from radiographic images (34), using features from chemotherapy images may be easier and less costly to identify hot and cold tumors (35).

Recommendations

Further studies are required to understand the role of the microbiome in cancer and cancer treatment but ECTs should consider collection, including rapid freezing of stool samples, use of standard protocols to collect and analyze, and use of standardized food and concomitant drug diaries.

Simple blood-based biomarkers can be included as exploratory endpoints in larger or randomized ECT, such as lactate dehydrogenase (LDH), C-reactive protein, leukocytes, neutrophils, platelets, and low albumin and lymphocyte counts, and have been extensively investigated as markers of an "inflammatory" state and associated with poor prognosis in different cancers (36, 37). Stratification of patients with metastatic renal cell carcinoma using the International Metastatic Renal Cell Carcinoma Consortium classification in the landmark study with first-line nivolumab + ipilimumab identified potentially less benefit in good-risk patients, although this analysis was exploratory (38). The Lung Immune Prognostic Index, which incorporates neutrophils, leukocytes, and LDH, has recently been shown to potentially be predictive in patients with non–small cell lung cancer (NSCLC) treated with IO, and could be considered for patient stratification for IO trials (39).

However, patients should not be selected for ECTs on the basis of these unvalidated prognostic/predictive signatures as they may not reflect the true activity of an IO combination, may underestimate toxicity, and subsequently lead to failure in later stage development. The scores could be considered as stratification factors in later phase trials.

Tumor mutational burden (TMB) in circulating tumor DNA (ctDNA) is a promising biomarker given emerging data, which suggests patients with NSCLC might be selected for treatment with atezolizumab on the basis of high TMB in plasma (40). However, TMB cutoffs remain to be refined, and may be different for patients treated with combinations. Finally, ctDNA dynamics may identify responding and, even more important, hyperprogressing and pseudoprogressing patients to IO agents much earlier than conventional imaging (41, 42), and should be further evaluated.

For ECTs, combining imaging with tumor biopsies might be particularly fruitful.

Evaluation of PD-L1 and immune cell infiltrates/inflammatory gene expression is reasonable especially if serial samples can be obtained, but is costly and may limit accrual; incorporation into later, larger trials may be most appropriate.

iRECIST should be incorporated into ECTs, as a secondary or exploratory objective, to allow the creation of warehouses to develop and test novel endpoints (43) and to more fully elucidate the frequency and outcomes of unusual responses such as hyperprogression, especially in randomized or placebo-controlled trials.

Table 1. 2019 MDICT Task Force recommendations for IO drug development.

Topic	Recommendations
Strategy	• Minimize redundancy and increase efficiency–more informative data • Carefully consider the most important questions to be answered
Dose and schedule	• Redefine definitions to aid optimal dose selection, including new concepts such as TLT and IRD • Data rich early trials with PK/PD across range of doses to assist in determining TLT and IRD • Critically evaluate chemotherapy timing and dose in combination with IO agents
Trial design go/no-go decisions	• Good clinical trial methodology remains critical despite recent successes; consider phase 0, window of opportunity trials • Larger, Bayesian, or randomized trials may be required to fully explore schedule and dose • Follow published guidelines for seamless designs • Set the bar high so only the best drugs continue in development
Core clinical and imaging biomarkers	• Liquid biopsy development is critical, but tissue biopsies remain important for PD studies • Standardize methodology and optimal timing for novel biomarkers such as the microbiome • Include exploratory biomarkers, but do not use for patient selection until validated • Imaging: iRECIST should be used in IO clinical trials to develop data warehouses to develop and test novel endpoints and explore pseudoprogression and hyperprogression. Explore the use of molecular imaging and radiomics.

Abbreviation: PK/PD, pharmacokinetic/pharmacodynamic.

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Conclusions

Immune check point inhibitor and other IO therapies have brought new challenges, and the speed of development has left many questions unanswered. Recruitment challenges may begin to limit our ability to answer questions as the number of trials with IO agents in combination has expanded to exceed and widespread clinical use has reduced the need for clinical trial opportunities. MDICT has generated a series of recommendations (**Table 1**).

Disclosure of Potential Conflicts of Interest

J. Tabernero is an employee/paid consultant for Array Biopharma, AstraZeneca, Bayer, BeiGene, Boehringer Ingelheim, Chugai, Genentech, Inc., Genmab A/S, Halozyme, Imugene Limited, Inflection Biosciences Limited, Ipsen, Kura Oncology, Lilly, MSD, Menarini, Merck Serono, Merrimack, Merus, Molecular Partners, Novartis, Peptomyc, Pfizer, Pharmacyclics, ProteoDesign SL, Rafael Pharmaceuticals, F. Hoffmann-La Roche Ltd, Sanofi, SeaGen, Seattle Genetics, Servier, Symphogen, Taiho, VCN Biosciences, Biocartis, Foundation Medicine, HalioDX SAS, and Roche Diagnostics. E.G.E. de Vries reports receiving commercial research grants (to institution) from Amgen, Genentech, Roche, Bayer, Servier, Regeneron, Chugai Pharma, CytomX Therapeutics, Nordic Nanovector, G1 Therapeutics, AstraZeneca, Radius Health, and Synthon, and is an advisory board member/unpaid consultant (payment to institution) for NSABP, Sanofi, Synthon, and Daiichi Sankyo. J.-Y. Douillard is an employee/paid consultant for the European Society for Medical Oncology. L. Seymour is an employee/paid consultant for Boehringer Ingelheim, reports receiving commercial research grants from AstraZeneca, Bayer, Senhwa, and Roche, and holds ownership interest (including patents) in AstraZeneca. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: M. Smoragiewicz, A.A. Adjei, E. Calvo, J. Tabernero, A. Marabelle, C. Massard, J. Tang, J.-Y. Douillard, L. Seymour
Development of methodology: M. Smoragiewicz, A.A. Adjei, E. Calvo, J. Tabernero, A. Marabelle, C. Massard, E.G.E. de Vries, J.-Y. Douillard, L. Seymour
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J. Tabernero, L. Seymour
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Smoragiewicz, J. Tabernero, C. Massard, J.-Y. Douillard, L. Seymour
Writing, review, and/or revision of the manuscript: M. Smoragiewicz, A.A. Adjei, E. Calvo, J. Tabernero, A. Marabelle, C. Massard, J. Tang, E.G.E. de Vries, J.-Y. Douillard, L. Seymour
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.-Y. Douillard
Study supervision: E. Calvo

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