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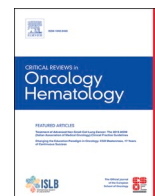


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Patients' selection and trial matching in early-phase oncology clinical trials

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ABSTRACT

Background: Early-phase clinical trials (EPCT) represent an important part of innovations in medical oncology and a valuable therapeutic option for patients with metastatic cancers, particularly in the era of precision medicine. Nevertheless, adult patients' participation in oncology clinical trials is low, ranging from 2% to 8% worldwide, with unequal access, and up to 40% risk of early discontinuation in EPCT, mostly due to cancer-related complications.

Design: We review the tools and initiatives to increase patients' orientation and access to early phase cancer clinical trials, and to limit early discontinuation.

Results: New approaches to optimize the early-phase clinical trial referring process in oncology include automatic trial matching, tools to facilitate the estimation of patients' prognostic and/or to better predict patients' eligibility to clinical trials. Classical and innovative approaches should be associated to double patient recruitment, improve clinical trial enrollment experience and reduce early discontinuation rates.

Conclusions: Whereas EPCT are essential for patients to access the latest medical innovations in oncology, offering the appropriate trial when it is relevant for patients should increase by organizational and technological innovations. The oncologic community will need to closely monitor their performance, portability and simplicity for implementation in daily clinical practice.

1. Introduction

Worldwide, adult cancer patient participation in oncology trials is low, ranging from 2% to 8% (Unger et al., 2023). During 2020 and 2021, Covid-19 pandemic slightly affected the inclusion of patients in oncology clinical trials. Nevertheless the overall participation rapidly increased with time after a temporary slowdown in activity (Sayyid et al., 2022; Bakouny et al., 2022; Bayle et al., 2021). The overall objective set few years ago was to include more than 10% in clinical trial (Tran et al., 2020; Le Plan Cancer). We are still not there yet, but new development in technologies and policies could lead us to match this objective.

Early phase clinical trials (EPCTs) represent 20% of all clinical trials in oncology with 11,000 active clinical trials in 2022 worldwide (WHO Global observatory on health research and development (1999–2022), 2023). During the past 20 years, the response rate in phase 1 trials nearly doubled without an increase in the treatment-related death rate

(Chihara et al., 2022). Before 2000, EPCTs, including phase I and/or phase II trials, mainly involved chemotherapeutic agents. Reported objective response rates were less than 5% (Estey et al., 1986; Decoster et al., 1990; Horstmann et al., 2005; Italiano et al., 2008; Postel-Vinay et al., 2016; Chakiba et al., 2018). Afterward, the early development of molecular targeted agents, and concomitantly, the more frequent evaluation of chemotherapies in combination, increased the global response rate in EPCTs up to 10% (Italiano et al., 2008; Postel-Vinay et al., 2009). After 2013, the development of immunotherapies, in monotherapy or in combination, together with next generation molecular targeted agents, further pushed the overall response rates up to 15% - 20% (Chihara et al., 2022; Chakiba et al., 2018). Nowadays, when EPCTs design include biomarker selection, the overall response rate can even reach 30% (Alouani et al., 2023; Griguolo et al., 2022). With such results, EPCTs are becoming a recommended therapeutic option for patients with refractory cancers.

The low participation rate can be explained by several factors.

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Patients' access to EPCT depends on travel distances from early-phase centers (Unger et al., 2018), health professional habits (Jacobs et al., 2014), social disparities (Besle et al., 2018; Perni et al., 2021; Mohd Noor et al., 2013; Dunlop et al., 2022) and patients' characteristics matching with often complex selection criteria, including biomarker selection (Desai et al., 2023). The molecular analysis of tumors is a cornerstone of current oncology drug development as 90% of compounds are FDA-approved with a companion biomarker (Scott et al., 2023). Decision makers highlight the importance of improving the ways for patients to access EPCT through a more optimized identification of patients matching selection criteria and a better communication on clinical trials in oncology (LEEM, 2022). They suggest that the use of patient data could support these efforts.

Here, we review the initiatives and tools that could contribute to improve patient recruitment in EPCTs, and evaluate how to implement them in clinical routine.

2. Patients selection in EPCT

2.1. EPCT objectives and classical selection criteria

EPCTs in oncology aim at evaluating the toxicity and the early anti-tumor efficacy of newly developed anticancer drugs or combinations and identifying dose levels for further investigations. Phase I clinical trials usually include healthy subjects for many medical specialties. For neurodegenerative diseases or transplantation interventions they usually involve patients, and this is also classical in oncology (FDA, 2022; Roberts et al., 2004). The main ethical justification is to spare healthy participants from potential toxicities of anti-tumor compounds, and to provide opportunity for early access to innovations for patients with cancers refractory to conventional treatments (Cox and Avis, 1996; Daugherty et al., 1995). EPCT usually includes a limited number of participants; around 30 patients in dose-escalation phases, and a few hundred in expansion phases (Postel-Vinay et al., 2016). During the dose escalation phase, the first period of treatment (usually 21–28 days) is usually critical to evaluate the adverse events related to the investigational compound (Fig. 1). The absence of significant toxicity during this period, defined as Dose Limiting Toxicity (DLT) period, allows continuing dose escalation, by increasing the dose of treatment for the next cohort of patients (Le Tourneau et al., 2009). When a patient cannot complete the DLT period, he or she is not evaluable for DLT, and thus needs to be replaced by another patient. Up to 15% of patients included in EPCT discontinue the study during this period (Olmos et al., 2012). Early patient discontinuation usually prolongs the whole duration of the clinical trial, increases the cost of research and means a waste of time and quality of life for these patients, underscoring the ethical limits of inappropriate patients' selection. Therefore, an upfront appropriate selection of patients is justified 1) to maximize the probability that the patient will complete the DLT period, 2) to ensure patients' safety (by minimizing the risk and consequences of potential adverse events), 3) to spare unfit patients from demanding procedures that could compromise

their quality of end of life, and 4) to avoid factors that might hinder the assessment of adverse events causality, such as cancer-related symptoms that may significantly worsen during the trial.

This is why classical selection criteria for EPCT usually include adequate organ functions (e.g., liver, kidney, and bone marrow), no uncontrolled and/or severe symptoms, a performance status ≤ 1 , and a life expectancy of more than 3 months at the time of inclusion. Other classical eligibility criteria require that the tumor lesions can be measured according to RECIST 1.1 criteria, that the tumor site is accessible to biopsy and that it bears a specific molecular alteration related to the mechanism of the treatment under evaluation. Selection criteria are reviewed during a screening period. Depending on the complexity of the criteria, this screening phase can last between one week and one month, for example if a biopsy is required, or even more if a molecular biomarker is required. At the end of the screening period, 15–25% of patients are not eligible any more for the clinical trial (Kempf et al., 2016; Mckane et al., 2013). The most frequent reasons for screen failures include abnormal imaging results (such as new diagnosis of brain metastasis), abnormal blood tests, deterioration of the performance status, or a new clinical event that meets an exclusion criterion (Kempf et al., 2016; Mckane et al., 2013; Fogel, 2018; NCRI Cancer Conference, 2023).

When pooling screening and DLT periods, approximately 40% of participants discontinue the trial (Fig. 2) (Kempf et al., 2016). Early discontinuation is deleterious for both the patient and the study. Patients can feel disappointed and think they have missed a potential therapeutic option (Yang et al., 2023), and it extends the duration of the study.

The attempts to improve the recruitment of patients in EPCT aimed to optimize the care path organization, and better estimate patients' prognosis at 3 months and/or patient eligibility (Al Darazi et al., 2021; Bigot et al., 2017; Garrido-Laguna et al., 2012).

2.2. Care paths organization

Running EPCTs requires teams and infrastructures adapted to the close assessment of toxicities, pharmacology, the delivery of new drugs from the patient's bedside to the collection and management of data (Brown et al., 2017; The START Center). Therefore, few hospitals or private clinics have the certification to run such trials in a territory or country. As a result to this limited number of centers, some patients have to travel long distances to access these trials. Some inequalities exist in the access to EPCT, based on three mechanisms: care path organization of the access to trials, screening of patients prior to inclusion, and constraints linked to participation in a research protocol (Besle et al., 2021; Charton et al., 2023).

During the selection phase of an EPCT, the physician investigator of the clinical trial need relatively complete information about the patient to verify the inclusion criteria. This situation is simple when the patient is known to the hospital. It is often more difficult when the patient comes from another hospital because of the limited number of shared documents (Besle et al., 2018). Sharing patient health data, ideally in a

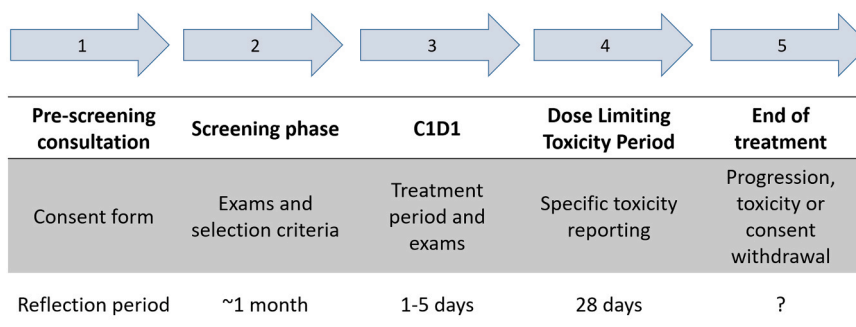


Fig. 1. Classical steps of a phase 1 clinical trial. Abbreviations: C1D1, first day of first cycle.

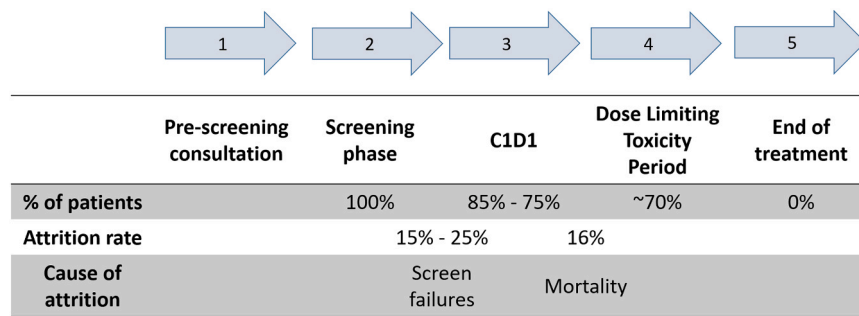


Fig. 2. Attrition rate of patients in phase 1 clinical trials. Abbreviations: C1D1, first day of first cycle.

computerized and secure manner, before the first consultation for EPCT screening, would avoid redundant laboratory tests or radiologic examinations already carried out (Vrijssen et al., 2021; Lysdahl and Hofmann, 2009) and thus potentially reduce the duration of the screening period. Most sites have in house organization to share patients' data between hospitals, and most often not interoperable with other sites. Consequently, when no trial is available in one site, it is rare for the patient to be referred to another center in the region, and if so, the search for a clinical trial is relatively laborious. This deprives the patient of a therapeutic opportunity at an advanced stage of the disease.

The vast majority of oncology EPCTs evaluate compounds with identified targets (Scott et al., 2023). Sometimes it concerns molecular alterations, such as KRAS G12C or NTRK fusions (Ou et al., 2022; Hong et al., 2020, 2019). Ongoing molecular profiling programs led in many institutions around the globe can provide the biomarkers required for patient inclusion in EPCTs (Trédan et al., 2019; Debieu et al., 2023; American Society of Clinical Oncology, 2023; Canadian Cancer Trials Group, 2023; Helland et al., 2022; Kringelbach et al., 2023; Nygren et al., 2023). Specific biomarkers and analysis methods are still often required for EPCTs that are not routinely implemented in sites (for example an immunohistochemistry analysis with a specific antibody), making this type of selection criteria a persisting challenge (Bayle et al., 2023). When a dedicated molecular analysis is required for the study, this is performed during a pre-screening period that can last between 15 days and more than a month.

In parallel, political efforts are made to facilitate the orientation of patients to targeted treatments in clinical trials, such as consortiums of European countries for patients' access to personalized oncology (PCM4EU; PRIME-ROSE). Moreover, the FDA recently incented to improve diversity of clinical trial enrollment. Broadening the usually restrictive eligibility criteria in EPCTs may help addressing these disproportions (Snyder et al., 2022). Altogether, improving the access to EPCTs for patients in a region would benefit from better health data exchange, optimized care path organizations, more rapid and distributed prescreening analysis and automatic trial matching.

3. Trial matching

Orientation of patients to oncology EPCTs is traditionally made by physicians, who are aware of active clinical trials in their or the nearby institutions, and know the patients. Several tools aim at facilitating and automating this process referred to as trial matching tools (Table 1). These tools require information about the EPCT status on sites, the selection criteria of the trial and the matched clinical characteristics. Several tools for the extraction of structured information from clinical trial eligibility criteria have been published under open source licenses, including MatchMiner (Nierengarten et al., 2023; Klein et al., 2022), the Clinical Trial Parser developed by Facebook research (Open-Sourcing), and digitalECMT (O'Regan et al., 2023). Moreover, several organizations provide databases and search platforms for trial registries, notably ClinicalTrials.gov (https://clinicaltrials.gov/), the WHO (https://www.

Table 1
Trial-matching tools' characteristics.

Generation	Manual (1st generation)	Semi-automatic (2nd generation)	Automatic (3rd generation)
Method	Manual search	Semi-automatic search	Automatic search with push notification
Platform type	None	Cloud	Electronic health records
Advantages	Easy to set up	Automatic update of trial data Efficient search Better matching	Automatic update of patient data Automatic notification without requiring a search
Disadvantages	Time and workforce consuming (manual update of trial and patient data) Inefficient search Risk of error	Manual or semi-automatic update of patient data Requires a search	Complex and numerous data with risk of false positive Need for a solution for structuring trial data to match patient data
Maturity	Available	Implementation in progress	Research and development stage

who.int), the Clip2 (https://e-cancer.shinyapps.io/DATAVIZ_SCREEN/) and others, and some initiatives proposed to aggregated these databases (Kreutzfeldt et al., 2023). In addition, more and more private initiatives are under development such as those in the US detailed in a recent editorial (Desai et al., 2023) and for Europe, for example in Spain Trialing (Hardy-Werbin et al., 2023; Adashek and Kurzrock, 2023), CancerTrials (https://www.cancertrials.be/), and in France Klineo (https://www.klineo.fr/), OncoClic (https://www.oncoclic.fr/), ScreenAct (https://screenact.fr).

In these applications, EPCT status, such as: open, have slots, on hold, closed to enrollment, and EPCT selection criteria, are often downloaded from the public databases. The selection criteria are available in plain text, transformed into structured variables, and used to match the patient's clinical characteristics. For example, the criteria "Histologically confirmed unresectable (Stage IIIB, IIIC, or IIID) or metastatic (Stage IV) cutaneous melanoma, according to the AJCC 8th edition" can be turned into "cutaneous melanoma", "locally advanced" and/or "metastatic", so that a patient or a clinician can select it in a rolling menu.

Most web platforms propose manual entry of patients' characteristics (referred as semi-automatic - 2nd generation trial matching tools in Table 1). The variables can be either molecular alterations and/or combined clinical descriptions. Tools that can connect to hospitals databases could in theory automatically structure the patients' data and thus scan any patient corresponding to a clinical trial in a hospital. Several tools for automatic structuration of medical reports exist (task known as name entity recognition in Natural Language Processing) such as MEDomics (Morin et al., 2021), Coder (Yuan et al., 2022), GatorTron (Yang et al., 2022), ConSore (Heudel et al., 2016), or Intelligence For

Health (<https://intelligenthealth.ai/>). In practice, the performance for these tools are heterogeneous and depend on the type of variable considered. For example, the tumor type is often adequately structured, but dates of tumor events (such as recurrence or progression), or other diagnoses can be limited (L. Verlingue, P.A. Cassier, unpublished observations).

A third generation of fully automatic trial matching tools is rising relying on recent Natural Language Processing methods. A meta-analysis on 10 studies has demonstrated a summary sensitivity of 90.5% and a summary specificity of 99.3% for automatic cancer clinical trial enrollment (Chow et al., 2023). Some authors even estimated that automatic trial matching can reduce by 85–90% the workload of oncologist and consequently increase the number of patients reviewed for eligibility (Ni et al., 2015). Newer initiatives use Large Language Models can even automatically process free text for both the clinical trial selection criteria and the patients' notes. The first attempt (using one-shot in-context learning with GPT3.5 on 185 patients) have reached an overall accuracy of 0.86 and 0.84 for the inclusion and exclusion criteria, respectively (Jin et al., 2023). Ongoing works attempt to reproduce human reasoning by asking a sequence of questions (multi-hop reasoning) related to the selection criteria (Jullien et al., 2023). Some of these applications can perform conversions and calculations for numeric values and synonyms and could potentially improve the results. The implementation of performant automatic trial matching approaches rely on updated information about the clinical trial status and access to patients' data.

4. Outcome prediction from clinical and biological variables

As stated in the introduction, 40% of patients discontinue early the EPCT during the screening or the DLT periods mainly because of disease related events, including cancer related mortality (Kempf et al., 2016; Mckane et al., 2013; Fogel, 2018; NCI Cancer Conference Abstracts, 2023) (Fig. 2). Prognosis estimation is a notoriously difficult task (Krishnan et al., 2013). Most recent prospective evaluation of the performance of physicians nevertheless tempered the old paradigm: Area Under the Receiver Operating Curve was between 72% and 81% to predict the 2-year survival of patients affected by cancer (Estey et al., 1986; Decoster et al., 1990; Horstmann et al., 2005b; Smith-Uffen et al., 2020; Kiely et al., 2013). The oldest but still used clinical variable related to prognosis estimation is the Eastern Cooperative Oncology Group performance status (Oken et al., 1982). Various models were then developed to predict the short-term prognosis of patients with metastatic cancers from several clinical and biological variables (Table 2). They have been established through classical statistical methods, to select the most significant ones from a set of variables of interest. However, few direct comparisons are available to date (Al Darazi et al., 2021). The Royal Marsden Hospital (RMH) (Arkenau et al., 2008, 2009) is the oldest and most used score in practice. It was validated for patients treated with chemotherapies and targeted therapies. RMH is based on three markers: the number of sites of metastases; the lactate dehydrogenase (LDH) level and the albumin level. The MDACC and PMH scores were similar to the RMH score but included the performance status, and the MDACC had slightly better accuracy for prognosis estimation when externally compared to RMH (Wheler et al., 2012; Chau et al., 2011). Several tools are also dedicated to patients enrolled in trials with immune-checkpoint inhibitors (Bigot et al., 2017; Hierro et al., 2018).

More recently, machine and deep learning methods were used to significantly increase the number of clinical and biological variables used to predict prognosis or patient eligibility, with improved performances (Heudel et al., 2016; Garcelon et al., 2018; Delorme et al., 2021; Becker et al., 2020). For example, the ROPRO score, included 27 variables reflecting host fitness and tumor biology, and clearly outperformed most of the prognosis estimators developed to date (Becker et al., 2020). Another model directly used the clinical notes to estimate patient overall survival with similar performance as ROPRO score for

bad prognosis patients, but without manual curation of the data (K-memBERT) (Piat et al., 2023). The generalization performance of the most recent tools, such as the PIPO-score, are currently under multi-centric evaluation (Matos et al., 2021; UpSMART, 2023).

5. Eligibility prediction

In theory, trial matching and prognosis estimation could provide sufficient information to improve the selection of patients for EPCT. Nevertheless, there remains some limitations, including that 1) it can be laborious to manually input the variables related to prognosis, up to 27 in some cases, and the clinical characteristics of the patients and 2) it can be challenging to review the results of two different tools, with the uncertainty related to each prediction (trials proposed and survival estimation), and use it in the timeframe of a patient visit. A more direct application would be to immediately predict if the patient is a good candidate or not to ECPTs, meaning that he/she could successfully pass the screening and DLT period. Similar to what humans do, the tool could use as input both the patient health reports and the clinical trial protocols. To do so, consultation reports in free text can be fed into Natural Language Processing tools to predict patients' eligibility. Such approach reached high performance and a reduction of the early discontinuation rate from 39.8% to 12.8% in a retrospective cohort (Delorme et al., 2021) (Table 1). Natural Language Processing have the advantages of being user friendly (often requiring a simple copy-paste, writing, or data flow in the backend to run a prediction), and easily interpreted (for example, highlighting the most important words used for the predictions). Finally, patient reported assessment can also relate to early trial discontinuation, opening new applications on this source of data (Ouali et al., 2023).

6. Perspectives

Inclusion of patients in oncology EPCTs are *per se* limited to patients matching the protocol defined selection criteria of individual studies, and nevertheless burdened with a significant number of early discontinuations. The evolving landscape of EPCTs, particularly with biomarker driven compounds, raises new challenges for patient selection. Moreover, a tsunami of new compounds is expected following the implementation of artificial intelligence-based virtual screening and optimized preclinical development (Rifaioğlu et al., 2019). We have identified leverage points in EPCTs that can be addressed by 1) optimized care pathways organization to improve communication from and within sites running EPCTs, 2) automatic trial matching for a large number of patients, and 3) improving outcome prediction including screening, DLT period completion and/or survival. Altogether, we estimate that these efforts could move from 5% up to more than 20% of adult patients referred to EPCTs, and from 40% to less than 20% the early discontinuation rate in EPCTs (Fig. 3). These applications can also limit the bias in patient selection, such as the place of residence of patients, facilitate and accelerate the process of patient referral, increasing the number of candidates and limiting the number of patients with early discontinuation. By recruiting more diverse population of patients, those initiatives could even limit the discrepancies sometimes observed in response rates between early and late phase clinical trial, for example with PD-1/PD-L1 immunotherapies (Li et al., 2024). Other initiatives such as decentralized clinical trials could synergize to reach these goals (Adashek et al., 2023).

To make this feasible, the new tools should be scalable (i.e. continue to function well for new patients and for new clinical trials), portable (can be easily installed in hospitals, accessible on new platforms), user-friendly (do not need a long training to be used) and time saving. Saving time with high performance can improve the confidence of healthcare practitioners and facilitate the implementation in routine. Therefore, the tools should be carefully positioned in the care pathway of the patients participating in oncology clinical trials, adapted to the clinical practice

Table 2

Main prognostic scores and eligibility support tools for early-phase oncology clinical trials. The table highlights the types of compounds, the outcome considered for application. It also describes the pros and cons of each approach.

Scores	RMH	MDACC	PMH	GRIm-score	MDA-ICI	LIPI	PIPO-score	Natural Language Processing	ROPRO
References	Arkenau et al. (2008, 2009)	Wheler et al. (2012)	Chau et al. (2011)	Bigot et al. (2017)	Sen et al. (2018)	Varga et al. (2019)	Matos et al. (2021)	Delorme et al. (2021)	Becker et al. (2020)
Investigated treatment types	Chemotherapy; Targeted therapies	Chemotherapy; Targeted therapies	Chemotherapy; Targeted therapies	Immune-Checkpoint Therapies	Immune-Checkpoint Therapies	Immune-Checkpoint Therapies	Immune-Checkpoint Therapies; Targeted therapies	Immune-Checkpoint Therapies; Targeted therapies	Immune-Checkpoint Therapies; Targeted therapies
Risk factors	LDH > ULN; Albumin < 35 g/L; Site of metastases > 2	LDH > ULN; Albumin < 35 g/L; Site of metastases > 2; ECOG PS > 1; Gastrointestinal tumor type	Albumin < 35 g/L; ECOG PS > 0; Site of metastases > 2	LDH > ULN; Albumin < 35 g/L; dNLR > 6	Age > 52 years; ECOG PS > 1; LDH > 466 UI/L; Platelets > 300 G/L; ANC > 4.9 G/L; ALC < 1.8 G/L; Liver metastases	dNLR > 3; LDH > ULN	ECOG PS; Number of metastatic sites; Presence of liver metastases; dNLR; Albumin; LDH levels	Free text from consultation reports	27 demographic, clinical, hematologic, and blood chemistry parameters
Risk-groups									
Low	0–1	Low 0 Low-I 1	0–1	0–1	0–2	0	0–2	successful screening and DLT period completion	ROPRO ≤ 1.18 (≤ 90% quantile)
Intermediate	-	Interm. 2 High-I 3	-	-	3 4	1	3–4	-	-
High	2–3	High 4–5	2–3	2–3	5–6	2	5–6	screen failure	ROPRO > 1.18 (> 90% quantile)
Number of patients	212 78 (prospective validation)	1181	223	268	172	360	799	1858	201 (retrospective validation on the phase I study BP29428)
OS	Median OS (months), 10.6 vs 3.6 4.7 vs 2.2 (prospective validation)	Median OS (months), 24.0 vs 15.2 vs 8.4 vs 6.2 vs 4.1	-	Median OS (months), 68.9 vs 20.4	Median OS (months), 24.2 vs 11.6 vs 8.0 vs 3.8	Median OS (months), 17.8 vs 11.7 vs 3.9	Median OS (months), 16.3 vs 6.6 vs 2.9	-	HR 11.29 (95% CI 5.52–23.12)
90-day mortality (%)	-	-	37% vs 7%	-	-	-	-	-	-
C-index for OS	-	0.67 (95% CI, 0.62 – 0.71)	0.89 (95% CI, 0.76 – 0.98)	0.70 (95% CI, 0.64–0.77)	0.72 (95% CI, 0.64 – 0.80)	-	0.71 (95% CI, 0.64–0.78)	-	0.81, p = 6.08.10 ⁻¹⁵
Pros	simple; objective factors; prospectively validated	more accurate than RMH score	prediction of 90-day mortality	simple; objective; specifically designed for ICT	specifically designed for ICT	simple; objective factors; specifically designed for ICT	patient-specific risk prediction for any given time point; easily accessible online; no dichotomization of continuous and ordinal variables; evaluated for ICT and for TT	good performances: F1 score 0.80, recall 0.81, area under the curve 0.88, reduction of screen fail rate from 39.8% to 12.8% (relative risk, 0.322; 95% CI, 0.209–0.498; P, 0.0001)	strongest performances; largest dataset used for prognostic modeling to date
Cons	not evaluated for ICT; low specificity	multiple variables and prognostic categories; not evaluated for ICT	not evaluated for ICT	not initially developed for patients treated with both TT and ICT	not initially developed for patients treated with both Tt and ICT; multiple variables	not initially developed for phase I trials	not evaluated for ICI and TT combinations	restricted to French language and to a unique center; order of the words within the sentence	not specifically developed for patients involved in EPCT; 27 variables to be entered

(continued on next page)

Table 2 (continued)

Scores	RMH	MDACC	PMH	GRIm-score	MDA-ICI	LIPI	PIPO-score	Natural Language Processing	ROPRO
					and prognostic categories			not considered; does not support structured data format to date; need to be prospectively validated	into the formula; only one retrospective analysis on patients from EPCT

Abbreviations: dNLR, derived neutrophil-to-lymphocytes ratio; ECOG PS, Eastern Cooperative Oncology Group performance status; GRIm-score, Gustave Roussy Immune Score; HR, Hazard Ratio; ICT, immune-checkpoint therapy; LDH, Lactate Dehydrogenase; LIPI, Lung Immune Prognostic Index; Low-I, Low-Intermediate; MDACC, MD Anderson Cancer Center; MDA-ICI, MD Anderson immune checkpoint inhibitor; OS, overall survival; PIPO-score, Phase I prognostic online; PMH, Princess Margaret Hospital; RMH, Royal Marsden Hospital; TT, targeted therapy; ULN, upper limit normal.

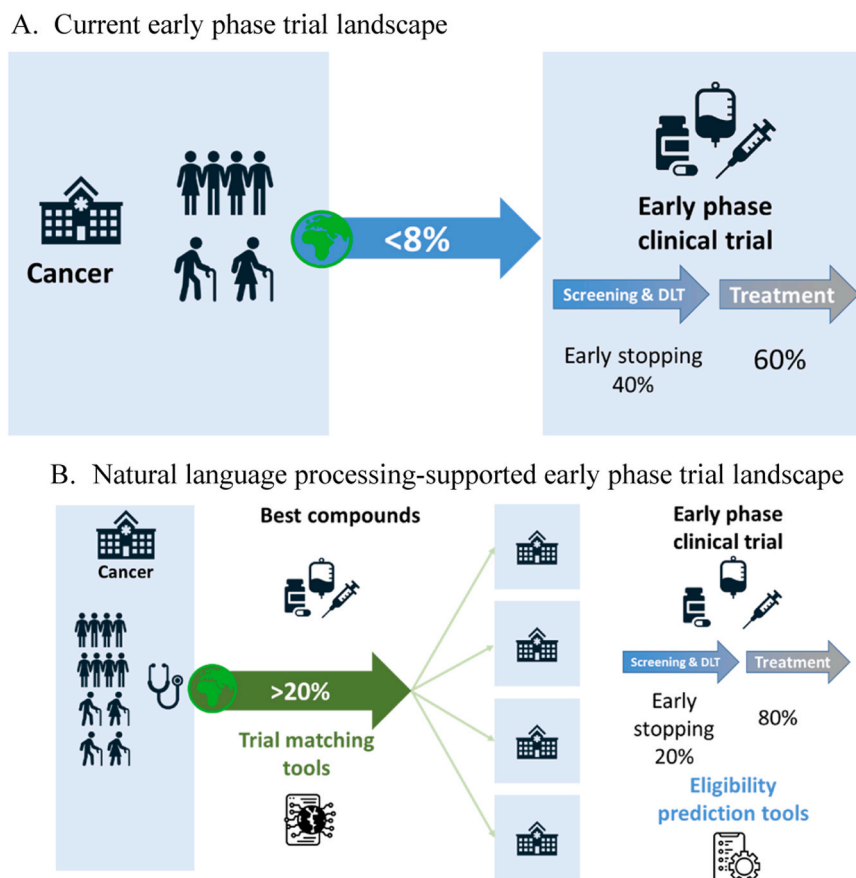


Fig. 3. The attrition rate of patients in early phase trials. Abbreviations: DLT, Dose Limiting Toxicity.

and to the regulatory requirements specific to clinical research.

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CRedit authorship contribution statement

P. Corbaux: Methodology, Investigation, Formal analysis, Writing – original draft. **A. Bayle:** Investigation, Writing – review & editing. **S. Besle:** Investigation, Writing – review & editing, **A. Vinceneux:** Writing – review & editing. **H. Vanacker:** Writing – review & editing. **B. Hanvic:** Writing – review & editing. **C. Baldini:** Writing – review &

editing. **P. Cassier:** Writing – review & editing. **C. Terret:** Writing – review & editing. **L. Verlingue:** Conceptualization, Methodology, Visualization, writing – original draft, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

LV: reports personal fees from Adaptherapy, is CEO of RESOLVED, has received non-personal fees from Pierre-Fabre and Servier, and a grant from Bristol-Myers Squibb, all outside the submitted work. AB is the CEO and co-founder of Klinéo. PAC received consulting/honoraria by Boehringer Ingelheim Ose Immunotherapeutics, Bristol Meyer Squibb. As Principal-Investigator in the Phase 1 unit at CLB of Clinical Trials

the relations are:

AV with Astra Zeneca, BIONTECH RNA, EXSCIENZA LTD, Exelixis, Hoffmann La Roche Ag, IPSEN, Janssen Cilag, Kinnate Biopharma, Lilly France, Loxo Oncology, Novartis, TAKEDA.

LV with Genmab, Bicycle Therapeutics, Revolution Medicine, Daiichi, Astra Zeneca, Hoffmann La Roche.

PAC with Abbvie, Adlai Nortye, Alligator, Amgen, Boehringer Ingelheim, Blueprint, Bristol Meyer Squibb, Debio, Dragonfly, Exelixis, Incyte, Iteos, Janssen, Kinnate, Kazia, Lilly/Loxo, Merck Sharp Dohme, Molecular Partners, Novartis, Ose immunotherapeutics, Pierre Fabre, Relay, Roche/Genentech, Sotio, Taiho, Tango, Toray, Turning Point, Transgene.

As part of the Drug Development Department (DITEP) at Gustave Roussy CB, KO, and AB declare being/having:

Principal/sub-Investigator of Clinical Trials for Abbvie, Adaptimmune, Adlai Nortye USA Inc, Aduro Biotech, Agios Pharmaceuticals, Amgen, Astra Zeneca Ab, Astra Zeneca, Aveo, Basilea Pharmaceutica International Ltd, Bayer Healthcare Ag, Beigene, BicycleTx Ltd, Blueprint Medicines, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Ca, Capi Pharmaceuticals, Inc, Cato Research, Celgene Corporation, Cellcentric, Chugai Pharmaceutical Co, Cullinan-Apollo, Daiichi Sankyo, Debiopharm, Eisai, Eisai Limited, Eli Lilly, Ever-Immune, Exelixis, Faron Pharmaceuticals Ltd, Foghorn Therapeutics Inc, Forma Therapeutics, Gamamabs, Genentech, Genmab, Glaxosmithkline, H3 Biomedicine, Hoffmann La Roche Ag, IGM Biosciences, Imcheck Therapeutics, Incyte Corporation, Innate Pharma, Iris Servier, Iteos Belgium SA, Janssen Cilag, Janssen Research Foundation, Janssen R&D LLC, K-Group Beta, Kinnate Biopharma, Kura Oncology, Kyowa Kirin Pharm. Dev, Lilly France, Loxo Oncology, Medimmune, Menarini Ricerche, Merck Sharp & Dohme Chibret, Merus, Molecular Partners Ag, Nanobiotix, Nektar Therapeutics, Novartis Pharma, Nuvalent, Octimet Oncology Nv, Oncoethix, Oncopeptides, Orion Pharma, Ose Pharma, Pfizer, Pharma Mar, Phio Pharmaceuticals Corp, Pierre Fabre Medicament, Pyramid Bioscience, Regeneron Pharmaceuticals, Relay Therapeutics, Roche, Sanofi Aventis, Seattle Genetics, Sotio A.S, Syros Pharmaceuticals, Taiho Pharma, Tesaro, Transgene S.A, Turning Point Therapeutics, Xencor.

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All other authors don't declare any conflict of interest.

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