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The opportunity of patient-journey studies for academic clinical research in oncology

Francesco Perrone ,[1] Raimondo Di Liello ,[1] Piera Gargiulo,[1] Laura Arenare,[1] Lorenzo Guizzaro,[2,3] Paolo Chiodini ,[2] Ciro Gallo ,[2] Maria Carmela Piccirillo[1]

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[1]Clinical Trial Unit, Istituto Nazionale Tumori IRCCS Fondazione Pascale, Napoli, Italy
[2]Medical Statistics Unit, Università degli Studi della Campania Luigi Vanvitelli, Napoli, Italy
[3]Human Medicines, European Medicines Agency, Amsterdam, Netherlands

Correspondence to
Dr Francesco Perrone;
f.perrone@istitutotumori.na.it

ABSTRACT

A wave of new treatments and treatment combinations are becoming available for solid tumours. Trials performed to obtain registration establish a positive benefit-risk but unavoidably leave many questions unanswered on place-in-therapy and the relative efficacy of different treatment sequences. Such limitations create problems in terms of strength of treatment guidelines and reimbursement (in countries where a public payer exists). Data on new drugs arriving during the last 10 years for the treatment of hepatocellular carcinoma and renal cancer are reported as an example of how the fortunate condition of having new effective treatments may translate into uncertainty regarding the optimal treatment plan. We suggest that academic research should react to such limitations and propose a model of patient-journey study (PJS), where patients are followed from the initial diagnosis across subsequent lines of treatment. A PJS master protocol might include at each node of clinical decision either the possibility of choosing treatment according to guidelines (generating prospective real-world evidence) or the possibility to randomise where uncertainty exists (generating comparative effectiveness data). PJS protocols might be adaptively modified every time a new drug arrives on the market. Overall, methodologically sound analyses of PJS will produce knowledge on the efficacy and the effectiveness of different treatment pathways and might significantly optimise treatment of patients in clinical practice. PJS would represent a jump from a few snapshots (trials performed to get regulatory approval) to a full movie (evidence on the relative value of treatment pathways).

INTRODUCTION

Oncology is living along contrasting trajectories. As knowledge on molecular causes and drivers of cancer growth increases, a large part of the scientific community tries to translate it into therapeutic options; notwithstanding such efforts, precision oncology is not yet established as an effective strategy beyond any reasonable doubt. On the other side, a wave of combination of immune checkpoint inhibitors with other new or old drugs is showing to be effective in several settings.[1] This is a fortunate situation, because it is much better to have several therapeutic options than none or very few. Figure 1 shows, for example, how the number of available treatments (detailed in the online supplemental table 1) has rapidly expanded within the last 10 years for hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC), two types of cancers characterised in the past by the availability of few or very few therapeutic options.

Introducing new drugs into market

Pharmaceutical industries drive the arrival of new drugs to the market, often building on academic research discovering new therapeutic mechanisms and treatment strategies. The system might be virtuous, but unfortunately it is suffering a severe shortness of breath. More and more problems derive from the rising cost of new drugs.[2] Problems also arise from limitations of clinical trials designed to obtain regulatory approval.[3 4] Such trials, indeed, are snapshots on the efficacy of new drugs. As a consequence, what comes before (eg, characteristics of eligible patients and acceptability of the comparator treatment) might be no longer consistent with clinical practice when the drug arrives to the market. And, what comes after the snapshot (eg, outcome after subsequent lines of treatment) is by design excluded from what the trials are able to robustly characterise.

Introducing new drugs into clinical practice

Therefore, the place-in-therapy of some new drugs is far from being clear when they arrive to the market, and the wave of innovation might turn into chaos, causing both unsustainability and confusion of scientific evidence, resulting in an inability to identify and address the needs of patients. To find the best treatment algorithm in HCC and RCC, for example, is becoming complex due to shortcomings of available evidence (see ESMO guidelines at https://www.esmo.org/guidelines/gastrointestinal-cancers/

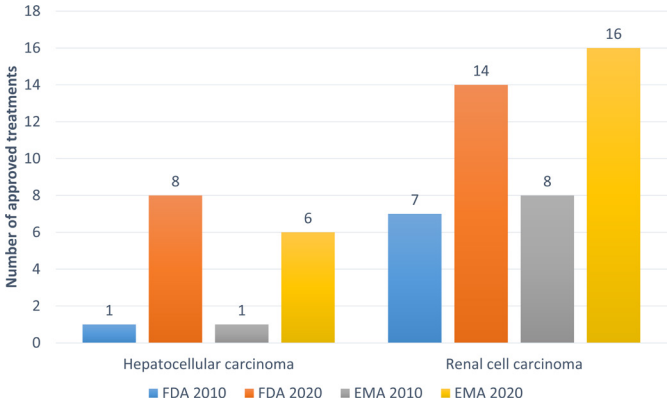

Figure 1 Treatments approved by the FDA and EMA for hepatocellular carcinoma and renal cell cancer in 2010 and 2020. EMA: European Medicines Agency; FDA: US Food and Drug Administration.

hepatocellular-carcinoma/eupdate-hepatocellular-carcinoma-treatment-recommendations and https://www.esmo.org/guidelines/genitourinary-cancers/renal-cell-carcinoma/eupdate-renal-cell-carcinoma-treatment-recommendations-3). New drug combinations, indeed, are being approved because proved better than the same drug that was standard when trials were planned (sorafenib in HCC and sunitinib in RCC).[5 6] Nevertheless, nobody knows the relative efficacy of such combinations (lacking head-to-head trials) or which is the best treatment sequence where multiple options exist that can be used at different stages of the disease (lacking clinical trials comparing different treatment sequences). Consequently, decisions of all stakeholders that come after regulatory approval are made more difficult.

Moving from the snapshot to the movie

We propose that academy, in collaboration with patient organisations, should react implementing a research strategy focused on the therapeutic pathways of patients (patient-journey study (PJS)) rather than on the efficacy of single treatments. A PJS might enrol patients at diagnosis and follow them across subsequent lines of treatment. At each treatment-decision node, within a desirable framework of shared decision-making,[7] to the patient would be offered the option to choose according to guidelines, randomise where uncertainty exists (according to a formal protocol with its own study design) or access to other trials (regardless of phase and sponsor) when available and reasonable. Therefore, the master protocol of a PJS will prospectively integrate trials and real-world evidence, overcoming the existing dualism and favouring the quality of both.[8] It will empower shared decision-making and might be inclusive for biomarker studies and precision oncology trials, loco-regional treatments, supportive care and pharmaco-economic analyses. In countries where public coverage of cancer drug exists, knowledge generated through appropriate analyses of such studies might allow to implement reimbursement according to the model of coverage with evidence development.[9] Globally, it might be useful to strengthen the evidence base for international guidelines, frequently self-limiting to a listing approach, being unable to select which options are the best. Particularly, a PJS might be instrumental to describe and value how patients' preferences might usefully be considered and reflected in developing or updating guidelines.[10 11]

Overall, such research strategy might be a way for moving from a few snapshots to a full movie, that moght also open new chances for on-stage photographers.[12]

Correction notice This article has been corrected since it first published. The disclaimer statement has been included.

Twitter Francesco Perrone @fperrone62

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ORCID iDs
Francesco Perrone http://orcid.org/0000-0002-9738-0526
Raimondo Di Liello http://orcid.org/0000-0003-4511-7969
Paolo Chiodini http://orcid.org/0000-0003-0139-2264
Ciro Gallo http://orcid.org/0000-0002-7939-3104

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