



Drug development in the era of precision medicine in oncology— Clues beyond randomization

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The primary objective of any treatment in oncology is the improve patients' overall survival (OS) and/or quality of life (QoL). Patients with solid tumors may often be cured thanks to local treatments including surgery and radiotherapy when then are free of distant metastases. In this setting, anticancer drugs may improve cure rates when combined to local treatments. In the recurrent and/or metastatic setting, drugs represent the main treatment option, while surgery and radiotherapy might still be used in a palliative intent in most cases. With the exception of germline tumors and lymphoma, drugs have a limited ability to cure patients in this setting, and patients most often need to receive sequential treatments for life.

In the ancestral paradigm of drug development in oncology, drugs used to be developed per cancer type following a well-established path that well suited chemotherapeutic agents for which antitumor activity largely depended on cancer types in preclinical models (*Table 1*). The first evaluation of new drugs in patients in phase I clinical trials was usually performed in patients who had exhausted standard of care, and not in healthy volunteers given the toxic nature of the drugs and their narrow therapeutic index. Dose escalation used to be open to patients with any type of cancer however, in order not to miss a serendipitous antitumor activity in unexpected cancer types. Phase I trials were not randomized, and enabled to establish the schedule and the recommended phase II dose that was the highest dose to be considered safe for

further evaluation. Based on antitumor activity observed in preclinical models and during phase I trials, preliminary drug efficacy was then assessed in a specific cancer type and setting (usually in the recurrent and/or metastatic setting) in single-arm or randomized phase II clinical trials. Surrogate endpoints such as the objective response rate (ORR) or progression-free survival (PFS) were commonly used to have a rapid read-out of the efficacy. These surrogate endpoints were assessed by following over time the tumor burden, formerly the sum of the product of the two diameters of the target lesions (WHO criteria) (1), and more recently the sum of the largest diameter of up to five target lesions (RECIST) (2). Randomized phase III clinical trials were performed in a similar patient population in order to demonstrate an improvement in OS and/or QoL of the new treatment over the current standard of care. Randomization is the gold-standard approach for market access in order to avoid selection biases. Recently, seamless drug development led to increasingly replace phase II clinical trials with large expansion cohorts performed during phase I trials, in order to accelerate drug development (3). This paradigm based on the randomization for drug approval nicely fitted to drugs developed in specific but common cancer types, but is less suited to rare cancer types.

A better understanding of cancer biology led to the development of molecularly targeted agents (MTAs) that were specifically designed to modulate a molecular pathway in the tumor cells or their microenvironment, and

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Table 1 Drug development paradigms

	Not biomarker-driven	Biomarker-driven	
		1 single molecular alteration	Several molecular alterations
Per cancer type	Ancestral paradigm	Ancestral paradigm	Umbrella trials
Across cancer types	–	Basket trials	Algorithm-testing trials

immunotherapies that reactivate the immune system against cancer cells. Several MTAs, such as antiangiogenic agents or mammalian target of rapamycin (mTOR) inhibitors, were developed in specific cancer types without any molecular selection based on a biomarker, whereas the identification of molecular alterations in some cancer types formed the basis for a biomarker-driven drug development following a drug-diagnostic codevelopment (*Table 1*) (4). Most of MTAs developed with a companion diagnostic were initially tested in one single cancer type, such as crizotinib in anaplastic lymphoma kinase (ALK)-translocated non-small cell lung cancer (NSCLC) patients (5). The assumption that the predictive value of a molecular alteration in one cancer type would hold true in other cancer types led to the design of basket trials in which the selection was based on the occurrence of the molecular alteration in different cancer types (6-9). The example of vemurafenib in patients with BRAF V600E-mutated cancers however suggested that the predictive value of a molecular alteration might vary depending on the cancer type (6). Intratumor heterogeneity and coexisting molecular alterations might explain primary and secondary resistance to MTAs. Despite these caveats, MTAs have substantially improved the outcome of patients in several cancer types, although a minority of patients are eligible to these drugs (10).

Biomarker-driven drug development represents a challenge when the prevalence of the biomarker is low. In the pivotal phase III trial that compared crizotinib to chemotherapy in ALK-translocated NSCLC patients, 4,967 patients had to be screened in order to treat 347 patients (7%) (11). Umbrella trials were designed in specific cancer types in order to allow proposing different MTAs and/or immunotherapies depending on identified molecular alterations following a broad screening, with the advantage of being able to propose a treatment to all included patients (12). Overall, basket and umbrella trials are generally set up as simple parallel phase II clinical trials performed in histologically- and molecularly-defined subgroups of patients (13). They both accelerate drug development, although the ideal clinical trial would test

simultaneously the efficacy of multiple drugs in multiple molecularly- and histologically-defined subgroups of patients. This trial however would unrealistically require tens of thousands of patients to evaluate the efficacy of each drug in each subgroup of patients with enough statistical power. Clinical trials that mix cancer types, molecular alterations and drugs have been conducted (14-19). These trials were actually not designed to assess the efficacy of any of the drugs tested in any subgroup of patients, but only to inform about the ability of the treatment algorithm used to allocate drugs to patients to improve their outcome (20). Treatment algorithms evaluated in these trials may be “marketed” in the same way than drugs, as did the company CureMatch[®] that was created following the results of the WINTHER trial (17,21).

The ancestral paradigm of drug development in oncology is further challenged by (I) the ever-expanding molecular segmentation of cancer with ever-smaller subgroups of patients who might benefit from specific MTAs or immunotherapies, and (II) the discovery of molecular alterations against which drugs may be effective across cancer types. A striking example is the NTRK gene fusions that are present in 0.3% of all cancer patients and efficiently targeted with NTRK inhibitors (22). While we strongly believe randomization should remain the gold-standard in large patient populations, novel ways of evaluating the efficacy of drugs are highly needed in small patient populations (*Figure 1*).

One approach is to use each patient as his/her own control by comparing the efficacy a drug to the efficacy of prior treatments received (14,16,17,23). The assumption made that tumor growth is linear over time is likely a fair approximation over a short period in the recurrent and/or metastatic setting, knowing that it takes decades for a cancer to become macroscopic. This approach avoids dealing with interpatient’ heterogeneity, especially for a tissue-agnostic drug development. The comparison of drugs’ efficacy in a same patient is however only valid if drug efficacy has been assessed using the same evaluation criteria (e.g., RECIST) and the same timing for tumor evaluations. The SHIVA02

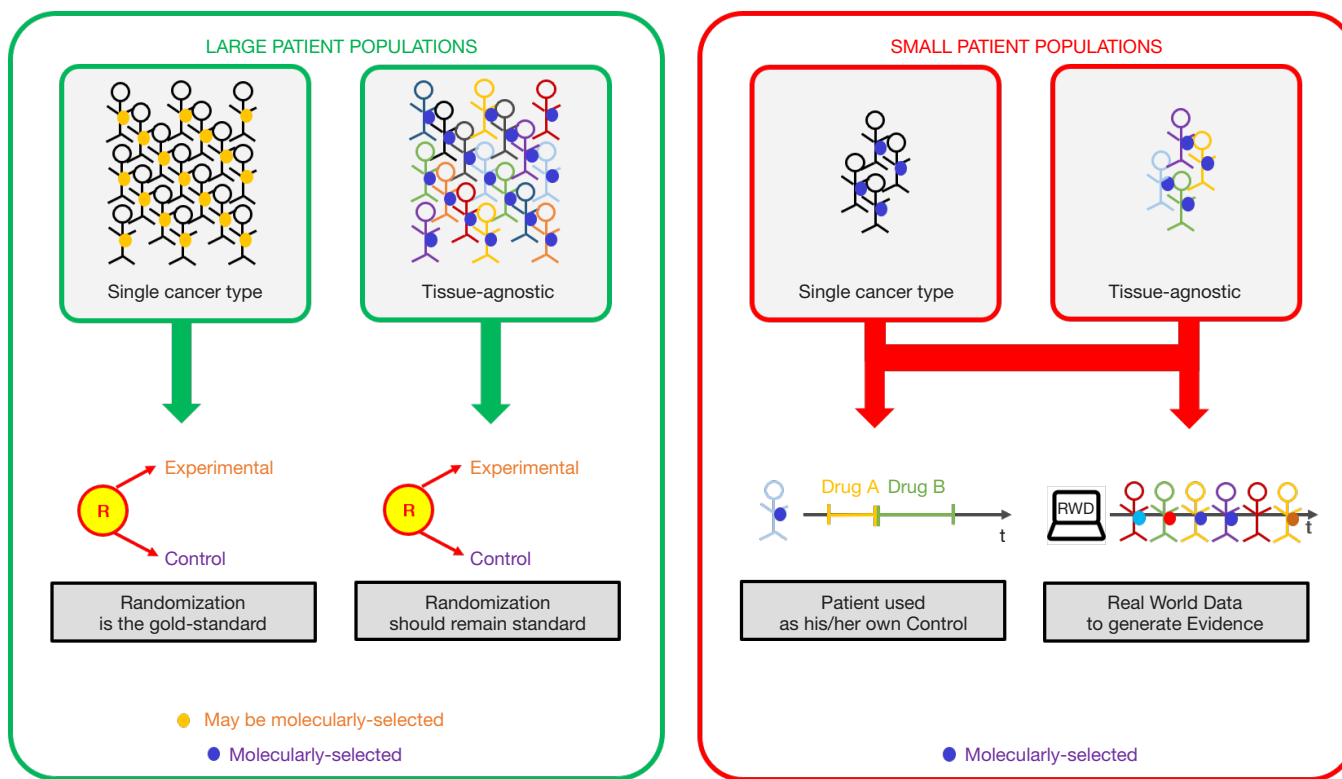


Figure 1 Drug development approaches for large and small cancer patient populations. RWD, Real-World Data.

clinical trial has been designed considering this by mandating to use the same tumor assessment method and timing during the two treatment periods (NCT03084757).

A second approach is the use of real-world data to generate evidence, by comparing the outcomes of treated and non-treated patient populations (24,25). Comparisons can be made using randomization and while adjusting on clinical and/or molecular parameters. Similar patient’s groups may also be selected using propensity score matching. This approach provides the additional advantage of representing a non-selected patient population as opposed to clinical trials. Major regulatory authorities, including the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), have recognized the importance of real-world data as a source of complementary evidence for regulatory decisions (26,27). Many current retrospective real-world data efforts are however not of high enough quality to answer all outstanding questions. The key requirements indeed are to have a large, as heterogeneous as possible, patient population with curated and standardized clinical and molecular data. The quality of the data needs to be as high as the one collected in clinical trials, especially in

terms of response to treatments received.

To conclude, there is an urgent need to develop new methods to foster drug development in the era of precision medicine, due the molecular segmentation of cancer and the tissue-agnostic predictive value of some molecular alterations. However, it is essential to keep in mind that local treatments, including surgery and radiotherapy, remain the main pillars of cancer therapy for which the ancestral paradigm per cancer type applies, and that randomization should still be considered the gold-standard approach to evaluate the efficacy of new treatments whenever feasible in large enough patient populations. For small patient populations, the use of each patient as his/her own control and real-world data represent appealing tools to generate robust evidence.

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