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Cancer treatment paradigms in the precision medicine era

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To fully harness precision medicine and transform cancer care for the better will require a strategic shift to highly personalized interventions that embrace innovation and adaptability.

With advances in genomic sequencing and molecular profiling, the ability to tailor therapies to individual patients based on their unique molecular makeup is no longer a distant vision but a reality. To propel the field forward and keep pace with the revelations emerging from genomics, immunology and other omics fields, we must adopt a strategic approach that embraces innovation and adaptability. Traditional research methodologies, though valuable in their time, may no longer align with the nuanced demands of precision medicine[1]. By re-evaluating and refining our research strategies, we can ensure that our work not only advances scientific understanding but also translates into tangible benefits for patients. This means investing in new methodologies, fostering interdisciplinary collaboration and remaining agile despite ever-evolving scientific discoveries. In doing so, we can unlock the full potential of precision medicine and transform cancer care for the better. However, to fully harness the potential of precision medicine, a comprehensive re-evaluation of current treatment strategies is needed.

Below we outline five strategic recommendations aimed at modernizing cancer treatment paradigms, facilitating a shift from traditional, one-size-fits-all approaches to highly personalized interventions.

Re-evaluate RCT requirements in lethal cancers

In patients with lethal cancers with poor prognosis (including but not limited to glioblastoma and pancreatic cancer), consider accepting evidence from phase 1/2 studies and real-world data as sufficient justification for treatment changes, especially when current randomized controlled trial (RCT)-validated treatments show minimal outcome benefits. In the case of glioblastoma, standard therapy has not changed in 20 years, since a RCT published in 2005 established benefit for temozolomide together with radiation, though the probability of progression-free survival (important for glioblastoma because of its impact on brain function) approaches zero at 3 years[2]. In pancreatic cancer, a large-scale randomized trial for all stages, published in 2024, showed that best practices were associated with a 23% one-year survival versus 24% for patients in whom best practices were not implemented[3]. For patients with metastatic disease, which is the majority, outcomes are even worse. These dismal statistics result from innumerable RCTs with thousands of enrolled patients over decades. A new strategy is needed.

The traditional gold-standard RCT may be too rigid for rapidly fatal cancers, and a positive trial too often means a statistically significant *P* value with an insignificant effect on clinical outcome[1]. Moreover, once the result of the RCT becomes 'standard of care', regardless of the bleak outcome, patients are encouraged to accept this therapy. Physicians often cannot administer an investigational approach from a clinical trial until the patient's cancer has 'failed standard-of-care therapy', which is a routine clinical trial inclusion criterion. In addition, RCTs often take 5–7 years to complete, during which thousands of patients may die while waiting for treatment approval.

For cancers with very poor survival, the ethical balance shifts toward accepting greater uncertainty in exchange for faster access to potentially effective treatments. Anaplastic thyroid cancer is a stark example of a deadly disease, with a median survival of just 5 months after diagnosis and a bleak 1-year survival rate of <20%. However, the discovery of *BRAF-V600* mutations and the innovative use of the BRAF plus MEK inhibitor combination has revolutionized treatment[4]. This approach, validated by a single-arm study from a basket trial, received approval because of its remarkable efficacy[4]. Long-term follow-up confirmed significant clinical benefit, making this non-randomized trial a practice-changing study in the field.

Platform phase 2 studies are a non-randomized approach that can effectively investigate multiple cohorts quickly and in parallel. For instance, DART (NCT02834013), a national National Cancer Institute (NCI)/Southwest Oncology Group (SWOG) immunotherapy study included 53 rare cancer cohorts. Dual immunotherapy (nivolumab and ipilimumab) in this platform trial showed high response rates, including durable complete remissions in multiple rare cancers, such as aggressive angiosarcomas and high-grade neuroendocrine cancers, leading to changes in National Comprehensive Cancer Network (NCCN) guidelines (with most payors reimbursing according to the NCCN guidelines).

Another emerging clinical trial platform in Europe is based on the Dutch Drug Rediscovery Protocol (DRUP) trial[5]. In the EU Cancer Mission project PRIME-ROSE (www.prime-rose.eu), 11 national DRUP-like trials are joined together and aggregate their data to generate evidence faster (>200 cohorts aligned, >20 merged so far). To implement fast-track approvals or guideline changes for drugs that show benefit after phase 1/2 trials would require creating specialized approval pathways for treatments targeting lethal cancers, developing robust frameworks for evaluating non-RCT evidence including synthetic control arms[6] and establishing clear criteria for when this approach is appropriate.

Implement early molecular profiling and early matched therapies

Establish comprehensive molecular testing at initial diagnosis rather than waiting until late-stage disease[7]. Recent insights reveal that

oncogene-targeted therapies as well as immunotherapies deliver much greater efficacy when administered in earlier stages. The poster child for this observation is chronic myelogenous leukemia (CML), a previously fatal leukemia with a near-normal life expectancy today because of the use of molecularly matched therapy (such as imatinib and similar drugs). However, although the response rate approaches 100% when treatment is started at diagnosis and patients can then expect to live a lifespan that approximates that of healthy adults, response rates are low for end-stage disease, and the treatment has only a small impact on life expectancy[1]. Another striking example is immunotherapy for mismatch repair-deficient/microsatellite instability-high (D-MMR/MSI-H) rectal cancers, which has an impressive 100% response rate when applied at diagnosis[8].

Early treatment enables the identification and targeting of molecular alterations before tumors evolve complex genomics and multiple co-drivers. This recommendation goes beyond the current practice of molecular testing at progression by advocating for comprehensive molecular profiling at diagnosis, even before metastatic spread. Comprehensive initial profiling also provides baseline data to track tumor evolution. Early molecular data can inform clinical trial eligibility before standard treatments fail. Ultimately, we need to implement universal somatic and germline testing in all patients with cancer if we are serious about beating most cancer types[7]. Practical considerations include overall costs, testing platforms and development of clinical-decision support tools for complex molecular data.

Create a strategy for identifying and addressing pan-cancer and tumor-agnostic targets across all potential markers and cancers

Breakthroughs in cancer research have gone hand in hand with diagnostic technical advancements, uncovering new molecular targets. This shift is steering us from traditional organ-specific therapies to biomarker-guided precision medicine[9]. Targeting common molecular changes can hasten the development of precision therapies across cancers. Traditional histology-based methods of drug approval frequently deny medications to patients, particularly those battling rare cancers[10]. Tumor-agnostic treatment approvals based on non-RCT data mark a pivotal moment, emphasizing the need for strategic, biomarker-driven precision oncology. First approved by the US Food and Drug Administration (FDA), many of these drugs are not yet approved in other countries, creating global inequities. Consider *NTRK* fusion-positive tumors as a prime example. Diverse cancers exhibit remarkably high rates of response to NTRK inhibitors in a tumor-agnostic and age-agnostic manner; however, *NTRK* fusions occur in only ~0.3% of diverse cancers. This makes it impractical to conduct RCTs with standard-of-care arms for each tumor type individually, as it is estimated that such an undertaking would require nearly 50 years to complete.

Tumor-agnostic drug development should not be the exception but rather the rule for cancers. The proposed ESMO Tumour-Agnostic Classifier (ETAC) emphasizes the interaction between targeted molecular anomalies and the unique biology of tumors, which influences the therapeutic outcomes of molecularly guided treatment option[11]. We recommend establishing baseline criteria for evaluating tumor-agnostic potentia as an integral component of developing tumor-agnostic therapies.

This recommendation necessitates collaboration across multiple stakeholders, including academia, industry, regulatory agencies, patient advocacy groups and clinical trial specialists.

Develop alternative evidence-generation methods and set outcome-based thresholds for innovation beyond and/or before standard of care for fatal cancers

Create and validate new approaches to generating clinical evidence beyond traditional RCTs, including *N*-of-1 trial methodology, synthetic control arms[6] and systematic collection of real-world data. These methods should better accommodate the granularity required for precision oncology. This recommendation seeks to develop new approaches to clinical evidence that better match the realities of precision medicine. *N*-of-1 trials, in this context, refer to trials in which each patient is given a molecularly matched customized treatment; because each patient may get a different treatment combination, the ability of an algorithm (sometimes referred to as a matching score) to choose therapy with improved outcomes is evaluated, rather than the outcome of each set of drugs in each tumor type[12]. Real-world data collection systems may also be invaluable and need to capture detailed molecular and clinical information, track outcomes and enable rapid learning from treatment experiences as described — for example, for DRUP-like trials combined with real-world data from the DigiONE project[13].

There is a need to establish specific survival thresholds (say, 50% mortality at 2 years) below which standard treatments, even if validated by RCT, should be actively challenged through research and alternative treatment approaches, balancing the 'do no harm' principle with the imperative for therapeutic innovation. This recommendation proposes using specific metrics to trigger systematic re-evaluation of the standard of care and to encourage the use of investigational agents and paradigms before standard of care, when standard-of-care management results in poor outcomes. The latter is important because ineffective therapy may increase tumor resistance, even to an active therapy.

The threshold concept provides objective criteria for when current standards are inadequate and balances the need to protect patients from unproven treatments, the imperative to improve poor outcomes and the risk of maintaining ineffective standards. Implementation requires consensus on appropriate thresholds for different types of cancer, systems to track outcomes against these thresholds, mechanisms to initiate and fund advanced treatment research and processes to modify standard-of-care recommendations

Create supportive regulatory frameworks

Develop new regulatory structures that facilitate biomarker-based gene- and immune-targeted therapy application in neoadjuvant and early-line settings while ensuring that proper informed consent and data collection processes are in place to advance therapeutic knowledge rapidly. This recommendation focuses on adapting regulatory systems to support precision medicine approaches. Current frameworks often focus on large population effects rather than molecular subgroups and favor late-stage testing over early intervention. Moreover, they have limited provisions for biomarker-driven treatment selection.

New frameworks should include clear pathways for biomarker-based approval and tissue collection for molecular testing, as well as standards for informed consent in precision medicine trials, especially when moving precision medicine quickly to the first-line setting; requirements for data sharing; and mechanisms for rapid incorporation of new evidence into clinical practice. The FDA's accelerated approval program is one such program that has clearly helped precision oncology[14]. We need global adoption of such programs for more universal patient access[15].

How to implement next-generation strategies? These recommendations signal a transformative change in cancer treatment, transitioning from a broad, population-focused approach to a precise, personalized paradigm based on optimizing outcomes via the science of tumor molecular biology. As we navigate this dynamic landscape, it is crucial to recognize that traditional paradigms might not adequately address the complexities and personalized nature of modern oncology. Precision medicine calls for a more tailored approach — one that uses cutting-edge technologies and real-time data-driven insights to deliver individualized treatments.

In implementing precision oncology, several cross-cutting factors are essential for success. First, robust data infrastructure is crucial. This involves establishing advanced and evolving reporting for molecular testing, enabling real-time outcomes tracking, creating systems for data sharing across institutions and enhancing analytics capabilities to handle complex datasets. Second, the economic implications must be addressed. This includes developing payment models for multi-omic testing and precision treatments, securing research funding, and creating 'living guidelines' that adapt to rapidly evolving discoveries. Lastly, education has a pivotal role. Training physicians in molecular oncology and clinical trial design is vital. Additionally, educating patients and caregivers about precision medicine is essential.

To advance our field, we must embrace innovation rather than repeating the same approaches and expecting different outcomes. This requires openness from reviewers, regulators, funding agencies, researchers and institutions. By adopting these strategies, the field of oncology has the potential to significantly enhance therapeutic effectiveness, achieve improved patient outcomes and ultimately fulfil the central mantra of 'precision medicine': delivering the right drug to the right patient with the right biology at the right time.

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