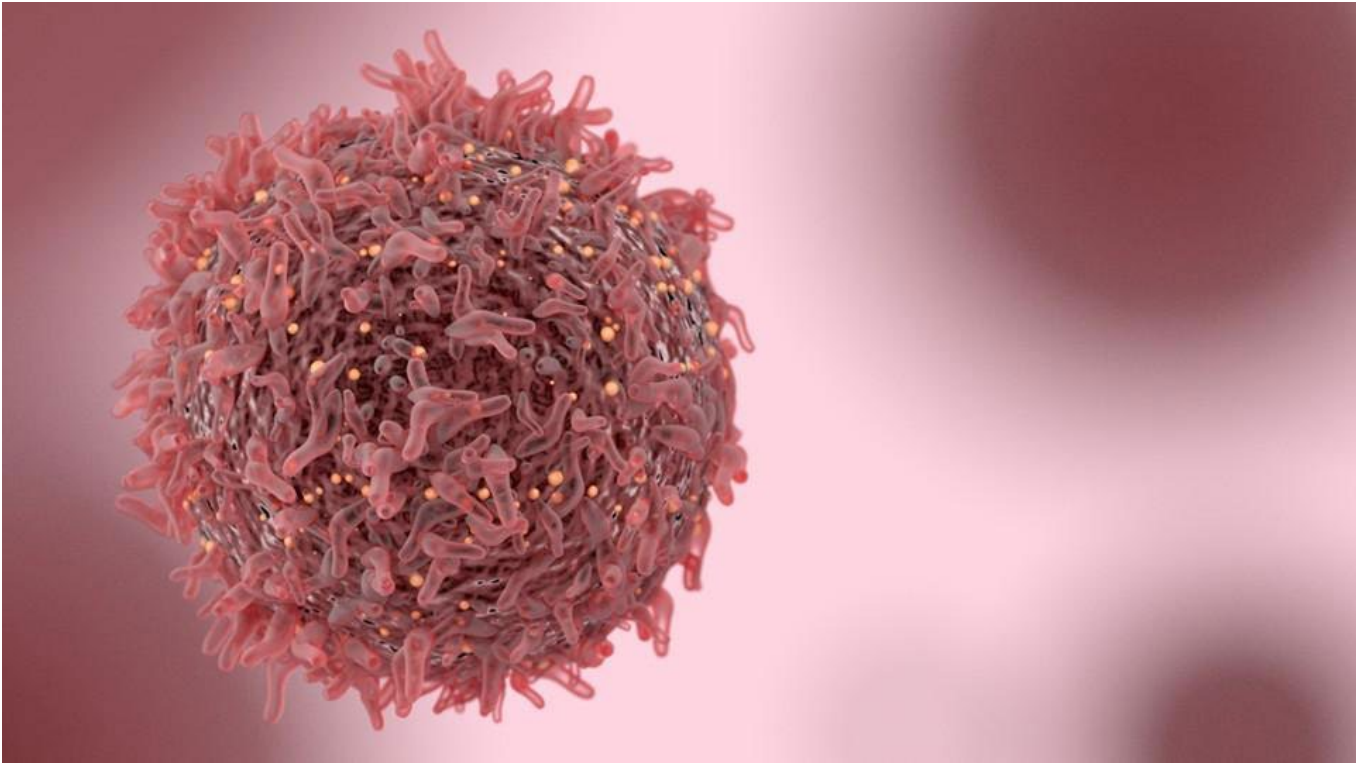




ASCO 2026 reshapes oncology trial design



The American Society of Clinical Oncology 2026 annual meeting showcased how, across tumour types, new cancer therapies are achieving deeper responses, extending survival and increasingly moving treatment into earlier-stage and, in some cases, potentially curative settings.

Yet, alongside this exciting progress, a new set of considerations is coming into focus. The clinical development ecosystem, which encompasses trial design, operational execution, and regulatory pathways, is being challenged to evolve in lockstep with scientific advances.

The question is no longer what science enables, but whether the research and development and regulatory ecosystem can keep pace. Discussions at ASCO 2026 reinforced that translating increasingly complex, biomarker-driven innovations into trials that are feasible, scalable, and patient-focused is a key priority for the industry.

Raising the bar: When “practice-changing” becomes the expectation

A defining feature of ASCO 2026 was the number of studies delivering clear, practice-changing results.

Among the most widely discussed and lauded plenary presentations was the RASolute 302 Phase III study of daraxonrasib, a RAS(ON) multi-selective inhibitor. In a historic achievement, daraxonrasib demonstrated a substantial survival benefit over chemotherapy in previously treated metastatic pancreatic cancer – a setting where progress has historically been limited. The therapy reduced the risk of death by approximately 60% compared to chemotherapy, with median overall survival nearly doubling.



These results reinforce the potential of targeting the RAS pathway to redefine not only the standard of care in this setting but, indeed, the expectations of treatment in this challenging disease.

At the same time, earlier-phase innovation is also beginning to meet this rising bar. Initial results from the Phase I NT-175 study, a T-cell receptor therapy targeting TP53-mutated tumours, demonstrated encouraging safety and early signs of efficacy across solid tumours. As one of the most advanced TP53-directed TCR programmes currently in development, NT-175 highlights the potential to address a mutation that is prevalent across multiple tumour types and signals a move toward broader applicability even within highly targeted approaches.

The OPTIMA Phase III study in early breast cancer highlighted a different dimension of innovation. By using genomic testing to guide treatment decisions, the study showed that a significant proportion of patients with high clinical risk ER-positive HER2-negative early breast cancer could safely avoid chemotherapy without compromising outcomes.

Collectively, these findings point to a dual change in oncology innovation. New therapies may be expected to not only outperform existing standards, but also in some cases reduce treatment burden by avoiding unnecessary interventions. This raises the bar for clinical development. Sponsors are no longer competing against limited or potentially ineffective options and are instead designing trials within the context of highly effective standard-of-care therapies and increasingly personalised treatment pathways.

As a result, trial design is moving beyond incremental benefit toward clear clinical value and meaningful differentiation in real-world decision-making. For R&D leaders, this raises the bar to where future trials must be designed to deliver practice-changing outcomes, as incremental gains may no longer suffice.



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Moving earlier: Trials in the curative setting introduce new implications

One of the most prominent trends at ASCO 2026 was the movement of promising therapies into earlier stages of disease.

The LIBRETTO-432 Phase III study demonstrated a significant reduction in recurrence risk with adjuvant selpercatinib, a highly selective, potent, and brain-penetrant RET inhibitor, in RET fusion-positive non-small cell lung cancer following surgical resection. These findings reflect the growing push to intervene earlier in the disease course, before progression occurs.

Similarly, perioperative approaches in prostate cancer, such as those explored in the PROTEUS Phase III study, aim to improve long-term outcomes by introducing therapy around the time of prostatectomy.

While these advances offer the promise of improved event-free and overall survival, they also introduce new layers of design and operational considerations for clinical trials. Trials in earlier stages of disease tend to require longer follow-up periods, as endpoints like disease-free or metastasis-free survival can take years to mature.

At the same time, there is increasing acceptance and reliance on surrogate endpoints, such as minimal residual disease or pathologic complete response, which can introduce variability and raise regulatory considerations. This means trial designers need to



plan for extended follow-up and carefully select endpoints to balance speed and regulatory acceptability. They must also ensure robust strategies are in place to manage operational challenges, such as sustaining site engagement over longer study durations.

There is another important clinical consideration. Treating patients earlier increases the potential for benefit. However, it also raises the risk that some patients may receive treatment they would not otherwise need, potentially exposing them to unnecessary side effects without a corresponding benefit.

These factors can fundamentally reshape oncology trial design. Endpoint selection, trial duration, and patient targeting become critical not only for scientific validity, but also for feasibility.

Biomarker-driven trials: Precision can introduce fragmentation

As ASCO 2026 presentations indicate, biomarkers are central to oncology research and development, but their increasing use is introducing new operational realities.

Biomarker testing is no longer limited to determining eligibility at trial entry. It is increasingly used to stratify patients into subgroups, guide treatment decisions throughout studies, and enable more adaptive designs. For example, the SERENA-6 Phase III study in patients with HR-positive, HER2-negative advanced breast cancer demonstrated how biomarkers such as circulating tumour DNA can be used dynamically within a study and enable treatment adjustments based on molecular changes detected before clinical progression.



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This shift is also evident in colorectal cancer. Studies such as CIRCULATE-US (Phase II/III) are using ctDNA to guide treatment decisions in earlier-stage disease, including identifying patients who may benefit from therapy escalation or de-escalation based on minimal residual disease status. Also, the CodeBreak 300 Phase III study highlights how increasingly precise molecular selection is shaping narrowly defined patient populations while also necessitating combination strategies to achieve meaningful clinical benefit. This reflects a broader transition toward making precision oncology actionable at every stage of development.

However, this also introduces some degree of fragmentation of the study population in the development plan. As biomarker strategies become more refined, patient populations become smaller and more difficult to identify. Recruitment timelines may be lengthier, screening processes may need adjustments, and ensuring consistent testing across global trial sites can become more challenging. In parallel, there is increased expectation for biomarker testing to be conducted earlier and more routinely, reinforcing its role not only in scientific discovery, but in trial execution.

New modalities, new design challenges

The breadth of innovation at ASCO 2026 reflects an increasingly complex and heterogeneous development landscape. In addition to high-profile datasets, such as those discussed above, a notable number of first-in-class and first-in-human assets were presented across tumour types, underscoring both the pace and breadth of early-stage development. These programmes span a wide range of mechanisms and targets, reinforcing the industry's progress toward increasingly precise and differentiated therapeutic approaches.



Antibody-drug conjugates continue to be a widely studied modality, but with greater structural and functional variation. Emerging approaches include dual-payload and bispecific ADC designs, reflecting efforts to enhance efficacy, overcome resistance, and expand targetability through more sophisticated engineering. For example, early clinical development of first-in-class dual-payload ADCs, such as the CLIO-8221 Phase I/II study, highlights how multiple therapeutic mechanisms can be delivered within a single construct to address resistance while also increasing complexity in understanding safety and mechanism-specific effects.

First-in-human studies of next-generation targeted therapies are also expanding the boundaries of precision oncology. Early clinical data from selective KRAS G12D inhibitors, such as TSN1611, demonstrate encouraging safety and preliminary efficacy signals across multiple solid tumour types. This supports the potential to address previously difficult-to-treat mutations while introducing new considerations for biomarker selection and patient identification.

Together, these trends reflect a pipeline expanding in both scope and complexity. Many of these therapies are designed for combination use or incorporate multiple mechanisms within a single construct. While this creates opportunities for synergistic efficacy, it also makes it more challenging to isolate drivers of clinical benefit and fully characterise safety profiles. As a result, traditional trial frameworks, which often optimise for single agents, are becoming less applicable.

These changes are placing greater emphasis on more flexible and adaptive trial designs, including more nuanced endpoint strategies, combination-aware study structures, and approaches better suited to smaller, more segmented patient populations. Ensuring that these trials remain operationally feasible while capturing the full clinical value of increasingly complex therapies is becoming a defining priority for oncology development.

Closing the gap: New tools for a new era of oncology R&D

Real-world evidence is increasingly being integrated into trial design, particularly to supplement traditional study arms or support evidence generation where randomised trials may be difficult to conduct. In recent years, the US Food and Drug Administration has increasingly clarified the role of real-world data in regulatory decision-making through draft guidance. The FDA's Oncology Center of Excellence has reinforced this direction through its Real-World Evidence Program, focused on advancing the use of real-world data across both pre- and post-approval settings.

At ASCO 2026, presenters used real-world datasets to evaluate treatment patterns, outcomes, and biomarker dynamics at scale. A metastatic colorectal cancer study incorporated longitudinal ctDNA data with real-world outcomes to assess treatment response and survival while large observational analyses explored associations between commonly used therapies and outcomes across various patient populations.

Aligning scientific innovation with delivery

ASCO 2026 underscored how the field is entering an era when scientific innovation is no longer the primary constraint. Instead, success will depend on the industry's ability to adapt clinical development frameworks to match the complexity and pace of new therapies that have the potential to benefit patients in unprecedented ways.

This will require trial design that brings together biomarkers, data, technology, and patient-centred models from the outset. The impact of the next generation of oncology therapies will be determined not only by their scientific promise, but by the oncology community's ability to deliver them efficiently, consistently, and at scale.



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