New endpoints for early-stage cancer are gaining regulatory traction

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Using the standard regulatory endpoints of overall survival (OS) and progression-free survival (PFS) may not be feasible in some early-stage cancer trials due to the time it would take to reach the number of patient deaths and disease progression events to demonstrate efficacy. Novel endpoints that can offer quicker insights into the short- or long-term clinical benefits of new cancer drugs are needed, especially for early-stage cancer and immediately before (neoadjuvant) and after (adjuvant) primary treatment.

The FDA and EMA have shown some flexibility in accepting new endpoints in regulatory decision-making for early-stage cancer treatments. For example, the agency has accepted minimal residual disease (MRD), pathologic complete response (pCR), and metastasis-free survival (MFS), among others, for both accelerated and regular approvals (Table 1).

Regulatory acceptance of a surrogate endpoint depends on whether and how well its relationship to long-term clinical benefits can be demonstrated and whether it can be accurately measured. In some circumstances, new disease measures may be accepted as valuable stand-alone endpoints, capable of showing a clinically meaningful delay in the appearance of distant disease (metastases).

Three promising new endpoints

Some of the most promising novel and intermediate endpoints for early-stage cancers are:

1 Minimal residual disease in blood cancer

Minimal residual disease (MRD) is defined as when cancer cells remaining after treatment can't be detected by scans or lab tests, but cancer has not been fully eradicated. Regulatory acceptance of this endpoint as the basis for full marketing approval (versus conditional or accelerated approval) has been slow, even though it may have prognostic value for OS in many blood cancers.

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One problem has been the lack of a standardized threshold for MRD detection linked to improved long-term outcomes. Different studies use different thresholds, and there is currently no expert consensus.

Regulators have not yet established MRD as a surrogate endpoint, and, to date, it has only supported accelerated approval. But a closely related endpoint, known as major molecular response (MMR), has long been accepted as evidence of efficacy for regular approval of drugs to treat chronic myeloid leukemia (CML) because there is evidence that MMR predicts improved long-term outcomes.

2 Pathologic complete response in neoadjuvant breast cancer

In 2018, in its first-ever decision on a molecular assay to detect MRD, the FDA granted Blincyto (blinatumomab) accelerated approval for relapsed or refractory acute lymphocytic leukemia (ALL) with MRD greater than or equal to 0.1%. The primary efficacy endpoint of the single-arm pivotal Phase II trial was complete MRD response status after one blinatumomab cycle; the secondary endpoint was hematologic relapse-free survival (RFS) at 18 months.

In January 2020, the FDA issued guidance which established that MRD may be acceptable evidence of efficacy in ALL. However, the guidance specified that MRD cannot be used as the basis for marketing approval in multiple myeloma, chronic lymphocytic leukemia, or acute myeloid leukemia. In CML, sponsors can use MMR—with clearly defined thresholds and methodology—along with evidence that MMR predicts improved long-term outcomes in PFS and event-free survival (EFS).

Long-term outcome data is needed to support MRD as a surrogate endpoint for clinical benefit in most hematologic cancers.

Pathologic complete response (pCR) is not yet an established surrogate endpoint for regular approval in the neoadjuvant breast cancer setting, in part

Table 1. Novel and intermediate endpoints in cancer

Endpoint	Definition	Example
Minimal residual disease (MRD)	*In ALL:* the presence of leukemic cells not detectable by microscopy and measurable by standardized methods with a sensitivity of 0.01%.	March 2018 accelerated approval* – Blincyto for B-cell precursor ALL
Pathologic complete response (pCR)	*In neoadjuvant therapy of breast cancer:* the absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following the completion of neoadjuvant systemic therapy.	September 2013 accelerated approval – Perjeta combination neoadjuvant and adjuvant therapy for early-stage breast cancer
Metastasis-free survival (MFS)	*In prostate cancer:* the time from randomization to the time of first evidence of distant metastasis (new bone or soft tissue lesions or enlarged lymph nodes outside the pelvis), or death due to any cause, whichever occurred first.	February 2018 regular approval – Erleada for non-metastatic, castrate-resistant prostate cancer

**Accelerated approval based on MRD with supportive data from a prior approval based on OS.*

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because the data are mixed. For example, the FDA and an international working group performed a meta-analysis of 12 clinical trials that enrolled almost 12,000 patients and did not find a correlation at the trial level between pCR and improved OS or EFS. However, at the patient level, the meta-analysis found that breast cancer patients who attained pCR had improved survival, especially those with aggressive tumor subtypes.

A July 2020 FDA guidance established development pathways for products in neoadjuvant indications. It specified the pCR endpoint for accelerated approval and the EFS, OS, and disease-free survival (DFS) endpoints for regular approval.

To date, the FDA has approved one breast cancer drug with pCR as the primary endpoint—Perjeta (pertuzumab) in combination with trastuzumab and chemotherapy for neoadjuvant treatment of patients with HER2-positive, locally advanced, inflammatory, or early-stage breast cancer. This approval was based on a two-trial model: a neoadjuvant study demonstrating a 17.8% absolute improvement in pCR rate led to accelerated approval, and an adjuvant study demonstrated improvement in invasive disease-free survival (IDFS), the time from randomization to invasive recurrence or death.

For regulatory purposes, it's unclear whether pCR can be introduced as an endpoint in other solid tumors, but there are reasons it might not work. Definition(s) for pCR in breast cancer are well-developed because pCR rates have been investigated and published in the medical literature for multiple therapies. Breast cancer screening results are available in the neoadjuvant, curative-intent setting for a large population. Other solid tumors with less routine screening do not have such large datasets.

3 Metastasis-free survival in prostate cancer

In 2018, the FDA approved Erleada for non-metastatic prostate cancer using the metastasis-free survival (MFS) endpoint for the first time. Cancer researchers cheered the agency's recognition of MFS. But while it sounds commonsensical that not having metastases is to a patient's benefit, it remains to be proven whether they live longer or have a better quality of life.

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The rationale is as follows: MFS may be related to time to symptomatic progression (TTSP), an endpoint that relies on delayed symptoms increasing patients' quality of life. Symptom delay may have the added benefit of postponing other treatments for metastatic disease, which could help patients avoid the toxicities of those treatments.

Acceptance of MFS was important for men at a certain point in their journey with prostate cancer. Assessing the benefits of new therapies for men with non-metastatic castrate-resistant prostate cancer was difficult because trials using traditional endpoints took too long. MFS, on the other hand, allowed sponsors to measure an earlier endpoint that is clinically meaningful for a patient population that had no treatment options until their disease metastasized. Thus, the use of MFS to measure clinical benefit brought new therapies to patients who otherwise had to wait and watch.

Former regulators Amy McKee and Jorge Camarero bring more than two decades of experience reviewing oncology drug applications at the Food and Drug Administration (FDA) and European Medicines Agency (EMA), respectively. Amy most recently served as Deputy Center Director at the FDA's Oncology Center of Excellence (OCE) and Supervisory Associate Director of the Office of Hematology and Oncology Products (OHOP) within the FDA's Center for Drug Evaluation and Research (CDER). She managed four divisions performing the scientific review and evaluation of hematology and oncology drugs and biologics.

> "Companies that incorporate surrogate intermediate endpoints in developing early-stage cancer drugs may determine efficacy faster and more efficiently than those that don't."

Jorge served as an alternate member of the Committee for Medicinal Products for Human Use (CHMP) and as a member of the EMA's Oncology Working Party. Before that, he was Head of the Oncology Area for the Spanish Agency for Medicines and Medical Devices (AEMPS); a Pharmaceutical Inspector for the Spanish Government's Health Department delegation; and a Regulatory Clinical Assessor in Oncology for the AEMPS.

Jorge and Amy now use their regulatory and life science experience to help Parexel's clients through the regulatory process, navigating rapidly evolving landscapes related to oncology endpoint selection, regulatory meetings and submissions, compliance, and market access.

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