Novel Therapeutic Interventions Early in the Disease Trajectory: Drug Development Beyond the Refractory Setting

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ABSTRACT

The 2019 Accelerating Anticancer Agent Development Workshop assembled a panel of experts for an in-depth discussion session to present "novel therapeutic interventions early in the disease trajectory." The panel reviewed the limitations of evaluating investigational cancer therapeutics solely in advanced metastatic and relapsed/refractory disease settings, and recommended strategies for drug evaluation earlier in the disease course, including in the first line in combination with standard chemotherapy, and in the maintenance and neoadjuvant disease settings. Advantages of earlier drug evaluation were discussed, including expanding the population of evaluable patients, earlier response assessment via surrogate endpoints, earlier clinical benefit in the disease course, tailoring of therapies based on response, and furthering our understanding of biomarker-driven therapies.

Introduction

The evaluation of novel anticancer therapies traditionally takes place in the advanced metastatic or the relapsed/refractory disease setting. This is an ethically sound and mutually beneficial space for drug evaluation, prioritizing available therapeutic options of proven benefit over investigational agents of unproven efficacy. It also allows patients with refractory disease and no standard options to access potentially beneficial therapies, while contributing to the clinical development of novel agents. However, the traditional strategy of late-stage drug evaluation may limit our ability to leverage recent advances in the understanding of the molecular and pathologic underpinnings of cancer and the large-scale expansion of drug development, particularly in select histologic or molecular disease subtypes. In addition, testing novel agents in the late-stage setting complicates assessment of efficacy due to the evolution of multiple mechanisms of resistance, and visceral organ involvement may increase toxicity. Expanding our drug evaluation efforts to include patients earlier in their disease trajectory provides valuable and necessary opportunities for furthering our understanding of biomarker-driven therapies, drug development in rare and aggressive diseases, the tailoring of therapies based on response or disease characteristics, and ultimately our overall ability to provide therapies to patients in need.

The 16th Annual Accelerating Anticancer Agent Development Workshop, held in May 2019, and cosponsored by the FDA, the American Society of Clinical Oncology, the American Association of Cancer Research, and Duke University (Durham, NC), assembled a panel of experts from the clinical sciences, pharmaceutical industry, the FDA, and patient advocacy organizations with the expressed goal of accelerating the drug evaluation and approval process so that effective therapies may reach patients more quickly. As part of this workshop, a panel of experts was assembled for an in-depth discussion session to present "novel therapeutic interventions early in the disease trajectory." The panelists discussed opportunities for, and examples of, early-phase clinical oncology drug development beyond the traditional refractory metastatic setting, including clinical trial design strategies for first- and second-line treatment of metastatic disease, maintenance treatment after initial metastatic therapeutic response, and neoadjuvant treatment. In this article we aim to summarize these discussions, review examples of early-disease drug evaluation, and make recommendations to help guide the field moving forward.

The case for drug development beyond the refractory setting

The current clinical trial paradigm relies on an inverse relationship between the evaluable patient population and the investigational agent. Newly diagnosed, treatment-naïve patients have limited opportunities to participate in clinical trials investigating agents in early development. The investigational agents available for first-line evaluation are drugs that are in later stages of drug development, namely phase III efficacy studies. Alternatively, the newest agents are often restricted to patients with significantly more advanced disease, namely those with metastatic disease or those with disease refractory to standard therapies. Realigning newer drugs with less heavily pretreated patients may expand the population of evaluable patients. Confining drug evaluation to the advanced metastatic setting neglects opportunities for drug evaluation, and most importantly clinical benefit, due to differential safety and efficacy effects late in the disease course. Moving investigational agents earlier in the disease process allows for a better understanding of drug safety and clinical activity in populations beyond the late-stage refractory patient. Earlier evaluation can provide enhanced value in oncology, but is of compound importance in the case of both rare and aggressive diseases, where opportunities for drug evaluation are the most limited.

It is clear that efficacy analysis can be largely influenced by nuanced patient selection, for example, with the use of biomarkers. However, adding biomarker selection can further limit the potential patient population in rare or aggressive diseases, thereby slowing accrual and endpoint data to advance agents into later stage (phase III) clinical

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Clin Cancer Res 2020;26:4743–7

doi: 10.1158/1078-0432.CCR-19-4035

Translational Relevance

The traditional strategy of cancer drug evaluation in the advanced metastatic and relapsed/refractory disease settings may limit our ability to leverage recent advances in the understanding of the molecular and pathologic underpinnings of cancer and the large-scale expansion of drug development, particularly in select histologic or molecular disease subtypes. In addition, testing novel agents in the late-stage setting complicates assessment of efficacy due to the evolution of multiple mechanisms of resistance, and visceral organ involvement may increase toxicity. Expanding our drug evaluation efforts to include patients earlier in their disease trajectory provides valuable and necessary opportunities for furthering our understanding of biomarker-driven therapies, drug development in rare and aggressive diseases, the tailoring of therapies based on response or disease characteristics, and ultimately our overall ability to provide therapies to patients in need.

investigation. Investigating drugs earlier in the treatment trajectory of the disease process offers a larger population of potentially eligible and evaluable patients from which to offer more nuanced selection. Furthermore, small absolute clinical benefit earlier in the disease and/or treatment course allows the potential for larger relative benefit for patients with rarer cancers or aggressive disease.

In January 2019, the FDA released a draft guidance on studying rare disease and looking at treatment earlier in the disease course, including indications beyond oncology. It included meaningful inclusion/exclusion criteria to expand patient accrual and allow adequate representation of the target population, early randomization in all phases of drug development, and a realigning of appropriate endpoints for earlier stages of disease (1).

Real-World Examples of Drug Development Earlier in the Disease Course

Drug evaluation in the first line as additive or synergistic with standard chemotherapy

Rare and aggressive cancers often do not allow time for the evaluation of novel therapies in late-refractory settings. With a limited median survival of 3 months without effective therapy, pancreatic cancer is an example of an aggressive malignancy with limited opportunity for drug evaluation beyond the second line. After receiving both available standard options with regimens such as FOLFIRINOX and gemcitabine/Abraxane, most patients are debilitated and no longer meet eligibility to afford them the opportunity for protocol therapies. Even potentially small absolute benefits earlier in the treatment armamentarium, such as first-, or at most, second-line treatment, can have a significant relative impact for patients. The ability to evaluate drugs earlier in the first-line setting is exemplified in the evaluation of the CD40 agonistic mAb APX005M. A phase Ib study (NCT02482168) was performed in patients with previously untreated pancreatic ductal adenocarcinoma. Within the 24 evaluable patients in the treatment arm containing gemcitabine/Abraxane/nivolumab and APX005M, there were 14 partial responses (PR; 58%), and 8 patients (33%) with stable disease. Twenty of 24 patients (83%) had tumor shrinkage (2). This study was not designed to examine efficacy. Nonetheless, a 58% PR rate is an incredibly encouraging result for pancreatic ductal adenocarcinoma, especially in a phase I clinical trial. The efficacy of this combination is currently being formally evaluated as first-line therapy in patients with pancreatic ductal adenocarcinoma in a randomized phase II trial (NCT03214250; ref. 3). Evaluating APX005M in combination with standard chemotherapy as first-line treatment provided an expedited route to phase II.

Drug Evaluation in Maintenance Therapy with the Goal of Prolonged Duration of Response

The ideal endpoint for clinical drug evaluation studies, in the maintenance setting or otherwise, is overall survival. Given the considerable challenges with this approach, progression-free survival (PFS) is a valuable endpoint. However, both of these approaches, while ideal, yield significant feasibility challenges including funding and following patients through the course of subsequent therapies. Interim endpoints are needed that balance real-world clinical benefit with regulatory demands. For patients early in the disease course, time to first progression (TFP), or PFS in the maintenance setting, is a clinically meaningful endpoint, differentiated from PFS in subsequent lines. This is particularly the case in patients with aggressive diseases with limited subsequent therapeutic options, allowing drug evaluation and potential clinical benefit prior to clinical progression.

The POLO-1 trial (NCT02184195) used a biomarker-driven strategy to evaluate the PARP inhibitor, olaparib, in the maintenance setting for patients with germline BRCA mutations and pancreatic cancer. Patients who had not progressed after platinum-based treatment were randomized to receive olaparib or placebo. The primary endpoint was PFS, in this case TFP. Olaparib in this setting resulted in a significantly increased TFP PFS of 7.4 months compared with 3.4 months in patients receiving placebo. After 2 years, 22.5% of patients receiving olaparib were progression free compared with 9.6% of those receiving placebo (4). Evaluating olaparib in this manner allowed for a rare and valuable opportunity for clinical benefit in this difficult-to-treat population. The rucaparib experience in pancreatic cancer more clearly demonstrates the importance of evaluating therapies in earlier disease settings. The RUCAPANC study (NCT02042378) investigating rucaparib in previously treated BRCA1/2-mutated pancreatic cancers stopped enrollment early due to insufficient clinical activity (5). However, preliminary results from a phase II study evaluating rucaparib in the maintenance setting in patients with BRCA1/2- or PALB2-mutated pancreatic cancer who had not progressed after platinum-based chemotherapy showed encouraging disease activity in the 19 evaluable patients, with an objective response rate of 36.8% (six PRs and one CR) and a median PFS of 9.1 months (6).

Large platform phase II trials maximize the utility of a single standard-of-care control arm by allowing the simultaneous comparison of a number of investigational drug arms. The coordinated evaluation of multiple treatment arms in comparison with a single control arm with the flexibility to open and close investigational arms based on early signals of efficacy, futility, or toxicity, is particularly important in populations with high unmet needs. These platform designs are increasingly common in the advanced disease setting, but can also be utilized in the first-line and maintenance settings. FOCUS4 (ISRCTN 90061546) and MODUL (NCT02291289) are examples of biomarker-driven platform trials extending this strategy to early

disease, specifically in patients with treatment-naïve colorectal cancers. In both studies, all patients receive standard first-line chemotherapy, during which time tumor biomarker testing will allocate those patients with initial tumor response to different targeted therapies, if they are responding to their first-line regimen (7, 8).

Drug Development in the Neoadjuvant Setting

Developing drugs in the nonmetastatic setting is important in its own right, metastatic response does not always translate to neoadjuvant or adjuvant benefit, and vice versa. Neoadjuvant or adjuvant benefit may be missed if agents are assessed only in heavily treated populations, and development of multiple mechanisms of resistance under pressure of treatment further complicates assessment of efficacy. The neoadjuvant setting, in particular, offers several distinct advantages. Treatment can be focused on specific biologic subsets, assessed by biopsy in a treatment-naïve setting. Dynamic imaging and biopsies during therapy, as well as primary surgical samples following neoadjuvant therapy allow *in vivo* assessment of pharmacodynamic markers, provide evidence of biologic effect, and can be assessed for new predictive and prognostic biomarkers. Early surrogates, including clinical, radiographic, and pathologic assessment, can provide proximate measures of response, correlating with long-term outcomes. These early surrogates can decrease the time, cost, and number of patients needed to bring new drugs to market. The relatively fixed time-to-surrogate endpoint (i.e., time-to-surgery) in neoadjuvant drug development can in turn spare larger numbers of adjuvant patients from receiving therapies of limited benefit. Beyond the benefits to clinical research, there is the potential for direct clinical benefit to the patient through the possibility of increasing the cure rate.

To maximize the utility of drug development in the neoadjuvant setting, it is important to establish baseline benchmarks for neoadjuvant cytotoxic or standard therapies across the spectrum of solid tumors under investigation, to use as a comparison when adding in investigational agents. The importance of surrogate benchmarks in neoadjuvant treatment are exemplified in breast cancer, where pathologic complete response (pCR, defined as absence of invasive disease in breast and axillary nodes) has become an accepted surrogate efficacy standpoint, and in diseases such as bladder and rectal cancer where organ preservation is a commonly reported and clinically meaningful endpoint, despite unclear benchmarks. The DNA-PK inhibitor, M3814, is currently being investigated in combination with capecitabine and radiotherapy in locally advanced rectal cancer (NCT03770689). Primary endpoints include pCR and clinical complete response, while secondary endpoints include the number of patients with R0 resections. Sphincter preservation, while not a formal endpoint, could be meaningfully considered in future trials if clear benchmarks are established. Surrogate benchmarks also allow for endpoint evaluation to occur with far fewer patients. This is particularly important in rare diseases or in specific disease subsets. The development of the anti-HER2 antibody, pertuzumab, highlights this point. The APHINITY trial (NCT01358877), which investigated the addition of pertuzumab to standard adjuvant therapy for $HER2^{+}$ breast cancers, recruited more than 4,800 patients and showed a 0.9% benefit in the 3-year rate of invasive disease–free survival (94.1% vs. 93.2%), although the benefit was more than 3% in patients with node-positive disease (9). In comparison, in the neoadjuvant setting, the randomized multicenter NeoSphere trial (NCT00545688) investigating the addition of pertuzumab to neoadjuvant trastuzumab-docetaxel therapy randomized only 417 patients and showed a near doubling of the rate of pCR (39.3% vs. 21.5%), suggesting that the neoadjuvant setting also allows focus on patients with higher risk disease, who have the greatest need for improvements in therapy (10). The CLEOPATRA trial (NCT00567190) testing the addition of pertuzumab in the metastatic setting had an intent-to-treat population of 808 patients (11).

A number of trials designed could be employed in each of these clinical settings. Options include (i) basket trials, wherein a single experimental agent or regimen is evaluated simultaneously in multiple histologies, (ii) umbrella trials, which assign patients with one histology to different experimental arms, or (iii) platform trials, essentially an extension of umbrella trials, wherein the experimental arms can be adapted on the basis of early outcome measures (12, 13). The use of surrogate benchmarks in umbrella–platform trials are particularly valuable, allowing a new paradigm of drug development, through the tailoring of subsequent therapies to response data in the neoadjuvant setting. Clinical trials can be designed to include early response as selection or decision-making criteria. Adjuvant therapy can then be deescalated in excellent responders, whereas new therapies can be investigated in poor responders. This can decrease the number of patients needed to understand efficacy and provide a better understanding of biologic subtypes of disease. This adaptively randomized neoadjuvant investigational paradigm is exemplified in the phase II I-SPY2 trial (NCT01042379). In this adaptive platform trial, various novel agents are added to standard neoadjuvant therapy in different treatment cohorts of patients with high-risk breast cancer (defined as high risk using the 70-gene signature assay MammaPrint). There is one shared control arm for all experimental arms, maximizing the impact of control patients. The initial diagnostic pathology informs adaptive randomization into different biomarker subtypes. The primary endpoint is pCR in the surgical resection, and the outcomes are further used to update the probabilities used in the initial adaptive randomization for the neoadjuvant biomarker subtype cohorts. Drugs can be dropped for futility or can graduate for efficacy. Using one master protocol with an adaptive design allows continuing enrollment in open arms, with additional agents requiring only a new appendix as opposed to a whole new protocol. Biomarker studies allow further refinement of treatment options for specific patients. For example, in patients with triple-negative breast cancer (TNBC), the arms evaluating the addition of pembrolizumab and the addition of veliparib/carboplatin both graduated for efficacy. Patients with TNBC classified by MammaPrint as "ultra-high risk" (MP2) had an estimated 67% pCR rate with the addition of pembrolizumab, compared with 23% of unselected control patients (14). Unselected TNBC had an estimated pCR rate of 51% with veliparib/carboplatin compared with 26% in the control arm. When selecting for patients with TNBC classified as high sensitivity on a 7-gene DNA repair deficiency expression signature (PARPi7-high), the estimated pCR rate to veliparib/carboplatin improved to between 56% and 70%. Dual biomarker selection allowed an even further improvement in pCR rates, up to 75% in patients who were both MP2 and PARPi7-high in this preliminary data (15). Although, the phase III BrighTNess study (NCT02032277) found that the improved pCR rate with carboplatin and veliparib added to paclitaxel in patients with TNBC was due to carboplatin, with no added benefit to veliparib, the biomarker data from both ISPY2 and BrighTNess can be used to further select patients who could benefit from a DNA damaging approach, whether chemotherapy alone, or chemotherapy with targeted agent (16). Larger phase III neoadjuvant trials powered for both pCR and event-free survival (EFS) may allow us to more tightly

Table 1. Key recommendations for drug development beyond the refractory setting.

In addition to the clinical investigation of novel therapies in patients with advanced and refractory cancers, we recommend

• Investigating novel therapies
  ◦ in the first-line as additive to the accepted standard of care
  ◦ in the maintenance setting, in patients responding to first-line therapy
  ◦ in the neoadjuvant setting as additive to the accepted standard of care

• Increased use of umbrella and platform study designs to maximize opportunities for investigation and allow for shared control arms in earlier disease settings
• Increased development and acceptance of surrogate endpoints, as a means toward accelerated approvals for novel therapeutics

correlate both response and biomarkers to long-term outcome. The neoadjuvant KEYNOTE 522 trial (NCT03036488) is a larger randomized trial powered for both endpoints that has already demonstrated an improvement in pCR with the addition of the checkpoint inhibitor, pembrolizumab, to weekly paclitaxel with carboplatin followed by cyclophosphamide and either doxorubicin or epirubicin in patients with TNBC (64.8% vs. 51.2% in the chemotherapy alone arm). pCR was assessed after half of the approximately 1,200 patients had completed surgery, with EFS to be determined with longer follow-up (17).

Early findings from smaller studies using surrogate endpoints such as radiographic or pathologic response can provide a path to accelerated drug approval from the FDA. The accelerated approval can subsequently be converted to regular approvals. In a review of all FDA drug approvals between January 2006 and November 2017, 67 of 226 (30%) received accelerated approval. The vast majority of these, 59 (88%) were approved on the basis of response endpoints (including pCR), with eight based on time to event endpoints (EFS or disease-free survival). Of the 33 of 67 accelerated approvals that were subsequently converted to regular approvals, 82% had a confirmatory trial, and 18% simply had longer follow-up of the same trial demonstrating sustained treatment effect (18).

Conclusions

To maximize patient benefit, drug development should continue to expand evaluation efforts earlier in the disease process. The neoadjuvant, as well as first-line and maintenance settings in patients with advanced disease, provide distinct advantages compared with late-stage and refractory disease populations. Investigations in these settings have successfully demonstrated statistically significant clinical benefits in these early populations. Established biomarker studies should be sufficient to initiate trials in newly diagnosed patients. Appropriate surrogate endpoints need to be established and validated across disease types to maximize opportunities for meaningful evaluation in neoadjuvant and first-line patients. Prospective biomarker and early-endpoint analyses should be used to inform adaptive randomization into multicohort early-disease studies. Together, these strategies can meaningfully advance drug development and accelerate drug delivery to patients in need.

Disclosure of Potential Conflicts of Interest

H.S. Rugo reports other from Pfizer (clinical trial support to UC), Merck (clinical trial support to UC), Novartis (clinical trial support to UC), Lily (clinical trial support to UC), Genentech (clinical trial support to UC), OBI (clinical trial support to UC), Odonate (clinical trial support to UC), Daichi (clinical trial support to UC), Seattle Genetics (clinical trial support to UC), MacroGenics (clinical trial support to UC), Immunomedics (clinical trial support to UC), and Sermonix (clinical trial support to UC) outside the submitted work, as well as one time consulting with Samsung and Puma. M.A. Tempero reports personal fees from AstraZeneca (advisory board), Advance Medical | Teladoc Health (consultant), Bristol-Myers Squibb (advisory board), CPRIT (advisory board), EcoR1 Capital, LLC (consultant), Elicio Therapeutics, Inc. (consultant), FibroGen, Inc. (advisory board), and GlaxoSmithKline, LLC (advisory board), and ISPEN, Inc. (consultant), Immunovia (advisory board), Karyopharm Therapeutics (consultant), Merck & Co., Inc. (advisory board), Ontario Bordet Institute (consultant), Swedish Orphan Biovitrum (consultant), outside the submitted work, other from Halozyme (grant support), Astellas Pharma Global Development, Inc. (DSMC), and Celgene (grant support) outside the submitted work. P.M. LoRusso reports personal fees from AbbVie (advisory board member, 2018–2019), Agios (data safety monitoring board, 2016–2019), Five Prime (data safety monitoring board, 2017–2020), GenMab (advisory board member, 2016–2019), Halozyme (data safety monitoring board, 2016–2019), Roche-Genentech imCORE Alliance (2016–2019), Genentech (advisory board, 2016–2019), CytomX (advisory board member, 2016–2019), Takeda (advisory board, 2017–2020), Sotio (consultant, 2018–2019), Cybrexa (advisory board, 2018–2019), Agenus (advisory board, 2018–2020), Tyme (data safety monitoring committee, 2018–2020), IQVIA (advisory board, 2019–2020), TRIGR (advisory board, 2019–2020), Pfizer (advisory board, 2019–2020), I-MAB (advisory board, 2019–2020), ImmunoMet (advisory board, 2018–2020), Black Diamond (advisory board, 2019–2020), GlaxoSmithKline (advisory board, 2019–2020), QED Therapeutics (advisory board, 2019–2020), AstraZeneca (advisory board, 2019–2020), EMD Serono (advisory board, 2019–2020), Shattuck (advisory board, 2019–2020), Astellas (advisory board, 2019–2020), Salarius (advisory board, 2019–2020), Silverback (advisory board, 2019–2020), MacroGenics (advisory board, 2019–2020), Kyowa Kirin Pharmaceutical (advisory board, 2020–2021), Kineta (advisory board, 2020–2021), Zentalis Pharmaceuticals (advisory board, 2020–2021), and Molecular Templates (advisory board, 2020–2021) outside the submitted work. No potential conflicts of interest were disclosed by the other authors.

Received December 10, 2019; revised May 18, 2020; accepted June 17, 2020; published first June 22, 2020.

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