The failure of figitumumab: the danger of taking shortcuts in drug development

With such a complex and evolving adversary as cancer, it is never a surprise to learn of a negative randomized phase for a novel anti-cancer therapy. In this issue of Annals of Oncology, we learn the results of the randomized phase III trial of erlotinib combined with either the insulin-like growth factor-1 receptor (IGF-1R) inhibiting antibody figitumumab or placebo, a study that was discontinued for futility after the Data Safety Monitoring Board reviewed the ongoing results crossed a futility border, such that the investigational arm could not achieve a significant improvement in the primary end point of overall survival (OS) [1]. It is safe to say that these results will not move the field forward in terms of new treatment options, but we should only consider this negative trial a very regrettable disappointment if we fail to learn from this experience. The study by Scagliotti et al. provides a fertile learning opportunity as we attempt to develop future trials that respect the limited resource of patients for clinical trials while maximizing our shared goal of improve patient outcomes with novel targeted therapies.

This randomized trial of an epidermal growth factor receptor (EGFR) inhibitor combined with an IGF-1R inhibitor is predicated on the preclinical finding that the combination of inhibitors of IGF-1R and the EGFR prolongs time to development of resistance in cell line [2, 3] and xenograft models [4]. Notably, the current study was not preceded by phase I or II trials to demonstrate an absence of toxicity concerns or promising efficacy in a few dozen patients relative to erlotinib alone. Not coincidently, the phase III trial demonstrated increased toxicity with the erlotinib/figitumumab combination, with nonfatal serious adverse events recorded in 18% versus 5% of patients on the combination with figitumumab versus placebo, respectively.

There is a clear value to identifying toxicity issues early, before enrolling hundreds of patients on a phase III trial of a combination that has never been tested but merely presumed to be feasible and without excessive toxicity. Had the phase II randomized trial of chemotherapy with bevacizumab in patients with all histologies of advanced non-small-cell lung cancer (NSCLC) [5] never been conducted and carefully analyzed, we would never have identified the excessive risk of life-threatening or fatal bleeding complications in patients with squamous NSCLC. Had this combination been rushed to phase III and enrolled hundreds of patients before the recognition of this association, dozens of patients would likely have died from pulmonary hemorrhage, and bevacizumab would almost certainly have failed to have been an approved agent that contributes to improving survival in well-selected patients, but rather as an agent that leads to the dramatic hemorrhagic deaths of a significant fraction of its recipients.

Compounding the challenges introduced by building a large randomized phase III trial without a proper foundation of preceding phase I and II experiences to provide reassuring safety and encouraging efficacy data, the study not only enrolled a relatively unselected population but actually preferentially focused on a study population especially ‘unlikely’ to benefit significantly from erlotinib—namely the subgroup of patients with non-adenocarcinoma NSCLC, with its very low incidence of EGFR mutations [6]. Erlotinib in this clinical setting provides a very low bar for improvement, but this is not clearly a setting in which the combination of erlotinib and figitumumab would be expected to be uniquely or especially effective. Not only was there no significant improvement in OS with figitumumab, survival in the placebo arm was numerically superior.

Finally, there are the potential challenges encountered even when phase III trials are developed based on the results of very promising phase II trials. The last several years have seen such negative results with the MET inhibitors tivantinib [7] and onartuzumab [8], as well as the vascular disrupting agent vandetanib [9], to name just a few. Such discrepancies may be explained by any of a number of factors. Larger phase III trials should provide a more accurate representation of the true clinical population that can overcome the potential selection bias in smaller phase II trials run in a limited number of specialized centers. Larger trials also may bring into relief the possibility of difficulty recognizing and managing toxicities in a broader, community-based setting where patient volumes may be higher and experience with these novel agents may be less. Finally, larger randomized phase III trials markedly the potential for sampling error seen in the results in a few dozen patients who may simply happen to do unusually well.

In summary, while the present trial of second-line treatment with erlotinib paired with either the IGF-1R inhibiting antibody figitumumab in nonadenocarcinoma NSCLC was profoundly negative, illustrating no hint of improved survival alongside increased toxicity in subsets of patients, we can hope learn from this experience. This trial should serve as an important reminder of the negative consequences of bypassing the potentially valuable stages of drug development provided by careful phase I testing to assess safety/tolerability followed by phase II efforts to identify the presence of a signal of efficacy and perhaps also reveal subsets especially likely to benefit. There are many potential pitfalls in the clinical testing of novel agents even when this process is thoughtful and methodical, but it is our destiny to repeat this history and squander the resources of our patients and optimal utility of these approaches if we court failure by taking blind potential shortcuts through the road of drug development.
Nit-Picking around second line in EGFRwt NSCLC: just an academic effort

During the last decade, several new drugs emerged as effective in patients with advanced nonsmall-cell lung cancer (NSCLC). Agents targeting the epidermal growth factor receptor (EGFR), such as gefitinib, erlotinib or afatinib, induced dramatic and durable responses in patients with activating EGFR mutations (EGFRmut+), demonstrating superiority versus platinum-based chemotherapy in front-line setting [1–3]. More recently, crizotinib, a potent ALK-MET-ROS1 inhibitor demonstrated superiority versus chemotherapy in chemonaive and in pretreated patients with ALK translocations [4, 5]. The striking superiority of targeted agents versus chemotherapy in molecularly selected patients demonstrated that today, in daily clinical practice, identification of biological characteristics of the tumor is crucial for defining the correct therapeutic strategy. Unfortunately, ~85% of all NSCLCs are EGFR and ALK wild type and no targeted therapy is available outside clinical trials. In front-line setting, platinum-based chemotherapy remains the best treatment, with regimens including pemetrexed and/or bevacizumab for individuals with nonsquamous histology [6]. In 2000, docetaxel was the first agent approved for second-line therapy in NSCLC [7] and few years later two other agents, pemetrexed and erlotinib, reached the approval based on the results of phase II trials showing noninferiority in terms of survival versus docetaxel [8] or superiority versus placebo [9]. Additional trials were conducted with the aim of identifying the best second-line therapy [6]. All trials, conducted in a general and unselected population of pretreated NSCLC, showed only minimal differences in terms of efficacy leading to the conclusion that pemetrexed, docetaxel and erlotinib represent an acceptable option as second-line treatment [6]. In second-line setting, gefitinib showed superiority versus docetaxel only in EGFRmut+ patients [10], with no survival improvement over placebo in unselected NSCLC [11]. For such reason, in the UE, gefitinib use is restricted to individuals harboring EGFR mutations.

In the present issue, Zhou et al. reported the results of a phase II randomized trial comparing pemetrexed versus gefitinib as second-line therapy in patients with nonsquamous EGFR wild-type (EGFRwt) advanced NSCLC [12]. The study, conducted in 161 Asiatic patients, showed that pemetrexed is superior to gefitinib in terms of progression-free survival (PFS), with a nonsignificant difference in terms of overall survival (OS). In addition to the clinical end point, authors also re-analyzed the EGFR status using a highly sensitive method, showing that a consistent percentage of the study population, ~30%, harbored an activating EGFR mutation despite the initial assessment with direct sequencing did not detect any EGFR alteration. Interestingly, in such population of EGFRmut+ patients, no difference in PFS was observed in the two arms.

This study raises an important clinical question that is whether chemotherapy should be preferred as second-line treatment in EGFRwt patients. In such population, the efficacy of standard chemotherapy is modest, with a response rate below 10%, a median PFS of 3–4 months and a median OS of 7–8 months [6]. Even if disappointing, these results seem superior to what achievable with EGFR-TKIs as demonstrated in two phase III trials, the TAILOR and DELTA, and in two meta-analyses [13–16]. In addition, both TAILOR and DELTA trials used a highly sensitive method for EGFR mutation test, reducing the risk of including false-negative patients. Nevertheless, ‘pure’ EGFRwt patients did not survive longer with chemotherapy [13, 14] or, in other words, EGFR-TKIs are not detrimental in...