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2011 Therapeutic Additions and Possible Deletions in Oncology

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Introduction

Approval of agents for the treatment of cancers by the US Food and Drug Administration (FDA) was granted to only six new chemical entities in the three years spanning 2008 to 2010. By contrast, in the first nine months of 2011, six new chemical entities were approved for use in cancer. This approval rate is unprecedented and takes advantage of the advances in science since the approval of the first monoclonal antibody (rituximab) in 1997 and the first targeted small molecule tyrosine kinase inhibitor (imatinib) in 2001 for non-Hodgkin's lymphoma and chronic myelogenous leukemia, respectively. Here we briefly discuss the newly approved agents, a possible deletion from the therapeutic armamentarium, and the use of the FDA accelerated approval process.

There was a particular emphasis on molecularly targeted agents, including four different kinase inhibitors and two antibody-based agents (Table 1). As is characteristic for many targeted agents, these are applicable either to patients with rare cancers or to a small subset of those with common cancers. 2011 was also marked by the controversy surrounding the use of bevacizumab in metastatic breast cancer.

One of the year's most noted developments was the approval of two drugs (ipilimumab and vemurafenib) for the treatment of metastatic melanoma. Until now, only one drug (dacarbazine) had ever been approved for metastatic melanoma, and that drug has never shown a survival advantage compared with placebo or best supportive care. Ipilimumab (Yervoy) is a fully human monoclonal antibody that targets CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4), resulting in the unchecked activation of the immune response, thereby enhancing T-cell mediated anti-tumor activity. Approval of ipilimumab was based on a phase III trial of 676 patients with unresectable or metastatic disease. In this trial, subjects were randomized to ipilimumab alone, in combination with an investigational peptide vaccine (gp100), or gp100 alone. A survival advantage was found for the two groups who received ipilimumab (approximately 10 months) compared to the vaccine alone (6.4 months).¹ It should be noted that the vaccine-alone arm had a lower overall survival than what has been seen historically. Although the best overall response rate was only 10.9%, some patients maintained their response for at least two years. Not surprisingly, the majority of the adverse events were immune-related, primarily related to the gastrointestinal tract (diarrhea and colitis) and the skin. Seven of the fourteen drug-related deaths were associated with immune-related events.

The second drug approved for melanoma was vemurafenib (Zelboraf), a selective inhibitor of activated BRAF. Mutated BRAF is present in 40–60% of advanced melanomas, with the vast majority involving the V600E mutation. Vemurafenib has been approved for the treatment of unresectable or metastatic BRAF V600E-positive melanoma. The approval for treatment-naïve patients was based on a phase III study of 675 patients who were randomized to either vemurafenib or dacarbazine.² All patients were BRAF V600E positive. Following a planned interim analysis, patients were allowed to cross-over to the vemurafenib arm. Overall survival (84% vs. 64% 6-month), progression free survival (5.3 vs. 1.6 months), and objective response rate (48% vs. 4%) were all significantly better on the vemurafenib arm. Interestingly, the most common side effects included the development of squamous cell carcinomas and keratoacanthomas, however these did not necessitate cessation of therapy. Approval for patients who had previously received systemic therapy followed the results of a phase II trial involving 132 patients that showed an objective response rate of 52%, including a 2% complete response rate.³

The first molecularly targeted agents for pancreatic neuroendocrine tumors were approved in 2011: sunitinib (Sutent) and everolimus (Afinitor). Sunitinib, an oral tyrosine kinase inhibitor that targets multiple kinases, including VEGFR, PDGFR, and RET, had previously been approved for the treatment of advanced renal cell cancer and gastrointestinal stromal tumor. Everolimus, an oral mammalian target of rapamycin (mTOR) inhibitor, had previously been approved for advanced renal cell cancer following sunitinib or sorafenib failure, subependymal giant cell astrocytoma associated with tuberous sclerosis, and as prophylaxis of organ rejection in patients at low-moderate immunologic risk receiving renal transplants. Although phase III trials were conducted for these agents, the primary endpoints were improvement in progression-free survival.^{4,5} Neither agent displayed impressive objective response rates (5–9%).

Two other TKIs were approved: vandetanib for medullary thyroid cancer and crizotinib (Xalkori) for ALK-positive non-small cell lung cancer (NSCLC). Approval for vandetanib, an oral tyrosine kinase inhibitor which targets VEGFR, EGFR, and RET, was based on a placebo-controlled phase III trial of 331 patients.⁶ A significant improvement in progression-free survival was noted, however a survival benefit has not yet been observed. The overall objective response rate was 44% compared to 1% on the placebo arm. Serious adverse events have included QT prolongation, torsades de pointes, hypertensive crisis, and colitis. Because of the potential cardiac effects, vandetanib was approved with a risk evaluation and mitigation strategy program, which limits the distribution of the drug to certified prescribers and pharmacists. Crizotinib is an oral inhibitor of the ALK and mesenchymal epithelial transition growth factor tyrosine kinases. Approximately 2–7% of patients with NSCLC have an inversion of chromosome 2 which leads to the generation of a fusion oncogene of EML4-ALK. Crizotinib underwent an accelerated approval for the treatment of ALK-positive locally advanced or metastatic NSCLC based on the response rates observed in two phase II trials. The overall response rate was 55%, with several complete responses observed. Mutations in ELM4-ALK that cause resistance to ALK inhibitors are already being identified.⁷

Abiraterone acetate (Zytiga), an orally active CYP17 inhibitor, was approved for use in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer patients who have previously received docetaxel. A comprehensive discussion of this agent can be found later in this issue.⁸ Briefly, approval was based on a phase III trial involving 1195 patients who were randomized to either abiraterone/prednisone or placebo/prednisone.⁹ A statistically significant overall survival benefit was observed (14.8 vs. 10.9 months, respectively).

Brentuximab vedotin (Adcetris) is an immunotoxin consisting of a chimeric anti-CD30 antibody, a protease-cleavable linker, and the microtubule-disrupting agent monomethyl auristatin E (MMAE). Upon binding and internalization of the drug to CD30-expressing cells, the linker is cleaved, releasing the cytotoxic MMAE. This agent has undergone accelerated approval for two types of lymphoma: Hodgkin lymphoma failing autologous stem cell transplant or failing at least two prior regimens in non-transplant candidates or systemic anaplastic large cell lymphoma after failure of at least one prior regimen. For both diseases, the approval was based on objective response rate data from phase II trials.^{10,11}

Perhaps the most controversial oncology therapeutic issue in 2011 was the recommendation to withdraw the approval for bevacizumab (Avastin) in metastatic breast cancer. This agent was first approved in 2008 via the FDA's accelerated approval process. At that time, a trial involving paclitaxel with or without bevacizumab showed a significant improvement in progression free survival (11.3 vs. 5.8 months) without an overall survival benefit.¹² Since then, several other trials involving bevacizumab in combination with chemotherapeutic agents have shown no overall survival benefit, less benefit with respect to progression-free survival, and excess toxicity.^{13,14} In December 2010, the FDA had proposed withdrawing this indication because of lack of evidence that the drug was safe and effective. On 29 June 2011, the Oncology Drugs Advisory Committee voted unanimously to recommend withdrawing approval for this indication. This has generated much debate amongst clinicians, industry, regulators, and patient-interest groups. As of the beginning of November 2011, the FDA's final decision had yet to be announced.

Regardless of the outcome, the bevacizumab case underscores the limitations inherent to the accelerated approval process. This process allows approval based on positive results for surrogate endpoints (e.g., response rate or progression free survival) as opposed to overall survival benefit, with the underlying goal of allowing new drugs to reach patients sooner. From December 1992 to July 2010, 35 agents were approved for 47 new indications. As of July 2010, only 26 out of the 47 new indications have been confirmed in post-approval trials.¹⁵ It is worth noting that whereas only two (crizotinib and brentuximab) of the eight agents approved this year were in the accelerated approval program, three other agents (sunitinib, everolimus, and vandetanib) were approved without evidence of survival benefit. As the national debt and health care crises loom, and as the cost of newly developed agents skyrockets, it remains to be determined whether this country can continue to justify the approval of costly oncology treatments which have not yet been demonstrated to improve overall survival.

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Table 1

Summary of new oncology drugs approved in 2011.*

Agent	Mechanism of action	Disease	Accelerated Approval	Study	Primary Outcome	Estimated cost
Abiraterone (Abi)	CYP17 inhibitor	Metastatic castrate-resistant prostate cancer	No	Phase III: Abi + prednisone vs. placebo + prednisone	OS	\$5,000 per month
Brentuximab	Anti-CD30 antibody conjugated to MMAE	Hodgkin lymphoma and anaplastic large cell lymphoma	Yes	Two phase II trials	ORR	\$13,500 per dose
Crizotinib	ALK TKI	ALK+ NSCLC	Yes	Two phase II trials	ORR	\$9,600 per month
Everolimus (Ever)	mTOR inhibitor	Pancreatic neuro-endocrine tumor	No	Phase III: Ever vs. placebo	PFS	\$8750 per month
Ipilimumab (Ipi)	Anti-CTLA-4 antibody	Metastatic melanoma	No	Phase III: Ipi vs. Ipi + gp100 vs. gp100 Phase III: Ipi + dacarbazine vs. dacarbazine	OS OS	\$30,000 per dose
Sunitinib (Sut)	TKI	Pancreatic neuro-endocrine tumor	No	Phase III: Sut vs. placebo	PFS	\$8,850 per month
Vandetanib (Van)	VEGFR and EGFR TKI	Medullary thyroid cancer	No	Phase III: Van vs. placebo	PFS	\$10,500 per month
Vemurafenib (Vem)	BRAF inhibitor	BRAF V600E-positive metastatic melanoma	No	Phase III: Vem vs. dacarbazine Phase II	OS & PFS ORR	\$9,400 per month

Abbreviations: ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

* January – October 6.