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Gabriel Carabulea, M.D.
665 Camino de los Mares, Suite 208
San Clemente, Ca 92673

26800 Crown Valley Pkwy, Suite 475
Mission Viejo, Ca 92691
(949) 218-2800

OCEAN VIEW HEMATOLOGY/ ONCOLOGY MEDICAL GROUP NEWSLETTER

Special issue: Melanoma

EVOLVING TREATMENT OPTIONS IN ADVANCED MELANOMA: BRAF and MEK inhibitors, immune checkpoints inhibitors.

In 1981, interleukin-2 became the first immunotherapy approved for treating patients with melanoma. The drug reliably produces an approximate 15% response rate and a "cure" rate of around 5%.
A key development that led to the real expansion of immunotherapy for melanoma was the observation that blockade of a negative regulator of T-cell activity, CTLA-4, could result in melanoma regression.

IPILIMUMAB (Yervoy) ANTI-CTLA-4 MONOCLONAL ANTIBODY, was approved for the treatment of melanoma in March 2011. Follow-up studies have shown impressive rates of survival following CTLA-4 therapy, with 4-year survival rates of approximately 40% in previously untreated patients. While most patients do not experience immediate tumor shrinkage, tumor may respond later in the treatment course, resulting in improved survival.

COMBINATION BRAF + MEK INHIBITION - DABRAFENIB AND TRAMETINIB COMBO - BOOSTS MELANOMA SURVIVAL

Despite the high rate of initial tumor regression associated with BRAF or MEK inhibitor monotherapy, disease progression eventually ensues in most patients. Several randomized phase III trials comparing dual inhibition versus BRAF inhibition alone have been completed. In these trials, patients with previously untreated metastatic melanoma with a BRAF V600E or V600K mutation received either the combination of dabrafenib plus trametinib, or dabrafenib plus placebo. Outcomes favored the combination arm by ORR (67% vs 51% respectively), PFS (median PFS, 9.3 vs 8.8 months), and 6-month OS (93% 85%). These observations have defined dual BRAF and MEK inhibition as the new standard of care for selected patients with advanced melanoma with BRAF V600-mutation.
The combination of dabrafenib plus trametinib was approved by FDA in January 2014.

PEMBROLIZUMAB: FIRST PD-1 INHIBITOR APPROVED BY FDA.

This drug is the first in an exciting new class of cancer therapies known as programed cell death inhibitors. It works by releasing a brake to the immune system, and then the immune system can attack the tumor. With pembrolizumab, we get better responses and fewer side effects than with ipilimumab. In initial clinical trials, one-third of the patients with metastatic melanoma responded long term to this agent alone. For years, we were trying to turn the immune system against the cancer. What we realized afterwards was that we needed to take off the brakes instead of trying to turn it on. So that's where ipilimumab and pembrolizumab come in. This class of drugs is going to have a big impact on cancer care. These drugs are also being tested in about 30 types of cancer,but melanoma is the front line.

NIVOLUMAB (Opdivo): Second PD-1 Inhibitor receives FDA approval for unresectable or metastatic melanoma.

Nivolumab yielded an "impressive" duration of response when used as second- or third-line treatment for patients with advanced melanoma. In this phase III trial, nivolumab as a single agent produced responses in 32% of patients, compared with 11% of the chemotherapy arm. Among responders, 95% were still in remission after 24 weeks of follow up. Overall survival data are not yet mature. These results will likely spell the end of chemotherapy in advanced melanoma.

IPILIMUMAB as adjuvant therapy?

Patients with resected stage III melanoma are at a substantially increased risk for the development of metastatic disease. In a large phase III trial, adjuvant therapy with ipilimumab, an anti-CTLA-4 monoclonal antibody, significantly prolonged relapse-free survival compared with placebo (median relapse-free survival 26.1 months in the ipilimumab group vs. 17.1 months in the placebo group). Additional follow-up data are required from this trial to assess the impact on overall survival. Many oncologists would like to see a significant overall survival benefit before recommending potentially toxic adjuvant therapy to a patient who is disease-free after surgery. The toxicity of ipilimumab in this trial also raised concern. Adjuvant ipilimumab at this dose and schedule will require additional assessment. In addition, another phase III trial is comparing ipilimumab to high-dose interferon, the current standard of care for adjuvant therapy. Also, randomized adjuvant trials of PD-1-blocking antibodies are eagerly anticipated, in view of their more favorable safety profile and substantial activity.

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