PHARMA NEWS

Liposomal Irinotecan Regimen: New Option for Pretreated Pancreatic Cancer

On 22 October 2015, the US Food and Drug Administration (FDA) approved liposomal irinotecan (Onivyde®, Merrimack) in combination with fluorouracil (5FU) and leucovorin (LV), for patients with metastatic pancreatic cancer who have been previously treated with gemcitabine-based chemotherapy. This approval was based on evidence of a significant overall survival (OS) benefit in the randomized, phase III NAPOLI-1 trial that enrolled 417 patients with metastatic pancreatic adenocarcinoma who had progressed after standard first-line gemcitabine-based therapy. Updated results presented earlier this year at the 2015 Gastrointestinal Cancers Symposium showed that median OS in the combination arm was 8.9 months compared with 5.1 months in those receiving 5FU/LV alone (hazard ratio [HR] = 0.47; \( P = .0018 \)). The approved labeling will include a boxed warning regarding the risk of severe neutropenia and diarrhea with this combination.
First Oncolytic Virus Therapy Approved for Melanoma

On 27 October 2015, the FDA approved talimogene laherparepvec (T-VEC; Imlygic™, BioVex, a subsidiary of Amgen) for the local treatment of unresectable cutaneous, subcutaneous, and nodal melanoma lesions that recurred after initial surgery. T-VEC is a genetically modified, live, oncolytic, herpes virus that can be injected directly into melanoma lesions where it replicates and causes the tumor cells to rupture and die. This is the first approval of an oncolytic viral therapy. The decision was based on data from the phase III OPTiM trial that randomized 436 patients with unresected stage IIIB/C or IV melanoma to T-VEC or subcutaneous granulocyte macrophage colony stimulating factor (GM-CSF). The durable response rate (primary endpoint) was 16.3% with T-VEC compared with 2.1% for GM-CSF, the objective response rate (ORR) was 26.4% versus 5.7%, and the complete response (CR) rate was 11% versus 1%, respectively. Local treatment with T-VEC may also improve survival. Median OS was 23.3 months with T-VEC compared to 18.9 months with GM-CSF (HR = 0.79; \( P = .051 \)). Although T-VEC is generally well tolerated—mostly flu-like symptoms and injection site pain—it should not be given to individuals with suppressed immune systems or those who are pregnant because it can cause herpes infection. Full approval of T-VEC for this indication is also expected in European Union based on the positive opinion of European Medical Agency (EMA) given on October 22.

FDA Says Yes to Trabectedin for Recurrent Soft Tissue Sarcomas

On 23 October 2015, the FDA approved trabectedin (Yondelis®, Janssen) as second-line therapy for unresectable, locally advanced, or metastatic liposarcoma and leiomyosarcoma in patients previously treated with anthracycline-based chemotherapy. Trabectedin was approved in Europe in 2007 for previously treated advanced soft tissue sarcoma based on phase II data. The FDA approval is based on recently published results of a randomized phase III trial (\( N = 518 \)) comparing trabectedin with dacarbazine (\textit{J Clin Oncol.} 2015 Sep 14). In this study, median progression-free survival (PFS) in the
trabectedin arm was 4.2 months compared to 1.5 months in the control arm (HR = 0.55; P<.0001). Trabectedin also significantly delayed time to subsequent salvage therapy. However, the interim analysis of OS (64% censored) failed to demonstrate significant survival benefit of trabectedin. Nevertheless, trabectedin is viewed as an important new treatment option for a group of patients with few effective therapeutic choices available to them.

**Crizotinib Finally Poised for European Approval for Newly Diagnosed ALK-Positive Non-Small Cell Lung Cancer**

On 22 October 2015, the EMA handed down a positive opinion regarding a supplemental indication for crizotinib (Xalkori®, Pfizer) for the first-line treatment of anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). This approval in Europe is eagerly awaited by physicians and patients with ALK-positive NSCLC. The EMA decision is based on data from the phase III PROFILE 1014 trial showing a significant improvement in PFS compared to the PFS with standard chemotherapy (pemetrexed plus either cisplatin or carboplatin). Median PFS was 10.9 months with crizotinib versus 7.0 months with chemotherapy (HR = 0.45; P<.001). Crizotinib was first approved in the United States in 2011 under the accelerated approval program and was subsequently granted full FDA approval in 2013 for any ALK-positive NSCLC, irrespective of prior therapy, based on data from the PROFILE 1007 trial in patients previously treated with platinum-based chemotherapy. In contrast, the European approval at that time was restricted to second-line therapy.

**FROM THE LITERATURE**

**Adjuvant Bisphosphonates: New Standard of Care for Postmenopausal Breast Cancer Patients**

Results of a large meta-analysis conducted by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) demonstrated that adjuvant bisphosphonate therapy
significantly reduced the rate of breast cancer recurrence in the bone and improved breast cancer survival among women who were postmenopausal when treatment began. Individual patient data from randomized controlled trials conducted over the past 20 years and involving more than 18,000 women were analyzed. These trials randomized patients to 2-5 years of adjuvant bisphosphonate therapy or control and had a median follow-up of 5.6 years. For all patients, bisphosphonate therapy was associated with borderline significant reductions at 10 years in rates of distant recurrence, bone recurrence, breast cancer mortality, and all-cause mortality. Whereas in postmenopausal women, highly significant reductions were observed in the 10-year rates for bone recurrence (6.6% vs 8.8%; rate ratio [RR] = 0.72; \( P = .0002 \)) and breast cancer mortality (14.7% vs 18.0%; RR = 0.82; \( P = .002 \)). Moreover, the benefit was independent of the type or schedule of bisphosphonate, the estrogen receptor status of the primary tumor, lymph node involvement, or use of concomitant systemic chemotherapy. The authors pointed out in their conclusion that definite benefit of adjuvant bisphosphonates was demonstrated only in postmenopausal women. In their commentary, Adam Brufsky, MD, PhD, and Aju Mathew, MD (University of Pittsburgh Cancer Institute, Pennsylvania, United States), called this a landmark report and predicted it should lead to widespread adoption of adjuvant bisphosphonate therapy (for at least 2 years) as a standard of care for postmenopausal women with early-stage breast cancer, particularly given the low cost and relatively mild toxicity of bisphosphonates. They also pointed out that the observed 3.3% absolute reduction in the risk of breast cancer deaths at 10 years is similar to that achieved with anthracycline-based versus nonanthracycline chemotherapy.


Prognostic Factors for Prolonged Survival of Patients with ALK-Rearranged NSCLC and Brain Metastases

A retrospective, multicenter study of 90 patients with ALK-rearranged NSCLC and brain metastases showed median OS of 49.5 months after diagnosis of brain metastasis and benefit from treatment with stereotactic radiosurgery (SRS) or whole-brain radiotherapy (WBRT) and ALK inhibitors. Intracranial PFS after treatment was nearly a year. These favorable survival outcomes were observed despite almost half of the patients having four or more brain metastases. Multivariable analysis identified three favorable prognostic factors that were independent predictors of improved OS in patients with brain metastases. These included no treatment with an ALK tyrosine kinase inhibitor (TKI) before developing brain metastases ($P<.001$), absence of extracranial metastases ($P = .003$), and Karnofsky performance status (KPS) $\geq 90$ ($P<.001$). These three prognostic factors defined four distinct subgroups of patients with estimated 2-year OS rates ranging from 33% to 100%. Patients with KPS <90, extracranial metastases, and prior TKI therapy had an estimated 2-year OS rate of 33%. For patients with one, two, or three of these favorable prognostic factors, estimated 2-year OS rates were 59%, 76%, and 100%, respectively ($P<.001$). In contrast, age, smoking history, number of metastatic lesions in the brain (one vs multiple), initial radiotherapy (SRS vs WBRT) did not significantly influence prognosis. The authors pointed out that findings from this trial reinforce the need for brain surveillance with magnetic resonance imaging (MRI) and evaluation for repeat treatment of brain metastases and that clinical factors that classify patients into prognostic groups may guide local therapy decision making. For example, based on findings from this study, the authors would recommended local treatment of brain metastases with SRS, particularly if patients have either KPS $\geq 90$, no extracranial metastases, or did not receive a prior TKI.

**Impressive Antitumor Activity of PARP Inhibitor in Castration Resistant Prostate Cancer With DNA-Repair Defects**

In the phase II TOPARP-A trial that included 50 patients with heavily pretreated, metastatic, castration-resistant prostate cancer (CRPC), treatment with olaparib (400 mg twice daily) yielded an 88% ORR in a subset of patients with tumors that exhibited known DNA-repair defects. All 50 patients had received prior treatment with docetaxel, 98% had received abiraterone or enzalutamide, and 58% had received cabazitaxel, and their tumors were no longer responding to these standard treatments. Among 49 patients with tumor samples that could be evaluated by next-generation sequencing, 16 (33%) were found to have tumors harboring either homozygous deletions, loss-of-function mutations, or both in several DNA-repair genes, including BRCA1/2, ATM, Fanconi’s anemia genes, and CHEK2. Among these 16 patients, 14 (88%) had an objective response to olaparib, including all 7 patients with BRCA2 loss-of-function mutations, and 4 of 5 with ATM deletions and/or mutations. Responses to treatment commonly lasted for more than 6 months and were associated with prolonged radiologic PFS and substantial falls of circulating tumor cell counts. These findings support the hypothesis that advanced CRPC harboring DNA-repair defects, which represents 25% to 30% of all sporadic cases, respond to a poly (ADP-ribose) polymerase (PARP) inhibitor such as olaparib. Importantly, this study also showed that next-generation sequencing analysis of tumor-biopsy samples is feasible and can identify patients who may benefit from targeted therapeutic approaches.


**PD-L1 Expression May Be a Predictive Factor of Lack of Response to VEGF-TKI in Metastatic Renal Cell Carcinoma**

A multivariate analysis of clinical outcomes in patients with metastatic renal cell carcinoma (mRCC) demonstrated that programmed death ligand-1 (PD-L1) expression
was significantly associated with lack of responsiveness to vascular endothelial growth factor receptor (VEGFR) TKIs and was an independent predictor of shorter OS. Expression of PD-L1 and PD-L2 was quantified in tumor cells and tumor-infiltrating lymphocytes from 91 patients with clear-cell mRCC who were treated with either sunitinib, sorafenib, or pazopanib. PD-L1 expression, but not PD-L2 expression, was significantly associated with a high International Society of Urological Pathology grade \((P = .031)\) and sarcomatoid features \((P = .014)\), and a multivariate OS analysis showed that PD-L1 expression was associated with worse OS \((P = .038)\) and PFS \((P = .013)\) outcomes compared with PD-L1−negative tumors. PD-L1−positive tumors were also poorly responsive to VEGFR-TKI therapy \((P = .012)\) compared with PD-L1−negative tumors. In total, 16 patients (17.6%) had PD-L1−positive tumors. Of those, only 2 patients (12.5%) had an objective response to antiangiogenic therapy. In contrast, 35 of 75 patients (46.7%) with a PD-L1−negative tumor had an objective response. PD-L2 expression did not show any association with response to VEGFR TKIs. The authors concluded that these results, which are consistent with other reported studies, suggest that PD-L1 may be a potential biomarker that could help guide treatment of mRCC, where VEGFR TKIs are the mainstay of treatment. This disease suffers from a lack of predictive markers to help select the most appropriate treatment. The results of this study also provide a compelling rationale for combining PD-1/PD-L1 blockade with VEGFR-TKI therapy for the treatment of mRCC.


**Role of Corticosteroids to Attenuate Radiation-Induced Pain Flare**

Radiation therapy is effective in treatment of symptomatic bone metastases, but with an incidence of pain flare in 30% to 40%. Results of a Canadian, randomized, placebo-controlled, phase III study in 298 patients with solid tumors showed that low-dose dexamethasone significantly reduced radiation-induced pain flare in the treatment of painful bone metastases. Patients were randomized to either dexamethasone (8 mg/day)
or placebo, starting on the day of radiotherapy and continuing for 4 days afterward. Among 148 patients assigned to dexamethasone, 39 (26%) had a pain flare compared with 53 of 150 patients (35%) in the placebo group ($P = .05$). The biggest difference between the two groups was observed in the first 5 days, during which 29 patients (20%) in the dexamethasone group and 46 patients (31%) in the placebo group had a pain flare; an 11% absolute difference ($P = .03$). A thorough assessment of quality of life (QoL) using three validated instruments (European Organisation for Research and Treatment of Cancer [EORTC] quality of life questionnaire [QLQ-C15-PAL], the bone metastases module [EORTC QLQ-BM22], and the Dexamethasone Symptom Questionnaire) showed that patients receiving dexamethasone had significantly reduced nausea, improved appetite, and reduced functional interference at Day 10 compared with the placebo group. At day 42, patients in the dexamethasone group also had slight improvements in the physical domain ($P = .05$) and insomnia ($P = .09$). Based on these findings, the authors concluded that prophylactic dexamethasone use should be adopted as standard of care for patients receiving palliative radiotherapy for treatment of painful bone metastases. However, in their commentary, Barry Laird, MD, and Marie Fallon, MD (European Palliative Care Research Centre, Norwegian University of Science and Technology, Trondheim, Norway and University of Edinburgh, Edinburgh, United Kingdom), advise caution before dexamethasone is used routinely. They point out that observed reduction in the incidence of pain flare with dexamethasone was only modest, and that corticosteroids can have adverse effects on muscle mass and glycemic control. They encourage further translational research to better understand the neuroimmunomodulatory mechanisms that might predispose patients to pain flare, identify patients who are likely to respond to palliative radiotherapy, and identify those at risk for pain flare.


ADDITIONAL PUBLICATIONS WORTH READING

- **Advances in Immuno-Oncology: Immune Checkpoint Inhibitors in NSCLC.** Advances in the understanding of immunology and the role of the immune system to eliminate cancer have led to the development of immunotherapies, including cancer vaccines and monoclonal antibodies, that inhibit immune checkpoint pathways. Clinical activity of these therapeutic strategies have first been demonstrated in melanoma that is a known immunogenic tumor. Although lung cancer was historically considered nonimmunogenic, recent evidence clearly support use of immune checkpoint inhibitors, such as nivolumab and pembrolizumab, in both squamous and nonsquamous NSCLC and further research with these and other PD-1/PD-L1 inhibitors and their combinations with other treatment modalities are ongoing. This supplement contains an overview of advances of immunotherapy in NSCLC and include three articles that comprehensively cover the rationale for immunotherapy in the treatment of NSCLC, the currently available data on the benefits and risks associated with immune checkpoint inhibitors in patients with advanced NSCLC. The articles provide useful practical guidance on how to incorporate immunotherapy into the treatment of NSCLC in the clinic, how to evaluate response of immunotherapy, and manage immune-related toxicity. *Semin Oncol. 42*(Suppl 2):S1-S28.

- **Cancer-Treatment-Induced Neurotoxicity—Focus on Newer Treatments.** This review article explores the main neurotoxicities associated with various cancer therapies with a focus on newer biologic and immunotherapeutic agents. These therapies may affect both central and peripheral nervous systems. The authors emphasize importance of recognition of neurotoxicity, as drug discontinuation or dose-adjustment may prevent further neurologic injury. In addition, it is important to differentiate treatment-related symptoms from progression of cancer into the nervous system. The goal should be to minimize the risk of neurologic damage, thereby preserving patients’ quality of life. *Nat Rev Clin Oncol. 2015 Sep 22* [Epub ahead of print].
• **Benefits of Lenalidomide in Lower-Risk del(5q) Myelodysplastic Syndromes.** In this review article, the authors discuss the role of lenalidomide and provide practical recommendations for the use of lenalidomide in the treatment of transfusion-dependent, lower-risk, del(5q) myelodysplastic syndromes (MDS). The pivotal phase II (MDS-003) and phase III (MDS-004) studies showed that lenalidomide effectively reduces red blood cell transfusion burden and acts as a disease modifying agent, altering the natural history of the disease by suppressing the del(5q) clone. Hematologic and/or cytogenetic responses correlated with delayed AML progression and better OS. *Ann Oncol.* 2015 Oct 26. [Epub ahead of print].

**UPCOMING prIME EVENTS**

**THINKING OUTSIDE THE BOX IN GLIOBLASTOMA: 2015 AND BEYOND**

2 December 2015 | Boston, Massachusetts  
3 December 2015 | Shreveport, Louisiana  
7 December 2015 | Summit, New Jersey  
7 December 2015 | West Palm Beach, Florida  
10 December 2015 | Chattanooga, Tennessee  
10 December 2015 | Albuquerque, New Mexico  
14 December 2015 | Providence, Rhode Island  
14 December 2015 | Atlanta, Georgia  
15 December 2015 | Tucson, Arizona  
17 December 2015 | Oklahoma City, Oklahoma  
17 December 2015 | Indianapolis, Indiana  
17 December 2015 | Palo Alto, California  

**Expert Practice in Lung Cancer**

5 December 2015 | Barcelona, Spain
2016 Progress and Controversies in Gynecologic Oncology Conference
22-23 January 2016 | Barcelona, Spain

23 January 2016 | New York, New York
30 January 2016 | Chicago, Illinois
20 February 2016 | Houston, Texas
27 February 2016 | San Francisco, California

OTHER prIME ACTIVITIES

Oncology Guru: Test Your Knowledge in Oncology/Hematology

Symposium Webcast—New Therapeutic Strategies for Glioblastoma in 2015

prIME Rounds Webcast—Practical Guidance for the Contemporary Management of CML
Downloadable Slides—2015 Debates and Didactics in Hematology and Oncology

prIME News Webcast—Updates from the World Conference on Lung Cancer

Do You Think Like the Experts? Refining the Management of Advanced Non-Small Cell Lung Cancer with ALK Rearrangement

prIME Rounds Webcast—Chronic Lymphocytic Leukemia and Indolent Non-Hodgkin Lymphoma

Downloadable Slides—The Biosimilar Era: Opportunities and Considerations

Virtual Journal Club—Front-Line Therapy and Beyond: Recent Perspectives on ALK-Positive Non-Small Cell Lung Cancer
Expert Review—Perspectives and Treatment Options for Recurrent Glioblastoma

prIME Decision Points—Navigating the Treatment Landscape for Chronic Lymphocytic Leukemia