Oncology Pharmacy Newsletter

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New Indication for Nivolumab (Opdivo®)

Nivolumab is now approved for combination treatment with ipilimumab of BRAF wild type, unresectable or metastatic melanoma. During combination therapy, nivolumab is administered at a dose of 1mg/kg every 3 weeks with ipilimumab 3mg/kg every 3 weeks for 4 cycles. Once 4 cycles are completed, ipilimumab is discontinued and nivolumab is continued at 3mg/kg every 2 weeks until disease progression or toxicity.

New Safety Warnings for Nivolumab

Bristol Myers Squibb recently announced that ongoing clinical monitoring has noted the occurrence of encephalitis or toxic epidermal necrolysis (TEN) in patients receiving nivolumab (Opdivo®) as a single agent in non-small cell lung cancer, or as a single agent, or in combination with ipilimumab (Yervoy®) in melanoma patients.

Encephalitis can occur as part of the clinical picture for many oncologic disease processes, including melanoma and lung cancer, and infections. Five cases of encephalitis believed to be associated with nivolumab or combination nivolumab-ipilimumab treatment have been accumulated in the ongoing post-marketing surveillance.

Although TEN is very rare, occurring in 0.03% of patients receiving nivolumab or 0.5% of patients on combination nivolumab-ipilimumab therapy, it was fatal in all of the 3 patients reported.

Combination Nivolumab and Ipilimumab in Melanoma

The phase III, CheckMate 067 Trial looked at the combination of nivolumab and ipilimumab in untreated, advanced melanoma (stage III-IV) as compared to nivolumab alone or ipilimumab alone in standard doses in 945 patients. BRAF mutations were present in 31.5% of patients and 23.6% of patients were positive for PD-L1.

In the combination arm, nivolumab was dose reduced to 1mg every 3 weeks for 4 cycles when administered with ipilimumab in standard, 3mg/kg doses, then increased to 3mg/kg every 2 weeks which continued until toxicity or progression. Both monotherapies were dosed at their usual doses of 3mg/kg per dose with ipilimumab given every 3 weeks for 4 doses, or nivolumab given every 2 weeks until progression or toxicity, and were double blinded with placebo for the alternative drug.

Overall, patients in the combination nivolumab and ipilimumab arm experienced an 11.5 month median progression free survival, as compared to 6.9 months for nivolumab and 2.9 months for ipilimumab patients. Those patients with little to no PD-L1 expression experienced the most benefit from combination therapy, increasing their progression free survival from 5.3 months with nivolumab alone or 2.9 months with ipilimumab alone to 11.2 months with combination treatment. BRAF status did not confer a major difference in response. Relative overall survival benefits can not yet be determined.

Combination therapy lead to grade 3-4 adverse effects in 55% of patients, while single agent therapy with nivolumab lead to grade 3-4 adverse effects in 16.3% of patients and 27.3% of those receiving ipilimumab. Greater than 82% of all patients in each treatment group experienced some side effect. More than 1/3 of patients in the combination therapy group discontinued treatment due to side effects. Discontinuation was most commonly due to disease progression in the single agent arms, or for toxicity in the combination arms.

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NEW BASAL CELL CARCINOMA TREATMENT

Hui "Maya" Chang, PharmD Candidate, 2015, UConn School of Pharmacy

Overview: Sonidegib (Odomzo®), a hedgehog pathway inhibitor, is indicated for the treatment of adults in locally advanced basal cell carcinoma (BCC) that has recurred following surgery or radiation therapy, or those who are not candidates for surgery or radiation.

Mechanism: Sonidegib works through binding and inhibiting Smoothened, a transmembrane protein involved in the Hedgehog signal transduction. The Hedgehog signaling plays a key role in a variety of processes, such as embryogenesis, maintenance of adult tissue homeostasis, tissue during chronic persistent inflammation, and carcinogenesis. The approval was based on BOLT clinical trial that showed 58% overall response rate with confirmed complete or partial tumor response in patients.

Dosing and Monitoring: The current recommended dose is 200-mg capsule orally once daily taken on an empty stomach, at least 1 hour before or 2 hours after a meal. Patients should be monitored for serum creatine kinase (CK) and creatinine levels prior to initiating therapy, periodically during treatment, and as clinically indicated.

Sonidegib should be discontinued for severe or intolerable musculoskeletal adverse reactions, first occurrence of serum CK elevation between 2.5 and 10 times upper limit of normal (ULN), or recurrent serum CK elevation between 2.5 and 5 times ULN. Currently no dose adjustment recommendation exist for patients with renal impairment or mild hepatic impairment. Sonidegib has not been studied in patients with moderate or severe hepatic impairment.

Adverse Effects: Patients most commonly experience the following symptoms when taking Sonidegib: muscle spasms (54%), alopecia (53%), dysgeusia (46%), fatigue (41%), nausea (39%), musculoskeletal pain (32%), diarrhea (32%), decreased weight (30%), decreased appetite (23%), myalgia (19%), abdominal pain (18%), headache (15%), pain (14%), vomiting (11%), and pruritus (10%).

Drug Interactions: Sonidegib is primarily metabolized by hepatic enzymes, CYP3A4. Patients should avoid strong CYP3A4 inhibitors including but not limited to saquinavir, telithromycin, and ketoconazole, and long-term (greater than 14 days) use of moderate CYP3A4 inhibitors including but not limited to atanzavir, diltiazem, and fluconazole. Patients should also avoid concomitant administration of Sonidegib with strong and moderate CYP3A4 inducers, including but not limited to carbamazepine, efavirenz, modafinil, and St. John's Wort.

Contraindications and Precautions: Currently no contraindications for Sonidegib exist. However, Sonidegib can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Female patients should be advised to use effective contraception during treatment with Sonidegib for at least 20 months after the last dose. Male patients with female partners should be advised to use condoms, even after a vasectomy, during treatment with Sonidegib and for at least 8 months after the last dose to avoid potential drug exposure in pregnant females or females of reproductive potential. Advise females who may have been exposed to Sonidegib during pregnancy, either directly or through seminal fluid, to contact the Novartis Pharmaceuticals Corporation at 1-888-669-6682.

No data are available regarding the presence of Sonidegib in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Nursing women should be advised not to breastfeed during treatment with Sonidegib and for 20 months after the last dose.

Patients should also be advised to not donate blood or blood products during treatment with Sonidegib for at least 20 months after the last dose.

References: Odomzo New Drug Approval. Available at: http://www.centerwatch.com/drug-information/fda-approved-drugs/drug/100088/odomzo-sonidegib. Accessed 21 September, 2015.

Odomzo [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.

Katoh et al. Hedgehog signaling pathway and gastrointestinal stem cell signaling network (review). Int J Mol Med. 2006;18:1019-1023.

Suggestions for topics, questions, and comments are welcome! Just reply to sender of this newsletter or email: Susan Glassman glassman@uchc.edu
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COMING IN NOVEMBER

Standard Volume Rituximab Infusions

The rate calculator has passed the test! It will be added to the Pharmacy web-page in the near future and in-servicing will be done for the Infusion Center, MS5, and Oncology 6 RNs. All the nurse needs to do is type in the dose and hit "enter". Please see the sample calculations below.

All of the COS order sets are being modified by Chris Niemann to reflect this new admixture. Anticipated launch has been delayed to early November 2015. If an order is mid-cycle, we can continue to use the 1mg/ml concentration until the cycle is completed.

Due to the way in which rituximab is programmed into the Alaris pump, the pump programming process will not change.

Changes in available Pharmacy technology has made it necessary to mix all rituximab infusions in a total volume of 500ml NS. Many institutions already administer rituximab in this fashion.

Rituximab must be diluted to a final concentration of 1-4mg/ml before infusion, and the final volume of 500ml will accomplish this for the vast majority of doses administered here. For those few patients that we administer doses under 500mg, Pharmacy will mix the rituximab in an appropriately reduced final volume to maintain this concentration.

Enter Dose Ordered **640** mg in 500mL NS **Conc. =** 1.28 mg/mL

Titration for 50mg/hr for initial infusion

Initial rate x 30 minutes	50 mg/hr	=	**39.06 mL/hr**
After 30 minutes increase to	100 mg/hr	=	**78.13 mL/hr**
After 30 minutes increase to	150 mg/hr	=	**117.19 mL/hr**
After 30 minutes increase to	200 mg/hr	=	**156.25 mL/hr**
After 30 minutes increase to	250 mg/hr	=	**195.31 mL/hr**
After 30 minutes increase to	300 mg/hr	=	**234.38 mL/hr**
After 30 minutes increase to	350 mg/hr	=	**273.44 mL/hr**
After 30 minutes increase to	*400mg/hr	=	**312.50 mL/hr**

***400 mg/hr = maximum rate**

Titration for 100mg/hr for subsiquent infusions

Initial rate x 30 minutes	100 mg/hr	=	**78.13 mL/hr**
After 30 minutes increase to	200 mg/hr	=	**156.25 mL/hr**
After 30 minutes increase to	300 mg/hr	=	**234.38 mL/hr**
After 30 minutes increase to	*400 mg/hr	=	**312.50 mL/hr**

***400 mg/hr = maximum rate**