Best Pharmaceuticals for Children Act (BPCA)
Pediatric Oncology Core Working Group Conference Call
January 14, 2014
11:00 a.m.–11:45 a.m. ET

Participants

Peter Adamson, M.D.
Martha Donoghue, M.D.
Lori Gorski, M.D.
Kate Matthay, M.D.
Gregory H. Reaman, M.D.
C. Patrick Reynolds, M.D., Ph.D.
Malcolm Smith, M.D., Ph.D.
Perdita Taylor-Zapata, M.D.
Anne Zajicek, M.D., Pharm.D.

Purpose

The purpose of this call was to discuss the following:

- Recent initial Pediatric Study Plans (PSPs) waiver considerations and potential pediatric relevance:
  - Baricitinib, a Janus kinase (JAK) 1/2 inhibitor
  - Ganetespib, a heat shock protein 90 (Hsp90) inhibitor
  - Radium-223 (Ra-223) dichloride (Xofigo), a bone seeking alpha-emitter used for bone metastases in metastatic castration-resistant prostate cancer (MCRPC)
  - Etirinotecan pegol (NKT-102)
- Follow up on priorities and plans for off patent Written Requests (WRs) for oncology drugs
- Future conference calls.

Recent Initial PSPs Waiver Considerations and Potential Pediatric Relevance

Dr. Reaman said that if there is interest in the agents discussed, he could invite the sponsors to make presentations and discuss WRs at the next meeting of the Pediatric Subcommittee of the Oncology Drugs Advisory Committee (ODAC).

Baricitinib. Baricitinib inhibits JAK 1 and 2. The Children's Oncology Group (COG) Acute Lymphoblastic Leukemia (ALL) Committee is interested in JAK inhibitors for high-risk patients, particularly patients with Ph+ like ALL. The committee has had difficulty obtaining another JAK inhibitor for clinical evaluation due to the sponsor's lack of willingness. Dr. Reaman asked whether baricitinib, which two companies are jointly developing, could be an alternative.

Dr. Adamson said that interest was likely, but he did not know about adult development of the drug. Dr. Reaman said that the initial PSPs were submitted at the end of phase 2 trials. Baricitinib is in the late stage of development for a number of adult malignancies, starting with

metastatic breast cancer. The compound was initially developed to treat rheumatoid arthritis, and there are positive phase 3 studies for that indication.

Dr. Matthay asked how baricitinib compared to ruxolitinib. Dr. Reaman did not think there had been comparisons. Ruxolitinib is a preferential JAK 2 inhibitor; baricitinib inhibits JAK 1 and 2 and inhibits JAK 3 to a lesser extent.

Dr. Adamson said there was a high degree of interest in JAK inhibitors, and developing more than one is a good idea, at least in the early phases. The ALL Committee would be supportive. Dr. Matthay said that Dr. Mignon Loh would be interested.

Dr. Matthay asked whether Incyte, which developed ruxolitinib, was also developing baricitinib. Dr. Reaman said that Incyte and Eli Lilly were jointly developing baricitinib. COG investigators recently met with Eli Lilly to discuss the company's drug pipeline. Baricitinib may provide an opportunity to work with a more pediatric-friendly sponsor.

Dr. Matthay said that the group would have to look at the advantages of baricitinib based on preclinical studies and adult pharmacokinetic (PK) studies. Phase 1 studies of ruxolitinib have already been performed in juvenile myelomonocytic leukemia.

Dr. Smith cautioned that JAK inhibitors in myeloproliferative neoplasms have not reduced clonal burden, despite the presence of JAK 2 mutation, and these drugs have not shown spectacular activity in the ALL point mutations for JAK 2 xenografts. Perhaps JAK 2 inhibitors target translocations more effectively. There has not been dramatic proof of principle, unlike with *BCR-ABL* and dasatinib. An agent may be needed for JAK 2 translocations, but this is not a large group. Dr. Reaman agreed that the drug would have a niche indication, but he was not aware of the difference in sensitivity of point mutations and translocations. This difference would make the niche smaller.

Dr. Matthay added that resistance can evolve very quickly, as with ruxolitinib, and the agent may need to be combined with something else.

Dr. Reaman asked if there were some interest in the drug. Dr. Adamson said that the drug could be used in a small population; whether the agent could be used beyond that is an open question.

Ganetespib. Dr. Reaman explained that this agent, an Hsp90 inhibitor, is being developed to treat several adult cancers. Hsp90 inhibitors have been explored in pediatric cancers, but no real activity has been demonstrated. In preclinical and early phase settings, there has been interest in triple-negative breast cancer and a number of other refractory adult cancers. He asked whether Dr. Smith had updates from the Pediatric Preclinical Testing Program (PPTP).

Dr. Smith said that the rationale for this class of agent is compelling, as these agents block pathways that are important to the cancer. However, clinical activity for this class has been limited. Despite years of work, no agents in this class have been approved, and ganetespib is probably the best in the class. He did not see single-agent activity against models that have

various dependencies on oxygenic signaling pathways. Researchers have been frustrated in finding therapeutic windows for this class.

Dr. Reaman said he understood the frustration with other Hsp90 inhibitors, but ganetespib appeared to be the best in its class in adults. Dr. Smith said that PPTP looked at ganetespib selectively but not across the entire panel. Like other agents, ganetespib was potent *in vitro* and showed good cytotoxic activity. He saw growth delay in some models but not regression. The researchers did not screen ganetespib extensively because they had looked at other Hsp90 agents and did not see effects. This agent induced regression in non-small cell lung cancer patients with *ALK* mutations, but the researchers did not see activity in an *ALK*-mutated neuroblastoma.

Dr. Matthay said ganetespib was studied in p53 mutant ovarian cancer and asked whether the compound should be studied in patients with p53 mutations in other cancers. Dr. Smith said that almost all ovarian cancer is p53 mutated. He was not aware of data that ganetespib is preferentially active in p53 mutated cancers. Dr. Matthay said that preclinical data show that the compound sensitizes p53 mutant cells to treatment with chemotherapy.

Dr. Reaman said the sponsor could give a presentation on preclinical, early, and mid-stage clinical activity in adults, if there is interest. The activity in the *ALK*-positive non-small cell lung cancer is interesting because there was activity in patients who were resistant to *ALK* inhibitors. The group can wait and consider this agent later.

Dr. Smith said that a phase 3 trial in non-small cell lung cancer may be ongoing. If the results are positive, ganetespib would be on the path toward licensing; if not, the future of the compound is uncertain. Dr. Reaman suggested that the group wait for the results of the phase 3 trial.

Ra-223 dichloride (Xofigo). Dr. Reaman explained that this compound, a bone-seeking alpha emitter, was recently approved in adults with MCRPC. The compound has little toxicity and significant activity. Treatment of multiple or isolated bone metastases in pediatric cancers is occasionally needed, usually in late-stage patients. He asked whether there was concern with potential toxicity with external beam radiotherapy.

Dr. Adamson said that others have made a case for developing this compound in metastatic osteosarcoma, which would be difficult. The samarium study for pulmonary metastases was not positive. Interest in Ra-223 dichloride in osteosarcoma is not universal because of experience with radioisotopes and their inability to affect the pulmonary metastatic course of disease. Developing the compound for symptom management for bone metastases would also be difficult. Generally, other systemic therapy would be attempted, and external beam radiotherapy can manage most patients. There is not an overwhelming need to develop this compound.

Dr. Matthay asked whether myelosuppression was a problem with samarium. Dr. Adamson said this was part of the problem. The other part was the lack of uniform uptake in pulmonary metastases. The drug cannot have a significant impact if it does not get to the disease. An advantage is that Ra-223 dichloride is an alpha emitter and may be less toxic.

Dr. Reaman said the drug had an integral relationship with calcium metabolism and incorporation in bone, but he did not know if this effect was seen in osteosarcoma. If this effect exists in pulmonary metastatic osteosarcoma lesions, it may be worth considering and checking with the COG Bone Tumor Committee because of its relative safety compared to samarium.

Etirinotecan pegol (NKT-102). Dr. Reaman said that this drug has demonstrated considerable activity in platinum-resistant ovarian cancer. Because of its PEGylation, the drug is thought to be 1,000 times more potent *in vitro* in inhibiting topoisomerase I. Because of the linkage to polyethylene glycol (PEG), it penetrates tumor cells and has delayed clearance. The drug has a unique PK profile, with reduced peaks following administration, and has less myelosuppression than irinotecan. The parent compound is used in a number of diseases, and this compound may be worth considering in pediatrics.

Dr. Matthay asked whether diarrhea was as significant a toxicity with etirinotecan pegol, and Dr. Reaman said that it was not. Dr. Reynolds said that the Merrimack compound MM-398, a liposomal irinotecan, cures multidrug-resistant Ewing tumor xenograft. He is about to submit a paper on MM-398. Researchers found that Ewing sarcomas overexpress *SLFN11*, which sensitizes them to SN-38. Exposure levels of SN-38 are inadequate with the old irinotecan. MM-398 can achieve adequate levels, and etirinotecan pegol may have the same effect. He asked whether etirinotecan pegol had been studied with Ewing sarcomas.

Dr. Matthay asked whether Dr. Reynolds was referring to a nanoparticle preparation. Dr. Reynolds said that the nanoparticle preparation was a third preparation of irinotecan. He is beginning a phase 1 clinical trial of MM-398. Most of the patients have Ewing sarcoma, but MM-398 does have activity in rhabdomyosarcoma and neuroblastomas in xenografts. Modified irinotecans may have activity, especially in tumors sensitized by *SLFN11* expression.

Dr. Adamson said that he had studied enzyme 2208 (EZN-2208), which is PEG SN-38. In pediatrics, a PEG SN-38 or irinotecan drug would have some appeal because of ease of use. Whether these drugs are more effective than irinotecan is not known. He asked whether these drugs had been compared with irinotecan in adult cancers.

Dr. Reaman said he was not aware of a comparison, but activity was demonstrated in platinum-resistant ovarian cancer. Dr. Reynolds said that MM-398 activity was seen in a phase 2 trial with pancreatic carcinoma, and that trial will be finished in a few months. Dr. Reaman said that he could invite Nektar Therapeutics to give a presentation, if there is interest. Dr. Adamson said there was interest, but developing definitive efficacy studies would be difficult.

Iniparib. Dr. Reaman said that this drug, a benzamide structurally related to nicotinamide, was originally developed as a poly adenosine diphosphate ribose polymerase (PARP) inhibitor. Preclinical studies suggest that iniparib is not a PARP inhibitor but a prodrug. The reactive intermediates covalently bind to a number of cellular targets: cysteine and selenocysteine residues, resulting in the induction of oxidative stress. Iniparib is a classic cytotoxic drug, although the mechanism of action is unique. The current development is in triple-negative breast cancer, so a waiver for the PSP would likely be granted.

Drs. Adamson and Smith said they did not know enough about the drug. Dr. Smith said he would need to know more about the expected therapeutic window. Dr. Reaman said that the group could wait until more information is available to consider this drug.

MDM2 inhibitors. Dr. Reaman said that in a previous call, there had been interest in looking at MDM2 inhibitors. He asked whether there was still interest and, if so, in which compounds. Dr. Smith said that Roche, Merck, and Eli Lilly have compounds, but they are deciding whether to continue development. The PPTP results with RG7112 show that a set of tumors respond to MDM2 inhibitors as single agents. There is interest, but the adult drug development has not moved forward quickly.

Dr. Reaman asked whether the group should wait until there is a better adult development plan. He asked whether phase 1 studies had been completed. Dr. Matthay thought that Dr. Jason Shohet had done some work with the MDM2 inhibitor nutlin in pediatric neuroblastoma, but he said the drug was not ready for clinical trials.

Dr. Smith said that if a company was moving a drug forward, there would be a lot of interest. Dr. Reaman said he spoke with Dr. Sandra Horning at Genentech, and that company may be interested. He suggested that the group wait and discuss these drugs in the future. Dr. Smith said that Dr. Susan Blaney has been interested in MDM2 inhibitors for brain tumors.

Priorities and Plans for Off Patent WRs for Oncology Drugs

Dr. Zajicek said that she did not have any updates. The group had mentioned cyclophosphamide and glucocorticosteroids, but she was not sure if there was interest. Dr. Reaman said that etopicide may have been on the list. He asked about resources for studies. Dr. Zajicek said that in the past, she had a $25 million annual budget. About half of that is set aside for out-years. The majority of funds are going to the Pediatric Trials Network, which has begun many neonatal trials. Funds were also spent on the vincristine, actinomycin D, and daunomycin trials, which are complete. Methotrexate and isotretinoin studies may begin this year or next, depending on the company. Dr. Zajicek would be happy to discuss working with COG and would have funds for this work.

Dr. Reaman said that labeling information is incomplete for a number of widely used drugs. He did not know whether labeling was necessary and whether many practicing clinicians refer to the product label for dosing and toxicity information. He will raise the issue with the ODAC and would be interested in hearing if there are any agents that should be prioritized.

Dr. Zajicek said she would follow up with Dr. Smith about COG infrastructure capabilities. She asked whether the Pediatric Subcommittee would meet this year. Dr. Reaman said there would be one meeting, possibly in early October, and he will make sure there are no conflicts. The COG fall meeting is in September, the International Society of Paediatric Oncology meeting is in late October, and the American Association for Cancer Research meeting is the last week in October.

Future Conference Calls

The group has been meeting quarterly. Circle Solutions, Inc., will poll the group to determine a fixed day and time for future meetings.

Action Items:

- Etirinotecan pegol and possibly baricitinib will be considered for the next ODAC meeting. Dr. Reaman will wait for feedback from the COG ALL Committee on JAK 2 inhibitor studies and working with Incyte.
- Dr. Zajicek will follow up with Dr. Smith about COG infrastructure capabilities.
- Circle will poll the group to determine a fixed day and time for future meetings.