TRENDS-in-MEDICINE

BULLETIN:

AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) – PREVIEW

May 13, 2015
by Lynne Peterson

In a web and teleconference with reporters, ASCO officials highlighted the results of four studies to be presented at ASCO's annual meeting in Chicago May 29-June 2, 2015. ASCO president Peter Yu, MD, director of cancer research at the Palo Alto Medical Foundation, said the theme this year is "Illumination and Innovation: Transforming Data into Learning."

BRISTOL-MYERS SQUIBB and ABBVIE's elotuzumab (HuLuc63) – positive Phase III results in relapsed/refractory multiple myeloma

The results of the open-label, 646-patient Phase III ELOQUENT-2 trial in multiple myeloma patients who had failed 1-3 prior lines of therapy clearly showed that adding this monoclonal antibody to Celgene's Revlimid (lenalidomide) + dexamethasone significantly improved both progression-free survival (PFS) and overall response rate (ORR). The principal investigator, Sagar Lonial, MD, from Emory University School of Medicine, said elotuzumab has a dual mode of action, targeting both the tumor and the host, "a bit of a double whammy." He said the overall survival (OS) data are still "relatively immature" and need another six months, "but there are very encouraging signs, not just on duration of remission but on overall survival."

ELOQUENT-2 Results with Elotuzumab in Multiple Myeloma

Measurement	Revlimid + dexamethasone +		p-value
	Elotuzumab n=321	Placebo n=325	
Primary endpoint #1: PFS at 1 year	68%	57%	<0.05
Primary endpoint #2: PFS at 2 years	41%	27%	0.0004 HR 0.70
Secondary endpoint: OS at 1 year	Data not yet available		
ORR	79%	66%	0.0002

Asked about the cost of adding another, presumably expensive drug, to Revlimid, which is already expensive, Dr. Lonial said the cost of elotuzumab is not yet known, but answered, "You also have to look at outcomes in terms of benefits…For me, it is where the plateau is in the curve…If we are curing some people, that in many ways changes the game. Cost is one factor, but what is the benefit you get at that price. And for that we need a little more follow-up."

Elotuzumab already has breakthrough therapy status by the FDA.

Asked how elotuzumab would be positioned since Amgen/Onyx's Kyprolis (carfilzomib) has shown longer PFS than this, Dr. Lonial said, "The ASPIRE trial [of carfilzomib in multiple myeloma] and ELOQUENT-2 had two very different patient populations. Patients in ELOQUENT-2 were more refractory and had more high-risk genetics. And the control in ELOQUENT-2 is something I can't answer today…I can say the benefit for the three-drug arm was the same for age <65 and age >65 across the board, and there were high-risk genetic subsets nicely identified who did better with the 3-drug arm. It will take time to understand the risk stratification…For me the 3-drug regimen was better and introduced a new mechanism of action."

Metastatic prostate cancer – using docetaxel earlier improves survival

The first survival results from the STAMPEDE trial appear to be game changing. The study found that giving chemotherapy (docetaxel) along with Novartis' Zometa (zoledronic acid) to men with locally-advanced, lymph node-positive, metastatic prostate cancer when they initiate long-term hormone therapy improves survival. Normally, chemotherapy is reserved for patients who progress on androgen deprivation therapy, but this study clearly showed that it should be used much earlier.

There was a statistically significant and clinically meaningful increase of:

- 38% in failure-free survival. This was true regardless of how many metastases the patient had at entry (M0, M1, or overall).
- 24% in overall survival. This was true for M1 and overall metastatic status, but the numbers were too low (so far) to draw a conclusion for the M0 men.

ASCO president Dr. Yu said, "We have treated this with hormone therapy until it is exhausted and there is no response left, and at the last moment using chemotherapy…That may be a self-defeating strategy because you are using it when the disease has evolved to where it is more aggressive…Last year, we started to see evidence that that may be wrong, that giving it [chemotherapy] early may be better than hormone therapy followed by chemotherapy at the last stages…This is a chemotherapy drug that has been around a long time. We know it is tolerable by men. This is not a treatment that is very difficult to take…So, there is a paradigm shift occurring…And the really interesting thing is the very strong hint that this strategy of bringing chemotherapy early on can have a benefit even in men who don't have evidence of metastases at the time of starting hormone therapy (adjuvant use of hormone therapy)."

Asked what the guidelines say about using docetaxel upfront with hormone therapy, Nicholas James, MD, PhD, from the University of Warwick, U.K., who presented the data, said docetaxel is licensed in Europe only for hormone-refractory prostate cancer, so using it earlier would be off-label. However, he said this will be discussed with European regulators who have the authorization to change an indication based on an academic trial like this. The researchers are recommending routine use of docetaxel in men with newly diagnosed metastatic disease and selected high-risk non-metastatic men. He added, "I expect the guidelines will change to recommend upfront use of docetaxel."

What do these findings mean for use of Astellas and Medivation's Xtandi (enzalutamide) and Johnson & Johnson's Zytiga (abiraterone)? Dr. James said it is possible that either abiraterone or enzalutamide might be better than docetaxel, but those data are not yet available. The first data will come from this same trial, STAMPEDE, for abiraterone, but it won't be available until 2017.

Over-the-counter nicotinamide (vitamin B3) – prevents non-melanoma skin cancers and pre-cancerous lesions

An Australian study, ONTRAC, found that this oral form of vitamin B3 – which is distinctly different from niacin – is effective in preventing new basal cell or squamous cell carcinomas in patients who already had at least 2 non-melanoma skin cancers. The 386-patient, 1-year study found that over-the-counter, inexpensive (<$10/month) nicotinamide, taken BID:

- Significantly reduced new non-melanoma skin cancers – 1.77 new lesions (cancers) vs. 2.42 new lesions (p=0.02), a 23% reduction. And the effect was the same for basal cell carcinoma as for squamous cell cancer.
- Significantly reduced premalignant actinic keratoses, a 15% reduction.

However, there was only a benefit as long as the nicotinamide was taken. When patients stopped, their benefit wears off pretty quickly.

Unlike niacin, oral nicotinamide is well tolerated and does not cause headache, flushing, or low blood pressure.

The principal investigator, Diona Damian, MD, a dermatologist from the University of Sydney, Australia, said, "This is ready to go to the clinic. It is for people who already have skin cancer. It is not something we would recommend at this stage for the general population…This is a non-toxic, inexpensive agent that has been in clinical use in dermatology for decades with no safety concerns…It has hardly any drug-drug interactions…My message would be that this is a preventive treatment for people who have a track record of skin cancer. At this stage we don't recommend it to the general population who may or may not be at risk of skin cancer later on…At the moment, it is not something for the general population."

Asked if these results can be extrapolated to countries with less sunlight than Australia, Dr. Damian said they can. While nicotinamide is more effective in people with a lot of skin cancers, it also works in people with less sun exposure, provided they already have skin cancer. She added, "We don't know any downside to these compounds…but we are encouraging use in skin cancer patients."

Renal cancer
– augmented chemotherapy for kids with rare form of Wilms

Two studies by the Children's Oncology Group found that children with Wilms tumor who have a loss of heterozygosity (LOH) of chromosomes 1p and 16q have a poorer outcome, but that can be overcome by escalating therapy. Likewise, children with no loss of heterozygosity can do just as well with scaled back therapy.

Four-year overall survival for Wilms tumor patients is ≥86% regardless of stage, but 4-year event-free survival (EFS) is only 75%. LOH was found to be a prospective biomarker. About 5% of patients had a loss of both 1p and 16q, and they had significantly worse 4-year outcomes.

The AREN0532 (Stage I/II) and AREN0533 (Stage III/IV) studies looked at whether augmenting therapy would improve event-free survival for these LOH patients vs. standard therapy. And it did.

- In Stage I/II patients, augmented therapy increased 4-year EFS from 75% to 83.9%.
- In Stage III/IV patients, augmented therapy increased 4-year EFS from 66% to 91.5%.

Any additional toxicity with the augmented therapy was "manageable."

ASCO press conferences

ASCO is hosting five press conferences ***during*** the annual meeting. The topics are:

- Immunotherapy – Friday at 1 pm CDT.
- Targeted therapy – Saturday at 8 am CDT.
- Progress against rare and common cancers – Saturday at 10:30 am CDT.
- Late breakers from the plenary session – Sunday at 8 am CDT.
- Innovation in precision medicine – Monday at 8 am CDT.