ESMO: Cancer Immunotherapy on the Road

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by Neil Canavan

Since cancer immunotherapy was declared the Breakthrough of the Year in 2013 by Science magazine the field has been on fire, and its relatively few experts have been on the run– explaining the nascent technology and related data to oncologists at venues from the April meeting of AACR in San Diego, to the June meeting of ASCO in Chicago, to the September meeting of ESMO in Madrid.

The overall message is clear: cancer immunotherapy is here to stay. It’s effective, and it’s sexy: as Jedd Wolchok, M.D., Ph.D., of the Memorial Sloan Kettering Cancer Center, said at ASCO, “We treat the patient. It’s the patient that treats the tumor.”

Immunotherapy at ESMO
Education on the topic is much needed, and oncologists can’t get enough. As observed by Mario Sznol, M.D., as he chaired an immunotherapy education session at AACR 2014, “I chaired this same session seven years ago, and there were 30 people in the room – now look at it.” Standing room only.

There were crowds at ESMO as well, in particular, clinicians eager to hear the latest on PD-1 (programmed cell death 1) inhibitors, such as nivolumab.

Nivolumab, a monoclonal antibody, blocks the interaction between the receptor PD-1 and its ligand, PD-L1. What Wolchok meant about treating the patient is that the interaction blocked is between the patients’ tumor-attacking T-cells and the tumor cells being attacked. PD-1 signaling by the tumor shuts off this immune response.

As a class, these signals controlling the immune response (there are many) are called, “checkpoint inhibitors.”

In the CHECKMATE 037 study, nivolumab, was given to patients with advanced melanoma who progressed after treatment with the first approved checkpoint inhibitor, ipilimumab (more on this drug in a moment) or BRAF inhibitors (standard of care for those with the BRAF mutation).

The trial recruited 405 patients and randomized them to nivolumab, or “physician’s choice” of either dacarbazine, or a combination of carboplatin and paclitaxel.

Results for this gravely ill patient population were impressive. There was a 32% response rate for nivolumab versus 11% for physicians’ choice. “And 95% of these responses are ongoing,” reported study investigator, Jeffrey Weber, MD, Lee Moffitt Cancer Center, adding that, “In my view nivolumab should replace chemotherapy in routine practice in second- or third-line treatment for melanoma patients.”

Based on these data alone, nivolumab is now under priority review with the U.S. Food and Drug Administration (FDA).

**Ipilimumab**

Leading the immunotherapy charge is ipilimumab, approved in 2011. Ipilimumab blocks the down-regulatory interaction between the attacking T cell and the antigen presenting cell that’s telling the T cell what to attack.

Approved in melanoma, where extraordinary responses have been observed, data for ipilimumab in prostate cancer was reported at ESMO.

Results of a study of 799 patients with metastatic, castrate-resistant prostate cancer treated with ipilimumab, plus a single dose of radiation therapy, or radiation treatment alone showed the ipilimumab doubled the survival rate at 3 years: 12% for immunotherapy versus 6% for radiation alone.

Some immune-related adverse events were noted (gastrointestinal, dermatologic, endocrine), but these events were considered manageable.
IMA950
Recently elucidated features of the immune system have helped to resurrect the field of cancer vaccines (Provenge, the first approved cancer vaccine, is largely considered to be ineffective).

IMA950 is a vaccine in development to treat glioblastoma.

Sergio Quezada, Ph.D., of the University of College London Cancer Institute commented on the results for the IMA950 vaccine, tested in a Phase 1 investigation (N=40): “The basic concept here is that peptide vaccines injected together with an adjuvant, in this case GM-CSF, will promote effector T-cell responses.” GM-CSF is known to activate antigen-presenting cells, and to mobilize them in the tumor microenvironment.

“Most old-school vaccines use a single peptide,” Quezada explained. IMA950 incorporates nine different glioblastoma epitopes. “To me, what’s most important is two of these are helper epitopes,” which pull in helper CD4 immune cells along with CD8 (killer) T cells to boost overall response.

Results for the IMA950 phase 1 study showed that 90% of patients responded to at least one peptide, and 50% showed a response to more than one.

“The problem here is that this also activates regulatory T-cells,” said. Quezada, and that eventually squashes the immune response. “Perhaps a combination with agents such as anti-CTLA-4 may yield the biggest benefit – that would be a fantastic combination.”

recMAGE-A3
As is the nature of experimentation, there were failures at ESMO as well, such as the Phase 3 MAGRIT trial, which looked at the efficacy of the MAGE-A3 vaccine in patients with non-small cell lung cancer (NSCLC).

The vaccine, delivered with the adjuvant AS15, is based on the MAGE-A3 peptide. The function of MAGE-A3 in healthy cells is unknown, but its presence on the surface of tumor cells is a marker of poor prognosis. The marker is present in roughly a third of NSCLC patients.

The adjuvant AS15 is comprised of immune-stimulatory components: CpG 7909; monophosphoryl lipid; and QS-21, a plant derivative.

“The rationale here is two-fold,” explained MAGRIT investigator, Johan Vansteenkiste, M.D., Ph.D., University Hospital, Leuven, Belgium. “One, it’s a disease setting where cure rates are very hard to achieve, and two, studies to date suggest that the vaccine is a very well tolerated and promising treatment approach.”

Unfortunately, that promise went unfulfilled. Results for MAGRIT, which randomized 2,272 NSCLC patients after having lung resections to vaccine or placebo showed no statistical difference between the two cohorts.

“A definitive but disappointing answer for patients and investigators,” said Vansteenkiste.

The loss also represents a lack of information. “We need a better understanding of mechanisms,”
Vansteenkiste said. “Lung cancer has a very immunosuppressive environment, meaning that strategies like MAGE-A3 do create effective soldiers – antibodies that kill tumor cells – but the question now is, do the soldiers act on the battlefield?”

For MAGRIT, obviously not. However, in what is rapidly becoming a mantra in the immuno-oncology space, Vansteenkiste is eager to combine his vaccine with a checkpoint inhibitor, thinking that may be the key to a sustained therapeutic response.

**PLX3397**

PLX3397 is a small molecule drug targeting colony-stimulating factor-1 (CSF-1), a moiety thought to control the number and phenotype of tumor-associated macrophages (TAMs). The presence of TAMs have been linked to poor prognoses in a number of tumor types.

The present dose-escalation study looked at PLX3397 activity in patients who are being treated with paclitaxel – a drug that stimulates CSF-1 production, and TAM infiltration. It’s hoped that this approach will boost the efficacy of taxanes, like paclitaxel.

Results for this cohort of 88 patients showed a response rate ranging from 33% to 67%, depending on the dose level.

Lead investigator on the study, Hope Rugo, M.D., University of California San Francisco, said that the results were good enough to fold further investigation of PLX3397 into the I-SPY2 trial.

**I-SPY2 and beyond**

The way drugs are being tested is changing, partly due to the excessive time and expense it takes to bring a drug to market with historical methods and, relative to the current topic, due the nature of immunotherapies.

One such new way of testing is the so-called, adaptive trial design; I-SPY2 is an adaptive trial.

“This is a shift that we’ve thought about for a long time,” said Rugo, who has long been involved in I-SPY. She explained that, rather than enrolling X hundreds of patients, dividing them up into treatment groups A and B and comparing outcomes after months or years on trial, an adaptive design allows for obtaining the same, or better, information using fewer patients over less experimental time.

It works like this: you take the same X hundred patients as before, but this time you characterize them according to, say, molecular subtypes, like those with overexpression of HER2. You identify all the types of patients according to the given criteria and then randomize them, as before, into A or B treatment arms.

However, rather than running the trial and waiting for the final results, in an adaptive design there are planned interim analyses, and these analyses identify early on which types of patients are responding to which therapies. This information is then used to enrich a given treatment arm with the subtype of patient that best responds.

The enrichment phase – which patient goes into which group – is handled by computer, so as to maintain the investigation as a blinded study.
“By the time you’re done with your trial you’ll actually have the statistical power to detect the benefit of your treatment in that patient subtype population,” said Rugo.

How might this apply to immunotherapies? “Say you decide that PD-L1 expression is the critical factor for (nivolumab) response. Okay, but I still want to know if this drug works at all in patients who don’t have PD-L1 expression,” Rugo said. “So, I’m going to enroll everybody and I’m going to evaluate PD-L1 expression in everybody up front so over time you will be able to figure out who the responders are.”

Is this type of trial design necessary for immunotherapies? According to the number of trials being proposed for immunotherapy combinations, absolutely. Because checkpoint inhibitors, in theory, should boost response to most any targeted agent that has already shown activity, a multitude of combinations are on the horizon.

A recent analysis by Leerink Partners, a healthcare investment bank, places the minimum number of trials to be run at 798— and that’s just using a PD-1 inhibitor backbone. “Which is staggering,” said Leerink lead analyst, Seamus Fernandez. “And that doesn’t even consider which line of therapy.”

Nor does it take into account the fact that immunotherapy strategies also increasingly include the direct manipulation of the patients’ T-cells themselves – removing T-cells from the patient, genetically optimizing their performance and then infusing them back into the patient. This approach – not seen much in evidence at ESMO because most such trials are still small, and mostly ongoing – has still generated an enormous interest in the investment, and clinical communities.

Regardless of how the trials are done, the motivation is strong, the science is largely in place and the patients are ready to pitch in.
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