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ASCO Review: Progress Is Where You Find It

by Mary Jo Laffler

In another year roundly critiqued as being “quiet” on major clinical advances, the American Society of Clinical Oncology annual meeting allowed other areas to shine.

Without a definitive new drug ready to change practice, many observers rejected this year’s American Society of Clinical Oncology as slow.

But coming out of the meeting, the trends highlighted show a remarkable amount of progress and the tremendous efforts underway to realize the full potential of genomic research to identify new therapies, find the best treatment settings and combinations and match them to the right patients.

True, none of the plenary abstracts featured a new molecular entity (and one was on a drug already withdrawn for lack of effect). But that allowed ASCO to put a spotlight on other areas of progress.

As Credit Suisse analysts put it going into the 31 May-4 June conference in Chicago, “the intense scrutiny on detailed data points from numerous pivotal trials from our large cap companies (most notably Merck and Bristol-Myers) has been replaced by what we expect to be some still-important data presentations, but also with a focus now on bigger picture themes as we think about the emerging oncology landscape,” including “how patients/physicians are managing the costs/side effects related to various therapies, as well as how our healthcare system may need to evolve to accommodate the large number of novel but expensive therapies that have shown impressive clinical results in recent years.”

Signature Achievements

That’s not to say there weren’t signature achievements. The POLO study showed a dramatic effect in a subset of patients with a notoriously difficult cancer – in pancreatic cancer patients with germline BRCA mutations, *AstraZeneca PLC*/*Merck & Co. Inc.*’s PARP inhibitor *Lynparza* (olaparib) yielded median progression-free survival (PFS) of 7.4 months compared to

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3.8 months for placebo, with more than twice as many patients remaining progression-free at both one year (34% vs. 15%) and two years (22% vs. 10%). (Also see "*AZ/Merck & Co's Lynparza POLO Study 'Practice Changing' For Pancreatic Cancer Subgroup* " - Scrip, 3 Jun, 2019.)

Astellas Pharma Inc./*Pfizer Inc.* got confirmation that enzalutamide has a role when added to testosterone in first-line treatment of hormone-sensitive prostate cancer from ENZAMET, with longer overall survival but also some increased toxicity.

But progress doesn't always come with great leaps forward; sometimes it's a matter of incremental advance. Going fast can miss things – the checkpoint inhibitors rightly made a big splash and have come to dominate many cancers (and billboards around the city of Chicago).

But the first few years were filled with questions about how to identify the right patients, better information on dosing and appreciating differences between the PD-x drugs (remember when it was thought *Keytruda* (pembrolizumab) and *Opdivo* (nivolumab) might be interchangeable?) – the sort of thing that isn't fleshed out when moving on a fast track.

In recent years, there's been a lot of filling in around the edges as more information rolled in. Researchers have clarified differences between the drugs in terms of efficacy and tolerability, better dosing regimens have been established in some cases, and the utility of the PD-L1 biomarker has been debated. This year there was a notable focus on emerging

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So Far, Still So Good For Seattle

biomarkers for IO as well as understanding resistance patterns.

And Merck presented five-year survival data from the KEYNOTE-001 study with Keytruda in non-small cell lung cancer – a landmark analysis that codifies the impact IO is having on the cancer landscape.

Whereas traditionally lung cancer has had a five-year survival rate of 5% or less, Merck Research Labs' chief medical officer Roy Baynes noted, the five-year overall survival (OS) rate was 23.2% in treatment-naïve patients and 15.5% in previously treated patients. In patients with high levels of PD-L1, five-year OS was 29.6% in treatment-naïve patients and 25.0% in previously treated patients.

Genetics/Astellas' Bladder Cancer ADC, 4 June, Scrip

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The trial also supports longer-term use. In patients who had been on therapy for two or more years, the five-year OS rate was 78.6% in treatment-naïve patients and 15.5% in previously treated patients. "The data also bodes well for Merck's ability to gain traction with payers, including those outside of the US who may look for more longer-term data to fully support a product," Credit Suisse analyst Vamil Divan said in a 2 June note.

Landmark data were also presented for *Roche*/*Genentech Inc.*'s *Perjeta* (pertuzumab) in combination with *Herceptin* (trastuzumab) and docetaxel in patients with previously untreated HER2-positive metastatic breast cancer, with an "unprecedented" effects seen at an end-of-study analysis.

After eight years of follow up, patients on the Roche regimen had a 16.3 month improvement in survival over patients on the comparator – a statistically significant 31% reduction in the risk of death.

Pricing Remains A Pain Point

Long-term use does raise financial issues, however, and cost concerns came up again and again in scientific presentations, especially regarding combination therapy. ASCO 2019 featured more than a handful of talks on value assessment, including a town hall on drug pricing and a specific session on oncology reimbursement reform that reviewed lessons learned from the oncology care model.

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In addition, health services/quality of care research took prominence with the presentation of research in the plenary session showing how Medicaid expansion under the Affordable Care Act almost eradicated racial disparity in cancer care compared to states that did not expand Medicaid.

It was one of several abstracts showing almost 10 years into Obamacare that access to care and better insurance are connected to better survival. (Also see "*US Affordable Care Act Impact On Cancer Care Quantified At ASCO*" - Pink Sheet, 2 Jun, 2019.)

Finding A Way With Big Data

There was a dedicated education session on big data, and the role of artificial intelligence and data analytics to process vast amounts of information – and the potential to better harness real-world evidence – came up in multiple tracks. The exhibit hall also reflected a shift toward more incorporation of a wide spectrum of technology into drug development and clinical practice, with splashy booths for sequencing and AI companies. And the plenary abstract on racial disparities was conducted using Flatiron Health claims data.

Big pharma continues to explore ways to exploit data analytics. Roche has fully embraced it, making it a centerpiece of its oncology strategy with its early alliances (and later acquisitions) of Flatiron Health and Foundation Medicine. (Also see "*Next-Generation Roche: How Data Analytics Will Keep It In The Lead In Oncology*" - Scrip, 8 Jun, 2018.)

Lilly announced a deal with AI specialist Atomwise during ASCO. (Also see "*Time For AI To Deliver In Drug Discovery, Says Atomwise CEO*" - Scrip, 4 Jun, 2019.)

Two Years Of Artificial Intelligence Deals: A Pharma Snapshot

By Daniel Chancellor

30 May 2019
INFOGRAPHIC: major alliance deals focused on artificial intelligence and machine learning, signed by pharmaceutical companies over the past two years.

Read the full article here

While using non-traditional data sources like electronic health records and claims databases "are not designed with clinical evidence generation in mind, and analyses of these databases are retrospective rather than prospective, they can yield important insights into real-world practice and include many more patients than is typical for an oncology trial," Informa Pharma Intelligence analyst Dan Chancellor told *Scrip*. "This is particularly useful for studying niche populations, such as those with rare tumors or unique molecular/genetic signatures."

Data analytics companies are eager to expand the role of real world evidence (RWE). Private AI play ConcertoHealthAI, which had a fairly large booth in the exhibit hall, has come up with a

model for prospective research and is working with Pfizer, *Bristol-Myers Squibb Co.*, Astellas and other undisclosed partners, including payers.

President Jeff Elton talked about how encouraging the US FDA has been in embracing RWE and modernizing data collection and analysis in an interview at ASCO. "FDA has been spectacular leadership in this," he said. "They are ready for innovation and want to see protocols."

Big data is generating big buzz, Merck's Baynes agreed, as companies look to systematize datasets for pattern recognition and clues – but it's early days yet.

"You're only as good as the algorithms you employ," he commented. "There's tremendous enthusiasm around [data analytics] and it's important to pursue, but at the end of the day you need to recognize that the findings are hypothesis-generating."

Checking In On New Checkpoints

Analysts and physicians alike are keenly tracking the emergence of new checkpoint inhibitors beyond the PD-1/L1 family, and ASCO featured early data on a few hotly watched targets.

The data on *Aduro Biotech Inc.*/*Novartis AG*'s ADU-S100, a stimulator of interferon genes (STING) activator, were from a dose escalation study, but they showed an encouraging 100% disease control rate among the eight patients with triple-negative breast cancer evaluable for response, "strengthening the value of STING activation as a novel immunotherapy approach for solid tumors. There is now preliminary efficacy across TNBC, melanoma, adding to previous data for Merck's MK-1454 in head and neck cancer and thyroid carcinoma," according to Biomedtracker analysts.

Both ADU-S100 and MK-1454 are delivered intra-tumorally. Merck's Baynes noted that there was "no question of local effect" for STING and that Merck is in the process of expanding its trials. Aduro noted that enrollment in a study of ADU-S100 and ipilimumab in relapsed/refractory melanoma is ongoing and it anticipates initiating a trial with pembrolizumab in first-line head and neck cancer in the second half of 2019.

There were also early data on LAG-3, another next wave checkpoint inhibitor. But no monotherapy patients responded to *Regeneron Pharmaceuticals Inc.*/*Sanofi*'s REGN3767 and only 5% of patients receiving it with the anti-PD-1 cemiplimab achieved a partial response. Patients who converted to PD-1 monotherapy after receiving the LAG-3 drug did the best.

"It suggests that LAG-3 may be best used as a sequential agent and it does sensitize tumors to PD-1 inhibition, but the effect in this trial was weak (16% PR). This was a dose escalation study and not designed to determine efficacy, but you can't ignore the low overall response rates," Chancellor told *Scrip*.

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What Can We Learn From Failure?

ASCO threw the interesting twist of highlighting a trial failure for one of the four plenary spots, which served as a post-mortem on the accelerated approval and subsequent withdrawal of *Eli Lilly & Co.*'s *Lartruvo* (olaratumab) and an examination of what it was about soft tissue sarcoma (STS) that contributed to the failure.

It played out like a mystery – here was a drug that had a significant survival benefit in a large randomized Phase II trial, but then missed the survival endpoint in the Phase III study.

The principal investigator William Tap, Memorial Sloan Kettering Cancer Center, walked through the Phase II evidence, the sound decision for accelerated approval and the rigor and quality of the Phase III study. Both he and the discussant on the trial, Erasmus University's Jaap Verweij, identified issues about the heterogeneity of the STS classification and the likelihood of differential responses in subgroups.

The public debate of the findings seem to put to rest any concerns about the accelerated/conditional approval mechanisms – this is an example of a "successful failure" and a confirmation that these programs that push for new advances on early evidence must necessarily have some that don't work out.

> ***Lartruvo Could Be A Failure Of The Drug, The Design Or The Disease***
>
> By Mary Jo Laffler
>
> 04 Jun 2019 The presentation of the ANNOUNCE results, the failed confirmatory trial for Lilly's Lartruvo, at ASCO re-opened questions about the accelerated approval and the appropriate way to study soft tissue sarcoma. *Read the full article here*

Failure is of course an all too common part of the drug development process. Focusing on the olaratumab experience showed how much can be learned out of failure, and how it can inform future development.

When Merck comes up with a failed trial, it rallies a team to pull it apart – look at the setting, the degree that it missed the endpoint, if there were crossover effects or there might be a subgroup that is responding, Baynes explained in an interview at ASCO.

Even a positive trial is picked apart to glean intelligence about subgroups and response patterns, Baynes said, "but if a study fails, we spend a lot of time trying to [understand what happened]."

Failed trials are tremendous learning opportunities. As Genentech oncology product development leader Alan Sandler told *Scrip*, "the only mistake in clinical development is if you think you know more than you do."

Not Actually So Quiet?

It may have been a year that investors and analysts found quiet – although according to Baynes, ASCO was "anything but quiet." Of course Merck now has the leading IO franchise in Keytruda and the leading PARP inhibitor in Lynparza, and presented some of the biggest results of the conference.

But the different areas of focus at ASCO 2019 drive home the changing landscape in oncology, as IO falls into place as an established pillar of oncology, political and commercial pressure tightens on reimbursement and pricing, and new technologies raise new possibilities for R&D.

It sets the stage for what to look out for in 2020.