The American Society of Clinical Oncology Conference Just Weeks After the First New Drug for Metastatic Bladder Cancer in 38 years

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I had the privilege of attending the information-rich American Society of Clinical Oncology (ASCO) conference in Chicago as a patient advocate on behalf of BCAN as well as through a program sponsored by the Research Advocacy Network (RAN) that trains patient advocates to interact with researchers.

With regard to bladder cancer, the most significant news was reporting on the results of various immunotherapy clinical trials specific to metastatic disease. But in addition to that, there was discussion of trials of immunotherapies as potential treatment for earlier stages of bladder cancer; the search for biomarkers and circulating tumor cells to help predict recurrences or treatment response; and initiatives to build databases on targeted therapies and relevant mutations and patient responses to inform clinical practice going forward.

Immunotherapies for Metastatic Disease

The conference began just weeks after the F.D.A. had approved Tecentriq™ (Atezolizumab), an immunotherapy drug, as a second-line treatment for metastatic bladder cancer following Cisplatin/Carboplatin, the first line platinum-based chemotherapies. This was historic. It was 38 years since Cisplatin was approved in 1978, representing last time a treatment was approved for metastatic bladder cancer. The excitement and hope among the researchers and medical oncologists at the conference was palpable.

While there is much excitement surrounding these immunotherapy drugs (and for good reason), they are not a cure for bladder cancer nor do they work for all patients. Research going forward is trying to identify why they work for some and not others as well as determining the optimal length of treatment and the durability of response. They are so new that there is not yet five-year survival data.

The three major immunotherapies currently or recently in clinical trials for bladder cancer are:

(1) Tecentriq – Roche/Genentech – (generic Atezolizumab) – F.D.A. approved in May 2016 as second-line treatment for metastatic disease after platinum-based chemotherapy.
(2) Opdivo® – Bristol Myers Squibb – (generic nivolumab) – Clinical trials are ongoing for this drug for bladder cancer. It was approved in May for certain Hodgkin lymphomas.
(3) Durvalumab – AstraZeneca – Received breakthrough therapy designation from the F.D.A. in February 2016, which will expedite its review.

In addition to these, Keytruda® (Merck…generic is Pembrolizumab), an immunotherapy that has been F.D.A. approved for melanoma and non-small cell lung cancer is being tested for earlier stages of bladder cancer, both on its own and in conjunction with BCG or chemotherapy (see Table 3) below. Similarly, AstraZeneca's Tremelimumab is in trial for metastatic disease.

The information provided here is based on a discussion session at ASCO of four abstracts (LBA4500, 4501, 4502, 4515, summarized by Dr. Elizabeth Plimack of Fox Chase Cancer Center). While it is exciting that these new treatments becoming available, the bar for "success" in treating metastatic urothelial carcinoma (the type of bladder cancer that most patients have) is low. Systemic chemotherapy as a first-line treatment for metastatic disease historically has produced an overall response rate (ORR) of 50-60 percent with Cisplatin and an ORR of about 36 percent with Carboplatin is substituted (as shown in Table 1).

Table 1 – Response Rate and Survival Information on Certain Treatments for Metastatic Disease

	1st Line Metastatic - Cisplatin	1st Line Metastatic – Carboplatin	2nd Line Metastatic - Atezolizumab	Next Line Metastatic – Paclitaxel/Docetaxel
Overall Response Rate	50-60%	36%	15% (per the package insert)	12%
Median Overall Survival	15 months	9 months	14.8 months	7 months
One-Year Overall Survival	60%	37%		26%

Atezolizumab (per the package insert), which was FDA approved in May, as a *second-line treatment* has an ORR of about 15 percent compared to an ORR of second-line chemotherapy (Paclitaxel/Docetaxel) of about 12 percent. In the various trials, the three immunotherapy drugs showed ORRs ranging from 15 to the mid-30s percent. Table 2 provides summary data on four trials of the three immunotherapy drugs.

Table 2 – Summary of Four Major Immunotherapy Clinical Trials

Immunotherapy Drug Studied	As first or second line treatment for metastatic disease?	Phase I or Phase II trial?	Number of patients enrolled	Target
Durvalumab	Post platinum	Phase I basket*	42	PDL-1
Nivolumab	Post platinum	Phase I basket*	78	PD-1
Atezolizumab	Post platinum	Phase II	310	PDL-1
Atezolizumab	First line for Cisplatin-ineligible patients	Phase II	119	PDL-1

* A basket trial is one in which patients with different types of cancers may be included as the trial drug is focused on a particular mutation rather than the cancer's organ of origin.

One study explored the question of whether Atezolizumab could be used as a first-line treatment in Cisplatin-ineligible patients. These patients may be ineligible for cisplatin based on a variety of conditions: poor kidney function and hearing loss are examples. Historically, Carboplatin has been substituted for Cisplatin in most of these patients.

As a first-line treatment, the overall response rate was slightly better with chemotherapy than with Atezolizumab but the median overall survival rate was better with Atezolizumab: 14.8 months compared to 9.3 months. One-year survival with Atezolzumab was 57 percent compared to 37 percent with Gemcitabine-Carboplatin.

Fewer Side Effects From Immunotherapies Than From Chemotherapy

About 20 to 40 percent of patients in the immunotherapy trials reported not a single treatment-related side effect. This is a significant difference from chemotherapy in which most patients report side effects, sometimes significant ones. Of those experiencing side effects from immunotherapies, they tended to be less severe than those from chemotherapy.

Unanswered Questions

Researchers and clinicians are still trying determine the appropriate duration of treatment as well as how durable responses are once a patient goes off an immunotherapy drug. More and larger trials are in the works to explore those questions.

Immunotherapies for Muscle Invasive and Non-Muscle Invasive Disease

Clinical trials are in the works regarding whether immunotherapies could potentially be used to treat bladder cancer in its earlier stages.

Table 3 – Future Development of Immunotherapies (PD1 inhibitors) in Bladder Cancer

	Non-Muscle Invasive Bladder Cancer	Muscle-Invasive Bladder Cancer	Metastatic Bladder Cancer
Low Grade	In development		
High Grade	Pembrolizumab+BCG		
BCG Unresponsive	Pembrolizumab		
Neoadjuvant		Atezolizumab+Pembrolizumab+ Chemo	
Adjuvant		Atezolizumab Phase III Nivolumab Phase III	
Trimodality		Pembrolizumbab+Radiotherapy	
Cisplatin-eligible (CE)			Durvalumab+Tremelimumab (Phase III)

CE Maintenance			Avelumab - Phase III
CE Platinum Refractory (recurrence after Cisplatin)			Pembrolizumab (Phase III vs. chemo) Atezolizumab(Phase III vs. chemo)
Cisplatin-ineligible			Pembrolizumab

Circulating Tumor Cells and Identifying Biomarkers

A biomarker is the presence of a substance to help predict recurrence of a cancer or help predict response to a given drug. As biomarkers PDL-1 and PD1 are not yet useful, however, significant research continues in trying to identify useful biomarkers in bladder cancer treatment.

Large Datasets of Targeted Therapy Results Will Help Further Cancer Research

In September 2015, the Bladder Cancer Advocacy Network (BCAN) launched a Bladder Cancer Genomics Consortium (BCGC) to enroll 200 metastatic patients and provide them with genomic testing and access to a targeted therapy based on the results. The goal was to provide access to these patients as well as to move the research forward.

Similar efforts were announced at ASCO (across cancers). One, sponsored by ASCO is the Targeted Agent and Profiling Utilization Registry (TAPUR) that will work in conjunction with pharmaceutical companies and provide free access to F.D.A.-approved drugs based on a patient's genomic sequencing. The purpose is to gather treatment and results data on targeted therapies and use that information to advance research.

In addition, at ASCO Vice President Joe Biden announced the launch of the Genomics Data Consortium. The National Cancer Institute's website states:

> *An initiative of the National Cancer Institute (NCI), the GDC will be a core component of the National Cancer Moonshot and the President's Precision Medicine Initiative (PMI), and benefits from $70 million allocated to NCI to lead efforts in cancer genomics as part of PMI for Oncology….[these datasets will] represent some of the largest and most comprehensive cancer genomics datasets in the world…In addition, the GDC will accept submissions of cancer genomic and clinical data from researchers around the world who wish to share their data broadly. In so doing, researchers will be able to use the state-of-the-art analytic methods of the GDC, allowing them to compare their findings with other data in the GDC.*
>
> *Data in the GDC, representing thousands of cancer patients and tumors, will be harmonized using standardized software algorithms so that they are accessible and broadly useful to any cancer researcher.*