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Durvalumab: a newly approved checkpoint inhibitor for the treatment of urothelial carcinoma

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ABSTRACT

Until a recent introduction to checkpoint inhibitors, there were limited second-line chemotherapy options for urothelial carcinoma (UC) patients with disease progression after first-line, platinum-based treatment. Outcomes for patients with advanced disease over the past 30 years have highlighted a need for new and better therapy. In response to evolving interest, durvalumab (MEDI4736) was introduced as a potential treatment for advanced stages of UC. Durvalumab is a selective, high-affinity, human IgG1 kappa monoclonal antibody engineered with a triple mutation to reduce toxicity. This checkpoint inhibitor has shown promise in advanced UC and is currently the topic of much discussion in the cancer research community. This review article will explore the details surrounding durvalumab, while also giving a brief overview of additional immunotherapeutic agents utilized for UC.

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Key issues.

- Bladder cancer has a high rate of recurrence and a history of poor survival rate.
- Until the recent approval of checkpoint inhibitors, limited options existed for this cancer population subset.
- Many patients excluded from first line therapies are in dire need of additional second line alternatives such as checkpoint inhibitors like durvalumab.
- Monoclonal antibodies that target immune checkpoints prevent cancer from circumventing the checkpoint process and proliferating.
- Response rates vary based on PD-L1 expression status but even patients with low expression show some benefit, with response often lasting months after discontinuation of therapy.
- Durvalumab demonstrates a manageable safety profile in patients with advanced or metastatic urothelial cancer, many of whom have exhausted other options.

Introduction

Checkpoint pathways: regulating the immune system

One of cancer's unique defense mechanisms is it's ability to protect tumor cells from immune system attack. Understanding this mechanism has led to novel treatment options that have shown much potential. In a healthy individual, the body's immune system contains ligand-receptor interactions that trigger the immune checkpoint process, which serves to control the extent of immune response by regulating T-cell activity.[1] This prevents autoimmunity and damage to healthy tissue. In the setting of cancer, protective mechanisms provided by immune checkpoints can be circumvented, allowing cancer cells to avoid being recognized and degraded by cytotoxic T-cells. In other words, certain cancers have evolved to disguise themselves as non-foreign to the immune system by expressing normal checkpoint proteins.[1] Therefore, cancer cells proliferate and overwhelm the body, eventually blocking an appropriate T-cell response. Revealing cancer's remarkable ability to defend itself has led researchers to utilize monoclonal antibodies such as immune checkpoint inhibitors, which are designed to block certain receptor-ligand interactions, preventing T-cells from becoming inactivated.[1,2] As a result of this novel mechanism, immunotherapeutic agents such as durvalumab are under intense clinical investigation in multiple tumor types and in combination with other interventions.

Cytotoxic T-lymphocyte antigen-4 (CTLA-4)

CTLA-4 is a naturally occurring immune checkpoint receptor located on cytotoxic T-cells. Through binding interactions with its ligands, B7.1 and B7.2, T-cell activation is regulated.[3] CTLA-4 is thought to work primarily in the lymph nodes to control T-cell activity early in the immune response.[4] Cancers that express normal checkpoint proteins such as CTLA-4 can render the immune system's antitumor effects inactive. In response to this challenge, antibodies have been designed to block the interaction between CTLA-4 and its ligands.[3] A CTLA-4 blocking antibody called ipilimumab was the first immunotherapeutic in its class to gain Food and Drug Administration (FDA) approval. The drug has been shown to enhance the immune response, including antitumor activity.[3,5] In general, anti–CTLA-4 therapy has shown promising effects in a number of cancers, particularly melanoma (Table 1).[6]

Programmed death-1 (PD-1)

PD-1 is an immune checkpoint protein with 2 corresponding ligands, PD-L1 and PD-L2. Unlike CTLA-4, which is T cell-specific, PD-1 is present on many other immune cells, in addition to T-cells. In certain cancers, tumor cells can overexpress normal, regulatory proteins. This allows cancer cells to bypass the immune system's screening process. Interactions between PD-L1/PD-1 can then lead to inhibition of cytotoxic T-cell activation. As a result, dysregulation of T-cell activity occurs, and cancer cell death is not achieved.[2,7] Immunotherapy agents such as, nivolumab and pembrolizumab, are two PD-1 blocking antibodies that are currently FDA approved for metastatic melanoma, nonsmall cell lung cancer (NSCLC), urothelial carcinoma (UC), as well as many other cancer types (Table 1).[8,9]

Programmed death-ligand 1 (PD-L1) pathway

In certain cancer types, PD-L1 is commonly overexpressed on tumor cells, more so than PD-1 expression. When these ligands bind to PD-1 receptors located on immune cells, cytotoxicity inhibition occurs, rendering the immune system's antitumor effects inactive.[2,7] Newer agents target PD-L1, to prevent the binding interaction with PD-1 located on immune cells. These agents

Table 1
Checkpoint inhibitor summary.

Target	IgG subclass	Agent (generic)	Year of approval	FDA-approved indications
CTLA-4	I	Yervoy (ipilimumab)	2011	- Metastatic melanoma in adults and pediatric patients (12 years and older). - Adjuvant treatment in cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1mm who have undergone complete resection, including total lymphadectomy.
PD-1	IV	Opdivo (nivolumab)	2014	- BRAF V600 mutation-positive unresectable or metastatic melanoma as a single agent - Unresectable or metastatic melanoma, in combination with ipilimumab - Metastatic nonsmall cell lung cancer and progression on or after platinum-based chemotherapy - Advanced renal cell carcinoma who have received prior anti-angiogenic therapy - Classical Hodgkin lymphoma (adult patients) that have relapsed or progressed after receiving certain treatment - Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy - Locally advanced or metastatic urothelial carcinoma who have received certain treatment
	IV	Keytruda (pembrolizumab)	2014	- Unresectable or metastatic melanoma - Nonsmall cell lung cancer with tumors that have high expression of PD-L1 - Recurrent or metastatic head and neck squamous cell cancer - Adult and pediatric patients with refractory classical Hodgkin lymphoma, or who have relapsed after 3 or more lines of therapy - Locally advanced or metastatic urothelial carcinoma - Adult and pediatric patients with unresectable or metastatic microsatellite instability-high cancer
PD-L1	I	Tecentriq (atezolizumab)	2016	- Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have had disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
	I	Bavencio (avelumab)	2017	- Adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma - Patients with locally advanced or metastatic urothelial cell carcinoma
	I	Imfinzi (durvalumab)	2017	- Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

Checkpoint pathway comparison.[5,8–11, 12]

include durvalumab, avelumab, and atezolizumab (Table 1). Unlike CTLA-4, PD-L1 activity occurs later in the immune response within peripheral tissues. As such, targeting multiple checkpoint pathways has the potential for additive or synergistic effects on antitumor responses and is being further investigated at this time (Tables 2–9).[4]

Table 2
2017 US cancer estimates based on sex.

	New cancer cases			Cancer deaths		
Sex	Both	Male	Female	Both	Male	Female
All cancer sites	1,688,780	836,150	852,630	600,920	318,420	282,500
Urinary system	146,650	103,480	43,170	32,190	22,260	9,930
Urinary bladder	79,030	60,490	18,540	16,870	12,240	4,630
Kidney & renal pelvis	63,990	40,610	23,380	14,400	9,470	4,930
Ureter & other	3,630	2,380	1,250	920	550	370

Estimated number of new cancer cases and deaths by sex in 2017.[18]

Table 3
US Mortality by race & ethnicity in kidney and renal pelvis cancer, 2010-2014[18].

Race	African American	Asian Pacific islander	American Indian Alaska native	Hispanic	Caucasian
Kidney & renal pelvis					
Male	5.7	2.7	8.9	4.9	5.8
Female	2.5	1.1	4.2	2.3	2.5

Table 4
US probability (%) of developing cancer of the kidney and renal pelvis, 2011-2013[18].

Age	Birth to 49	50-59	60-69	70 and up
Male	0.2	0.3	0.6	1.3
Female	0.1	0.2	0.3	0.7

Review of urothelial carcinoma

UC includes cancers of the bladder, ureters, and kidneys. These tumors are multifocal and occur at a ratio of 50:3:1, respectively. Invasion of cancer within the upper urinary tract has a 30%-50% chance of developing into bladder cancer. Whereas bladder cancer has a 2%-3% chance of developing into cancer of the upper urinary tract.[10] Although the reason for many cancers is unknown, established causes include both modifiable and nonmodifiable elements. Unfortunately, the time between exposure and detection of cancer can be as long as 10 years.[11]

Bladder cancer

Smoking is a commonly known risk factor for cancer, contributing to about half of all bladder cancer cases. In addition to smoking, individuals that are exposed to hazardous chemicals within certain work environments are at an increased risk for development of bladder cancer.[11] The incidence of bladder cancer is over 3 times higher in men than in women (Table 2).[11] In 2012, this type of cancer was in the top 5 leading causes of cancer deaths for males 80 years old or older.[12] Race also appeared to be a factor in developing bladder cancer, with Caucasian males carrying the highest risk. The risk for bladder cancer also increases with age as the majority of people diagnosed are 70 years or older.[13] Alterations in the p53 gene may suggest a poor prognosis and greater recurrence. In contrast, FGFR3 mutations are commonly found in less severe tumors and are indicative of a low relapse rate, as well as having a better prognosis.[14] Bladder cancer is typically discovered early due to signs and symptoms that become noticeable and concern-

Table 5
US incidence by race & ethnicity for kidney and renal pelvis cancer, 2009-2013[18].

Race	African American	Asian Pacific Islander	American Indian Alaska Native	Hispanic	Caucasian
Kidney & renal pelvis					
Male	24.4	10.8	29.9	20.7	21.9
Female	13.0	4.8	17.6	11.9	11.3

ing to the patient. Signs and symptoms include hematuria, increased frequency, urgency, pain, and irritation during urination.[11] However, clinical manifestations are often painless.[15] Invasive cystoscopy remains the gold standard for diagnosis and follow-up. Other methods of detection are current areas of research. Since carcinoma of this type may not always be detected early if the patient is not experiencing symptoms, screening in high-risk groups may be helpful.[16] The 5-year relative survival rate reported for Caucasian men is 79%, Caucasian women 74%, African American men 69%, and African American women 54%.[11] Bladder cancer has also shown to have a very high rate of recurrence (50%-70%). A high relapse rate allows progression to a more advanced tumor stage in 15%-25% of patients. Therefore, frequent follow-up throughout the course of treatment is crucial.[17] At diagnosis, about 30% of bladder carcinoma has metastasized to the muscle, which carries a higher mortality risk.[15]

Kidney cancer

Major risk factors for cancer of the kidney and renal pelvis include obesity, smoking, high blood pressure, chronic renal failure, as well as exposure to hazardous chemicals.[11] While the overall probability of developing kidney and renal pelvis cancer is low, most people developing this type of cancer are over 70 years old. It is slightly more common in males than in females, and mortality appears to be the highest among American Indian Alaskan Native males.[11] There are 7 known genes that are thought to be associated with kidney cancer: FH, FLCN, MET, SDH, TSC1, TSC2, and VHL.[18] Early stage kidney cancer is usually asymptomatic. With progression, symptoms often arise and can include hematuria, pain or a lump in the lower back or abdomen, tiredness, weight loss, pyrexia, and peripheral edema of the lower extremities.[11] Diagnosis techniques include ultrasound, computed tomography, magnetic resonance imaging, intravenous pyelogram, and cystoscopy.[19] Kidney cancer is usually identified inadvertently. Nearly all tumors are renal cell carcinomas.[16] The 5-year survival rate for cancer of the kidney and renal pelvis is 74%. Approximately 66% of cases are diagnosed at a local stage, for which the 5-year relative survival rate is 93%.[11]

Current treatment challenges in urothelial carcinoma

Platinum-based regimens have long been considered first-line for treatment of metastatic urinary bladder cancer.[20] However, therapy options have been stagnant for some time with little improvement in the outcomes of this patient population.[19] Bladder cancer responds to chemotherapy, however the survival for patients with advanced urothelial carcinoma has remained poor, with a median survival of 14 months and a 5-year survival rate of 15%. Since long-term survival in patients with metastatic disease is rare, palliative treatment is usually the best medicine and only option for these individuals.[20] Often, this lack of long-term survival is a result of various, evolving mechanisms that cancer cells utilize to become resistant to standard chemotherapy options.

Platinum resistance

Cancer patients are usually treated with repeated cycles of chemotherapy. This creates the potential for cancer cells to become resistant resulting in relapse or refractory disease. All of which contributes to the major limitation of current therapeutic options.[21] Currently, there are no diagnostic tests available to predict the response of bladder cancer to any chemotherapy. In addition, the reasons for patient variation in clinical response and development of toxicities are still relatively unclear. This may be due to not fully understanding the exact mechanism(s) of platinum-based drugs and how they access their target molecules. Researchers hypothesize that cellular repair mechanisms can affect the efficacy of cisplatin, which may contribute to patients' variable response to platinum-based medications.[22] Even if an initial response occurs, acquired resistance limits efficacy in terms of long-term treatment success. Of the numerous resistance mechanisms, it is still unknown which are most important clinically.[23]

Checkpoint inhibitor overview

Checkpoint inhibitors in the cancer guidelines

The National Comprehensive Cancer Network Panel (NCCN) establishes the clinical guidelines for cancer treatment. Treatment recommendations are categorized based on the level of evidence for each therapeutic option as well as the level of NCCN consensus. Category 1 is based on high-level of evidence and there is uniform NCCN consensus that the treatment is appropriate. Category 2 is based on lower-level evidence, and is further subdivided into 2A or 2B, where 2A represents a uniform NCCN consensus, while 2B indicates consensus. Conversely, category 3 recommendations can be based on any level of evidence, and there is major NCCN disagreement regarding the appropriateness of the invention. In general, NCCM guideline recommendations are category 2A unless specified otherwise.[24]

Bladder cancer

Per the NCCN, the use of pembrolizumab for locally advanced or metastatic bladder cancer is considered a Category 1 intervention, while atezolizumab, nivolumab, durvalumab, and avelumab are Category 2A interventions, all of which are second-line systemic therapy options after platinum-based therapy. Atezolizumab and pembrolizumab have been approved by the FDA as first-line treatment options by default for bladder cancer patients who are not eligible for cisplatin-containing chemotherapy.[24]

Kidney cancer

Nivolumab (Opdivo) is currently the only checkpoint inhibitor with an indication for renal cell carcinoma. It is listed in the NCCN Kidney Cancer guidelines as a Category 1 preferred intervention for subsequent therapy in patients with relapsed or stage IV and surgically unresectable clear cell carcinoma. For nonclear cell carcinoma patients with relapsed or stage IV and surgically unresectable disease, nivolumab is a Category 2A option for systemic therapy.[25]

Durvalumab

Preclinical study

Animal studies have shown durvalumab to be a promising treatment option due to the unique biology associated with PD-L1 blockade.[26] PD-L1 has been reported to regulate inflammatory responses in cancerous and noncancerous settings.[26] One preclinical study reported durvalumab to have a higher affinity to PD-L1 versus PD-L2, thereby inhibiting the interaction between PD-1 and CD80 significantly.[26] Designing a monoclonal antibody such as durvalumab to

Table 6
Study 1 - Bladder cancer cohort of study 1108 results[32].

PD-L1 Expression Status	Objective Response Rate (ORR)		Response	
	n/N (%)	95% confidence interval	Complete	Partial
All	31/182 (17%)	(11.9, 23.3)	5	26
High	25/95 (26.3%)	(17.8, 36.4)	3	22
Low/Negative	3/73 (4.1%)	(0.9, 11.5)	1	2
Not Evaluable	3/14 (21.4%)	(4.7, 50.8)	1	2

ORR, objective response rate by blinded independent review per RECIST 1.1.
PD-L1 Status was determined by the VENTANA PD-L1 (SP263) Assay.

specifically target PD-L1 can potentially decrease immune-related adverse events.[26] Preclinical study also reported that durvalumab significantly inhibited the growth of human tumors in mice. Researchers continue to further explore the biology of PD-L1 blockade. An anti–PD-L1 antibody (10F.9G2) was designed specifically to test immunocompetent mice, since durvalumab does not cross-react with mice PD-L1.[26] Results showed that the 10F.9G2 antibody used as monotherapy and in combination with oxaliplatin improved the survival rate of mice implanted with CT25 colorectal cancer cells.[26] The outcomes reported in this study provide a promising therapeutic approach for certain cancer types.

Approval history and clinical trials

Durvalumab was granted accelerated approval, priority review, and breakthrough therapy designation by the FDA on May 1, 2017. Durvalumab was evaluated and FDA-approved based on Study 1, which utilized the urothelial cancer cohort data from Study 1108.[25]

Study 1: Bladder cancer cohort of study 1108

Study 1 included a multicenter, multicohort, open-label trial consisting of 182 subjects with advanced urothelial carcinoma and disease progression after receiving platinum-containing chemotherapy. Participants in this study were administered 10 mg/kg of durvalumab intravenously over 60 minutes every 2 weeks for up to 12 months, unless the disease progressed, or the patients experienced intolerable toxicities. Patients were excluded if they had a history of immunodeficiency, need for systemic immunosuppression at $\geq$10 mg/day of prednisone equivalent, history of autoimmune disorders, untreated CNS metastases, HIV, tuberculosis (active), or hepatitis B or C infection. Assessment of the tumor was done at weeks 6, 12, and 16, then every 8 weeks for the first year and subsequently, every 12 weeks.[25]

Response

The median time to durvalumab response in Study 1 was 6 weeks. As shown in Table 6, patients whose immune cells expressed a higher amount of PD-L1 correlated with an increased response to durvalumab. However, even patients who expressed low amounts of PD-L1 seemed to derive some benefit. A partial response was achieved in 14.3% of all evaluable patients with 2.7% achieving a complete response. Among the 31 patients that responded, 14 patients (45%) had ongoing responses for 6 months or longer and 5 patients (16%) had responses for 12 months or longer.[27]

Safety

The most frequent adverse reactions noted in Study 1 were tiredness, musculoskeletal pain, constipation, decreased appetite, nausea, edema of the extremities, and urinary tract infection.

Table 7
Urothelial bladder cancer expansion cohort results (NCT01693562).[32]

PD-L1 expression location	PD-L1Expression status	Objective response rate (complete or partial)		Disease control rate(at 12 weeks)	
		n/N (%)	95% CI	n/N (%)	95% CI
Unselected		13/42 (31.0%)	(17.6, 47.1)	20/42 (47.6%)	(32.0, 63.6)
TC or IC	+	13/28 (46.4%)	(27.5, 66.1)	16/28 (57.1%)	(37.2, 75.5)
	-	0/14 (0.0%)	(0.0, 23.2)	4/14 (28.6%)	(8.4, 58.1)
TC	+	7/15 (46.7%)	(21.3, 73.4)	8/15 (53.3%)	(26.6, 78.7)
	-	6/27 (22.2%)	(8.6, 42.3)	12/27 (44.4%)	(25.5, 64.7)
IC	+	10/18 (55.6%)	(30.8, 78.5)	12/18 (66.7%)	(41.0, 86.7)
	-	3/24 (12.5%)	(2.7, 32.4)	8/24 (33.3%)	(15.6, 55.3)

IC, tumor-infiltrating immune cells; TC, tumor cells; PD-L1 negative defined as <25% expression;PD-L1 positive defined as >25% expression.

Table 8
Update on efficacy and tolerability of durvalumab (NCT01693562).[32]

	Confirmed Objective response rate		Response		Overall survival (at six months)	
PD-L1 status	n/N (%)	95% CI	Complete	Partial	%	95% CI
All	21/103 (20.4)	(13.1, 29.5)	4.9%	15.5%	60.3	(48.7, 70.1)
High	18/61 (29.5)	(18.5, 42.6)	4.9%	24.6%	68.4	(53.6, 79.3)
Low/Negative	3/39 (7.7)	(1.6, 20.9)	5.1%	2.6%	44.7	(26.5, 61.4)

About 43% of patients reported Grade 3-4 adverse events. In addition, severe adverse reactions occurred in 46% of patients. The most frequent of these serious adverse events were acute kidney injury (AKI) (4.9%), urinary tract infection (4.4%), musculoskeletal pain (4.4%), liver damage (3.3%), general physical deterioration (3.3%), sepsis, abdominal pain, pyrexia and/or tumor-associated fever (2.7%, each). Eight patients (4.4%) experienced grade 5 adverse events including cardiorespiratory arrest, general physical health deterioration, sepsis, ileus, pneumonitis or immune-mediated hepatitis. Three additional patients had infection and disease progression at the time of death. Durvalumab was discontinued due to adverse reactions in 3.3% of patients.[27]

Study advantages and limitations

Advantages of the study include a low discontinuation rate of 3.3% among participants. In addition a potential correlation between PD-L1 expression and response rate was also established. However, durvalumab showed activity even in patients those who had a lower expression of PD-L1.[27] Having activity in high or low levels of PD-L1 expression allows durvalumab to give patients more treatment options.

Disadvantages of the study include failure to reach the median duration of response in all patients. Only those in the PD-L1 low and /or negative group reached the median duration of response threshold (12.3 months). In addition, a significant number of patients experienced serious adverse reactions (46%).[27]

Study 2: NCT01693562

Study design and participants

This durvalumab study was a phase I/II multicenter, open-label dose escalation and dose-expansion study (NCT01693562) which was conducted in 70 centers worldwide. This study enrolled approximately 60 patients with urothelial bladder cancer in an expansion cohort. Inclusion criteria consisted of patients who had inoperable or metastatic transitional-cell urothelial carcinoma, had progressed on, been ineligible for, or refused any number of prior therapies. Subjects

received durvalumab 10 mg/kg every 2 weeks. The majority of patients were men (68.9%) and Caucasian (65.6%) with a median age of 66. Most participants (93.4%) had previously received one or more systemic therapy for advanced disease, and 31.1% had received 3 or more systemic therapies.[28]

Response

Of the 13 patients that had a partial or complete response, the median time for response in this study was 6.3 weeks (95% confidence interval, 5.6-12.1 weeks) 13. Of these patients, 92.3% had an ongoing response at the last follow-up. The median duration of exposure was 8 weeks (9.2 weeks for PD-L1 positive, and 6 weeks for PD-L1 negative subgroups). In the PD-L1 positive subgroup, 76.0% patients had a reduction in tumor size and 68.0% achieved a 30% or greater reduction from baseline. In the PD-L1 negative subgroup, 36.4% had a decrease in tumor size, and one study participant (9.1%) had a 30% or greater target lesion reduction from baseline. A single case of disease progression achieved initial response, but later discontinued treatment due to grade 3 AKI. However, even after durvalumab was stopped in this patient, imaging showed response persisting until 48 weeks, even in the absence of other therapy.[28]

Safety

The safety analysis included all 61 patients enrolled in the study. A similar number of adverse reactions were reported between PD-L1 positive and negative patients. The most frequently reported treatment-related adverse events were fatigue (13.1%), diarrhea (9.8%), decreased appetite (8.2%), itching (3.3%), and infusion-related reactions (3.3%). Three patients suffered from grade 3 treatment-related adverse events (AKI, infusion-related reaction, tumor flare). One patient with grade 3 treatment-related AKI discontinued treatment. No grade 4/5 adverse events, pneumonitis, colitis or deaths occurred related to treatment.[28]

Study advantages and limitations

Reduction in tumor size was notable in over a third of the study participants. In addition, responses to durvalumab treatment were durable and continued even after discontinuation. The majority of treatment-related adverse events were low grade and manageable.[28]

Due to limited follow-up and small sample size, not all adverse events may have been revealed. Additionally, not every tumor size reduction met Response Evaluation Criteria In Solid Tumors response criteria.[28]

NCT01693562 (Update)

Study design and participants

An update of study NCT01693562 further evaluated the efficacy of durvalumab. In this update, 37% of participants had received 2 or more regimens, 97% had previously received platinum treatment, 95% had cancer that had spread viscerally, and 49% had liver metastases at baseline.[27]

Response and safety

An ongoing response was seen in 18 patients and 16 patients had duration of response for 6 months or longer. Seven patients had a response duration lasting 9 months or longer.[27] Treatment-related grade 3-4 adverse reaction rates were infrequent.[27]

Study sdvantages and limitations

At 6 months, overall survival with durvalumab therapy was maintained in over half of the patients, with the most benefit seen in PD-L1 positive group. Responses occurred quickly (median time to response 1.4 months). Less benefit was seen in PD-L1 low and/or negative patients.[27]

Table 9
Durvalumab in bladder cancer trials based on clinicaltrials.gov.

Intervention	Estimated enrollment	Cancer type	Trial ID
Durvalumab + radiation, followed by adjuvant durvalumab	42	Urothelial	NCT02891161
Durvalumab +/- tremelimumab vs. standard of care (cisplatin + gemcitabine or carboplatin + gemcitabine	1005	Urothelial	NCT02516241
Durvalumab + epacadostat	185	Selected advanced solid tumors: NSCLC Melanoma Head & neck Gastric Gastroesophageal Urothelial Triple Negative Breast Cancer	NCT02318277
Durvalumab + radiation +/–tremelimumab	74	Bladder	NCT03150836
Durvalumab + Tremelimumab	15	Malignant neoplasms of urinary tract	NCT02812420
Durvalumab	34	Carcinoma in situ of Bladder Bladder	NCT02901548
Tremelimumab monotherapy, Durvalumab monotherapy, Durvalumab + tremelimumab	64	Urothelial bladder Triple-negative breast cancer Pancreatic ductal Adenocarcinoma	NCT02527434
AZD4547, Durvalumab, Olaparib, AZD1775, Vistusertib	110	Muscle invasive bladder cancer	NCT02546661
Durvalumab + Tremelimumab + tumor microenvironment (TME) modulator polyICLC	102	Head and neck squamous cell carcinoma Breast cancer Sarcoma Merkel cell carcinoma Cutaneous T-cell lymphoma Melanoma Renal Bladder Prostate	NCT02643303

A review of the development of Durvalumab: 5 year review

Publications mentioning durvalumab, using its research acronym MEDI4736, began appearing on PubMed as early as March 2013.[29] However, if one digs deeper, it can be discovered that just over 7 years ago, on 11/24/2010, a patent application was filed for "Targeted binding agents against B7-H1."[30] That is, binding to the specific B7 homolog 1 cluster of differentiation (CD274) to the programmed cell death protein 1 (PD-1; CD279) and CD80(B7-1). This patent was published on 06/03/2011 and included: "Human monoclonal antibodies directed against B7-H1 and uses of these antibodies in diagnostics and for the treatment of diseases associated with the activity and/or expression of B7-H1 are disclosed. Additionally, hybridomas or other cell lines expressing such antibodies are disclosed."[30] That patent application was then following by the preclinical and clinical development, and eventually the US FDA approval of durvalumab (Imfinzi; AstraZeneca).

The first published clinical trial for durvalumab appears in 2013 by Zielinski.[31] This brief report references a presentation at the 2014 Annual Meeting of American Society of Clinical Oncology. The Phase I clinical trial was described as a dose escalation study using the 3 + 3 study design,[32] treating 26 subjects. The author reports that, adverse effects were observed in 34% of the patients and were limited to Grade I and II toxicities, thus implying that MEDI4736 was

Table 10
Clinical trials involving durvalumab: 5 year review.[27,39,41–45,46]

Population	Phase	Intervention	Author	Date
Lung Cancer				
Stage IIIA (N2) nonsmall cell lung cancer (NSCLC).	Phase II	Durvalumab	Rothschild SI[18]	April 2016
EGFR-mutant nonsmall cell lung cancer. (TATTON trial)	Phase Ib	Durvalumab	Ahn MJ[15]	April 2016
Advanced stage IV NSCLC	Phase III	Durvalumab platinum	Peters S[16]	April 2016
Advanced or metastatic NSCLC (NEPTUNE trial)	Phase III	Durvalumab + tremelimumab vs Platinum-based Standard of care therapy	Mok T[19]	April 2016
TKI-naïve patients with EGFR mutant NSCLC	Phase I extension	Durvalumab + gefitinib	Gibbons DL[17]	April 2016
Stage III Nonsmall-cell lung cancer	Phase III	Durvalumab after Chemotherapy	Antonia SJ[23]	Nov. 2017
Advanced nonsmall-cell lung cancer, Third line treatment	Phase II	Durvalumab	Garassino MC[24]	April 2018
Mesothelioma (NIBIT-MESO-1)	Phase II	Durvalumab + Tremelimumab	Calabrò L[27]	June 2018
Bladder cancer				
Advanced urothelial bladder Cancer	Phase I	Durvalumab	Massard C[20]	June 2016
Locally advanced or metastatic urothelial carcinoma	Phase I/II	Durvalumab	Powles T[22]	Sept. 2017
Women's cancers				
Women's cancers	Phase I	Durvalumab + Olaparib or Durvalumab +Cediranib	Lee JM[21]	July 2017
Metastatic breast cancer	Pilot	Durvalumab + Tremelimumab and Immunogenomic Dynamics	Santa-Maria CA[26]	April 2018
Head and neck cancer				
Advanced squamous cell carcinoma of the head and neck (DUCRO trial)	Phase I/II	Durvalumab + Cetuximab and radiotherapy	Bonomo P[25]	Feb. 2018
Colorectal cancer				
Colorectal cancer	Phase Ib/II	Durvalumab + Tremelimumab	Fumet JD[28]	June 2018

well tolerated.[32] The authors also claimed that a positive clinical effect could be documented in 9 of the 26 of the patients.[32] Over the next several years many more clinical trials evaluating durvalumab were conducted. In 2016 durvalumab was mentioned in a review article titled "Antibodies to watch in 2016."[33] This review paper states that at the time of submission durvalumab was in Phase III studies for NSCLC and head and neck cancer. Shortly after this mention, many clinical trials were rapidly published over the next 2 years studying durvalumab alone and in combination with other anticancer modalities (Table 9).[28,34–45,46] Within 6 months of the 'Antibodies to Watch' paper being published, 6 clinical trials were published in PubMed searchable journals.[28,34–37,38]

Initially durvalumab was studied in NSCLC patients, and later investigated for several tumor types including studies in bladder cancer, women's cancers, head and neck cancers, mesothelioma, and colorectal cancer (Table 10).[27,39,41–45,46]

As of July 2018, durvalumab (Imfinzi) is approved in the USA by the FDA for the treatment of "Locally advanced or metastatic urothelial carcinoma who–– have disease progression during or following platinum-containing chemotherapy; have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy."[47] And it is approved for patients with "Unresectable, Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy."[47] Durvalumab was first

approved for urothelial carcinoma on May 1, 2017 after being granted a "Breakthrough Therapy Designation" and approved for accelerated review February 16, 2016.[48] It was then afforded for NSCLC on February 16, 2018.[48] Currently clinical trials are underway assessing the potential use of durvalumab in patients with other tumor types.

Expert commentary

Until recently, there has been little improvement in the outcomes of patients with advanced or metastatic urothelial disease. However, results from immunotherapy studies have shown promise; giving those who once had a poor prognosis additional treatment options. With more than half of urothelial cancer patients not being successful candidates for cisplatin therapy, checkpoint inhibitors may now play a vital role in their survival.[49] Durvalumab demonstrates a manageable safety profile and trials provide evidence of meaningful clinical benefit in patients with advanced or metastatic urothelial cancer, many of whom have exhausted other options.[28]

As a result of these clinical advances, durvalumab and other checkpoint inhibitors are currently supported by the NCCN guidelines and are changing the way metastatic disease is treated. The availability of checkpoint inhibitors is a large step for patients who are long overdue for treatment advances. In the future, medications in this class may potentially replace first-line platinum-based therapies as a personalized drug regimen, as well as improve survival in patients with advanced metastatic disease. However, current data remains insufficient to recommend durvalumab as a first-line option, and more research is needed to support its use.

Durvalumab (Imfinzi; MEDI4736) serves as a major advancement in the world of oncology. While the available data surrounding this agent is still very new and continued approval is contingent upon confirmatory trials, it shows much promise. Recently, in February of 2018, durvalumab was also approved by the FDA for locally advanced NSCLC. This immunotherapy option provides patients with a poor prognosis a chance for a better outcome without jeopardizing their quality of life.

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