Bladder Cancer Clinical Trials:

From Diagnostic Criteria to FDA-Approved Drugs and Emerging Therapies

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Introduction

Bladder cancer is a malignant condition originating predominantly in the urothelial cells lining the bladder.

The most common type, urothelial carcinoma (previously known as transitional cell carcinoma), accounts for more than 90% of all cases. Bladder cancer can range from non-invasive to invasive forms, with muscle-invasive bladder cancer (MIBC) posing a more significant health risk due to its higher propensity for metastasis.

Bladder cancer is the 10th most commonly diagnosed malignancy globally, with approximately 573,000 new cases and 213,000 deaths reported worldwide in 2020. It predominantly affects older adults, with a median age of diagnosis around 73 years in developed nations like the United States. The disease is also more common in men, who are about three to four times more likely to develop bladder cancer than women, a disparity driven by both biological and lifestyle factors.

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Insights on Bladder Cancer

Evolution of Understanding

The understanding of bladder cancer has evolved notably over the past decades. Historically, bladder cancer was primarily understood through its clinical presentation and basic histological classifications. The introduction of cystoscopy as a diagnostic tool allowed for earlier detection and more precise categorization of early-stage bladder cancer. In recent years, advancements in molecular profiling have revolutionized our understanding and treatment of bladder cancer. For instance, the identification of biomarkers such as COL4A1 and COL4A2 have shown promise as diagnostic markers for bladder cancer. These markers, along with genetic mutations like FGFR3 (common in low-grade bladder cancer) and TP53 (associated with more aggressive MIBC), have become essential in assessing cancer progression and prognosis.

Prevalence and Epidemiology

Bladder cancer is the 10th most common cancer worldwide, with an estimated 573,000 new cases and 212,000 deaths annually as of 2020. In the U.S., around 82,290 new cases were reported in 2023, with men being three to four times more likely to develop bladder cancer than women. The disease disproportionately affects older adults, with a median age of diagnosis of 73 years. Globally, bladder cancer incidence has been rising, particularly in developing countries where industrialization and exposure to carcinogens are prevalent.

Contributing Factors on Bladder Cancer

Key Contributing Factors

1. Biological Factors: Genetic mutations play a critical role in bladder cancer progression. FGFR3 mutations are commonly associated with low-grade, non-muscle-invasive bladder cancer, while mutations in TP53 and RB1 are linked to more aggressive forms of muscle-invasive cancer. The high recurrence rate of non-muscle-invasive bladder cancer (up to 50% after initial treatment) further complicates long-term management.

2. Environmental Factors: Smoking remains the most significant environmental risk factor, contributing to 50% of bladder cancer cases in men and about 30% in women. Tobacco smoke contains carcinogens like aromatic amines, which are processed in the liver and excreted in the urine, where they come into direct contact with the bladder lining, leading to DNA damage and malignancy. Occupational exposure to harmful chemicals in industries such as rubber, dye, leather, and paint is another established risk factor.

Key Contributing Factors

3. Psychological and Social Impact: The high recurrence rate of non-muscle-invasive bladder cancer contributes to anxiety and depression in patients. Additionally, the psychosocial effects of living with a urostomy bag post-cystectomy, such as social isolation and body image issues, can significantly impact a patient's quality of life.

4. Healthcare Costs: Bladder cancer is one of the most expensive cancers to treat due to its recurring nature and the need for long-term surveillance. In the U.S., bladder cancer treatment costs rank among the highest of any malignancy, driven by frequent monitoring, surgeries, chemotherapy, and immunotherapy.

Diagnostic Criteria

Evolution of Diagnostic Criteria

Bladder cancer diagnosis has evolved significantly with advances in molecular and imaging technologies. In recent years, biomarkers such as FGFR3 mutations have gained prominence, aiding in identifying subtypes of bladder cancer that may respond differently to treatment(Artificial Intelligence–based Detection of FGFR3 Mutational Status Directly from Routine Histology in Bladder Cancer: A Possible Preselection for Molecular Testing? - ScienceDirect). The shift towards precision medicine allows for more targeted therapies based on the tumor's genetic makeup

ICD-11 Code for Bladder Cancer: 2C94

Bladder cancer is classified under ICD-11 code 2C94. This category refers to primary or metastatic malignant neoplasms involving the bladder. The ICD-11 structure provides specificity by identifying different forms of bladder cancer, facilitating accurate diagnosis and reporting:

- 2C94.0: Adenocarcinoma of the urinary bladder
- 2C94.1: Squamous cell carcinoma of the urinary bladder
- 2C94.2: Urothelial carcinoma of the bladder
- 2C94.Y: Other specified malignant neoplasms of the bladder
- 2C94.Z: Malignant neoplasms of the bladder, unspecified

Diagnostic Criteria:

- **Clinical Assessment:** Symptoms such as hematuria (blood in urine), painful urination, and frequent urination often prompt initial diagnostic investigation.
- **Histopathological Examination:** Confirmation of malignancy is obtained through microscopic examination of tissue samples, typically acquired via transurethral resection or cystoscopic biopsy.
- **Imaging Studies:** Techniques such as ultrasound, CT, MRI, and PET scans help in assessing the tumor's size, spread within the bladder, and potential metastasis to other organs.
- **Urine Cytology:** Examination of urine for cancer cells can assist in the diagnosis, particularly for identifying urothelial carcinoma.
- **Molecular Testing:** Tests for specific genetic mutations or markers that may influence treatment options and prognosis are increasingly being used in the diagnostic process.

Exclusions:

- Malignant mesenchymal neoplasms (codes 2B50-2B52) are not included under this heading.
- Neoplasms of the brain or central nervous system (2A00-2A07), and haematopoietic or lymphoid tissues (2A20-2B37) are also excluded from this category.

TNM Classification

The TNM classification system is specifically tailored to describe the extent and spread of bladder cancer, helping clinicians to determine the most effective treatment strategies and to predict outcomes.

T (Tumor)
- **Ta**: Non-invasive papillary carcinoma
- **Tis**: Carcinoma in situ ("flat tumor")
- **T1**: Tumor invades the subepithelial connective tissue
- **T2**: Tumor invades the muscle
- **T3**: Tumor invades perivesical tissue:
  - **T3a**: Microscopically
  - **T3b**: Macroscopically (extravesical mass)
- **T4**: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
  - **T4a**: Tumor invades the prostate, uterus, or vagina
  - **T4b**: Tumor invades the pelvic wall or abdominal wall

N (Node)
- **NX**: Regional lymph nodes cannot be assessed
- **N0**: No regional lymph node metastasis
- **N1**: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
- **N2**: Multiple regional lymph node metastases in the true pelvis
- **N3**: Lymph node metastasis to the common iliac lymph nodes

M (Metastasis)
- **M0**: No distant metastasis
- **M1**: Distant metastasis
  - **M1a**: Non-regional lymph node(s)
  - **M1b**: Other distant metastases

Clinical Application

The detailed staging provided by the TNM system is crucial for:

- Determining Treatment: Treatment options for bladder cancer vary significantly based on stage. For example, non-muscle invasive cancers (Ta, Tis, T1) may be treated with transurethral resection and intravesical therapy, while muscle-invasive cancers (T2 and above) typically require more aggressive treatments, such as radical cystectomy or systemic chemotherapy.
- Prognostic Value: The stage of bladder cancer at diagnosis is a strong predictor of outcome. Higher stages generally correlate with a poorer prognosis.
  - Stage 0 - Indicates carcinoma in situ. Tis, N0, M0.
  - Stage I - Localized cancer. T1-T2, N0, M0.
  - Stage II - Locally advanced cancer, early stages. T1-T2, N1, M0.
  - Stage III - Locally advanced cancer, late stages. T1-T4, N2-N3, M0.
  - Stage IV - Metastatic cancer. T1-T4, N1-N3, M1.
- Research and Clinical Trials: Accurate staging is essential for enrolling patients in clinical trials and for comparing the efficacy of treatments across different studies.

Market Insights

Market for Bladder Cancer Treatments

The global market for bladder cancer therapies is experiencing rapid growth due to the introduction of new treatments, including immunotherapy and targeted therapies. In 2023, the market was valued at $3.65 billion and is projected to grow at a CAGR of 14.5%, reaching $7.28 billion by 2028. Immunotherapy drugs, such as Atezolizumab (Tecentriq) and Pembrolizumab (Keytruda), have shown substantial efficacy in treating advanced and metastatic bladder cancer, providing new treatment options for patients who do not respond to chemotherapy. Targeted therapies like Enfortumab Vedotin (Padcev) have also revolutionized treatment, offering a more precise approach.

Future Outlook

The future of bladder cancer treatment lies in the expansion of precision medicine and personalized therapies. Biomarker-driven treatments, such as those targeting FGFR mutations, and combination therapies involving immunotherapy and chemotherapy are likely to become more prevalent. Additionally, advances in early detection, such as liquid biopsy, have the potential to improve patient outcomes by identifying bladder cancer at more treatable stages.

Epidemiology of Bladder Cancer

Epidemiology of Bladder Cancer

Bladder cancer is the 10th most commonly diagnosed malignancy globally, with approximately 573,000 new cases and 213,000 deaths reported worldwide in 2020. It predominantly affects older adults, with a median age of diagnosis around 73 years in developed nations like the United States. The disease is also more common in men, who are about three to four times more likely to develop bladder cancer than women, a disparity driven by both biological and lifestyle factors. Bladder cancer incidence varies widely across the world, with higher rates observed in industrialized nations due to increased exposure to tobacco smoke and occupational carcinogens. Additionally, collagen type 4 alpha 1 (COL4A1) and alpha 2 (COL4A2) levels were found to be elevated in urine samples from patients with bladder cancer, indicating potential biomarkers for early detection.

Global Incidence and Prevalence

The global incidence of bladder cancer is concentrated in more industrialized regions, such as North America and Europe, where higher prevalence rates, especially among men, are reported. The highest rates are observed in Southern and Eastern Europe, where environmental and occupational exposures contribute significantly to the disease burden. In the U.S., bladder cancer is the fourth most common cancer in men, accounting for 6% of all new cancer cases diagnosed in 2023. Industrialized regions see a higher prevalence of urothelial carcinoma due to widespread smoking and occupational exposures, while developing regions struggle with bladder cancer linked to parasitic infections like schistosomiasis.

Interestingly, bladder cancer rates are rising in developing countries, particularly in regions of the Middle East and Africa. In these areas, schistosomiasis—a parasitic infection linked to chronic inflammation of the bladder—has been identified as a significant risk factor, contributing to the development of squamous cell carcinoma, a less common form of bladder cancer compared to the urothelial carcinoma commonly seen in Western countries. Schistosomiasis-related bladder cancer represents a unique subtype of squamous cell carcinoma, distinct from urothelial carcinoma, highlighting the importance of geographic and environmental influences on cancer subtype prevalence.

Epidemiology of Bladder Cancer (cont.)

Key Risk Factors

1. Smoking:

- Smoking remains the most significant risk factor for bladder cancer, contributing to approximately 50% of all cases in men and 30% in women. Tobacco smoke contains carcinogenic chemicals like aromatic amines and polycyclic aromatic hydrocarbons, which, when excreted in urine, come into direct contact with the bladder lining, increasing the risk of cellular mutations (Bray et al., 2018; Ahmadi et al., 2021). Smoking contributes to the recurrence of bladder cancer even after treatment, due to persistent exposure to carcinogens.

2. Occupational Exposures:

- Workers in the dye, rubber, leather, and paint industries face heightened bladder cancer risk due to prolonged exposure to industrial chemicals, particularly aromatic amines. Though regulatory measures have reduced this risk in developed countries, the problem persists in low- and middle-income countries with less stringent. Occupational exposures to chemicals such as aniline dyes, commonly found in industries like textile manufacturing, continue to be a major concern in both developed and developing countries, despite regulatory efforts.

3. Gender and Hormonal Influence:

- Bladder cancer disproportionately affects men, driven by higher smoking rates, occupational exposure, and possible hormonal differences. Estrogen may provide some protective effects for women, while androgen receptor signaling contributes to bladder cancer progression in men. However, the incidence of bladder cancer is three to four times higher in men than women, but women often present with more advanced disease at diagnosis, suggesting gender-based differences in disease awareness and access to healthcare.

4. Schistosomiasis and Parasitic Infections:

- In regions like Egypt and sub-Saharan Africa, schistosomiasis is a major cause of bladder cancer, significantly increasing the risk of squamous cell carcinoma through chronic inflammation of the bladder wall. Public health interventions have reduced this risk in some areas, but bladder cancer related to schistosomiasis remains a significant concern in endemic regions.

5. Diet and Lifestyle:

- Emerging evidence suggests that diet and hydration may influence bladder cancer risk, with high consumption of processed red meats and chronic dehydration increasing carcinogen concentration in the bladder.

Epidemiology of Bladder Cancer (cont.)

Genetic Predispositions and Molecular Factors:

- Bladder cancer is associated with specific genetic mutations, such as alterations in the FGFR3 gene, commonly found in low-grade, non-muscle-invasive bladder cancers, and TP53 mutations, more frequently associated with high-grade, muscle-invasive bladder cancer. These genetic factors influence disease onset and guide therapeutic approaches, such as targeted therapies for patients with FGFR3 mutations. Mutations in FGFR3 and TP53 are critical markers for bladder cancer progression and can also be used to tailor targeted therapeutic approaches, particularly in advanced cases.

Age, Ethnicity, and Racial Disparities:

- Age is one of the most significant risk factors for bladder cancer, with the majority of cases occurring in individuals over the age of 65. This trend has contributed to a steady increase in bladder cancer incidence in developed countries.
- Caucasian people have the highest incidence rates of bladder cancer, but African American and Hispanic populations tend to present with more advanced disease and worse survival outcomes, often due to delayed diagnoses and healthcare disparities.

Trends in Bladder Cancer Mortality:

- Despite advances in treatment, bladder cancer remains a leading cause of cancer-related mortality, especially among older adults. The 5-year survival rate for non-muscle-invasive bladder cancer exceeds 80%, but for muscle-invasive or metastatic bladder cancer, survival rates drop to around 30% or lower. While bladder cancer has a high recurrence rate, the development of novel immunotherapies has offered new hope, particularly in cases of muscle-invasive bladder cancer. The high recurrence rate of non-muscle-invasive bladder cancer, which can reach up to 70%, underscores the need for continuous surveillance and treatment.

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Pivotal Endpoints for Bladder Cancer Clinical Trials:

Key Challenges and Solutions

1. Overall Survival (OS)
2. Progression-Free Survival (PFS)
3. Disease-Free Survival (DFS)
4. Complete Response (CR)
5. Objective Response Rate (ORR)
6. Duration of Response (DOR)
7. Event-Free Survival (EFS)
8. Quality of Life (QoL)
9. Metastasis-Free Survival (MFS)
7. Patient-Reported Outcomes (PROs)

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1. Endpoint: Overall Survival (OS)

Correlation to Patient Outcome:

- Directly measures the length of time patients live post-treatment.

Challenge:

- Requires long follow-up times, especially for early-stage cancers. Confounding factors such as crossover treatments can impact results.

Solution:

- Use interim analyses to allow earlier decisions based on trends. Implement surrogate markers like PFS to estimate potential outcomes. Sensitivity analysis can adjust for confounding variables like subsequent therapies.

2. Endpoint: Progression-Free Survival (PFS)

Correlation to Patient Outcome:

- Time until disease progression or death.

Challenge:

- Variability in definitions of "progression," biased by assessment schedules, and informative censoring can misrepresent the true progression time.

Solution:

- Standardize imaging criteria (e.g., RECIST) and ensure consistency in assessment intervals. Use blinded central review of imaging to reduce bias. Sensitivity analysis can address data censoring challenges.

3. Endpoint: Disease-Free Survival (DFS)

Correlation to Patient Outcome:

- Assesses time post-treatment during which no cancer is detected.

Challenge:

- Long follow-up periods are needed, and patient adherence to follow-ups can be inconsistent.

Solution:

- Regular follow-ups, non-invasive biomarkers (e.g., liquid biopsies, imaging), and digital tools for patient engagement can help with tracking recurrence more effectively.

4. Endpoint: Complete Response (CR)

Correlation to Patient Outcome:

- Measures the percentage of patients with complete disappearance of disease.

Challenge:

- Detection methods vary, and some responses may be short-lived, complicating the accurate determination of CR.

Solution:

- Advanced imaging (e.g., PET-CT) and molecular markers can provide more precise tracking of tumor burden. Serial imaging at standard intervals can help capture transient or delayed responses.

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5. Endpoint: Objective Response Rate (ORR)

Correlation to Patient Outcome:

- Proportion of patients showing significant tumor reduction.

Challenge:

- Defining partial vs. complete responses can be challenging, especially in non-measurable or slowly growing tumors.

Solution:

- Use standardized response criteria like RECIST 1.1 to ensure consistent definitions of tumor response. Consider modified criteria for atypical responses in immunotherapies.

6. Endpoint: Duration of Response (DOR)

Correlation to Patient Outcome:

- Time during which a tumor remains in partial or complete response.

Challenge:

- Difficult to measure in slowly progressing cancers or those with pseudo-progression (immunotherapy) where tumor size may initially increase.

Solution:

- Consistent follow-up and real-time response assessment using advanced imaging techniques. Adaptive trial designs may allow for earlier assessment of duration.

7. Endpoint: Event-Free Survival (EFS)

Correlation to Patient Outcome:

- Time until any cancer-related event, including progression or death.

Challenge:

- Non-cancer-related events can confound results, leading to overestimation or underestimation of treatment effectiveness.

Solution:

- Precisely define cancer-specific events in trial protocols. Use censoring methods to exclude non-cancer events from analysis to maintain data accuracy.

8. Endpoint: Quality of Life (QoL)

Correlation to Patient Outcome:

- Reflects the overall well-being and function of patients post-treatment.

Challenge:

- QoL is subjective and highly dependent on patient-reported outcomes, which can vary greatly.

Solution:

- Standardize patient-reported outcome tools (e.g., EORTC QLQ-C30) across studies. Use multiple scales to validate responses and implement digital tools to collect real-time feedback on QoL.

9. Endpoint: Metastasis-Free Survival (MFS)

Correlation to Patient Outcome:

- Time until metastasis occurs.

Challenge:

- Early detection of metastasis can be challenging with some imaging techniques, leading to late identification of metastasis.

Solution:

- Use more sensitive imaging techniques such as PET-CT or MRI, and schedule regular follow-ups to catch early metastasis. Liquid biopsy can also provide early signals of metastasis.

10. Endpoint: Patient-Reported Outcomes (PROs)

Correlation to Patient Outcome:

- Provides insight into the patient's perspective on their health.

Challenge:

- Subjective reports can vary widely between patients, leading to variability in the data, and reporting tools may not always capture relevant patient experiences accurately.

Solution:

- Standardize survey tools and integrate digital platforms to track real-time patient feedback. Implement training for patients to ensure clarity and consistency in reporting. Use multiple validated tools to capture diverse aspects of health.

FDA-Approved Treatments for Bladder Cancer

Drug Name	Year of Approval	Class	Mechanism of Action	Therapeutic Effects
Cisplatin	1978	Chemotherapy	DNA crosslinking, inhibiting DNA replication	First-line treatment for advanced/metastatic bladder cancer
Carboplatin	1993	Chemotherapy	DNA crosslinking, inhibiting DNA replication	Alternative for patients ineligible for cisplatin
Gemcitabine (Gemzar)	1996	Chemotherapy	Inhibits DNA synthesis by incorporating into DNA	Combined with cisplatin for advanced/metastatic bladder cancer
MVAC (Methotrexate, Vinblastine, Doxorubicin, Cisplatin)	Combination (1980s)	Chemotherapy	Combination therapy affecting multiple pathways, primarily DNA replication	Combination therapy for advanced bladder cancer
Paclitaxel	1992	Chemotherapy	Inhibits microtubule disassembly, leading to cell death	Occasionally used in combination regimens for advanced bladder cancer
Docetaxel	1996	Chemotherapy	Inhibits microtubule disassembly, leading to cell death	Sometimes used for recurrent bladder cancer
Atezolizumab (Tecentriq)	2016	Immunotherapy (Checkpoint Inhibitor)	PD-L1 inhibitor that prevents immune evasion of cancer cells	Locally advanced/metastatic urothelial carcinoma post-chemotherapy
Pembrolizumab (Keytruda)	2017	Immunotherapy (Checkpoint Inhibitor)	PD-1 inhibitor that restores immune system's ability to attack cancer	Locally advanced/metastatic urothelial carcinoma post-chemotherapy
Nivolumab (Opdivo)	2017	Immunotherapy (Checkpoint Inhibitor)	PD-1 inhibitor that restores immune system's ability to attack cancer	Locally advanced/metastatic urothelial carcinoma post-chemotherapy
Durvalumab (Imfinzi)	2017	Immunotherapy (Checkpoint Inhibitor)	PD-L1 inhibitor that prevents immune evasion of cancer cells	Locally advanced/metastatic urothelial carcinoma post-chemotherapy
Avelumab (Bavencio)	2020	Immunotherapy (Checkpoint Inhibitor)	PD-L1 inhibitor that prevents immune evasion of cancer cells	Maintenance therapy for advanced urothelial carcinoma after chemotherapy
Erdafitinib (Balversa)	2019	Targeted Therapy	FGFR inhibitor targeting mutations in FGFR2/FGFR3	For patients with FGFR2/FGFR3 mutations who failed chemotherapy
Enfortumab vedotin (Padcev)	2019	Antibody-Drug Conjugate	Targets Nectin-4 on cancer cells and delivers cytotoxic agent	For patients post-chemotherapy and immunotherapy in advanced urothelial carcinoma
Sacituzumab govitecan (Trodelvy)	2021	Antibody-Drug Conjugate	Targets Trop-2 and delivers cytotoxic agent	For patients post-chemotherapy and immunotherapy in advanced urothelial carcinoma
Valrubicin (Valstar)	1998	Chemotherapy (Intravesical)	Topoisomerase inhibitor causing DNA strand breaks	Intravesical therapy for BCG-refractory non-muscle-invasive bladder cancer
Mitomycin (Jelmyto)	2020	Chemotherapy (Intravesical)	DNA synthesis inhibitor used intravesically	Intravesical therapy for non-muscle-invasive bladder cancer
Gemcitabine (Intravesical)	*Gemcitabine is FDA approved for bladder cancer(IV), Intravesical use is off-label	Chemotherapy (Intravesical)	Inhibits DNA synthesis by incorporating into DNA	Used intravesically for non-muscle-invasive bladder cancer

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Five Most Commonly Prescribed Drugs for Bladder Cancer

Drug		Year of Approval	Class	Mechanism of Action	Therapeutic Effects
Pembrolizumab (Keytruda)	Widely used as a first-line and second-line treatment for advanced bladder cancer.	2017	Immunotherapy (Checkpoint Inhibitor)	PD-1 inhibitor that restores immune system's ability to attack cancer	Locally advanced/metastatic urothelial carcinoma post-chemotherapy
Nivolumab (Opdivo)	A common option for adjuvant therapy in muscle-invasive bladder cancer.	2017	Immunotherapy (Checkpoint Inhibitor)	PD-1 inhibitor that restores immune system's ability to attack cancer	Locally advanced/metastatic urothelial carcinoma post-chemotherapy
Enfortumab Vedotin (Padcev)	Frequently used for patients who fail chemotherapy and immunotherapy.	2019	Antibody-Drug Conjugate	Targets Nectin-4 on cancer cells and delivers cytotoxic agent	For patients post-chemotherapy and immunotherapy in advanced urothelial carcinoma
Atezolizumab (Tecentriq)	Often employed as a maintenance therapy following chemotherapy.	2016	Immunotherapy (Checkpoint Inhibitor)	PD-L1 inhibitor that prevents immune evasion of cancer cells	Locally advanced/metastatic urothelial carcinoma post-chemotherapy
Avelumab (Bavencio)	A mainstay in maintenance therapy for patients who respond to platinum-based chemotherapy.	2020	Immunotherapy (Checkpoint Inhibitor)	PD-L1 inhibitor that prevents immune evasion of cancer cells	Maintenance therapy for advanced urothelial carcinoma after chemotherapy

Pivotal Clinical Trials Leading to FDA Approval

Drug Name	Study Name/Clinical Trial Identifier	Sample Size	Key Findings & Statistical Data
Pembrolizumab (Keytruda)	KEYNOTE-045	542	Demonstrated improved overall survival (OS) compared to chemotherapy (10.3 vs. 7.4 months; HR 0.73, p=0.002). Long-term OS benefits were observed with follow-up, with a 16.7% OS rate at 48 months.
Nivolumab (Opdivo)	CheckMate 274	709	Improved disease-free survival (DFS) in high-risk urothelial carcinoma post-surgery (median DFS: 21 months vs. 10.9 months, HR 0.70). Data from 2024 showed the first overall survival benefits, solidifying it as a standard for adjuvant therapy.
Enfortumab Vedotin + Pembrolizumab	EV-302/KEYNOTE-A39	886	Nearly doubled the median OS for advanced bladder cancer (31.5 months vs. 16.1 months, HR 0.47, p<0.0001). Marked improvement in progression-free survival (PFS) (12.5 months vs. 6.3 months, HR 0.45).
Atezolizumab (Tecentriq)	IMvigor 211	931	Did not meet its primary endpoint for OS, but significant responses were seen in PD-L1 positive patients (OS: 11.1 months vs. 10.6 months)
Avelumab (Bavencio)	JAVELIN Bladder 100	700	Demonstrated significant improvement in OS as maintenance therapy after chemotherapy for advanced urothelial carcinoma (OS: 21.4 months vs. 14.3 months, HR 0.69).

Approved Product Analysis: Keytruda

14.1 Melanoma

Ipilimumab-Naive Melanoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Unresectable or Metastatic Melanoma	Overall Survival (OS)	BICR using RECIST v1.1	Median: 9 months follow-up	KEYTRUDA 10 mg/kg every 2 weeks (n=279) KEYTRUDA 10 mg/kg every 3 weeks (n=277) Ipilimumab 3 mg/kg every 3 weeks (n=278)	KEYTRUDA 10 mg/kg every 2 weeks: HR = 0.63 (0.47, 0.83), p < 0.001 KEYTRUDA 10 mg/kg every 3 weeks: HR = 0.69 (0.52, 0.90), p = 0.004 Significant improvement in OS for both KEYTRUDA regimens vs. ipilimumab.
Unresectable or Metastatic Melanoma	Progression-Free Survival (PFS)	BICR using RECIST v1.1	Median: KEYTRUDA 10 mg/kg every 2 weeks: 5.5 months KEYTRUDA 10 mg/kg every 3 weeks: 4.1 months Ipilimumab: 2.8 months	KEYTRUDA 10 mg/kg every 2 weeks (n=279) KEYTRUDA 10 mg/kg every 3 weeks (n=277) Ipilimumab 3 mg/kg every 3 weeks (n=278)	KEYTRUDA 10 mg/kg every 2 weeks: HR = 0.58 (0.46, 0.72), p < 0.001 KEYTRUDA 10 mg/kg every 3 weeks: HR = 0.58 (0.47, 0.72), p < 0.001 Significant improvement in PFS for both KEYTRUDA regimens vs. ipilimumab.
Unresectable or Metastatic Melanoma	Objective Response Rate (ORR)	BICR using RECIST v1.1	Median: 9 months follow-up	KEYTRUDA 10 mg/kg every 2 weeks (n=279) KEYTRUDA 10 mg/kg every 3 weeks (n=277) Ipilimumab 3 mg/kg every 3 weeks (n=278)	KEYTRUDA 10 mg/kg every 2 weeks: ORR = 34% (28, 40) KEYTRUDA 10 mg/kg every 3 weeks: ORR = 33% (27, 39) Ipilimumab: ORR = 12% (8, 16) Significant improvement in ORR for both KEYTRUDA regimens vs. ipilimumab.
Unresectable or Metastatic Melanoma	Complete Response Rate	BICR using RECIST v1.1	Median: 9 months follow-up	KEYTRUDA 10 mg/kg every 2 weeks (n=279) KEYTRUDA 10 mg/kg every 3 weeks (n=277) Ipilimumab 3 mg/kg every 3 weeks (n=278)	KEYTRUDA 10 mg/kg every 2 weeks: 5% KEYTRUDA 10 mg/kg every 3 weeks: 6% Ipilimumab: 1%
Unresectable or Metastatic Melanoma	Partial Response Rate	BICR using RECIST v1.1	Median: 9 months follow-up	KEYTRUDA 10 mg/kg every 2 weeks (n=279) KEYTRUDA 10 mg/kg every 3 weeks (n=277) Ipilimumab 3 mg/kg every 3 weeks (n=278)	KEYTRUDA 10 mg/kg every 2 weeks: 29% KEYTRUDA 10 mg/kg every 3 weeks: 27% Ipilimumab: 10%

Approved Product Analysis: Keytruda (cont.)

Ipilimumab-Refractory Melanoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Unresectable or Metastatic Melanoma	Progression-Free Survival (PFS)	BICR using RECIST v1.1	Median: KEYTRUDA 2 mg/kg: 2.9 months KEYTRUDA 10 mg/kg: 2.9 months Chemotherapy: 2.7 months	KEYTRUDA 2 mg/kg every 3 weeks (n=180) KEYTRUDA 10 mg/kg every 3 weeks (n=181) Chemotherapy (n=179)	KEYTRUDA 2 mg/kg every 3 weeks: HR = 0.57 (0.45, 0.73), p < 0.001 KEYTRUDA 10 mg/kg every 3 weeks: HR = 0.50 (0.39, 0.64), p < 0.001 Significant improvement in PFS for both KEYTRUDA regimens vs. chemotherapy.
Unresectable or Metastatic Melanoma	Overall Survival (OS)	BICR using RECIST v1.1	Median: KEYTRUDA 2 mg/kg: 13.4 months KEYTRUDA 10 mg/kg: 14.7 months Chemotherapy: 11.0 months	KEYTRUDA 2 mg/kg every 3 weeks (n=180) KEYTRUDA 10 mg/kg every 3 weeks (n=181) Chemotherapy (n=179)	KEYTRUDA 2 mg/kg every 3 weeks: HR = 0.86 (0.67, 1.10), p = 0.117 KEYTRUDA 10 mg/kg every 3 weeks: HR = 0.74 (0.57, 0.96), p = 0.011* No statistically significant difference for KEYTRUDA 2 mg/kg vs. chemotherapy; significant improvement for KEYTRUDA 10 mg/kg vs. chemotherapy.
Unresectable or Metastatic Melanoma	Objective Response Rate (ORR)	BICR using RECIST v1.1	Not specified in data	KEYTRUDA 2 mg/kg every 3 weeks (n=180) KEYTRUDA 10 mg/kg every 3 weeks (n=181) Chemotherapy (n=179)	KEYTRUDA 2 mg/kg every 3 weeks: ORR = 21% (15, 28) KEYTRUDA 10 mg/kg every 3 weeks: ORR = 25% (19, 32) Chemotherapy: ORR = 4% (2, 9) Significant improvement in ORR for both KEYTRUDA regimens vs. chemotherapy.
Unresectable or Metastatic Melanoma	Complete Response Rate (secondary endpoint)	BICR using RECIST v1.1	Not specified in data	KEYTRUDA 2 mg/kg every 3 weeks (n=180) KEYTRUDA 10 mg/kg every 3 weeks (n=181) Chemotherapy (n=179)	KEYTRUDA 2 mg/kg every 3 weeks: 2% KEYTRUDA 10 mg/kg every 3 weeks: 3% Chemotherapy: 0%
Unresectable or Metastatic Melanoma	Partial Response Rate(secondary endpoint)	BICR using RECIST v1.1	Not specified in data	KEYTRUDA 2 mg/kg every 3 weeks (n=180) KEYTRUDA 10 mg/kg every 3 weeks (n=181) Chemotherapy (n=179)	KEYTRUDA 2 mg/kg every 3 weeks: 19% KEYTRUDA 10 mg/kg every 3 weeks: 23% Chemotherapy: 4%

Approved Product Analysis: Keytruda (cont.)

Adjuvant Treatment of Resected Melanoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Completely Resected Stage III Melanoma	Recurrence-Free Survival (RFS)	Investigator-assessed	Median: KEYTRUDA: Not Reached (NR) Placebo: 20.4 months (16.2, NR)	KEYTRUDA 200 mg every 3 weeks (n=514) Placebo (n=505)	KEYTRUDA 200 mg every 3 weeks: HR = 0.57 (0.46, 0.70), $p < 0.001$ Significant improvement in RFS for KEYTRUDA vs. placebo.
Completely Resected Stage III Melanoma (PD-L1 Positive Tumors)	Recurrence-Free Survival (RFS)	Investigator-assessed	Median: KEYTRUDA: NR Placebo: NR	KEYTRUDA 200 mg every 3 weeks (n=514) Placebo (n=505)	KEYTRUDA 200 mg every 3 weeks: HR = 0.54 (0.42, 0.69), $p < 0.001$ Significant improvement in RFS for KEYTRUDA vs. placebo regardless of PD-L1 expression.

Approved Product Analysis: Opdivo

14.1 Unresectable or Metastatic Melanoma

Previously Treated Metastatic Melanoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Unresectable or Metastatic Melanoma	Overall Survival (OS)	BICR using RECIST 1.1	Median: OPDIVO: 15.7 months (12.9, 19.9) Investigator's Choice: 14.4 months (11.7, 18.2)	OPDIVO 3 mg/kg every 2 weeks (n=272) Investigator's Choice of chemotherapy (n=133)	OPDIVO 3 mg/kg every 2 weeks: HR = 0.95 (0.73, 1.24) No significant difference in OS between OPDIVO and Investigator's Choice.
Unresectable or Metastatic Melanoma	Objective Response Rate (ORR)	BICR using RECIST 1.1	Duration:2.6+ to10+ months, 87% of responses were ongoing, with 13 patients having responses of 6 months or longer.	OPDIVO 3 mg/kg every 2 weeks (n=120)	OPDIVO 3 mg/kg every 2 weeks: ORR = 32% (23, 41) Consisting of 4 complete responses and 34 partial responses.
Unresectable or Metastatic Melanoma	Duration of Response (DoR)	BICR using RECIST 1.1	DoR ranged from 2.6+ to 10+ months 87% of responses were ongoing, with 13 patients having responses of 6 months or longer.	OPDIVO 3 mg/kg every 2 weeks (n=120)	OPDIVO 3 mg/kg every 2 weeks:

Approved Product Analysis: Opdivo (cont.)

Previously Untreated Metastatic Melanoma

CHECKMATE-066

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
BRAF V600 Wild-Type Unresectable or Metastatic Melanoma	Overall Survival (OS)	Investigator-assessed RECIST v1.1	Median: OPDIVO: Not Reached (NR) Dacarbazine: 10.8 months (9.3, 12.1)	OPDIVO 3 mg/kg every 2 weeks (n=210) Dacarbazine 1000 mg/m² every 3 weeks (n=208)	OPDIVO 3 mg/kg every 2 weeks: HR = 0.42 (0.30, 0.60), p < 0.0001 Significant improvement in OS for OPDIVO vs. dacarbazine.
BRAF V600 Wild-Type Unresectable or Metastatic Melanoma	Progression-Free Survival (PFS)	Investigator-assessed RECIST v1.1	Median: OPDIVO: 5.1 months (3.5, 10.8) Dacarbazine: 2.2 months (1.5, 2.4)	OPDIVO 3 mg/kg every 2 weeks (n=210) Dacarbazine 1000 mg/m² every 3 weeks (n=208)	OPDIVO 3 mg/kg every 2 weeks: HR = 0.43 (0.34, 0.56), p < 0.0001 Significant improvement in PFS for OPDIVO vs. dacarbazine.
BRAF V600 Wild-Type Unresectable or Metastatic Melanoma	Objective Response Rate (ORR)	Investigator-assessed RECIST v1.1	6 months+	OPDIVO 3 mg/kg every 2 weeks (n=210) Dacarbazine 1000 mg/m² every 3 weeks (n=208)	OPDIVO 3 mg/kg every 2 weeks: ORR = 34% (28, 41) Dacarbazine: ORR = 9% (5, 13) Significant improvement in ORR for OPDIVO vs. dacarbazine.
BRAF V600 Wild-Type Unresectable or Metastatic Melanoma	Complete Response Rate	Investigator-assessed RECIST v1.1	6 months+	OPDIVO 3 mg/kg every 2 weeks (n=210) Dacarbazine 1000 mg/m² every 3 weeks (n=208)	OPDIVO 3 mg/kg every 2 weeks: 4% Dacarbazine: 1%
BRAF V600 Wild-Type Unresectable or Metastatic Melanoma	Partial Response Rate	Investigator-assessed RECIST v1.1	6 months+	OPDIVO 3 mg/kg every 2 weeks (n=210) Dacarbazine 1000 mg/m² every 3 weeks (n=208)	OPDIVO 3 mg/kg every 2 weeks: 30% Dacarbazine: 8%

Approved Product Analysis: Opdivo (cont.)

Previously Untreated Metastatic Melanoma

CHECKMATE-067

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Previously Untreated, Unresectable or Metastatic Melanoma	Overall Survival (OS)	Investigator-assessed RECIST v1.1	Median: OPDIVO + Ipilimumab: Not Reached (NR) OPDIVO: 36.9 months Ipilimumab: 19.9 months	OPDIVO + Ipilimumab (n=314) OPDIVO (n=316) Ipilimumab (n=315)	OPDIVO + Ipilimumab vs. Ipilimumab: HR = 0.55 (0.44, 0.69), p < 0.0001 OPDIVO vs. Ipilimumab: HR = 0.63 (0.50, 0.78), p < 0.0001 Significant improvement in OS for both OPDIVO-containing arms vs. Ipilimumab alone.
Previously Untreated, Unresectable or Metastatic Melanoma	Progression-Free Survival (PFS)	Investigator-assessed RECIST v1.1	Median: OPDIVO + Ipilimumab: 11.5 months OPDIVO: 6.9 months Ipilimumab: 2.9 months	OPDIVO + Ipilimumab (n=314) OPDIVO (n=316) Ipilimumab (n=315)	OPDIVO + Ipilimumab vs. Ipilimumab: HR = 0.42 (0.34, 0.51), p < 0.0001 OPDIVO vs. Ipilimumab: HR = 0.57 (0.47, 0.69), p < 0.0001 Significant improvement in PFS for both OPDIVO-containing arms vs. Ipilimumab alone.
Previously Untreated, Unresectable or Metastatic Melanoma	Confirmed Overall Response Rate (ORR)	Investigator-assessed RECIST v1.1	Within 9 months follow-up	OPDIVO + Ipilimumab (n=314) OPDIVO (n=316) Ipilimumab (n=315)	OPDIVO + Ipilimumab: ORR = 50% (44, 55) OPDIVO: ORR = 40% (34, 46) Ipilimumab: ORR = 14% (10, 18) Significant improvement in ORR for both OPDIVO-containing arms vs. Ipilimumab alone.
Previously Untreated, Unresectable or Metastatic Melanoma	Complete Response Rate	Investigator-assessed RECIST v1.1	Within 9 months follow-up	OPDIVO + Ipilimumab (n=314) OPDIVO (n=316) Ipilimumab (n=315)	OPDIVO + Ipilimumab: 8.9% OPDIVO: 8.5% Ipilimumab: 1.9%
Previously Untreated, Unresectable or Metastatic Melanoma	Partial Response Rate	Investigator-assessed RECIST v1.1	Within 9 months follow-up	OPDIVO + Ipilimumab (n=314) OPDIVO (n=316) Ipilimumab (n=315)	OPDIVO + Ipilimumab: 41% OPDIVO: 31% Ipilimumab: 12%
Previously Untreated, Unresectable or Metastatic Melanoma	Duration of Response	Investigator-assessed RECIST v1.1	Range: OPDIVO + Ipilimumab: 1.2+ to 15.8+ months OPDIVO: 1.3+ to 14.6+ months Ipilimumab: 1.0+ to 13.8+ months	OPDIVO + Ipilimumab (n=314) OPDIVO (n=316) Ipilimumab (n=315)	Proportion with ≥6 months in duration: OPDIVO + Ipilimumab: 76% OPDIVO: 74% Ipilimumab: 63%

Approved Product Analysis: Opdivo (cont.)

14.2 Adjuvant Treatment of Melanoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
Completely Resected Stage IIIB/C or Stage IV Melanoma	Recurrence-Free Survival (RFS)	Investigator-assessed	Median: OPDIVO: Not Reached (NR) Ipilimumab: 16.56 months (NR)	OPDIVO 3 mg/kg every 2 weeks (n=453) Ipilimumab 10 mg/kg every 3 weeks (n=453)	OPDIVO vs. Ipilimumab: HR = 0.65 (0.53, 0.80), $p < 0.0001$ Significant improvement in RFS for OPDIVO vs. Ipilimumab.
Completely Resected Stage IIIB/C or Stage IV Melanoma	Overall Survival (OS)	Investigator-assessed	Median: Not Reached (NR) for both arms	OPDIVO 3 mg/kg every 2 weeks (n=453) Ipilimumab 10 mg/kg every 3 weeks (n=453)	OPDIVO vs. Ipilimumab: HR = 0.87 (0.67, 1.14), $p = 0.3148$ No statistically significant difference in OS between OPDIVO and Ipilimumab.

Approved Product Analysis: Padcev

14.1 Metastatic Urothelial Cancer

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
EV-301: Previously Treated patients with locally advanced or metastatic urothelial cancer	Overall Survival	RECIST v1.1	Median OS: 12.9 months (PADCEV) vs. 9.0 months (Chemotherapy)	n=608 (PADCEV n=301, Chemotherapy n=307)	Hazard ratio 0.70; significant improvement (p=0.0014)
EV-301: Previously Treated patients with locally advanced or metastatic urothelial cancer	Progression Free Survival	RECIST v1.1	Median PFS: 5.6 months (PADCEV) vs. 3.7 months (Chemotherapy)	n=608 (PADCEV n=301, Chemotherapy n=307)	Hazard ratio 0.62; significant improvement (p<0.0001)
EV-301: Previously Treated patients with locally advanced or metastatic urothelial cancer	Overall Response Rate	RECIST v1.1	Not specified	n=608 (PADCEV n=301, Chemotherapy n=307)	ORR: 40.6% (PADCEV) vs. 17.9% (Chemotherapy); significant improvement (p<0.0001)
EV-301: Previously Treated patients with locally advanced or metastatic urothelial cancer	Complete Response Rate (*Secondary endpoint*)	RECIST v1.1	Not specified	n=608 (PADCEV n=301, Chemotherapy n=307)	CR: 4.9% (PADCEV) vs. 2.7% (Chemotherapy)
EV-301: Previously Treated patients with locally advanced or metastatic urothelial cancer	Partial Response Rate(*Secondary endpoint*)	RECIST v1.1	Not specified	n=608 (PADCEV n=301, Chemotherapy n=307)	PR: 35.8% (PADCEV) vs. 15.2% (Chemotherapy)
EV-201, Cohort 1	Confirmed Overall Response Rate	RECIST v1.1	Not specified	n=125 (PADCEV)	ORR: 44% (95% CI 35.1, 53.2)
EV-201, Cohort 1	Complete Response Rate	RECIST v1.1	Not specified	n=125 (PADCEV)	CR: 12%
EV-201, Cohort 1	Partial Response Rate	RECIST v1.1	Not specified	n=125 (PADCEV)	PR: 32%
EV-201, Cohort 1	Duration of Response	RECIST v1.1	Median DOR: 7.6 months	n=55 (with response)	Median duration 7.6 months (95% CI 6.3, NE)

Note: NE = not estimable 1. Based on patients (n=55) with a response by BICR

Approved Product Analysis: Padcev (cont.)

Previously Treated Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
EV-201, Cohort 2	Confirmed Overall Response Rate	RECIST v1.1	Not specified	n=89	ORR: 51% (95% CI 39.8, 61.3)
EV-201, Cohort 2	Complete Response Rate	RECIST v1.1	Not specified	n=89	CR: 22%
EV-201, Cohort 2	Partial Response Rate	RECIST v1.1	Not specified	n=89	PR: 28%
EV-201, Cohort 2	Duration of Response	RECIST v1.1	Median DOR: 13.8 months	n=45 (with response)	Median duration 13.8 months (95% CI 6.4, NE)

Note: NE = not estimable 1. Based on patients (n=45) with a response by BICR

Approved Product Analysis: Padcev (cont.)

Previously Untreated Cisplatin Ineligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

Cohort	Sample Size	Dose	Endpoint	Magnitude of Improvement
Combined Dose Escalation	n=5	PADCEV 1.25 mg/kg as IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle	ORR	68% (95% CI 58.7, 76.0)
Combined Dose Escalation	n=5	Pembrolizumab 200 mg as IV infusion on Day 1 of a 21-day cycle	CR	12%
Combined Dose Escalation	n=5	Combined dose	PR	55%
Cohort A	n=40	PADCEV 1.25 mg/kg as IV infusion over 30 minutes on Days 1 and 8 of a 21-day cycle	ORR	Same as Combined
Cohort A	n=40	Pembrolizumab 200 mg as IV infusion on Day 1 of a 21-day cycle	DOR	Median DOR: 22.1 months (range: 0.6 to 26.2)
Cohort K	n=76	PADCEV 1.25 mg/kg + Pembrolizumab	ORR	Same as Combined
Cohort K	n=76	PADCEV 1.25 mg/kg + Pembrolizumab	ORR	Not reached (range: 1.2 to 24.1+ months)

Approved Product Analysis: Tecentriq

14.1 Locally Advanced or Metastatic Urothelial Carcinoma

Cisplatin-Ingeligible Patients with Locally Advanced or Metastatic Urothelial Carcinoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
IMvigor210, Cohort 1: Cisplatin-Ineligible Patients	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=119	ORR: 23.5% (95% CI 16.2, 32.2)
IMvigor210, Cohort 1: Cisplatin-Ineligible Patients	Complete Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=119	CR: 6.7%
IMvigor210, Cohort 1: Cisplatin-Ineligible Patients	Partial Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=119	PR: 16.8%
IMvigor210, Cohort 1: Cisplatin-Ineligible Patients	Median Duration of Response	RECIST v1.1	Range 3.7 months to 16.6+ months	n=28 (responders)	Median DOR not reached; range 3.7 to 16.6+ months
PD-L1 Expression <5% in ICs	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=87	ORR: 21.8% (95% CI 13.7, 32)
PD-L1 Expression <5% in ICs	Complete Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=87	CR: 6.9%
PD-L1 Expression <5% in ICs	Partial Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=87	PR: 14.9%
PD-L1 Expression <5% in ICs	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=19	NR (3.7 to 16.6+)
PD-L1 Expression ≥5% in ICs	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=32	ORR: 28.1% (95% CI 13.8, 46.8)
PD-L1 Expression ≥5% in ICs	Complete Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=32	CR: 6.3%
PD-L1 Expression ≥5% in ICs	Partial Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=32	PR: 21.9%
PD-L1 Expression ≥5% in ICs	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 14.4 months	n=9	NR (8.1, 15.6+)

Approved Product Analysis: Tecentriq (cont.)

Previously Treated Locally Advanced or Metastatic Urothelial Carcinoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
IMvigor210, Cohort 2: PD-L1 Expression All Patients	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=310	ORR: 14.8% (95% CI 11.2, 19.3)
IMvigor210, Cohort 2: PD-L1 Expression All Patients	Complete Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=310	CR: 5.5%
IMvigor210, Cohort 2: PD-L1 Expression All Patients	Partial Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=310	PR: 9.4%
IMvigor210, Cohort 2: PD-L1 Expression All Patients	Median Duration of Response	RECIST v1.1	Median DOR: 27.7 months	n=46 (responders)	Median DOR 27.7 months; range 2.1+ to 33.4+ months
PD-L1 Expression <5% in ICs	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=210	ORR: 9.5% (95% CI 5.9, 14.3)
PD-L1 Expression <5% in ICs	Complete Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=210	CR: 2.4%
PD-L1 Expression <5% in ICs	Partial Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=210	PR: 7.1%
PD-L1 Expression <5% in ICs	Median Duration of Response	RECIST v1.1	Median DOR: 20.9 months	n=20 (responders)	Median DOR 20.9 months; range 2.1+ to 33.4+ months
PD-L1 Expression ≥5% in ICs	Confirmed Overall Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=100	ORR: 26% (95% CI 17.7, 35.7)
PD-L1 Expression ≥5% in ICs	Complete Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=100	CR: 12.0%
PD-L1 Expression ≥5% in ICs	Partial Response Rate	RECIST v1.1	Median follow-up: 32.9 months	n=100	PR: 14.0%
PD-L1 Expression ≥5% in ICs	Median Duration of Response	RECIST v1.1	Median DOR: 29.7 months	n=26 (responders)	Median DOR 29.7 months; range 4.2 to 31.2+ months

Approved Product Analysis: Bavencio

14.1 Metastatic Merkel Cell Carcinoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
JAVELIN Merkel 200: Patients with Metastatic MCC	Confirmed Overall Response Rate	RECIST v1.1	After 12 months of follow-up	n=88	ORR: 33.0% (95% CI 23.3%, 43.8%)
JAVELIN Merkel 200: Patients with Metastatic MCC	Complete Response Rate	RECIST v1.1	After 12 months of follow-up	n=88	CR: 11.4% (95% CI 6.6%, 19.9%)
JAVELIN Merkel 200: Patients with Metastatic MCC	Partial Response Rate	RECIST v1.1	After 12 months of follow-up	n=88	PR: 21.6% (95% CI 13.5%, 31.7%)
JAVELIN Merkel 200: Patients with Metastatic MCC	Median Duration of Response	RECIST v1.1	Range 2.8 to 23.3+ months	n=29 (responders)	DOR ≥ 6 months: 86% (25 patients), DOR ≥ 12 months: 45% (13 patients)

14.2 Locally Advanced or Metastatic Urothelial Carcinoma

Population	Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
JAVELIN Bladder 100: Locally Advanced/Metastatic UC	Overall Survival	RECIST v1.1	Median OS: 21.4 months (BAVENCIO+BSC) vs. 14.3 months (BSC)	n=700 (BAVENCIO+BSC n=350, BSC n=350)	Hazard ratio 0.69 (95% CI 0.56, 0.86), p=0.001 ** OS improvement significant in PD-L1 positive tumors*

Approved Product Analysis: Bavencio (cont.)

Previously-Treated Urothelial Carcinoma

Population		Endpoint	Scales Used	Time Point	Sample Size	Magnitude of Improvement
JAVELIN Solid Tumor: Patients with Locally Advanced/ Metastatic UC	Confirmed Overall Response Rate	RECIST v1.1	Median time to response: 2.0 months	n=226/n=161	ORR: 13.3% (95% CI 9.1, 18.4)	ORR: 16.1% (95% CI 10.8, 22.8)
JAVELIN Solid Tumor: Patients with Locally Advanced/ Metastatic UC	Complete Response Rate	RECIST v1.1	Median time to response: 2.0 months	n=226/n=161	CR: 4.0%	CR: 5.6%
JAVELIN Solid Tumor: Patients with Locally Advanced/ Metastatic UC	Partial Response Rate	RECIST v1.1	Median time to response: 2.0 months	n=226/n=161	PR: 9.3%	PR: 10.6%
JAVELIN Solid Tumor: Patients with Locally Advanced/ Metastatic UC	Median Duration of Response	RECIST v1.1	NE (1.4+ to 17.4+ months)	n=30 (responders)	Median DOR not estimable; ongoing responses up to 17.4+ months	NE (1.4+ to 17.4+ months)

Note: CI: Confidence interval; NE: Not estimable; + denotes a censored value

Analysis of Failed Bladder Cancer Drug Candidates

Name of Drug	Clinical Trial Identifier	Reason for Termination / Drug Failure	Trend Analysis
Durvalumab (Imfinzi)	NCT02516241	Did not meet the primary endpoint of improving overall survival (OS) in subjects with unresectable stage IV urothelial cancer	Despite this, durvalumab remains an important treatment in other settings, and ongoing trials continue to explore its use, often in combination with other therapies, in different forms of urothelial cancer.
Rova-T (Rovalpituzumab Tesirine)	NCT02709889	While the drug showed manageable toxicity with common adverse events like anemia and thrombocytopenia, its objective response rate (ORR) was modest at around 10% overall, with 13% in neuroendocrine tumors	Safety concerns and limited response rates have been notable challenges for further development for this drug.
Vicinium	NCT02449239	Although the trial showed positive results, the FDA issued a complete response letter in 2021, requesting additional clinical data and addressing manufacturing issues before considering Vicinium for approval	The trial demonstrated promising efficacy for Vicinium in treating BCG-unresponsive NMIBC, but regulatory hurdles remain before it can be approved for broader use.
ALT-803	NCT03022825	The study reported promising outcomes, with a complete response (CR) rate of 71% in patients with carcinoma in situ (CIS) who received the BCG plus N-803 combination.	While the interim findings are encouraging, the trial will need to meet all endpoints and regulatory requirements to be officially deemed a success.
Apaziquone (EOquin)	NCT00461591	Lack of benefit in reducing recurrence rates	Phase III trials showed no significant improvement over placebo.

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Common Failure Points in Bladder Cancer Clinical Trials

1. High Recurrence Rates in NMIBC:

One of the most significant challenges in bladder cancer trials, especially for non-muscle-invasive types, is the high recurrence rate post-treatment. NMIBC has a recurrence rate of up to 70%, making it difficult to measure long-term treatment efficacy in trials.

2. BCG Failure and BCG-Unresponsive Subtypes:

BCG is a primary treatment for NMIBC, but many patients develop BCG-unresponsive disease. Clinical trials aimed at identifying alternative therapies for this subgroup have faced failures, primarily due to the difficulty in maintaining long-term tumor control.

3. Heterogeneity of the Disease:

Bladder cancer is highly heterogeneous, with multiple subtypes. This heterogeneity complicates patient selection in clinical trials, leading to failures in identifying treatment responses that apply broadly to all patients.

4. Impact of Comorbidities:

Many bladder cancer patients are elderly and often have significant comorbidities. These health issues make it difficult to standardize treatments and outcomes, as trial results are often influenced by these comorbid conditions rather than the cancer treatments themselves.

5. Cisplatin Ineligibility in MIBC:

Up to 50% of patients with muscle-invasive bladder cancer are ineligible for cisplatin-based chemotherapy due to poor kidney function or other comorbidities. This has led to numerous trial failures, as cisplatin is a cornerstone of bladder cancer treatment.

6. Difficulty in Measuring Immunotherapy Efficacy:

While immunotherapy has been a breakthrough in bladder cancer, clinical trials face challenges in accurately measuring its efficacy due to delayed responses or immune-related adverse effects.

7. Endpoints Challenged by Rapid Disease Progression:

In advanced or metastatic bladder cancer, the rapid progression of the disease can make it difficult to reach meaningful clinical trial endpoints such as overall survival (OS) or progression-free survival (PFS).

Safety Concerns for Bladder Cancer Treatment

1. Chemotherapy:

Chemotherapy, particularly cisplatin-based regimens, has been the cornerstone of bladder cancer treatment for decades. However, cisplatin is associated with notable safety concerns, including:

- Nephrotoxicity (kidney damage), which limits its use in patients with pre-existing kidney dysfunction.
- Ototoxicity, leading to hearing loss, particularly in older adults.
- Myelosuppression, causing low blood cell counts, which increases the risk of infection.

For cisplatin-ineligible patients, typically those with poor renal function, alternative chemotherapy regimens like carboplatin and gemcitabine are used.

2. Immunotherapy:

The advent of immune checkpoint inhibitors (ICIs) has transformed bladder cancer treatment, especially in advanced cases where cisplatin is not viable. These drugs, such as pembrolizumab (Keytruda) and nivolumab (Opdivo), have demonstrated efficacy by boosting the immune system's ability to attack cancer cells. However, they come with specific safety challenges:

- Immune-related adverse events (IRAEs): These can range from mild skin rashes to more severe conditions like pneumonitis, colitis, and hepatitis. IRAEs require careful monitoring and, in severe cases, corticosteroids or even immunotherapy discontinuation.

Management involves regular follow-up and early intervention, particularly with corticosteroids to control inflammation.

3. Targeted Therapy:

While generally better tolerated than chemotherapy, erdafitinib presents unique risks:

- Hyperphosphatemia: Elevated phosphate levels are common and may require dietary adjustments and the use of phosphate binders.
- Ocular toxicities: Blurred vision and dry eyes necessitate regular eye exams during treatment.

4. Antibody-Drug Conjugates

Enfortumab vedotin (Padcev) has demonstrated impressive results, especially when combined with pembrolizumab, showing nearly doubled survival times for advanced bladder cancer patients compared to chemotherapy alone. However, side effects include:

- Peripheral neuropathy, leading to pain and numbness in the hands and feet.
- Skin reactions and fatigue.

5. Surgical Options

For muscle-invasive bladder cancer (MIBC), the standard of care often involves radical cystectomy (complete removal of the bladder), frequently combined with neoadjuvant chemotherapy to reduce tumor size before surgery. This procedure comes with significant risks:

- Infection and bleeding are common immediate risks post-surgery.
- Urinary diversion methods (e.g., urostomy bags) post-cystectomy significantly impact a patient's quality of life, with social and psychological challenges becoming major considerations.

Standard of Care for Advanced Bladder Cancer

Standard of Care

In advanced or metastatic bladder cancer, the treatment landscape has shifted toward immunotherapies and combination regimens as first-line treatments. For example:

- **Pembrolizumab** has been approved for patients who are not eligible for cisplatin-based chemotherapy or whose disease has progressed after chemotherapy.
- **Avelumab** has been approved as a first-line maintenance therapy for patients whose disease has not progressed following platinum-based chemotherapy, providing longer overall survival.

Quality of Life Considerations

Bladder cancer treatments, particularly for advanced disease, have profound implications for patients' quality of life (QoL). Issues such as urinary incontinence, sexual dysfunction, and the psychological impact of life-altering surgeries like cystectomy are major concerns. Studies have found that the physical limitations imposed by treatment significantly lower QoL, and management of these side effects is essential in both early and late-stage treatments.

Efforts to improve QoL involve a multidisciplinary approach, including supportive care, psychological counseling, and early intervention for managing adverse effects of treatment. For patients undergoing immunotherapy, addressing fatigue and gastrointestinal issues through nutrition and lifestyle changes has proven beneficial.

Bladder cancer treatment has made significant strides, with new therapies offering hope to patients who previously had limited options. However, each treatment comes with its own safety challenges, from the toxicity of chemotherapy to the immune-related risks. Tailoring treatment plans to individual patient needs and managing side effects with proactive strategies is essential to ensuring the best possible outcomes. As clinical trials continue to refine these therapies, the standard of care will likely evolve further, focusing on both improving survival and maintaining a good quality of life for patients.

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Enhancing Clinical Trial Protocols for Bladder Cancer

Improving clinical trial protocols for bladder cancer is pivotal to advancing our understanding and treatment. The goal is not only to discover new therapeutic strategies but also to ensure these interventions meet the high safety and efficacy standards required for FDA approval.

1. Incorporation of Adaptive Trial Designs:
Adaptive trial designs allow researchers to modify various aspects of a study (such as dosage, patient cohort size, or even endpoints) based on interim data, enhancing efficiency and minimizing patient exposure to ineffective treatments. In bladder cancer, where patient populations can be heterogeneous, adaptive designs provide flexibility, making trials more responsive to real-time findings.

2. Biomarker-Driven Studies:
Biomarker-driven studies are essential in bladder cancer, particularly as treatments like FGFR inhibitors and PD-1/PD-L1 inhibitors become more widely used. Incorporating biomarkers into clinical trial designs not only helps tailor treatment to the specific genetic or molecular profile of a patient's cancer but also improves the likelihood of achieving significant clinical endpoints.

3. Focus on Combination Therapies:
The success of combination therapies in bladder cancer, such as enfortumab vedotin plus pembrolizumab, underscores the importance of exploring synergistic drug regimens in clinical trials. This approach has not only shown improved survival outcomes but has also set a new standard for treating advanced urothelial carcinoma. The combination outperformed standard cisplatin-based chemo in several key metrics.

4. Real-World Evidence (RWE) Integration:
Real-world evidence is increasingly valued by the FDA, especially in cases where long-term follow-up from randomized controlled trials (RCTs) is challenging. RWE provides additional data on treatment safety and efficacy in broader, more diverse patient populations outside of the controlled trial environment.

5. Long-Term Follow-Up for Durability:
Bladder cancer has a high recurrence rate, especially in non-muscle-invasive forms, making long-term follow-up crucial to assess treatment durability. This is particularly important for immunotherapies or gene therapies targeting extended recurrence-free survival (RFS). Extending clinical trials beyond initial response periods ensures more robust data on the long-term effectiveness of new therapies..

6. Regulatory Alignment and Early Consultation with the FDA:
Early engagement with the FDA during the design of clinical trials helps align the study's endpoints with the agency's expectations. For example, in trials where disease-free survival (DFS) is used as a primary endpoint, it is critical to confirm that the FDA views this as a valid surrogate for overall survival in the context of the specific treatment and patient population.

7. Use of Surrogate Endpoints:
For certain patient populations, particularly those with advanced bladder cancer, waiting for overall survival data can significantly delay treatment availability. Using surrogate endpoints like PFS, complete response rates, or biomarker responses can expedite regulatory approval while ensuring that the treatment demonstrates meaningful clinical benefit.

8. Global Harmonization of Trial Protocols:
As bladder cancer trials increasingly involve global populations, harmonizing clinical trial protocols across regions can facilitate faster patient recruitment and ensure that the data is applicable to diverse populations. This is especially important in rare subtypes of bladder cancer, where patient numbers may be limited.

Notable Key Opinion Leaders in Bladder Cancer Research

Name	Specialty	Designation	Location	Brief Bio
Howard Gurney (MBBS, FRACP, PhD)	Medical Oncology	Professor, Macquarie University	New South Wales. Australia	Howard Gurney is a leading figure in medical oncology, specializing in genitourinary cancers, including bladder cancer, prostate cancer, and kidney cancer. As Director of Clinical Trials at Macquarie University Hospital, he oversees a wide range of cancer research studies, particularly focusing on experimental therapeutics and immunotherapy for bladder cancer and other genitourinary malignancies.
Vinod O Ganju (MBBS, FRACP)	Hematology; Medical Oncology; Oncology	Director, Peninsula and Southeast Oncology	Victoria, Australia	Ganju is the Managing Director of Peninsula and Southeast Oncology (PASO), a renowned oncology and hematology center in Victoria. He has been instrumental in developing oncology services in the Mornington Peninsula area, co-founding a purpose-built day hospital at Frankston Private Hospital. His research interests include the development of new therapies for bladder cancer, and he leads several national and international clinical trials in this area.
Michael J Millward (MBBS, FRACP)	Medical Oncology	Professor, University of Western Australia	Western Australia, Australia	Michael J Millward is a Professor of Clinical Cancer Research at the University of Western Australia (UWA). He holds the position of the Cancer Council Professor and also serves as the Head of Medical Oncology at Sir Charles Gairdner Hospital in Perth. His academic and clinical work focuses on cancer research, particularly in the fields of bladder cancer, lung cancer, and melanoma. Millward is widely respected for his contributions to cancer research and has held leadership positions in organizations such as the Australasian Lung Cancer Trials Group. His efforts have been instrumental in advancing treatment protocols for both lung and bladder cancers.
Jayesh Desai (MBBS, FRACP)	Medical Oncology	Associate Professor, Peter MacCallum Cancer Centre	Victoria, Australia	Associate Professor Jayesh Desai is a medical oncologist at the Peter MacCallum Cancer Centre in Melbourne and recently appointed Associate Director Clinical Research. Jayesh Desai is a renowned medical oncologist with substantial expertise in bladder cancer and a wide range of other cancers, including colorectal cancer and sarcomas. He is deeply involved in translational research and the early development of novel cancer therapies. At Peter MacCallum Cancer Centre, one of the world's leading cancer research organizations, Desai leads numerous clinical trials focused on advancing treatment options for bladder cancer and other solid tumors.
Ben Tran (MBBS, FRACP)	Medical Oncology; Urology	Associate Professor, the Walter and Eliza Hall Institute of Medical Research	Victoria, Australia	Associate Professor Ben Tran is the Medical Oncologist at Peter MacCallum Cancer Centre and Senior Research Fellow at The Walter and Eliza Hall Institute of Medical Research (WEHI) in Melbourne. At WEHI, he plays a crucial role in researching and developing precision oncology approaches, with a strong focus on bladder cancer treatments. His work involves using real-world data and clinical trials to explore why some bladder cancer patients do not respond effectively to current therapies, such as immunotherapy. Tran is committed to matching the right treatments to patients based on molecular profiling, which is critical for personalized cancer care.

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If you would like further information on how iNGENū CRO can assist you to conduct your clinical trial, please contact Dr Sud Agarwal or Adam Moodie:

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