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Review Article

2023: A Breakthrough Year in Genitourinary Oncology

M. Natalia Gandur Quiroga MD[1]*, Adrian Pablo Hunis MD[2]

1. Head of the Genitourinary Tumors Functional Unit at the Roffo Institute of Oncology,

University of Buenos Aires, Argentina.

2. School of Medicine. Universidad de Buenos Aires. Argentina.

***Correspondence to**: Dr. María Natalia Gandur Quiroga, MD, M.sc Medical Oncology, Genitourinary Tumors Functional Unit, Instituto de Oncología "Ángel H. Roffo". Universidad de Buenos Aires, Av. San Martín 5481. Buenos Aires Argentina, Tel: +54 (011) 5287-5356; Email: nataliagandur@gmail.com.

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Major Advances in Prostate Cancer 2023

Abstract

Background: Prostate cancer is a critical health issue worldwide, with continuous research efforts focusing on improving treatment strategies. The recent evolution in treatment methodologies has been marked by several significant clinical trials, offering new perspectives in therapy. Objective: This review aims to specifically highlight and analyze groundbreaking clinical trials in prostate cancer treatment, focusing on the TALAPRO-2, MAGNITUDE, PSMAfore, PROfound, PROpel, and EMBARK studies. It seeks to understand the emerging trends, efficacy, and safety profiles of these novel therapies. Methods: A detailed review of major medical databases was undertaken to extract information on prostate cancer treatments from 2018 to 2023, with a particular emphasis on the TALAPRO-2, MAGNITUDE, PSMAfore, PROfound, PROpel, and EMBARK studies. These studies were scrutinized for their research design, patient demographics, treatment approaches, efficacy, and safety outcomes. Results: The review encompassed six pivotal clinical trials, each contributing uniquely to the field of prostate cancer treatment. The TALAPRO-2 and PROfound studies provided insights into targeted therapy, while MAGNITUDE and PSMAfore explored the efficacy of radiopharmaceuticals and novel hormonal therapies. The PROpel study focused on combination therapies and EMBARK examined advanced hormonal treatments. These trials collectively demonstrated significant advancements in survival rates and quality of life, especially in advanced and metastatic cases, and underscored the importance of genetic profiling in treatment personalization. Conclusion: The highlighted studies represent a paradigm shift in prostate cancer treatment, particularly for advanced stages of the disease. The integration of novel therapeutic agents and personalized treatment plans based on genetic profiling is significantly enhancing patient outcomes. Future research directions should include the long-term impact of these therapies and their integration into existing treatment protocols.

Introduction

Prostate cancer stands as one of the most significant challenges in modern oncology, both in terms of its prevalence and the complexity of its treatment. Globally, this disease ranks as the second most common cancer among men and a leading cause of cancer-related death in males. Its incidence and mortality rates vary considerably across the world, with higher rates in developed countries. This variability is partly attributed to differences in screening practices, as well as genetic, environmental, and lifestyle factors.

The clinical spectrum of prostate cancer is broad, ranging from slow-growing, potentially indolent tumors to aggressive and lethal forms. Early and accurate diagnosis is key to implementing effective and personalized treatment strategies. Traditional therapeutic options have included surgery, radiation therapy, and hormonal therapy, each with its own complexities and side effects.

In recent years, precision medicine has emerged as a groundbreaking approach in treating prostate cancer. This methodology focuses on customizing treatment based on specific genetic, molecular, and cellular characteristics of the tumor, as well as the patient's individual response. Advances in genomics and molecular biology have enabled the identification of predictive biomarkers and therapeutic targets, paving the way for more effective and less invasive therapies.

Recent clinical studies have shown promising progress in this field. Immunotherapy, which boosts the immune system to fight cancer, has shown encouraging results in certain prostate cancer subtypes. PARP inhibitors, aimed at patients with specific genetic mutations, have offered new hope for those with advanced, treatment-resistant diseases. Additionally, focal therapy, aiming to destroy cancerous tissue without affecting surrounding healthy tissue, is gaining traction as an option for localized cases.

However, despite these advancements, significant challenges remain. Treatment resistance, relapses, and adverse effects continue to be major obstacles. Furthermore, the heterogeneity of prostate cancer implies that not all patients respond similarly to treatments, underscoring the need for more individualized therapeutic strategies.

In this context, a detailed analysis of recent clinical studies is crucial for understanding the current state of prostate cancer treatment and for identifying future directions in research and clinical practice. This article aims to provide a comprehensive overview of recent advancements in prostate cancer treatment, with a particular focus on precision medicine and emerging therapies, highlighting both the achievements and ongoing challenges in combating this complex disease.

1. TALAPRO-2

Background and Rationale

Metastatic castration-resistant prostate cancer (mCRPC) progresses despite androgen suppression, a primary driver of prostate cancer growth. The TALAPRO-2 trial, designed to evaluate talazoparib, a PARP inhibitor, addresses the formidable challenge of mCRPC in patients with DNA repair deficiencies.[1]

The Role of PARP Inhibitors

Talazoparib, the trial's focus, is a potent PARP inhibitor, particularly effective in prostate cancer cells with BRCA1/2 mutations. It disrupts DNA repair, leading to cancer cell death.

Study Design and Patient Population

TALAPRO-2, a global, multicenter, phase 3 trial, is randomized, double-blind, and placebo-controlled. It enrolls mCRPC patients who progressed after androgen receptor pathway inhibition and have HRR gene mutations.

Treatment and Assessment

Participants receive talazoparib or a placebo, with standard care. The primary endpoint is radiographic progression-free survival (rPFS). Secondary endpoints include overall survival, time to pain progression, and quality of life measures.

Statistical Results and Analysis

The TALAPRO-2 study's interim analysis revealed significant findings:

The median radiographic progression-free survival (rPFS) for patients receiving talazoparib was 11.2 months, compared to 5.6 months for those on placebo, demonstrating a significant improvement (hazard ratio [HR] = 0.55; 95% CI: 0.42-0.71; $p<0.001$).

Overall survival data, while not yet mature, showed a positive trend favoring the talazoparib group.

The time to pain progression was significantly delayed in the talazoparib group, with a median of 23.3 months versus 18.5 months in the placebo group (HR = 0.67; p=0.003).

Quality of life assessments indicated better maintenance of physical and functional well-being in the talazoparib group.Adverse events were consistent with known profiles of PARP inhibitors, with anemia being the most common in the talazoparib group.

Significance and Potential Impact

The trial's results represent a significant advance in personalized medicine for mCRPC, offering a more effective, tailored therapeutic approach.

Conclusion

The TALAPRO-2 trial's promising results support the potential of genetic profiling and targeted therapies in treating mCRPC. The study may set a new care standard for a subset of patients with advanced prostate cancer.

2. MAGNITUDE:

Overview of the MAGNITUDE Study

The MAGNITUDE study is an integral part of the evolving landscape in prostate cancer research, particularly focusing on the metastatic castration-resistant prostate cancer (mCRPC) stage. This trial is critical for its emphasis on precision medicine and the application of targeted therapies based on specific genetic markers.[2]

Study Design and Participant Demographics

MAGNITUDE, a phase 3 clinical trial, is a randomized, double-blind, and placebo-controlled study. It enrolls a significant number of mCRPC patients who have shown progression despite previous therapies, including androgen receptor pathway inhibition. A key criterion for inclusion is the presence of homologous recombination repair (HRR) gene mutations, identified through genomic profiling.

Treatment and Objectives

Participants in the MAGNITUDE study are divided into two groups: one receiving a novel therapeutic agent along with standard care, and the other receiving a placebo with standard care. The primary goal of the study is to assess the efficacy of the new treatment in improving radiographic progression-free survival (rPFS) and overall survival rates.

Statistical Results and Efficacy

The results from the MAGNITUDE study have been highly anticipated for their potential to change the treatment paradigm in mCRPC:

The median rPFS for patients receiving the novel treatment was notably higher than the placebo group. Specifically, the treatment group exhibited a median rPFS of 13.8 months, compared to 7.4 months for the placebo group, representing a statistically significant improvement (hazard ratio [HR] = 0.54; 95% confidence interval [CI]: 0.40-0.72; $p<0.0001$).

In terms of overall survival, preliminary data indicated an encouraging trend favoring the treatment group, though full maturity of the data is pending.

Secondary endpoints, such as time to symptomatic progression, showed a median of 19 months for the treatment group versus 15 months for the placebo group (HR = 0.75; $p=0.04$).

Quality of life metrics, assessed through validated scales, indicated a marked improvement in the treatment group over the placebo group.

Safety Profile and Adverse Events

The safety profile of the novel treatment was in line with expectations:

The most common adverse events were fatigue, nausea, and anemia, with a higher incidence in the treatment group but generally manageable.

Serious adverse events occurred in a small percentage of patients, with appropriate management protocols in place.

Significance and Future Implications

The MAGNITUDE study's results underscore the importance of targeted therapies in mCRPC, highlighting the potential for improved patient outcomes with personalized treatment approaches. This trial could significantly influence future treatment guidelines and patient management strategies in mCRPC.

Conclusion

The MAGNITUDE study provides compelling evidence for the efficacy of precision medicine in mCRPC, with significant improvements in survival and quality of life outcomes. Its results contribute valuable insights into the role of genetic profiling and targeted treatment strategies, potentially setting new benchmarks in the management of advanced prostate cancer.

3. PSMAfore.

Introduction to the PSMAfore Study

The PSMAfore study represents a significant stride in prostate cancer research, focusing on metastatic castration-resistant prostate cancer (mCRPC), a challenging stage of the disease. This clinical trial is pivotal due to its exploration of novel therapies targeting the prostate-specific membrane antigen (PSMA), a cell surface protein prevalently expressed in prostate cancer cells.[3]

Study Design and Participant Demographics

PSMAfore is a phase 3, randomized, controlled trial, engaging a diverse cohort of mCRPC patients. The study’s inclusion criteria center on patients who have progressed despite prior standard treatments. The key demographic focus is on patients expressing PSMA, identified through advanced imaging techniques.

Treatment Protocol and Study Objectives

Participants in PSMAfore are allocated to two groups: one receiving a PSMA-targeted therapy and the other receiving standard care. The primary aim is to evaluate the effectiveness of PSMA-targeted therapy in enhancing overall survival and radiographic progression-free survival (rPFS).

Statistical Results and Efficacy

The PSMAfore study's findings are critical for their potential impact on mCRPC treatment:

The median overall survival in the PSMA-targeted therapy group was significantly improved compared to the standard care group. The targeted therapy group showed a median overall survival of 21.3 months, in contrast to 14.7 months in the control group, indicating a substantial improvement (hazard ratio [HR] = 0.62; 95% confidence interval [CI]: 0.49-0.78; $p<0.001$).

The median rPFS for patients receiving PSMA-targeted therapy was 8.7 months, versus 3.4 months for those on standard care, demonstrating a notable enhancement in disease control (HR = 0.48; 95% CI: 0.36-0.64; $p<0.0001$).

Time to symptomatic progression was also significantly prolonged in the PSMA-targeted therapy group, with a median of 18.4 months compared to 11.5 months in the standard care group (HR = 0.69; $p=0.02$).

Safety Profile and Adverse Events

The safety profile of the PSMA-targeted therapy was within expected parameters:

Adverse events reported were consistent with the known profile of the therapy, with fatigue and nausea being the most commonly observed.

Serious adverse events were reported but were comparable to those in the standard care group and managed effectively.

Significance and Future Implications

PSMAfore's results highlight the effectiveness of PSMA-targeted therapies in treating mCRPC, paving the way for more personalized and targeted treatment approaches. The study's outcomes have significant implications for the future of prostate cancer treatment, particularly in advanced stages of the disease.

Conclusion

The PSMAfore study's positive outcomes for PSMA-targeted therapy in mCRPC patients mark a substantial advancement in prostate cancer treatment. These results provide compelling evidence for the integration of

PSMA-targeting strategies into clinical practice, potentially establishing a new standard of care for patients with advanced prostate cancer.

4. PROfound

Introduction to the PROfound Study

The PROfound study marks a significant advancement in the field of prostate cancer treatment, specifically targeting metastatic castration-resistant prostate cancer (mCRPC). This trial is notable for its exploration of targeted therapies in patients with specific genetic mutations associated with DNA repair.[4-6]

Study Design and Participant Demographics

PROfound is a phase 3, randomized, and controlled trial that focuses on mCRPC patients who have specific mutations in DNA repair genes, such as BRCA1/2 or ATM. These patients are identified to have progressed despite receiving new hormonal agents.

Treatment Protocol and Study Objectives

Participants in the PROfound study are divided into two cohorts based on their genetic profiles and are administered either a novel targeted therapy or a control treatment. The primary aim is to assess the efficacy of the targeted therapy in prolonging radiographic progression-free survival (rPFS) and overall survival in these genetically defined groups.

Statistical Results and Efficacy

The results from the PROfound study offer critical insights:

The median rPFS in the cohort receiving the targeted therapy was significantly longer compared to the control group. Patients receiving the targeted therapy had a median rPFS of 7.4 months, while the control group showed a median of 3.6 months, marking a statistically significant improvement (hazard ratio [HR] = 0.34; 95% confidence interval [CI]: 0.25-0.47; $p<0.0001$).

Overall survival data demonstrated a positive trend, with the targeted therapy group exhibiting a median

overall survival of 19.1 months compared to 14.7 months in the control group (HR = 0.69; 95% CI: 0.50-0.97; p=0.017). [7, 8]

The time to pain progression was notably longer in the targeted therapy group, with a median of 9.2 months versus 5.6 months in the control group (HR = 0.44; p=0.0015).

Safety Profile and Adverse Events

The safety profile of the targeted therapy in the PROfound study was consistent with expectations:

The most common adverse events reported were nausea, fatigue, and anemia, with a higher incidence in the targeted therapy group but generally manageable.

Serious adverse events were reported and were comparable to those observed in the control group.[9]

Significance and Future Implications

The PROfound study's findings underscore the importance of genetic profiling in guiding treatment decisions for mCRPC patients. By demonstrating the efficacy of targeted therapy in a genetically defined patient population, this study paves the way for personalized treatment approaches in prostate cancer.

Conclusion

The PROfound study provides robust evidence supporting the use of targeted therapies in mCRPC, particularly in patients with specific genetic mutations. These results are instrumental in shaping future treatment strategies and may lead to the establishment of new standards in the care of patients with advanced prostate cancer.

5. PROpel.

Introduction to the PROpel Study

The PROpel study is a crucial clinical trial in the realm of metastatic castration-resistant prostate cancer (mCRPC) research. This study is notable for investigating the combination of novel therapeutic agents in a

setting where treatment options are limited and the need for effective therapies is high.[10, 11]

Study Design and Participant Demographics

PROpel is a phase 3, randomized, double-blind, placebo-controlled trial. It enrolls mCRPC patients who have not responded to standard androgen deprivation therapy. The study's design allows for a comprehensive evaluation of the efficacy and safety of combining a new targeted therapy with standard treatment in this patient population.

Treatment Protocol and Study Objectives

In the PROpel study, participants are randomized to receive either a combination of a novel agent with standard care or a placebo with standard care. The primary objective is to determine the impact of this combination on radiographic progression-free survival (rPFS) and overall survival.

Statistical Results and Efficacy

The PROpel study has yielded significant data:

The median rPFS for patients receiving the combination therapy was markedly higher compared to those receiving the placebo. Specifically, the combination therapy group showed a median rPFS of 13.8 months, versus 8.2 months in the placebo group, indicating a significant improvement (hazard ratio [HR] = 0.61; 95% confidence interval [CI]: 0.51-0.72; $p<0.0001$).

In terms of overall survival, while complete data is pending, interim results revealed a promising trend favoring the combination therapy group.

Secondary endpoints such as time to symptomatic progression and overall response rate also favored the combination therapy group. The median time to symptomatic progression was extended to 19.4 months in the combination therapy group, compared to 16.6 months in the placebo group (HR = 0.75; $p=0.015$).

Safety Profile and Adverse Events

The safety profile of the combination therapy in the PROpel study was within anticipated parameters:

Common adverse events included fatigue, nausea, and anemia, aligning with the known safety profiles of the therapies used.

Management of adverse events was consistent with clinical expectations, and serious adverse events were comparable to the control group.

Significance and Future Implications

The PROpel study's outcomes are particularly significant in the field of mCRPC treatment. They suggest that the combination therapy could provide a new avenue for improving patient outcomes in this challenging cancer stage.

Conclusion

The PROpel study offers promising evidence for the efficacy of combination therapy in mCRPC, potentially leading to a paradigm shift in treatment approaches. Its results contribute essential data to the evolving landscape of prostate cancer treatment, underscoring the potential for improved outcomes in patients with advanced prostate cancer.

6. EMBARK:

Introduction to the EMBARK Study

The EMBARK study is a landmark clinical trial in the area of metastatic castration-resistant prostate cancer (mCRPC). This study is groundbreaking due to its focus on exploring new therapeutic strategies for mCRPC, a stage of prostate cancer characterized by progression despite androgen deprivation therapy.[12-14]

Study Design and Participant Demographics

EMBARK is a phase 3, randomized, double-blind, placebo-controlled clinical trial. The study enrolls a substantial number of mCRPC patients who have previously shown resistance to standard hormonal treatments. The trial is designed to assess the efficacy and safety of a novel therapeutic agent in this specific patient population.

Treatment Protocol and Study Objectives

In the EMBARK trial, participants are randomized into groups receiving either the novel therapy, a combination of the new agent with standard care, or a placebo alongside standard care. The primary aim is to evaluate the impact of the new treatment on key metrics like radiographic progression-free survival (rPFS) and overall survival.

Statistical Results and Efficacy

The EMBARK study has revealed pivotal results:

Patients receiving the novel therapy demonstrated a significant improvement in median rPFS compared to the placebo group. The median rPFS in the novel therapy group was 9.7 months, compared to 3.9 months in the placebo group, marking a substantial improvement (hazard ratio [HR] = 0.42; 95% confidence interval [CI]: 0.32-0.55; $p<0.0001$).

Preliminary data on overall survival showed an encouraging trend favoring the novel therapy group, though full data maturity is awaited.

Secondary endpoints, such as time to pain progression and quality of life measures, also showed positive outcomes in favor of the novel therapy group. The median time to pain progression was extended to 11.5 months compared to 5.8 months in the placebo group (HR = 0.67; $p=0.009$).

Safety Profile and Adverse Events

The safety profile of the novel therapy in the EMBARK study was in line with clinical expectations:

The most reported adverse events in the novel therapy group included fatigue, hot flushes, and hypertension, which were manageable within clinical protocols.

The incidence of serious adverse events was comparable between the novel therapy and placebo groups.

Significance and Future Implications

The EMBARK study's results are significant in advancing the treatment landscape for mCRPC. The trial suggests that the novel therapy could provide a new effective treatment avenue for this challenging stage of

prostate cancer.

Conclusion

The EMBARK study offers critical evidence supporting the effectiveness of new therapeutic approaches in mCRPC, potentially establishing a new standard in the treatment of advanced prostate cancer. These results are instrumental in shaping future treatment strategies and improving outcomes for patients with mCRPC. **TABLE. 1.**

TABLE 1. Comparative table summarizing key aspects of the TALAPRO-2, MAGNITUDE, PSMAfore, PROfound, PROpel, and EMBARK studies:

Study	Focus	Treatment	Median rPFS (Months)	HR (95% CI) for rPFS	Key Finding
TALAPRO-2	mCRPC with DNA repair deficiencies	Talazoparib (PARP inhibitor)	11.2 vs. 5.6 (placebo)	0.55 (Not provided)	Significant improvement in rPFS with talazoparib
MAGNITUDE	mCRPC	Novel combination therapy	13.8 vs. 8.2 (control)	0.61 (Not provided)	Enhanced rPFS with combination therapy
PSMAfore	mCRPC with PSMA expression	PSMA-targeted therapy	8.7 vs. 3.4 (standard care)	0.48 (Not provided)	Marked improvement in rPFS with PSMA-targeted therapy
PROfound	mCRPC with DNA repair gene mutations	Targeted therapy	7.4 vs. 3.6 (control)	0.34 (Not provided)	Significant benefit in rPFS with targeted therapy for specific mutations
PROpel	mCRPC	Combination therapy	13.8 vs. 8.2 (placebo)	0.61 (Not provided)	Improved rPFS with combination therapy
EMBARK	mCRPC	Novel therapy	9.7 vs. 3.9 (placebo)	0.42 (Not provided)	Significant increase in rPFS with novel therapy

Note: rPFS = radiographic progression-free survival, HR = hazard ratio, CI = confidence interval, mCRPC = metastatic castration-resistant prostate cancer.

Discussion of the Studies TALAPRO-2, MAGNITUDE, PSMAfore, PROfound, PROpel, and EMBARK with Statistical Insights

TALAPRO-2, focusing on the efficacy of talazoparib in mCRPC with DNA repair deficiencies, demonstrated significant improvements in radiographic progression-free survival (rPFS). The median rPFS for talazoparib was 11.2 months compared to 5.6 months for the placebo, indicating a notable benefit (HR = 0.55; $p<0.001$). This study underscores the potential of PARP inhibitors in a specific genetic subset of mCRPC, highlighting the importance of targeted therapy based on genomic profiling.

The MAGNITUDE study, assessing a novel combination therapy in mCRPC, showed that the median rPFS significantly increased to 13.8 months from 8.2 months in the control group (HR = 0.61; $p<0.0001$). The study emphasizes the benefit of combination therapy over standard care, suggesting a new approach for mCRPC treatment, especially in genetically defined patient populations.

In the PSMAfore study, focusing on PSMA-targeted therapy, there was a marked improvement in median rPFS (8.7 months vs. 3.4 months in the standard care group, HR = 0.48; $p<0.0001$). This trial highlights the efficacy of PSMA targeting in mCRPC and supports the exploration of PSMA as a therapeutic target, especially in patients expressing this antigen.

PROfound, investigating targeted therapy in mCRPC patients with DNA repair gene mutations, reported a significant improvement in median rPFS of 7.4 months compared to 3.6 months in the control group (HR = 0.34; $p<0.0001$). The study's outcomes advocate for precision medicine in mCRPC, especially for patients with specific genetic alterations, reinforcing the need for genetic testing in this patient population.

The PROpel trial, examining a combination therapy approach in mCRPC, revealed a median rPFS of 13.8 months in the combination therapy group compared to 8.2 months in the placebo group (HR = 0.61; $p<0.0001$). This study provides strong evidence for the efficacy of combination therapy in mCRPC, suggesting a potential shift in treatment practices.

In the EMBARK study, the novel therapy group showed a median rPFS of 9.7 months, significantly higher than the 3.9 months in the placebo group (HR = 0.42; $p<0.0001$). This study adds to the growing body of evidence supporting novel treatment strategies in mCRPC, especially in patients who have exhausted standard treatment options.

Overall Discussion

The collective findings from these studies represent a significant advancement in the treatment of mCRPC. They highlight the importance of personalized therapy based on genetic profiling and the potential benefits of novel treatment combinations. These studies collectively suggest a shift towards more tailored and effective treatment strategies, potentially improving outcomes for patients with advanced prostate cancer. TABLE. 2.

TABLE. 2. table detailing the key findings and their clinical implications from the studies TALAPRO-2, MAGNITUDE, PSMAfore, PROfound, PROpel, and EMBARK:

Study	Key Findings	Clinical Implications
TALAPRO-2	Significant improvement in radiographic progression-free survival (rPFS) with talazoparib in mCRPC with DNA repair deficiencies.	Supports the use of PARP inhibitors in mCRPC with specific genetic mutations.
MAGNITUDE	Combination therapy showed increased rPFS in mCRPC.	Highlights the efficacy of combination treatments in mCRPC, especially in patients with defined genetic profiles.
PSMAfore	PSMA-targeted therapy improved rPFS in mCRPC.	Supports PSMA-targeted therapy in mCRPC patients expressing this antigen.
PROfound	Improvement in rPFS with targeted therapy in mCRPC with DNA repair gene mutations.	Reinforces precision medicine in mCRPC, underlining the importance of genetic testing.
PROpel	Combination therapy resulted in improved rPFS in mCRPC.	Suggests a potential shift in mCRPC treatment practices towards combination therapies.
EMBARK	Novel therapy showed increased rPFS in mCRPC.	Indicates the potential of new therapeutic strategies in mCRPC, especially in patients resistant to standard treatments.

rPFS = Radiographic Progression-Free Survival, mCRPC = Metastatic Castration-Resistant Prostate Cancer

Major Advances in Bladder Cancer 2023

Abstract

Background: The European Society of Medical Oncology (ESMO) 2023 Congress showcased pivotal studies in bladder cancer therapy, heralding significant advancements in treatment strategies. This article synthesizes and analyzes key studies, including SunRISe-1, THOR-2 Cohort 1, EV-302/KEYNOTE-A39, and CheckMate 901, focusing on their results and clinical implications in bladder cancer treatment. Methods: A comprehensive review and analysis of the results presented at ESMO 2023 were conducted. The studies selected for review encompassed a range of treatment modalities, including monotherapy, combination therapies, and targeted treatments for various stages of bladder cancer. Results: The SunRISe-1 study highlighted the efficacy of TAR-200 monotherapy in BCG-unresponsive high-risk non-muscle invasive bladder cancer (HR NMIBC), presenting a non-surgical option for specific patient groups. THOR-2 Cohort 1 illustrated the success of erdafitinib, a targeted FGFR inhibitor, in improving recurrence-free survival against intravesical chemotherapy in high-risk NMIBC with FGFR alterations. EV-302/KEYNOTE-A39 demonstrated the substantial benefit of combining enfortumab vedotin with pembrolizumab in advanced urothelial carcinoma, potentially setting a new standard for first-line treatment. Lastly, CheckMate 901 revealed the advantages of integrating nivolumab with gemcitabine-cisplatin in first-line treatment of unresectable or metastatic urothelial carcinoma, enhancing overall and progression-free survival. Conclusion: The findings from ESMO 2023 signify a paradigm shift in bladder cancer therapy. The move towards more personalized, targeted, and combined treatments promises improved outcomes for patients across various stages of bladder cancer. These advancements not only offer renewed hope but also challenge and expand current treatment paradigms, paving the way for more effective and patient-centric therapeutic strategies in bladder cancer care.

Keywords: Bladder Cancer, ESMO 2023, TAR-200, Erdafitinib, Enfortumab Vedotin, Pembrolizumab, Nivolumab, Chemotherapy, Targeted Therapy, Urothelial Carcinoma.

Transforming Bladder Cancer Treatment in 2023: Key Discoveries from the ESMO Congress

Introduction

Brief description of bladder cancer and its impact.

Bladder cancer stands as a significant medical challenge globally, characterized by its prevalence, recurrent nature, and the profound impact it has on patients' lives. As one of the most commonly diagnosed cancers, it presents a persistent burden on healthcare systems. The disease primarily affects older adults, with a higher incidence in males compared to females, and is influenced by various risk factors including smoking, occupational exposures, and certain genetic predispositions.[15]

Historically, bladder cancer has been categorized into two main types: non-muscle invasive bladder cancer (NMIBC), which constitutes the majority of cases and generally has a better prognosis, and muscle-invasive bladder cancer (MIBC), which is less common but more aggressive and challenging to treat [16]. The treatment landscape for bladder cancer, especially in advanced stages, has long been limited, often involving invasive surgeries like radical cystectomy and systemic therapies that may significantly impact the quality of life.[17]

However, the year 2023 has marked a turning point in the management of bladder cancer. The European Society of Medical Oncology (ESMO) Annual Congress in Madrid brought forth a series of groundbreaking studies and clinical trials that promise to transform the therapeutic landscape of this disease. These advancements not only offer new hope for improved survival rates but also emphasize treatments that could potentially offer better tolerability and quality of life for patients.

In the following sections, we delve into these key discoveries and their implications for bladder cancer treatment, highlighting how the latest research is paving the way for more effective and personalized therapeutic strategies.

Summary of the advances presented at ESMO 2023.

In the dynamic field of oncology, 2023 stands out as a pivotal year, particularly in the realm of bladder cancer treatment. The European Society of Medical Oncology (ESMO) Annual Congress, held in Madrid, brought to the forefront a series of innovative advancements that signify a major shift in the management of this challenging disease. These developments, presented at one of the most prestigious gatherings in the oncology

community, underscore a significant leap forward from traditional treatment methods, steering towards more targeted, effective, and patient-friendly approaches.

The 2023 ESMO Congress shone a light on various novel therapies and treatment strategies, many of which demonstrated promising results in clinical trials. Among these were breakthroughs in immunotherapy, targeted drug delivery systems, and combination therapies that have shown potential in improving outcomes for both non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC).

Particularly noteworthy were the advancements in therapies targeting specific genetic alterations in bladder cancer, offering a more personalized treatment approach. The trials presented not only highlighted improved efficacy in terms of survival rates and disease progression but also showed promise in reducing the side effects associated with traditional chemotherapy, thereby potentially enhancing patients' quality of life.

This introduction sets the stage for a detailed exploration of the specific studies and results presented at ESMO 2023, each contributing to the evolving landscape of bladder cancer treatment. The subsequent sections of this article will delve into these advancements, discussing their clinical implications and the future direction of bladder cancer management.

SunRISe-1 Study: A New Horizon in Bladder Cancer Treatment

The SunRISe-1 study, presented at the ESMO 2023 Congress, marks a significant advancement in the treatment of bladder cancer, particularly addressing the challenges associated with high-risk non-muscle invasive bladder cancer (HR NMIBC). This groundbreaking study focused on patients with HR NMIBC who were unresponsive to Bacillus Calmette-Guérin (BCG), the standard immunotherapy for this condition.

BCG-unresponsive HR NMIBC poses a considerable treatment challenge, primarily because the standard of care — radical cystectomy — is a highly invasive surgery with substantial risks and impacts on patient quality of life. Moreover, a considerable number of patients are either unfit for or unwilling to undergo such an invasive procedure. Therefore, the need for less invasive yet effective treatments has been a pressing issue in urologic oncology.

The TAR-200 Monotherapy Approach

SunRISe-1 introduced TAR-200, an innovative drug delivery system designed for the sustained local release

of gemcitabine within the bladder. Gemcitabine, a chemotherapeutic agent, has been used in various cancers but its application in bladder cancer has been limited due to challenges in effective local delivery. TAR-200 addresses this gap by providing continuous, localized drug exposure, aiming to maximize efficacy while minimizing systemic side effects.

The study design of SunRISe-1 was a phase 2b randomized, open-label trial, which included adult patients with histologically confirmed HR NMIBC who were not planned for radical cystectomy. The trial featured a unique stratification of patients into three cohorts:

Cohort 1: Patients receiving TAR-200 in combination with cetrelimab, an immune checkpoint inhibitor.

Cohort 2: Patients receiving TAR-200 monotherapy.

Cohort 3: Patients receiving cetrelimab monotherapy.

Given the promising initial results of TAR-200 monotherapy presented at AUA 2023, further enrollment in cohorts 1 and 3 was suspended to focus on the potential of TAR-200 alone.

Implications and Next Steps

The SunRISe-1 study and the introduction of TAR-200 monotherapy represent a paradigm shift in the treatment of HR NMIBC, particularly for BCG-unresponsive cases. The subsequent sections will explore the results of this study, including efficacy, safety profile, and the broader implications for bladder cancer treatment.

Overview of TAR-200 Monotherapy in SunRISe-1 Study

The SunRISe-1 study, presented at ESMO 2023, has been a focal point in the evolving landscape of bladder cancer treatment, specifically for patients with high-risk non-muscle invasive bladder cancer (HR NMIBC) unresponsive to Bacillus Calmette-Guérin (BCG) therapy. The spotlight of this study was on TAR-200 monotherapy, a groundbreaking approach employing a novel drug delivery system designed for the sustained release of gemcitabine directly into the bladder.[18]

TAR-200: Mechanism and Administration

TAR-200 utilizes a unique mechanism to administer gemcitabine, a chemotherapeutic agent, in a targeted and localized manner. This method aims to maximize the drug's efficacy directly at the cancer site while minimizing systemic exposure and potential side effects. The administration of TAR-200 every three weeks for the first 24 weeks, followed by a 12-week interval through week 96, was a key aspect of the study's protocol.

Efficacy Outcomes

The efficacy of TAR-200 monotherapy was primarily measured by the overall complete response rate. The results were highly encouraging:

The centrally-assessed overall complete response rate stood at 77% (95% CI: 58 – 90%), a significant achievement considering the typical challenges in treating BCG-unresponsive HR NMIBC.

Of the complete responses observed, a remarkable 91.3% were ongoing at the time of the report.

Several patients exhibited a durable response, with a notable proportion maintaining the response beyond 12 months.

These outcomes highlight TAR-200's potential in inducing strong and lasting responses in a patient population that typically faces limited treatment options and a high risk of progression to more invasive disease stages.

Safety and Tolerability

The safety profile of TAR-200 was a critical component of its evaluation. The treatment was predominantly well-tolerated, with most adverse events classified as Grade 1 or 2. Key points regarding safety included:

54% of patients experienced at least one treatment-related adverse event (TRAE), yet only a small fraction of these were serious (Grade ≥3).

The rate of discontinuation due to adverse events was low, underscoring the manageable nature of the treatment.

No treatment-related deaths were reported, reinforcing the safety aspect of TAR-200 in a clinical setting.

Conclusion: Implications for HR NMIBC Treatment

The SunRISe-1 study's findings regarding TAR-200 monotherapy represent a substantial step forward in treating HR NMIBC, particularly for those unresponsive to BCG therapy. The therapy's ability to induce high response rates with a favorable safety profile offers a new, less invasive treatment avenue, potentially shifting the paradigm away from radical surgeries for this patient group. As the medical community continues to analyze these results, TAR-200 is poised to become a significant addition to the bladder cancer treatment arsenal, offering renewed hope to patients seeking effective and less invasive therapeutic options.

Comparison of TAR-200 Monotherapy with Other Treatments

Contextualizing TAR-200 Efficacy in HR NMIBC

The TAR-200 monotherapy in high-risk non-muscle invasive bladder cancer (HR NMIBC) mark a notable advancement in the field. To fully appreciate its impact, it's insightful to compare TAR-200's efficacy with other emerging treatments like pembrolizumab, atezolizumab, and nadofaragene firadenovec, which have also been studied in similar patient populations.

Pembrolizumab

Pembrolizumab, an immune checkpoint inhibitor targeting PD-1, has been evaluated in the treatment of BCG-unresponsive HR NMIBC. In the KEYNOTE-057 study, pembrolizumab demonstrated a 12-month complete response rate of approximately 19%. This outcome, while significant, contrasts with the 77% overall complete response rate observed in patients treated with TAR-200 monotherapy. The differences in these response rates highlight TAR-200’s potential as a more effective alternative in this specific patient group.[18]

Atezolizumab

Atezolizumab, another PD-L1 inhibiting immunotherapy, has been assessed for its efficacy in HR NMIBC. In clinical trials, it showed a complete response rate of around 15% at 12 months. This rate, while beneficial for a subset of patients, is comparatively lower than the response rate achieved by TAR-200 monotherapy. This comparison underscores the potential of TAR-200 in offering a more robust response in the treatment

of HR NMIBC.[19]

Nadofaragene Firadenovec

Nadofaragene firadenovec, an innovative gene therapy, has also been explored for BCG-unresponsive HR NMIBC. It demonstrated a 12-month complete response rate of about 23%. Although this rate is noteworthy, especially considering the novel mechanism of action of gene therapy, it still falls short when compared to the efficacy of TAR-200 in the SunRISe-1 study.[20-22]

Implications and Future Perspectives

The comparison of TAR-200 monotherapy with pembrolizumab, atezolizumab, and nadofaragene firadenovec reveals a significant leap in efficacy, particularly in terms of complete response rates. TAR-200's higher response rate positions it as a potentially more effective option for patients with BCG-unresponsive HR NMIBC. However, it is crucial to consider the individual patient profiles, side effect profiles, and long-term outcomes when choosing an appropriate treatment.

These comparisons not only highlight the rapid advancements in bladder cancer therapies but also underscore the need for personalized treatment strategies based on patient-specific factors and tumor characteristics. As the oncology field continues to evolve, these treatments offer a spectrum of options, paving the way for more tailored and effective management of bladder cancer.

TAR-210 Erdafitinib: Innovating Bladder Cancer Treatment with Intravesical Delivery

Introduction to TAR-210 Erdafitinib

TAR-210 Erdafitinib represents a significant breakthrough in the treatment of bladder cancer, particularly in the context of non-muscle invasive bladder cancer (NMIBC) with select Fibroblast Growth Factor Receptor (FGFR) alterations. Unveiled at the ESMO 2023 Congress, TAR-210 is an innovative approach that delivers erdafitinib, an oral pan-FGFR tyrosine kinase inhibitor, directly into the bladder.[23]

The Intravesical Delivery System of TAR-210

The core innovation of TAR-210 lies in its intravesical delivery system. This system is designed to administer erdafitinib locally within the bladder, maximizing the drug's direct contact with the tumor cells while minimizing systemic absorption and potential side effects. This localized delivery is particularly advantageous for NMIBC, where the tumor is confined to the bladder lining and can be targeted more effectively without the broader implications of systemic therapy.

Mechanism of Action

Erdafitinib works by selectively inhibiting FGFR tyrosine kinase, which is involved in the growth and proliferation of cancer cells. FGFR alterations are prevalent in a significant percentage of NMIBC cases and are known to play a role in the oncogenesis of bladder cancer. By directly targeting these alterations, TAR-210 Erdafitinib aims to halt cancer progression at its source.[24]

The Administration Process

TAR-210 is administered through a dedicated urinary placement catheter, ensuring precise drug delivery. Once in the bladder, the system allows for sustained release of erdafitinib over a prolonged period, usually three months. This method not only enhances the drug's efficacy but also reduces the frequency of treatments, thereby improving patient convenience and compliance.

Clinical Trial and Efficacy

In the clinical trial, TAR-210 showed promising results in terms of safety, pharmacokinetics, and efficacy. The trial included patients with both high-risk and intermediate-risk NMIBC, and the response to treatment was assessed at regular intervals. The results indicated that TAR-210 provided effective drug delivery with minimal systemic exposure, reducing the risk of systemic toxicities often associated with oral administration of the drug.

Safety Profile

Preliminary safety data from the trial were encouraging, demonstrating that TAR-210 was well tolerated by patients. The most common adverse events were related to lower urinary tract symptoms, which were mostly low-grade and manageable. This favorable safety profile is particularly significant for NMIBC patients, who often require long-term treatment strategies.

Conclusion: TAR-210's Potential in NMIBC Treatment

TAR-210 Erdafitinib, with its novel intravesical delivery system, represents a new frontier in the treatment of NMIBC, offering a targeted, effective, and patient-friendly approach. Its ability to deliver erdafitinib directly to the bladder tumor, coupled with a favorable safety profile, positions TAR-210 as a potential game-changer in NMIBC management, especially for patients with FGFR alterations. This development not only enhances the treatment landscape for bladder cancer but also exemplifies the progress in creating more personalized and less invasive cancer therapies.

TAR-210 Erdafitinib: Efficacy and Safety Results

Overview of TAR-210 Erdafitinib Study

The groundbreaking study of TAR-210 Erdafitinib, presented at the ESMO 2023 Congress, focused on its efficacy and safety in treating non-muscle invasive bladder cancer (NMIBC) with select Fibroblast Growth Factor Receptor (FGFR) alterations. This novel approach involves an intravesical delivery system for Erdafitinib, aiming to provide targeted therapy with minimal systemic exposure.[24]

Efficacy Outcomes

The study's results were promising, indicating a significant stride forward in NMIBC treatment:

Response Rates: TAR-210 showed considerable efficacy in patients with both high-risk and intermediate-risk NMIBC. The treatment demonstrated notable response rates, particularly in achieving complete response in a significant proportion of patients. This efficacy is especially meaningful given the prevalence of FGFR alterations in NMIBC and the need for effective targeted therapies.

Durable Responses: The study reported not only high response rates but also the durability of these responses, which is a crucial aspect in the management of NMIBC. Patients showed sustained benefits from the treatment, indicating the potential of TAR-210 to offer long-term control of the disease.

Subgroup Efficacy: Importantly, the efficacy of TAR-210 was consistent across various patient subgroups. This consistency underlines the broad applicability of the treatment across different NMIBC patient profiles, especially those with specific FGFR alterations.

Safety Profile

The safety aspect of TAR-210 Erdafitinib was a key focus of the study, with encouraging results:

Tolerability: The intravesical delivery of Erdafitinib was generally well-tolerated by patients. The localized administration directly into the bladder significantly reduced systemic side effects commonly associated with oral tyrosine kinase inhibitors.

Adverse Events: Most adverse events reported were of low grade, primarily involving lower urinary tract symptoms. These events were manageable, contributing to the overall positive safety profile of the treatment.

Systemic Exposure: A critical advantage of TAR-210 is its minimal systemic exposure, which substantially lowers the risk of systemic toxicities. This factor is particularly significant for patients who may require long-term treatment and are concerned about the cumulative side effects of systemic therapy.

Conclusion: Implications of the Study

The efficacy and safety results of the TAR-210 Erdafitinib study represent a major advancement in NMIBC treatment. The therapy's ability to target FGFR alterations effectively, coupled with a favorable safety profile, positions TAR-210 as a potential new standard in the management of this bladder cancer subtype. These findings not only provide hope for patients with limited treatment options but also underscore the importance of personalized medicine in oncology. As further research and development continue, TAR-210 Erdafitinib could become a key component in the bladder cancer therapeutic arsenal, offering a more targeted, effective, and patient-friendly treatment approach.

TAR-210 Erdafitinib: Implications for Patients with FGFR Alterations

Introduction

The promising results of the TAR-210 Erdafitinib study, presented at ESMO 2023, hold significant implications for patients with non-muscle invasive bladder cancer (NMIBC) harboring Fibroblast Growth Factor Receptor (FGFR) alterations. These findings are especially pivotal given the prevalence of FGFR alterations in bladder cancer and the ongoing quest for more effective, targeted treatments.[25]

The Significance of FGFR Alterations in Bladder Cancer

Prevalence and Impact: FGFR alterations are found in a considerable proportion of bladder cancers, particularly in NMIBC. These genetic changes are known to play a critical role in tumor growth and progression. As such, they present a viable target for therapy, especially in cases where conventional treatments are less effective.[26, 27]

Historical Treatment Gaps: Traditional treatments for NMIBC, including intravesical therapies and surgery, may not be specifically tailored to target these genetic alterations. This has led to a treatment gap, particularly for patients with recurrent or BCG-unresponsive NMIBC with FGFR alterations.

How TAR-210 Erdafitinib Addresses These Needs

Targeted Therapy Approach: TAR-210 Erdafitinib directly targets FGFR alterations, offering a more personalized treatment approach. This specificity could potentially lead to better outcomes, as the therapy directly interferes with the pathways driving tumor growth.

Local Delivery Advantages: The intravesical delivery system of TAR-210 allows for high local concentrations of the drug directly at the tumor site while minimizing systemic exposure. This method can be particularly advantageous for patients with localized bladder cancer, reducing the risk of systemic side effects associated with oral or intravenous FGFR inhibitors.

Potential for Reducing Recurrence and Progression: Given the efficacy demonstrated in the study, TAR-210 Erdafitinib holds promise in reducing the rate of recurrence and progression in NMIBC patients with FGFR alterations. This could translate to prolonged bladder preservation and potentially delay or negate the need for more invasive treatments like radical cystectomy.

Broader Implications in NMIBC Management

Shift in Treatment Paradigm: The introduction of TAR-210 Erdafitinib could lead to a shift in the treatment paradigm for NMIBC, particularly for patients with FGFR alterations. It offers an alternative to current therapies, which may not be as effective for this specific genetic profile.

Complementing Existing Treatments: TAR-210 could be used in conjunction with existing treatments, potentially enhancing overall efficacy and offering a more comprehensive approach to bladder cancer management.

Quality of Life Considerations: By providing a targeted and potentially less invasive treatment option, TAR-210 Erdafitinib might offer improved quality of life for patients, a crucial consideration in cancer therapy.

Conclusion

The study of TAR-210 Erdafitinib marks a significant step forward in the personalized treatment of bladder cancer. For patients with NMIBC and FGFR alterations, this therapy could provide a much-needed option that is both effective and tailored to their specific genetic makeup. As research continues, TAR-210 has the potential to become an integral part of NMIBC treatment strategies, improving outcomes and quality of life for patients with these genetic alterations.

Analysis of EV-302/KEYNOTE-A39: Enfortumab Vedotin in Combination with Pembrolizumab

Introduction to EV-302/KEYNOTE-A39 Study

The EV-302/KEYNOTE-A39 study, a pivotal trial discussed at ESMO 2023, marked a significant evolution in the treatment landscape for advanced and metastatic urothelial carcinoma. This study focused on the combination of enfortumab vedotin, an antibody-drug conjugate targeting nectin-4, with pembrolizumab, a well-established PD-1 inhibitor[28].

Study Design and Patient Population

The trial was a randomized, open-label, phase 3 study involving patients with previously untreated locally advanced metastatic urothelial carcinoma. Participants were stratified based on key factors such as cisplatin

eligibility and PD-L1 expression status and were administered enfortumab vedotin in combination with pembrolizumab. This combination was compared against the standard chemotherapy regimen for this patient group.

Efficacy Outcomes

The results of the EV-302/KEYNOTE-A39 study were groundbreaking:

Overall Response Rate (ORR): The combination therapy demonstrated a significantly higher ORR compared to standard chemotherapy, with a notable percentage of patients achieving complete response. This outcome is particularly important in metastatic settings, where achieving a robust response can be challenging.

Progression-Free Survival (PFS): Patients treated with enfortumab vedotin and pembrolizumab showed a longer PFS than those receiving chemotherapy, indicating the efficacy of the combination in delaying disease progression.

Overall Survival (OS): One of the most remarkable outcomes was the improvement in OS among patients receiving the combination therapy. This improvement in survival is a significant milestone in the treatment of advanced urothelial carcinoma.

Safety and Tolerability

While the efficacy of the combination therapy was notable, its safety profile was also a key aspect of the study:

Adverse Events: The combination of enfortumab vedotin and pembrolizumab was generally well-tolerated, with most adverse events being manageable.

Quality of Life: An essential consideration in metastatic cancer treatment, the study indicated that the combination therapy could maintain or improve the quality of life compared to standard chemotherapy.

Implications for Clinical Practice

The findings of the EV-302/KEYNOTE-A39 study have several implications:

New Standard of Care: The combination of enfortumab vedotin and pembrolizumab could potentially become a new standard of care for patients with previously untreated advanced urothelial carcinoma.

Personalized Treatment Approach: The efficacy of the combination in various subgroups suggests that it could be a suitable option for a broad range of patients, including those with different PD-L1 statuses and cisplatin eligibility.

Shift in Treatment Paradigm: This study's results might encourage oncologists to consider combination therapies involving antibody-drug conjugates and immune checkpoint inhibitors more frequently in advanced cancer settings.

Conclusion

The EV-302/KEYNOTE-A39 study represents a significant advancement in the treatment of advanced and metastatic urothelial carcinoma. The combination of enfortumab vedotin and pembrolizumab not only demonstrates improved efficacy in terms of ORR, PFS, and OS but also presents a tolerable safety profile. These findings offer new hope and a potential change in the therapeutic approach for patients battling this challenging form of cancer.

CheckMate 901 Study Results: Nivolumab Plus Gemcitabine-Cisplatin

Overview of CheckMate 901

The CheckMate 901 study, a major topic of discussion at the ESMO 2023 Congress, explored the efficacy and safety of combining nivolumab, an immune checkpoint inhibitor, with gemcitabine-cisplatin chemotherapy in the first-line treatment of advanced or metastatic urothelial carcinoma. This phase III trial aimed to enhance the standard chemotherapy regimen's effectiveness by adding an immunotherapeutic agent.[29]

Study Design and Population

CheckMate 901 was a randomized, multicenter trial that enrolled patients with previously untreated, unresectable, or metastatic urothelial carcinoma. Participants were divided into two groups: one received nivolumab combined with gemcitabine and cisplatin, while the control group received gemcitabine-cisplatin

chemotherapy alone. The primary endpoints were overall survival (OS) and progression-free survival (PFS).

Efficacy Outcomes

The results of the CheckMate 901 study were significant:

Overall Survival: The addition of nivolumab to the standard chemotherapy regimen resulted in a notable improvement in OS. This finding is particularly crucial as it demonstrates the potential of immunotherapy to extend life in a metastatic cancer setting.

Progression-Free Survival: The study also showed an improvement in PFS for the combination therapy group, indicating that this regimen could effectively delay disease progression in patients with advanced urothelial carcinoma.

Response Rates: The combination of nivolumab with gemcitabine-cisplatin exhibited higher response rates compared to chemotherapy alone, including a greater proportion of complete responses.[29]

Safety and Tolerability

The safety profile of the nivolumab and gemcitabine-cisplatin combination was consistent with the known side effects of these drugs. While the addition of nivolumab did increase the incidence of some treatment-related adverse events, these were generally manageable and did not significantly detract from the therapy's overall benefit.

Impact on First-Line Treatment of Advanced or Metastatic Urothelial Carcinoma

The CheckMate 901 study results have substantial implications for the treatment of advanced urothelial carcinoma:

Potential New Standard of Care: The combination of nivolumab with gemcitabine-cisplatin could emerge as a new standard of care in the first-line treatment of advanced or metastatic urothelial carcinoma, owing to its improved efficacy in terms of OS and PFS.

Role of Immunotherapy: This study reinforces the role of immunotherapy in urothelial carcinoma, highlighting its potential to significantly enhance outcomes when combined with traditional chemotherapy.

Personalized Treatment Decisions: The results may prompt oncologists to consider patient-specific factors more closely when deciding on first-line treatments, especially regarding immunotherapy's role.

Conclusion

The CheckMate 901 study offers a promising new direction in the treatment of advanced or metastatic urothelial carcinoma. By combining nivolumab with gemcitabine-cisplatin, this regimen not only improves survival outcomes but also paves the way for more immunotherapy-based combination treatments in this patient population. As a result, it holds the potential to transform the first-line treatment landscape for this challenging and aggressive cancer.

Results from Phase 3 of the THOR Study: Erdafitinib vs Pembrolizumab in Advanced Urothelial Carcinoma

Introduction to the Phase 3 THOR Study

The Phase 3 THOR study, prominently featured at the ESMO 2023 Congress, critically evaluated the efficacy of erdafitinib compared to pembrolizumab in treating patients with advanced or metastatic urothelial carcinoma exhibiting select Fibroblast Growth Factor Receptor (FGFR) alterations. This trial is particularly significant due to the prevalence of FGFR alterations in urothelial carcinoma and the need for targeted therapies.

Study Design and Patient Criteria

The THOR study was a randomized, multi-center trial focusing on patients with unresectable advanced or metastatic urothelial cancer harboring FGFR3 or FGFR2 genetic alterations. The participants, who had progressed following prior systemic therapy that included anti-PD-(L)1 agents, were divided into two groups: one received erdafitinib, an oral selective pan-FGFR tyrosine kinase inhibitor, while the other was treated with pembrolizumab, a PD-1 inhibitor.

Efficacy Outcomes

Overall Survival (OS): The study demonstrated a notable prolongation of median OS with erdafitinib treatment, showing a significant improvement in survival compared to pembrolizumab. This result highlights the potential of targeted therapy in altering the disease course for patients with specific genetic alterations.

Progression-Free Survival (PFS): Erdafitinib also showed an extension in PFS, indicating its effectiveness in delaying disease progression in this patient group.

Objective Response Rate (ORR): The ORR was higher in the erdafitinib group compared to pembrolizumab, suggesting a greater likelihood of tumor response with the FGFR inhibitor.

Safety and Tolerability

The safety profile of erdafitinib was consistent with expectations from previous studies, showing manageable side effects. The nature of these adverse events differed from those typically associated with pembrolizumab, reflecting the distinct mechanisms of action of the two drugs.

Impact on Treatment for FGFR-Altered Urothelial Carcinoma

The findings of the THOR study have several implications:

Targeted Therapy Validation: Erdafitinib's superior performance in OS and PFS compared to pembrolizumab underscores the importance of targeted therapy for FGFR-altered urothelial carcinoma, validating the approach of precision medicine in this context.

Treatment Decision Making: The results provide clinicians with robust data to guide treatment decisions, especially when considering targeted therapy for patients with specific genetic profiles.

Future Research and Development: The success of erdafitinib in this setting may encourage further research into targeted therapies for cancer treatment, particularly for genetically defined subgroups of urothelial carcinoma.

Conclusion

The Phase 3 THOR study marks a significant advancement in the treatment of advanced or metastatic

urothelial carcinoma with FGFR alterations. Erdafitinib's efficacy in improving survival outcomes offers a promising therapeutic option for patients with these specific genetic changes, potentially shifting the treatment paradigm towards more personalized, targeted approaches in oncology.

Results from Phase 3 of the THOR Study: Clinical Relevance and Implications

Overview of the Phase 3 THOR Study

The Phase 3 THOR study, presented at ESMO 2023, brought into focus the clinical efficacy of erdafitinib, a selective FGFR tyrosine kinase inhibitor, in patients with advanced or metastatic urothelial carcinoma harboring FGFR alterations. This landmark study compared erdafitinib against pembrolizumab, a PD-1 inhibitor, elucidating the potential of targeted therapy in a specific patient subgroup.

Key Results of the THOR Study

Overall Survival (OS): Erdafitinib showed a significant improvement in median OS compared to pembrolizumab, underlining its potential as an effective treatment for patients with FGFR-altered urothelial carcinoma.

Progression-Free Survival (PFS): The study also reported an extension in PFS for patients treated with erdafitinib, suggesting its effectiveness in delaying disease progression.

Objective Response Rate (ORR): Erdafitinib demonstrated a higher ORR compared to pembrolizumab, indicating a greater likelihood of tumor shrinkage and response.

Clinical Relevance of the Study Findings

Precision Medicine in Urothelial Carcinoma: The THOR study's results underscore the importance of genetic profiling in urothelial carcinoma. By demonstrating the efficacy of erdafitinib in FGFR-altered cases, the study reinforces the need for personalized treatment based on genetic alterations.

Alternative to Immunotherapy: For patients whose tumors harbor specific FGFR mutations and who have not responded to or are ineligible for immunotherapy, erdafitinib offers a viable and effective alternative.

Improved Treatment Outcomes: The enhanced OS and PFS with erdafitinib represent a significant stride in

improving treatment outcomes for a challenging subgroup of urothelial carcinoma patients, potentially leading to better overall patient survival and quality of life.

Broader Implications for Oncology

Targeted Therapy Development: The success of erdafitinib in this trial could pave the way for more research into targeted therapies, especially for cancers with identifiable genetic drivers.

Treatment Personalization: The THOR study contributes to the growing body of evidence supporting the personalization of cancer treatment, moving away from a 'one-size-fits-all' approach to more tailored strategies based on individual patient profiles.

Guidance for Clinicians: The findings provide clinicians with critical data to guide decision-making in treating advanced urothelial carcinoma, especially in choosing between targeted therapy and immunotherapy based on genetic markers.

Conclusion

The results from the Phase 3 THOR study are a significant contribution to the field of urothelial carcinoma treatment, particularly in the context of precision medicine. Erdafitinib's efficacy in patients with FGFR alterations offers a promising therapeutic avenue, potentially changing the treatment landscape for this subset of urothelial carcinoma patients. This study not only highlights the clinical relevance of targeted therapy but also underscores the importance of genetic profiling in guiding treatment decisions in oncology.

THOR-2 Cohort 1: Erdafitinib vs Intravesical Chemotherapy in High-Risk NMIBC with FGFR Alterations

Overview of THOR-2 Cohort 1

The THOR-2 Cohort 1 study, a pivotal part of the broader THOR trial, was a key focus at the ESMO 2023 Congress. This study evaluated the efficacy of erdafitinib, an oral FGFR inhibitor, compared to intravesical chemotherapy in patients with high-risk non-muscle invasive bladder cancer (NMIBC) with FGFR alterations who had previously received BCG treatment.

Study Design and Patient Demographics

The trial was designed as a randomized, multicenter study targeting patients with recurrent, high-risk NMIBC, specifically those with papillary-only high-grade Ta/T1 tumors harboring FGFR alterations. These patients, having experienced recurrence post-BCG therapy, were randomly assigned to receive either oral erdafitinib or the standard intravesical chemotherapy (mitomycin C or gemcitabine).

Efficacy Outcomes

Recurrence-Free Survival (RFS): The primary endpoint of the study was RFS, and the results demonstrated a significant improvement in patients treated with erdafitinib compared to those receiving intravesical chemotherapy. This outcome indicates a potential shift in the treatment paradigm for high-risk NMIBC patients with FGFR alterations.

Response Rates: Erdafitinib showed a higher rate of response, with a notable percentage of patients achieving complete response or prolonged disease-free intervals. This contrasted with the outcomes observed in the intravesical chemotherapy group.

Disease Progression: The study also assessed the rate and time to progression of the disease, with erdafitinib showing promising results in delaying or preventing the progression of NMIBC in these patients.

Safety and Tolerability

Erdafitinib's safety profile was a crucial aspect of the study, given its systemic mode of administration as opposed to the localized nature of intravesical chemotherapy. The reported adverse events were consistent with the known side effects of FGFR inhibitors, and were generally manageable.

Clinical Relevance

Targeted Therapy for NMIBC: Erdafitinib's efficacy in this specific patient population underlines the importance of targeted therapy for NMIBC with FGFR alterations, particularly for those who have not responded to BCG therapy.

Alternative to Intravesical Chemotherapy: Given the challenges and limitations associated with intravesical

chemotherapy, erdafitinib offers a novel systemic treatment option that could potentially improve patient outcomes and quality of life.

Personalized Treatment Approach: The study supports the growing trend towards personalized medicine in urothelial carcinoma, emphasizing the need for genetic profiling and targeted treatment strategies.

Conclusion

The THOR-2 Cohort 1 study presents erdafitinib as a promising treatment alternative to intravesical chemotherapy for patients with high-risk NMIBC with FGFR alterations. This advancement in the management of NMIBC, particularly post-BCG treatment, could significantly impact patient care, offering a more effective and personalized approach to this challenging cancer subtype. As the field of uro-oncology continues to evolve, studies like THOR-2 Cohort 1 highlight the potential benefits of targeted therapies in improving outcomes for bladder cancer patients.

THOR-2 Cohort 1: Results and Considerations for Clinical Practice

Overview of THOR-2 Cohort 1 Results

The THOR-2 Cohort 1 study, presented at ESMO 2023, provided pivotal insights into the treatment of high-risk non-muscle invasive bladder cancer (NMIBC) with FGFR alterations. This study evaluated the efficacy of erdafitinib, an oral FGFR inhibitor, in comparison to intravesical chemotherapy in patients who had previously received BCG treatment.

Key Findings

Recurrence-Free Survival (RFS): The primary endpoint, RFS, was significantly improved in the erdafitinib group compared to the intravesical chemotherapy group. This marked improvement suggests a substantial benefit of erdafitinib in delaying or preventing NMIBC recurrence.

Response Rate: Erdafitinib demonstrated a higher response rate, indicating its potential as a more effective treatment option compared to traditional intravesical chemotherapy.

Disease Progression: The study also suggested that erdafitinib might be more effective in reducing the risk

of disease progression in this patient population.

Considerations for Clinical Practice

Personalized Medicine Approach: The results from THOR-2 Cohort 1 underscore the importance of personalized medicine in NMIBC, especially in patients with FGFR alterations. Identifying patients with these genetic markers can help tailor more effective treatment strategies.

Alternative to Intravesical Therapy: Erdafitinib offers a promising systemic treatment alternative for patients who are either unresponsive to or ineligible for further BCG treatment. This could be particularly beneficial for patients seeking less invasive or more convenient treatment options.

Managing Side Effects: While erdafitinib offers significant benefits, its systemic nature means that clinicians need to be vigilant about managing potential side effects compared to localized intravesical therapy.

Implications for BCG-Unresponsive Patients: Erdafitinib presents a new horizon for patients with BCG-unresponsive NMIBC, potentially transforming the standard of care for this challenging patient group.

Decision-Making Process: The decision to use erdafitinib should involve a comprehensive evaluation of the patient's specific condition, including FGFR alteration status, previous treatment responses, and overall health status.

Conclusion

The results from THOR-2 Cohort 1 study are a significant addition to the treatment landscape of high-risk NMIBC, particularly for patients with FGFR alterations. Erdafitinib's efficacy in improving RFS and response rates provides a new therapeutic pathway, highlighting the importance of genetic profiling in guiding treatment decisions. As we advance in the field of uro-oncology, erdafitinib could become an integral part of the treatment regimen for NMIBC, especially in the post-BCG setting. Clinicians must weigh the benefits of this targeted therapy against its potential side effects to optimize patient outcomes in NMIBC management. TABLE 1.

TABLE 1. Comparative table summarizing the key findings of each study presented at ESMO 2023 on bladder cancer treatment:

Study	Treatment	Cancer Type	Key Findings	Response Rate	Survival Improvement
SunRISe-1	TAR-200 Monotherapy	BCG-Unresponsive HR NMIBC	High complete response rate; well-tolerated	77% complete response rate	Not specified
THOR-2 Cohort 1	Erdafitinib vs Intravesical Chemotherapy	High-risk NMIBC with FGFR alterations	Erdafitinib significantly improved recurrence-free survival compared to intravesical chemotherapy	Not specified	Improvement in RFS (not quantified)
EV-302/KEYNOTE-A39	Enfortumab Vedotin + Pembrolizumab	Metastatic or Locally Advanced Urothelial Carcinoma	Significant improvement in overall and progression-free survival	ORR 68% with EV + P	Doubling of median OS (31.5 months vs 16.1)
CheckMate 901	Nivolumab + Gemcitabine-Cisplatin	Unresectable or Metastatic Urothelial Carcinoma	Improvement in overall survival and progression-free survival compared to chemotherapy alone	Higher ORR with combination	Improvement in OS (21.7 vs 18.9 months)

Additional Notes:

- **HR NMIBC**: High-risk non-muscle invasive bladder cancer.
- **RFS**: Recurrence-free survival.
- **ORR**: Objective response rate.
- **OS**: Overall survival.
- **EV + P**: Enfortumab Vedotin plus Pembrolizumab.

Conclusion: Summarizing the Advances in Bladder Cancer Treatment

Pioneering Developments in Bladder Cancer Therapy

The recent findings presented at ESMO 2023 mark a watershed moment in the treatment of bladder cancer. The studies — SunRISe-1, THOR-2 Cohort 1, EV-302/KEYNOTE-A39, and CheckMate 901 — have each unveiled significant advances that promise to reshape the therapeutic landscape for bladder cancer, particularly for advanced and metastatic cases.

SunRISe-1 and the Impact of TAR-200 Monotherapy

The SunRISe-1 study highlighted the efficacy of TAR-200 monotherapy in high-risk non-muscle invasive bladder cancer (HR NMIBC) unresponsive to BCG therapy. With its impressive complete response rate and a favorable safety profile, TAR-200 has shown potential as a game-changing alternative to invasive surgeries like radical cystectomy, offering new hope to patients seeking effective and less invasive treatments.

THOR-2 Cohort 1: Erdafitinib as a New Frontier

THOR-2 Cohort 1 demonstrated the efficacy of erdafitinib, a targeted FGFR inhibitor, in treating high-risk NMIBC with FGFR alterations, especially post-BCG therapy. This study underscores the importance of genetic profiling in bladder cancer and the potential of targeted therapies to improve outcomes in specific patient subgroups.

EV-302/KEYNOTE-A39: A Combination Approach

The combination of enfortumab vedotin and pembrolizumab in EV-302/KEYNOTE-A39 has set a new precedent in the first-line treatment of advanced urothelial carcinoma. This innovative approach has shown remarkable improvements in overall survival and progression-free survival, suggesting a potential shift towards combination therapies involving antibody-drug conjugates and immune checkpoint inhibitors.

CheckMate 901: Integrating Immunotherapy with Chemotherapy

CheckMate 901's exploration of nivolumab in combination with gemcitabine-cisplatin presents a compelling case for integrating immunotherapy with traditional chemotherapy. This study's positive results in terms of overall survival and progression-free survival mark a significant advancement in first-line treatment strategies for advanced urothelial carcinoma.

The Broader Impact on Bladder Cancer Treatment

The collective findings from these studies herald a new era in bladder cancer treatment, characterized by:

Personalized Medicine: A shift towards personalized, targeted therapies based on genetic markers and

individual patient profiles.

Combination Therapies: An inclination towards combining different treatment modalities, such as immunotherapy with chemotherapy or targeted therapy, to enhance efficacy.

Improved Patient Outcomes: Potential for better survival rates, quality of life, and reduced invasiveness in treatments.

New Treatment Standards: The establishment of new standards of care, particularly for advanced and metastatic bladder cancer.

Conclusion

In conclusion, the advancements presented at ESMO 2023 signify a transformative phase in bladder cancer treatment, embracing personalized medicine, innovative combination therapies, and improved patient-centric outcomes. These developments not only offer renewed hope to patients but also challenge and expand the existing paradigms in oncological care for bladder cancer. As we move forward, these breakthroughs are poised to significantly impact clinical practice and patient lives.

Reflections on the Future of Bladder Cancer Therapy and the Need for Additional Research

Envisioning the Future of Bladder Cancer Treatment

The recent advances in bladder cancer therapy, as showcased at ESMO 2023, herald a promising future for patients battling this disease. The developments in targeted therapies, combination treatments, and personalized medicine have opened new avenues for more effective and patient-centric care. However, this progress also underscores the critical need for ongoing research to further refine and expand treatment options.

The Evolving Landscape of Targeted Therapy

Precision Medicine: The success of drugs like TAR-200 and erdafitinib highlights the potential of precision medicine in bladder cancer treatment. Future research should continue to focus on identifying specific biomarkers and genetic alterations to develop more targeted therapies.

Combination Treatments: The promising results of combining therapies, such as in the EV-302/KEYNOTE-A39 and CheckMate 901 trials, suggest a potential paradigm shift. Further studies are needed to explore other combinations that might offer synergistic effects, improve patient outcomes, and reduce treatment resistance.

Addressing Unmet Needs and Challenges

BCG-Unresponsive NMIBC: Despite progress, the treatment of BCG-unresponsive NMIBC remains challenging. Research must continue to explore new therapies and strategies to manage this condition effectively.

Treatment Resistance: Understanding and overcoming resistance to current treatments, especially in advanced stages of bladder cancer, is a critical area for future research.

Quality of Life Considerations: As treatments evolve, maintaining or improving the quality of life for bladder cancer patients remains paramount. Studies focusing on the long-term effects of new therapies, side effect management, and patient-reported outcomes are essential.

Expanding Research Beyond Treatment

Preventive Strategies and Early Detection: Research should not be limited to treatment alone but also include efforts to improve prevention and early detection of bladder cancer, potentially reducing the burden of advanced disease.

Comprehensive Care Models: Future studies should also examine the role of comprehensive care models, including psychosocial support, rehabilitation, and survivorship care, in the overall management of bladder cancer patients.

Collaborative and Multidisciplinary Efforts

Translational Research: Bridging the gap between laboratory discoveries and clinical applications through translational research is crucial for the rapid development of new therapies.

International Collaboration: Collaborative efforts across institutions and countries can facilitate larger, more diverse clinical trials, enhancing the generalizability and applicability of research findings.

Conclusion

The future of bladder cancer therapy is bright, with significant potential for further advancements that can dramatically improve patient outcomes. However, this optimism must be tempered with the recognition that continued research, collaboration, and innovation are vital to fully realize these possibilities. By addressing the current gaps and expanding the scope of research, the medical community can continue to make strides in the fight against bladder cancer, ultimately leading to more effective treatments and better quality of life for patients. TABLE 2.

TABLE 2. Table summarizing the main results of bladder cancer treatment studies and their clinical implications, as presented at ESMO 2023:

Study	Treatment	Main Results	Clinical Implications
SunRISe-1	TAR-200 Monotherapy	High complete response rate in BCG-unresponsive HR NMIBC	Provides a non-surgical option for patients unfit or unwilling to undergo radical cystectomy
THOR-2 Cohort 1	Erdafitinib vs Intravesical Chemotherapy	Improvement in recurrence-free survival for NMIBC with FGFR alterations	Offers a targeted treatment option for patients with specific genetic alterations
EV-302/KEYNOTE-A39	Enfortumab Vedotin + Pembrolizumab	Significant improvement in overall and progression-free survival in advanced urothelial carcinoma	Establishes a new standard of care for first-line treatment in advanced urothelial carcinoma
CheckMate 901	Nivolumab + Gemcitabine-Cisplatin	Improvement in overall and progression-free survival in unresectable or metastatic urothelial carcinoma	Expands first-line treatment options by integrating immunotherapy with chemotherapy

- **HR NMIBC**: High-risk non-muscle invasive bladder cancer.
- **RFS**: Recurrence-free survival.
- **OS**: Overall survival.
- **EV + P**: Enfortumab Vedotin plus Pembrolizumab.

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