Review

Exploring the Link Between Malignant Melanoma and Urological Cancers: A Path Towards Personalized Medicine. Review of the Literature

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Review

Exploring the Link between Malignant Melanoma and Urological Cancers: A Path towards Personalized Medicine Review of the Literature

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Abstract: Malignant melanoma and urological cancers originate from different tissues and organs, yet several studies highlight connections between these malignancies, including common risk factors, genetic predispositions, and immunological pathways. Research indicates that individuals with a history of melanoma have an elevated risk of developing renal cell carcinoma (RCC), while those with RCC are more likely to develop melanoma. Shared factors such as a personal or family history of cancer, UV radiation exposure, smoking, and obesity have all been linked to an increased incidence of various cancer types. A major link between malignant melanoma and urological cancers is the presence of shared genetic mutations and familial cancer syndromes. Key mutations, including germline mutations in BRCA1, MITF, CDKN2A, TP53, and alterations in the PI3K/AKT pathway, significantly contribute to the risk of both types of malignancies. Personalized medicine, which tailors prevention and treatment strategies to an individual's genetic, environmental, and lifestyle factors, has significantly improved cancer care. The primary aim is to select the most effective treatment for each patient, maximizing therapeutic outcomes, reducing side effects, and minimizing the risk of drug resistance. Advances in genomics and immunology are driving the development of personalized therapies that target specific molecular pathways and immune responses common to both melanoma and urological cancers. Angiogenesis inhibitors and checkpoint inhibitors have demonstrated notable success in treating these cancers, with tumor mutational burden serving as a valuable biomarker for predicting the efficacy of immune checkpoint inhibitors.

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1. Introduction

Cancers are the leading cause of mortality. The global prevalence of cancer, as well as cancer-related mortality rates, has been hastily increasing as a result of rising population size, ageing, and higher exposure to cancer risk factors [1].

Malignant melanoma and urological cancers (renal, bladder, prostate, penis, testis or urethra cancer) are distinct malignancies arising from different tissues and organs. Multiple data from the literature describe connections between these types of cancers, including shared risk factors, genetic predispositions, and immunological mechanisms.

Understanding the correlation between malignant melanoma and urological cancers can lead to improved cancer detection, prevention, and treatment strategies.

Melanoma accounts for 1.7% of global cancer diagnoses and is the fifth most common cancer in the US. Although the overall 5-year survival has risen to 93.3% in the US, survival for stage IV disease remains only 29.8% [2].

Urological cancers, including kidney, bladder, prostate, testicular, penile, and urethral cancers, vary widely in terms of incidence, risk factors, and prognosis.

Renal cell carcinoma (RCC) represents around 3% of all cancers, with the highest incidence occurring in Western countries [3], with an estimated 431,288 new cases of RCC globally, of which 138,611 in Europe [4].

Urothelial carcinoma (UC) is the second most common urological malignancy in developed countries. They can be localised in the lower (bladder and urethra) and/or the upper (pyelocaliceal cavities and ureter) urinary tract. Upper tract urothelial carcinomas (UTUC) account for only 5–10% of UCs [5], bladder cancer (BC) accounts for 90–95% of UCs. Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, and it is the tenth when both genders are considered [6].

Primary urethral carcinoma is considered a rare cancer, accounting for < 1% of all genitourinary malignancies [7].

Prostate cancer (PCa) is the second most commonly diagnosed cancer in men, with an estimated 1.4 million diagnoses worldwide in 2020. In Europe it is the most common solid neoplasm, with an incidence rate of 370 000 per 100 000 men, outnumbering lung and colorectal cancer [8].

Testicular cancer (TC) represents 1% of adult neoplasms and 5% of urological tumors, with three to ten new cases per 100,000 males/per year in Western societies. The incidence of TC has increased during recent decades, predominantly in industrialized countries, and it continues to rise [9].

Penile cancer incidence varies across the world. Is uncommon disease in industrialized countries, with an overall incidence of around 1/100,000 males in Europe and 0.5 in the USA [10].

2. Epidemiological Links

There is a notable association between malignant melanoma and renal cell carcinoma (RCC). Research suggests that individuals with a history of melanoma have a higher risk of developing RCC, and those with RCC are at a greater risk of subsequent melanoma. This bidirectional association may be due to shared risk factors [11].

2.1. Environmental and Lifestyle Risk Factors for Malignant Melanoma and Urological Cancers

Factors such as advanced age, a personal or family history of cancer, certain viral infections like human papillomavirus (HPV), exposure to radiation (e.g., ultraviolet radiation from the sun), exposure to certain chemicals, smoking, alcohol consumption, and obesity have all been found to be associated with an increased incidence of various types of cancer.

2.1.1. Ultraviolet (UV) Exposure and Vitamin D

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The roll of ultraviolet (UV) sunlight radiation in the development of skin cancers, particularly malignant melanoma, is well-documented. UVA (320–400 nm) penetrates deeper into the skin, causing indirect DNA damage through reactive oxygen species (ROS) and UVB (280–320 nm) causes direct DNA damage by inducing cyclobutane pyrimidine dimers (CPDs) [12]. UVB radiation can also induces mutations in genes such as TP53 and BRAF, contributing to melanomagenesis [13].

However, the association between UV exposure and RCC remains unclear, recent studies have attempted to clarify the relationship but have produced mixed results. Grasso et al. [14] found no statistically significant differences between sun exposure in patients affected by kidney cancer and controls, both during childhood and adult life. Contrary to this, Karami et al. [15] suggest that among males there is an inverse association between occupational UV exposure and renal cancer risk. Replication studies are warranted to confirm these results.

Similar to the RCC, the role of vitamin D in bladder cancer and upper urinary tract urothelial cancer remains insufficiently evaluated. Epidemiological evidence regarding vitamin D levels and bladder cancer risk is inconclusive.

Most studies have shown that high dietary vitamin D intake in combination with low calcium intake were associated with a decreased risk of bladder cancer [16]. In a meta-analysis Zhang et al. [17] concluded that Vitamin D deficiency is associated with increased risk of bladder carcinoma. Recently, Gislefoss et al. [18] suggested that low-serum level of 25-hydroxy vitamin D (25(OH)D) and obesity have increase the BC risk, and leptin, which is important in weight regulation, may be involved in bladder carcinogenesis.

The role of vitamin D in prostate cancer is well established. The 2024 European Association of Urology (EAU) guideline mentions that with both low- and high vitamin-D concentrations being associated with an increased risk of PCa, and more strongly for high-grade disease [19,20]. Additionally, Murphy et al. demonstrated that Vitamin D deficiency was linked to higher Gleason scores and advanced tumor stages at diagnosis [21].

Ultraviolet A phototherapy represent risk factors for penile cancer [22].

There are no significant data regarding the involvement of UV exposure and vitamin D levels in testicular cancer.

2.1.2. Smoking

Smoking is a major risk factor for urological cancers, particularly bladder cancer, and has also been linked to an increased risk of melanoma. The carcinogenic compounds in tobacco can affect multiple organs, leading to the development of both skin and urological malignancies.

The effect of smoking in melanoma outcome still remains an enigma [23]. Recently, Arafa and colleagues [24] demonstrated that current smoking and heavy smoking is associated with a higher risk of squamous cell carcinoma (SCC) but a decreased risk of malignant melanoma, while former smoking was not associated with skin cancer risk. Conversely, in a case-control study published by Sondermeijer et al. [25] presented a strong inverse association between cigarette smoking and melanoma risk in men.

Smoking represent established risk factors for the urological cancers. The main mechanisms are: DNA damage by the tobacco carcinogens, increases oxidative stress, leading to cellular injury and carcinogenesis and angiogenesis, aiding tumor growth and metastasis.

Smokers have a 1.5-fold increased risk of RCC compared to non-smokers [26], but smoking cessation reduces RCC risk over time [27].

Multiple carcinogens (N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA), polycyclic aromatic hydrocarbons (PAHs), Cadmium and lead (Pb), 2-naphthylamine) are absorbed through the lungs into the bloodstream and then lipophilic carcinogens may accumulate in renal tissue [28].

Tobacco smoking is the most important risk factor for bladder cancer, accounting for approximately 50% of cases [29]. Low-tar cigarettes are not associated with a lower risk of developing BC. The risk associated with electronic cigarettes has not been adequately assessed. Bjurlin et al. demonstrated that biomarkers of carcinogens, several with a strong link to bladder cancer, are present in the urine of e-cigarette users.

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Kispert et al. [30] recently presented a study in wich smoking is associated with increased platelet-activating factor (PAF) accumulation and PAF receptor (PAF-R) expression and may contribute to tumor progression and metastasis in smokers.

Similarly, the carcinogens from cigarettes act on the entire urothelium, leading to the appearance of upper tract urothelial carcinomas or urethral cancer.

Current cigarette smoking was associated with an increased risk of PCa death and with aggressive tumor features and worse prognosis, even after quitting smoking [31].

Daling et al. [32] in a population-based case-control study in western Washington state that included 137 men presented that smoking do not increase the risk for in situ cancer, but proved significant risk factors for invasive penile cancer.

Even if previous studies suggested the existence of a correlation between maternal smoking and testicular cancer, Beck et al. [33] in a systematic review and meta-analysis concluded that evidence of an association between maternal exposure to cigarette smoke and risk of testicular cancer in offspring. An overall positive trend was suggested, but it had low statistical precision.

2.1.3. Obesity

Obesity promotes chronic inflammation, which is a known risk factor for cancer development. Inflammatory cytokines may promote the growth of both melanoma and RCC, providing a potential link between these malignancies [34].

Obesity with a BMI >35 is a well-established risk factor for RCC. At the same time, several retrospective studies have shown that obesity appears to be a factor that positively influences the prognosis of patients with RCC, call "obesity paradox". Recently, Graff and colleagues [35] provided a comprehensive review with the main purpose to disentangle the "obesity paradox" in renal cell carcinoma. The results support obesity as a risk factor for total and fatal RCC. They undermine the obesity paradox by suggesting that weight loss around diagnosis, and not low BMI itself, is associated with worse prognosis.

In the REDUCE study [36] obesity was associated with lower risk of low-grade PCa, and a higher risk of high-grade PCa.

The data regarding the role of obesity as a risk factor on other urological cancers (urothelial, penile, testicular) are inconclusive.

2.1.4. Occupational Exposure

Bladder cancer is known to be associated with occupational exposure to certain chemicals, such as aromatic amines found in dyes and rubber. There is limited evidence to suggest that these same carcinogens could also increase the risk of cutaneous melanoma, particularly in industrial workers exposed to multiple environmental carcinogens.

3. Shared Genetic Mutations and Molecular Pathways

3.1. Malignant Melanoma and Renal Cancer

One of the most significant connections between malignant melanoma and renal cell carcinoma lies in shared genetic mutations and familial cancer syndromes. Several key genetic mutations contribute to the risk of both malignancies.

3.1.1. BAP1 Tumor Predisposition Syndrome (BAP1-TPDS) is a hereditary cancer syndrome characterized by germline mutations in the BRCA1-associated protein 1 (BAP1) gene [37]. Located on chromosome 3p21.1, the main function of BAP1 is to encodes a nuclear deubiquitinating hydrolase that regulates cellular processes like DNA damage response, cell cycle progression, chromatin remodeling and regulation of gene expression [38]. The germline mutations is an inherited mutations in one or two allele of the BAP1 gene resulting in complete loss of BAP1 function. The consequences are genomic instability, uncontrolled cell proliferation and resistance to apoptosis. This can predispose individuals to uveal melanoma, cutaneous melanoma, and RCC [39].

In case of cutaneous melanoma patients with Germline mutations in BAP1 develop multiple atypical melanocytic lesions (dome-shaped, skin-colored to reddish papules), histologically distinct from conventional melanomas [40].

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Kapur et al [41] in a retrospective analysis on 145 patients with primary clear cell renal cell carcinoma (ccRCC) concluded that in RCC the clear cell subtype (ccRCC) germline mutations occur in approximately 10–15% of ccRCC. These patients are associated with poorer overall survival compared to those without mutation.

3.1.2. MITF Mutation

The Microphthalmia-associated Transcription Factor (MITF) regulates genes involved in melanogenesis, melanocyte survival and proliferation and DNA repair. The MITF-E318K variant is heterozygous missense mutation resulting in a glutamic acid to lysine substitution at position 318. Carriers have a higher risk of developing early-onset melanoma [42].

This mutation was also identified in patients with RCC, suggesting a shared genetic risk factor with melanoma. Lang et al. [43] concluded in a study that association of the pathogenic MITF variant with bilateral and multifocal type 1 papillary RCC in this family supports its role as a risk allele for the development of RCC and emphasizes the importance of screening for MITF variants irrelevant of the RCC histologic subtype .

3.1.3. CDKN2A Mutation

The roll of cyclin-dependent kinase inhibitor 2A gene is to prevent cell proliferation. Mutation of the CDKN2A gene leads to deregulated cell growth and increased tumorigenesis.

Carriers of CDKN2A mutations have a significantly higher risk of developing multiple primary melanomas at a younger age [44].

The role of CDKN2A mutations in renal cell carcinoma is less clear. Recently, in a study Kiatprungvech and colleagues [45] demonstrated that CDKN2A mutations may be associated higher tumor grade and poorer prognosis in RCC, development and sarcomatoid changes.

3.2. Malignant Melanoma and Urothelial Cancers

3.2.1. TP53 Mutation

TP53 gene in humans, is referred as the “guardian of the genome” due to its activities directed at maintaining genomic stability through the repair of damaged DNA [46].

Even though TP53 is rarely mutated in melanoma, reduced levels of p53 contribute to aggressiveness and resistance to therapy for patients with malign melanoma [47].

Wu et al. [48] found the TP53 mutation in 50% of bladder cancer patients and patients with muscle-invasive bladder cancers (MIBC) have more TP53 mutations than patients with non-muscle-invasive bladder cancers (NMIBC). Patients with the TP53 mutation were associated with a lower TP53 mRNA expression level, more advanced tumor stage and higher histologic grade.

3.2.2. CDKN2A Mutation

Deletions of CDKN2A is a molecular risk factors for tumour progression in NMIBC an indicator of increased aggressiveness and worse prognosis in MIBC [49].

3.2.3. PI3K/AKT Pathway

(phosphatidylinositol 3-kinase)-AKT pathway is one of the most important signaling networks in cancer.

The PI3K-AKT pathway plays a crucial role in both melanoma initiation and therapeutic resistance [50].

Various molecular alterations in PI3K/AKT/mTOR signaling have been described in bladder cancer, especially in metastatic form [51].

3.3. Malignant Melanoma and Prostate Cancer

3.3.1. CDKN2A Mutation

Cao et al. [52] in a meta-analysis of CDKN2A methylation to find its role in prostate cancer development and progression concluded that CDKN2A methylation may not be significantly

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associated with the development, progression of PCa. Although CDKN2A expression had an unfavorable prognosis in disease-free survival.

3.3.2. BRCA1 and BRCA2 Mutation

Nyberg and colleagues [53] in a prospective cohort study of male BRCA1 and BRCA2 carriers confirmed BRCA2 association with aggressive PCa.

3.4. Malign Melanoma and Penile Cancer

TP53 Mutation About half of HPV-negative penile cancers are driven by oncogenic activation of TP53, while a quarter is induced by loss of TP53 tumor suppressor function [54]. The CDKN2A mutation is rarely found in penile cancer.

3.5. Malignant Melanoma and Testicular Cancer

Few data from the literature suggest that *CDKN2A mutation* could have a role in testicular germ cell tumors [55].

4. Clinical Implications and Personalized Medicine

Personalized medicine, which customizes prevention and treatment strategies based on an individual's genetic, environmental, and lifestyle factors, has greatly advanced cancer care [56].

Understanding the link between malignant melanoma and urological cancers is a key advancement toward personalized medicine.

Identifying genetic mutations and syndromes that link melanoma to urological cancers highlights the importance of genomic profiling in cancer diagnosis and treatment. Advances in next-generation sequencing (NGS) now allow for the detection of specific mutations that may predispose individuals to multiple cancers or influence their response to treatment. NGS offers new opportunities for personalized precision medicine [57].

4.1. Tailoring Prevention Strategies (Table 1)

4.1.1. Reduce Ultraviolet Exposure and the Roll of Vitamin D

Excessive UV exposure is widely recognized as the leading environmental risk factor for melanoma. For those with a higher genetic risk [58], personalized prevention strategies include consistent use of broad-spectrum sunscreen, wearing protective clothing, and avoiding tanning beds.

Song et al. [59] in a systematic review and meta-analysis concluded that a moderate dietary vitamin D supplement to avoid the serum 25(OH)D deficient might be beneficial to the long-term survival of patients with melanoma.

In a prospective study Lin et al. [60] concluded that ultraviolet radiation exposure decreased the risk of PCa. Both low and high vitamin D concentrations have been associated with an increased risk of prostate cancer, with a stronger correlation for high-grade disease [19]. Maintaining normal vitamin D levels is essential.

4.1.2. Smoking Cessation in Malign Melanoma and Urological Cancers Prevention

Although the effect of smoking on malignant melanoma is still uncertain, smoking is a well-established risk factor for various urological cancers, particularly bladder cancer and RCC. Smoking cessation programs, aided by pharmacological treatments such as nicotine replacement therapy (NRT), have proven effective in reducing the incidence or recurrence of progression RCC [27] and bladder cancer [61]. In a network meta-analysis of 20 randomized controlled trials Gou et al. [62] concluded that Varenicline and Bupropion increased the odds of smoking abstinence.

4.1.3. Obesity and Dietary Interventions in Malignant Melanoma and Urological Cancers Prevention

Studies that focus specifically on the link between obesity and melanoma prognosis are limited [63]. Obesity may be a risk factor for bladder cancer recurrence [64] and higher risk of death from prostate cancer [65].

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The use of dietary antioxidants has shown promising results in studies, supporting the potential role of antioxidants in the prevention of malignant melanoma related to UV exposure.

Obesity and dietary habits are well-established risk factors for prostate cancer and RCC.

Personalized weight management programs guided by genetic and metabolic profiles, and dietary recommendations, such as reducing red and processed meats and increasing intake of plant-based foods rich in antioxidants (e.g., lycopene), regular physical activity, are essential for individuals at high risk for prostate cancer and RCC [66,67].

Table 1. Recommendations for lifestyle changes.

	Malignant melanoma	RCC	Urothelial cancer	Prostate cancer	Penile cancer	Testicular cancer
Smoking cessation	uncertain	yes	yes	yes	yes	uncertain
Reduce ultraviolet exposure	yes	-	-	No/ increase	ultraviolet A phototherapy	-
Vitamin D	moderate increase dietary	normal vitamin D levels	-	-	-	-
Obesity	uncertain	yes	yes	yes	-	-
Dietary antioxidants	yes	yes	yes	yes	uncertain	uncertain
	Malignant melanoma	**RCC**	**Urothelial cancer**	**Prostate cancer**	**Penile cancer**	**Testicular cancer**

4.2. Screening and Surveillance

Patients with a history of melanoma or urological cancer need careful monitoring for the potential development of additional malignancies. Routine screenings, such as skin examinations and urological assessments, can aid in early detection and improve patient outcomes.

Patients with germline mutations in BAP1, CDKN2A, MITF, and other cancer-related genes may benefit from more extensive cancer screening protocols. These could include regular skin examinations for melanoma, imaging studies to detect urological cancers, and continuous monitoring for other associated malignancies.

4.3. Personalized Treatment

The core idea of personalized medicine is to select the optimal treatment for each patient, with the goal of maximizing therapeutic effectiveness, minimizing side effects, and lowering the likelihood of drug resistance. Technological advancements and the significant reduction in DNA sequencing costs have led to the widespread integration of genetic testing into routine clinical practice [68]. Progress in genomics and immunology is propelling the creation of personalized treatments that target specific molecular pathways and immune responses shared by both melanoma and urological cancers. These overlapping genetic pathways present valuable opportunities for the development of targeted therapies.

In most cancer cases, treatment follows well-established standards that are outlined in specialized guidelines. It includes surgical therapy (nephrectomy, prostatectomy, radical cystectomy, melanoma surgery, etc.), radiotherapy, and/or hormone therapy.

In the final stages, palliative therapies are offered to patients with metastatic cancer, and these treatments can help enhance quality of life while potentially prolonging disease-free survival.

Angiogenesis inhibitors, such as vascular endothelial growth factor (VEGF) inhibitors, have proven effective in treating both urological cancers and melanoma.

Additionally, immunotherapies, including checkpoint inhibitors like programmed death-ligand 1 inhibitors (PD-L1 inh) with its receptor, programmed cell death protein 1 (PD-1) have shown considerable efficacy in these types of cancer.

An important marker for predicting the efficacy of immunotherapy is represented by tumor mutational burden (TMB). Tumor mutational burden (TMB) refers to the total number of somatic

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mutations present in a tumor's DNA. TMB does not impact the efficacy of angiogenesis inhibitors, but it is an useful biomarker for immune checkpoint inhibitors such as anti-PD-1, anti-PD-L1, and anti-CTLA-4 therapies [69].

Tumors with a high mutational burden typically generate more neoantigens—abnormal proteins caused by mutations—making them more likely to be recognized and targeted by the immune system [70].

Cancers like melanoma, lung cancer, and urothelial cancers commonly exhibit high TMB, whereas tumors such as prostate and breast cancers generally have lower TMB [71]. Tumors with high TMB are more likely to present a diverse range of neoantigens, increasing their susceptibility to immune system activation, especially when treated with checkpoint inhibitors. This is why immunotherapy tends to be more effective in tumors with high TMB [72].

4.3.1. Angiogenesis Inhibitors

VEGF inhibitors block the interaction between VEGF and its receptors (VEGFRs) on endothelial cells, preventing the signaling cascade responsible for new blood vessel formation [73]. VEGF inhibitors are primarily divided into two categories: monoclonal antibodies, which bind directly to VEGF ligands to block their interaction with receptors [74], and tyrosine kinase inhibitors (TKIs), which inhibit VEGFRs and other kinases involved in the angiogenesis signaling pathway [75]. he efficacy of these angiogenesis inhibitors has been particularly proven in RCC adjuvant therapy and in malignant melanoma. Their utility is limited in other types of urological cancers (Table 2).

Table 2. Angiogenesis inhibitors therapy for urological cancers and malignant melanoma.

	Malignant melanoma/ Urological Cancers	**Other cancers**
VEGF		
Monoclonal Antibodies		
Bevacizumab [76–81]	Malignant melanoma RCC Penile cancer*	Colorectal cancer Lung cancer Ovarian cancer
Tyrosine Kinase Inhibitors (TKIs)		
Sunitinib [82–84]	RCC	Gastrointestinal tumor Pancreatic neuroendocrine tumors
Pazopanib [85,86]	RCC Malignant melanoma*	
Axitinib [87]	RCC	

* Ongoing clinical trials.

4.3.2. Checkpoint Inhibitors

Angiogenesis inhibitors, such as VEGF inhibitors, have been effective in treating both urological cancers and melanoma. Furthermore, immunotherapies, including checkpoint inhibitors like anti-PD-1 and anti-CTLA-4, have demonstrated significant efficacy in this cancer types.

Both melanoma and RCC are highly immunogenic tumors, meaning they have the capacity to provoke an immune response. This immunogenicity has made both malignancies responsive to immunotherapy, particularly immune checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies. The use of PD-L1 inhibitors in RCC therapy is limited. Malignant melanoma and bladder cancer have demonstrated responsiveness to immune checkpoint inhibitors, with bladder cancer responding to PD-1/PD-L1 inhibitors and malignant melanoma showing efficacy with treatments targeting the CTLA-4 pathway (Table 3).

Table 3. Checkpoint inhibitors therapy for urological cancers and malignant melanoma.

	Malignant melanoma/	**Other cancers**

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Urological Cancers		
Checkpoint inhibitors		
PD-1 inhibitors		
Nivolumab [88–91]	Malignant melanoma RCC Urothelial cancers	Hepatocellular carcinoma Gastric and esophageal cancer
Pembrolizumab [92–96]	Metastatic melanoma RCC Urothelial cancers Penile cancer* [97]	Non-small cell lung carcinoma** Head and neck squamous cell carcinoma
PD-L1 inhibitors		
Atezolizumab [98–100]	Bladder cancer	Small and non-small lung cancer** Breast cancer
Durvalumab [101–103]	Bladder cancer	lung cancer Biliary tract cancer**
CTLA-4 inhibitors		
Ipilimumab [88]	Malignant melanoma	

* Ongoing clinical trial. * *Addition to chemotherapy

4.3.3. Combination Therapy

Even though treatment-related adverse events occur in a larger number of patients, combined therapies (VEGF and PD-1 inhibitors, CTLA-4 and PD-1 inhibitors) show the longest overall survival and progression-free survival. Rini et al. [77] presented the results of in an open-label, phase 3 trial with pembrolizumab plus axitinib for untreated advanced clear-cell renal-cell carcinoma. The combination treatment resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib.

Among patients with advanced melanoma, significantly longer overall survival occurred with combination therapy with nivolumab plus ipilimumab [104]. Similarly, Motzer et al. [105] highlighted that overall survival and objective response rates were significantly higher with nivolumab plus ipilimumab than with sunitinib among intermediate- and poor-risk patients with previously untreated advanced renal-cell carcinoma. Despite their efficacy, these agents also cause immune-related adverse effects that may be life-threatening if not detected and controlled appropriately [106].

Table 4. Combination therapy for urological cancers and malignant melanoma.

	Malignant melanoma/ Urological Cancers	**Other cancers**
Combination VEGF and PD-1 inhibitors		
Pembrolizumab + Axitinib [107]	RCC	
Combination CTLA-4 and PD-1 inhibitors		
Ipilimumab + nivolumab [104,105,108]	Malign Melanoma RCC Urothelial cancers Penile cancer*	

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Combination CTLA-4 and PD-L1 inhibitors		
Durvalumab with tremelimumab	-	Unresectable Hepatocellular Carcinoma [109]

* Ongoing clinical trial. * *Addition to chemotherapy

4. Conclusions

The connection between malignant melanoma and urological cancers is driven by shared epidemiological factors and genetic mutations, laying the groundwork for advancements in personalized medicine. As we gain deeper insights into the molecular pathways common to both cancer types, the opportunity to implement personalized prevention strategies, screening protocols, and customized treatments grows more evident. Early detection of genetic predispositions, such as BAP1 or CDKN2A mutations, coupled with the use of targeted therapies and immunotherapies, is poised to significantly improve patient care in the near future.

Personalized medicine offers significant potential for patients at higher risk of both melanoma and urological cancers. Through the use of genomic profiling and advancements in immunotherapy and targeted therapies, more tailored and effective treatments can be provided, leading to better patient outcomes. However, continued research and clinical trials are crucial to fully grasp the impact of shared genetic mutations and molecular pathways, and to establish comprehensive, individualized treatment protocols for these patients.

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References

1. Gluba-Brzózka A, Rysz J, Ławiński J, Franczyk B. Renal Cell Cancer and Obesity. Int J Mol Sci. 2022 Mar 21;23(6):3404.
2. Saginala K, Barsouk A, Aluru JS, Rawla P, Barsouk A. Epidemiology of Melanoma. Med Sci (Basel). 2021 Oct 20;9(4):63.
3. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of Renal Cell Carcinoma. Eur Urol. 2019 Jan;75(1):74–84.
4. Bukavina L, Bensalah K, Bray F, Carlo M, Challacombe B, Karam JA, et al. Epidemiology of Renal Cell Carcinoma: 2022 Update. Eur Urol. 2022 Nov;82(5):529–42.
5. Shariat SF, Favaretto RL, Gupta A, Fritsche HM, Matsumoto K, Kassouf W, et al. Gender differences in radical nephroureterectomy for upper tract urothelial carcinoma. World J Urol. 2011 Aug;29(4):481–6.
6. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–63.
7. Gatta G, van der Zwan JM, Casali PG, Siesling S, Dei Tos AP, Kunkler I, et al. Rare cancers are not so rare: the rare cancer burden in Europe. Eur J Cancer. 2011 Nov;47(17):2493–511.
8. Loghin, A.; Preda, O.; Bacârea, V.; Moldovan, C.; Porav-Hodade, D.; Dema, A.; Berger, N.; Borda, A. Predictive preoperatory variables of the prostate tumor volume. Romanian J. Morphol. Embryol. 2011, 52, 363–368.
9. Park JS, Kim J, Elghiaty A, Ham WS. Recent global trends in testicular cancer incidence and mortality. Medicine (Baltimore). 2018 Sep;97(37):e12390.
10. Fu L, Tian T, Yao K, Chen XF, Luo G, Gao Y, et al. Global Pattern and Trends in Penile Cancer Incidence: Population-Based Study. JMIR Public Health Surveill. 2022 Jul 6;8(7):e34874.

11. Kim K, Chung TH, Etzel CJ, Kim J, Ryu H, Kim DW, et al. Association between melanoma and renal-cell carcinoma for sequential diagnoses: A single-center retrospective study. Cancer Epidemiol. 2018 Dec;57:80–4.
12. Gandini S, Sera F, Cattaruzza MS, Pasquini P, Picconi O, Boyle P, et al. Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer. 2005 Jan;41(1):45–60.
13. Brash DE, Ziegler A, Jonason AS, Simon JA, Kunala S, Leffell DJ. Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. J Investig Dermatol Symp Proc. 1996 Apr;1(2):136–42.
14. Grasso AAC, Blanco S, Fantini G, Torelli F, Grasso M. Relationship between sun exposure and kidney cancer: preliminary experience with the evaluation of recreational UV exposure. Urologia. 2014;81(2):115–9.
15. Karami S, Boffetta P, Stewart P, Rothman N, Hunting KL, Dosemeci M, et al. Occupational sunlight exposure and risk of renal cell carcinoma. Cancer. 2010 Apr 15;116(8):2001–10.
16. Boot IWA, Wesselius A, Yu EYW, White E, Brustad M, Marques C, et al. Dietary vitamin D intake and the bladder cancer risk: A pooled analysis of prospective cohort studies. Clin Nutr. 2023 Aug;42(8):1462–74.
17. Zhang H, Zhang H, Wen X, Zhang Y, Wei X, Liu T. Vitamin D Deficiency and Increased Risk of Bladder Carcinoma: A Meta-Analysis. Cell Physiol Biochem. 2015;37(5):1686–92.
18. Gislefoss RE, Stenehjem JS, Hektoen HH, Andreassen BK, Langseth H, Axcrona K, et al. Vitamin D, obesity and leptin in relation to bladder cancer incidence and survival: prospective protocol study. BMJ Open. 2018 Mar 30;8(3):e019309.
19. Kristal AR, Till C, Song X, Tangen CM, Goodman PJ, Neuhauser ML, et al. Plasma vitamin D and prostate cancer risk: results from the Selenium and Vitamin E Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev. 2014 Aug;23(8):1494–504.
20. Tuohimaa P, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, et al. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. Int J Cancer. 2004 Jan 1;108(1):104–8.
21. Murphy AB, Nyame Y, Martin IK, Catalona WJ, Hollowell CMP, Nadler RB, et al. Vitamin D deficiency predicts prostate biopsy outcomes. Clin Cancer Res. 2014 May 1;20(9):2289–99.
22. Douglawi A, Masterson TA. Updates on the epidemiology and risk factors for penile cancer. Transl Androl Urol. 2017 Oct;6(5):785–90.
23. Stadler R. The effect of smoking in melanoma outcome still remains an enigma. J Eur Acad Dermatol Venereol. 2019 Dec;33(12):2219–20.
24. Arafa A, Mostafa A, Navarini AA, Dong JY. The association between smoking and risk of skin cancer: a meta-analysis of cohort studies. Cancer Causes Control. 2020 Aug;31(8):787–94.
25. Sondermeijer L, Lamboo LGE, de Waal AC, Galesloot TE, Kiemeney LALM, van Rossum M, et al. Cigarette Smoking and the Risk of Cutaneous Melanoma: A Case-Control Study. Dermatology. 2020;236(3):228–36.
26. Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer. 2005 Mar 10;114(1):101–8.
27. Sheikh M, Mukeriya A, Zahed H, Feng X, Robbins HA, Shangina O, et al. Smoking Cessation After Diagnosis of Kidney Cancer Is Associated With Reduced Risk of Mortality and Cancer Progression: A Prospective Cohort Study. J Clin Oncol. 2023 May 20;41(15):2747–55.
28. Hecht SS. Human urinary carcinogen metabolites: biomarkers for investigating tobacco and cancer. Carcinogenesis. 2002 Jun;23(6):907–22.
29. Freedman ND, Silverman DT, Hollenbeck AR, Schatzkin A, Abnet CC. Association between smoking and risk of bladder cancer among men and women. JAMA. 2011 Aug 17;306(7):737–45.
30. Kispert S, Marentette J, McHowat J. Cigarette smoking promotes bladder cancer via increased platelet-activating factor. Physiol Rep. 2019 Feb;7(3):e13981.
31. Islami F, Moreira DM, Boffetta P, Freedland SJ. A systematic review and meta-analysis of tobacco use and prostate cancer mortality and incidence in prospective cohort studies. Eur Urol. 2014 Dec;66(6):1054–64.
32. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. Int J Cancer. 2005 Sep 10;116(4):606–16.
33. Beck AL, Bräuner EV, Hauser R, Lim YH, Uldbjerg CS, Juul A. Maternal Exposure to Cigarette Smoke during Pregnancy and Testicular Cancer in Offspring: A Systematic Review and Meta-Analysis. Life (Basel). 2023 Feb 23;13(3):618.
34. Miracle CE, McCallister CL, Egleton RD, Salisbury TB. Mechanisms by which obesity regulates inflammation and anti-tumor immunity in cancer. Biochem Biophys Res Commun. 2024 Jul 23;733:150437.
35. Graff RE, Wilson KM, Sanchez A, Chang SL, McDermott DF, Choueiri TK, et al. Obesity in Relation to Renal Cell Carcinoma Incidence and Survival in Three Prospective Studies. Eur Urol. 2022 Sep;82(3):247–51.

36. Vidal AC, Howard LE, Moreira DM, Castro-Santamaria R, Andriole GL, Freedland SJ. Obesity increases the risk for high-grade prostate cancer: results from the REDUCE study. Cancer Epidemiol Biomarkers Prev. 2014 Dec;23(12):2936–42.
37. Sculco M, La Vecchia M, Aspesi A, Clavenna MG, Salvo M, Borgonovi G, et al. Diagnostics of BAP1-Tumor Predisposition Syndrome by a Multitesting Approach: A Ten-Year-Long Experience. Diagnostics (Basel). 2022 Jul 13;12(7):1710.
38. Louie BH, Kurzrock R. BAP1: Not just a BRCA1-associated protein. Cancer Treat Rev. 2020 Nov;90:102091.
39. Shao YF, DeBenedictis M, Yeaney G, Singh AD. Germ Line BAP1 Mutation in Patients with Uveal Melanoma and Renal Cell Carcinoma. Ocul Oncol Pathol. 2021 Oct;7(5):340–5.
40. Wiesner T, Obenauf AC, Murali R, Fried I, Griewank KG, Ulz P, et al. Germline mutations in BAP1 predispose to melanocytic tumors. Nat Genet. 2011 Aug 28;43(10):1018–21.
41. Kapur P, Peña-Llopis S, Christie A, Zhrebker L, Pavía-Jiménez A, Rathmell WK, et al. Effects on survival of BAP1 and PBRM1 mutations in sporadic clear-cell renal-cell carcinoma: a retrospective analysis with independent validation. Lancet Oncol. 2013 Feb;14(2):159–67.
42. Yokoyama S, Woods SL, Boyle GM, Aoude LG, MacGregor S, Zismann V, et al. A novel recurrent mutation in MITF predisposes to familial and sporadic melanoma. Nature. 2011 Dec 1;480(7375):99–103.
43. Lang M, Vocke CD, Ricketts CJ, Metwalli AR, Ball MW, Schmidt LS, et al. Clinical and Molecular Characterization of Microphthalmia-associated Transcription Factor (MITF)-related Renal Cell Carcinoma. Urology. 2021 Mar;149:89–97.
44. Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Bishop DT, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. J Med Genet. 2007 Feb;44(2):99–106.
45. Kiatprungvech N, Sangkum P, Malinee R, Sommaluan S, Korkiatsakul V, Worawichawong S, et al. Genetic study of the CDKN2A and CDKN2B genes in renal cell carcinoma patients. Pract Lab Med. 2024 May;40:e00410.
46. Park JH, Zhuang J, Li J, Hwang PM. p53 as guardian of the mitochondrial genome. FEBS Lett. 2016 Apr;590(7):924–34.
47. Ozretić P, Hanžić N, Proust B, Sabol M, Trnski D, Radić M, et al. Expression profiles of p53/p73, NME and GLI families in metastatic melanoma tissue and cell lines. Sci Rep. 2019 Aug 28;9(1):12470.
48. Wu G, Wang F, Li K, Li S, Zhao C, Fan C, et al. Significance of TP53 mutation in bladder cancer disease progression and drug selection. PeerJ. 2019;7:e8261.
49. Worst TS, Weis CA, Stöhr R, Bertz S, Eckstein M, Otto W, et al. CDKN2A as transcriptomic marker for muscle-invasive bladder cancer risk stratification and therapy decision-making. Sci Rep. 2018 Sep 26;8(1):14383.
50. Davies MA. The role of the PI3K-AKT pathway in melanoma. Cancer J. 2012;18(2):142–7.
51. Sathe A, Nawroth R. Targeting the PI3K/AKT/mTOR Pathway in Bladder Cancer. Methods Mol Biol. 2018;1655:335–50.
52. Cao Z, Wei L, Zhu W, Yao X. Meta-analysis of CDKN2A methylation to find its role in prostate cancer development and progression, and also to find the effect of CDKN2A expression on disease-free survival (PRISMA). Medicine (Baltimore). 2018 Mar;97(12):e0182.
53. Nyberg T, Frost D, Barrowdale D, Evans DG, Bancroft E, Adlard J, et al. Prostate Cancer Risks for Male BRCA1 and BRCA2 Mutation Carriers: A Prospective Cohort Study. Eur Urol. 2020 Jan;77(1):24–35.
54. Kashofer K, Winter E, Halbwedl I, Thueringer A, Kreiner M, Sauer S, et al. HPV-negative penile squamous cell carcinoma: disruptive mutations in the TP53 gene are common. Mod Pathol. 2017 Jul;30(7):1013–20.
55. Vladusic T, Hrascan R, Pecina-Slaus N, Vrhovac I, Gamulin M, Franekic J, et al. Loss of heterozygosity of CDKN2A (p16INK4a) and RB1 tumor suppressor genes in testicular germ cell tumors. Radiol Oncol. 2010 Sep;44(3):168–73.
56. Hoeben A, Joosten EAJ, van den Beuken-van Everdingen MHJ. Personalized Medicine: Recent Progress in Cancer Therapy. Cancers (Basel). 2021 Jan 11;13(2):242.
57. Qin D. Next-generation sequencing and its clinical application. Cancer Biol Med. 2019 Feb;16(1):4–10.
58. Sample A, He YY. Mechanisms and prevention of UV-induced melanoma. Photodermatol Photoimmunol Photomed. 2018 Jan;34(1):13–24.
59. Song Y, Lu H, Cheng Y. To identify the association between dietary vitamin D intake and serum levels and risk or prognostic factors for melanoma-systematic review and meta-analysis. BMJ Open. 2022 Aug 26;12(8):e052442.
60. Lin SW, Wheeler DC, Park Y, Cahoon EK, Hollenbeck AR, Freedman DM, et al. Prospective study of ultraviolet radiation exposure and risk of cancer in the United States. Int J Cancer. 2012 Sep 15;131(6):E1015-1023.
61. van Osch FHM, Jochems SHJ, Reulen RC, Pirrie SJ, Nekeman D, Wesselius A, et al. The association between smoking cessation before and after diagnosis and non-muscle-invasive bladder cancer recurrence: a prospective cohort study. Cancer Causes Control. 2018 Jul;29(7):675–83.

 doi:10.20944/preprints202410.0644.v1

62. Guo K, Wang S, Shang X, E F, Hou L, Li J, et al. The effect of Varenicline and Bupropion on smoking cessation: A network meta-analysis of 20 randomized controlled trials. Addict Behav. 2022 Aug;131:107329.
63. Cassano N, Caccavale S, Vena GA, Argenziano G. Body Mass Index and Melanoma Prognosis. Dermatol Pract Concept. 2021 Sep;11(4):e2021106.
64. Lin Y, Wang Y, Wu Q, Jin H, Ma G, Liu H, et al. Association between obesity and bladder cancer recurrence: A meta-analysis. Clin Chim Acta. 2018 May;480:41–6.
65. Tzenios N, Tazanios ME, Chahine M. The impact of body mass index on prostate cancer: An updated systematic review and meta-analysis. Medicine (Baltimore). 2022 Nov 11;101(45):e30191.
66. Nouri-Majd S, Salari-Moghaddam A, Aminianfar A, Larijani B, Esmaillzadeh A. Association Between Red and Processed Meat Consumption and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis. Front Nutr. 2022;9:801722.
67. Zhang S, Wang Q, He J. Intake of red and processed meat and risk of renal cell carcinoma: a meta-analysis of observational studies. Oncotarget. 2017 Sep 29;8(44):77942–56.
68. Brittain HK, Scott R, Thomas E. The rise of the genome and personalised medicine. Clin Med (Lond). 2017 Dec;17(6):545–51.
69. Chan TA, Yarchoan M, Jaffee E, Swanton C, Quezada SA, Stenzinger A, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. Ann Oncol. 2019 Jan 1;30(1):44–56.
70. Xie N, Shen G, Gao W, Huang Z, Huang C, Fu L. Neoantigens: promising targets for cancer therapy. Signal Transduct Target Ther. 2023 Jan 6;8(1):9.
71. Sha D, Jin Z, Budczies J, Kluck K, Stenzinger A, Sinicrope FA. Tumor Mutational Burden as a Predictive Biomarker in Solid Tumors. Cancer Discov. 2020 Dec;10(12):1808–25.
72. Palmeri M, Mehnert J, Silk AW, Jabbour SK, Ganesan S, Popli P, et al. Real-world application of tumor mutational burden-high (TMB-high) and microsatellite instability (MSI) confirms their utility as immunotherapy biomarkers. ESMO Open. 2022 Feb;7(1):100336.
73. El-Kenawi AE, El-Remessy AB. Angiogenesis inhibitors in cancer therapy: mechanistic perspective on classification and treatment rationales. Br J Pharmacol. 2013 Oct;170(4):712–29.
74. Hsu JY, Wakelee HA. Monoclonal antibodies targeting vascular endothelial growth factor: current status and future challenges in cancer therapy. BioDrugs. 2009;23(5):289–304.
75. Gotink KJ, Verheul HMW. Anti-angiogenic tyrosine kinase inhibitors: what is their mechanism of action? Angiogenesis. 2010 Mar;13(1):1–14.
76. Han X, Ge P, Liu S, Yang D, Zhang J, Wang X, et al. Efficacy and safety of bevacizumab in patients with malignant melanoma: a systematic review and PRISMA-compliant meta-analysis of randomized controlled trials and non-comparative clinical studies. Front Pharmacol. 2023;14:1163805.
77. Rini BI. Vascular endothelial growth factor-targeted therapy in renal cell carcinoma: current status and future directions. Clin Cancer Res. 2007 Feb 15;13(4):1098–106.
78. Cohen MH, Gootenberg J, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer. Oncologist. 2007 Mar;12(3):356–61.
79. Barlesi F, Scherpereel A, Gorbunova V, Gervais R, Vikström A, Chouaid C, et al. Maintenance bevacizumab-pemetrexed after first-line cisplatin-pemetrexed-bevacizumab for advanced nonsquamous nonsmall-cell lung cancer: updated survival analysis of the AVAPERL (MO22089) randomized phase III trial. Ann Oncol. 2014 May;25(5):1044–52.
80. Lazurko C, Linder R, Pulman K, Lennox G, Feigenberg T, Fazelzad R, et al. Bevacizumab Treatment for Low-Grade Serous Ovarian Cancer: A Systematic Review. Curr Oncol. 2023 Sep 3;30(9):8159–71.
81. Alencar AM, Sonpavde G. Emerging Therapies in Penile Cancer. Front Oncol. 2022;12:910335.
82. Méjean A, Ravaud A, Thezenas S, Colas S, Beauval JB, Bensalah K, et al. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N Engl J Med. 2018 Aug 2;379(5):417–27.
83. Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet. 2006 Oct 14;368(9544):1329–38.
84. Ma ZY, Gong YF, Zhuang HK, Zhou ZX, Huang SZ, Zou YP, et al. Pancreatic neuroendocrine tumors: A review of serum biomarkers, staging, and management. World J Gastroenterol. 2020 May 21;26(19):2305–22.
85. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med. 2013 Aug 22;369(8):722–31.
86. Thurneysen S, Cheng PF, Nagel HW, Kunz M, Jaberg-Bentele N, Nägeli M, et al. An exploratory study investigating the metabolic activity and local cytokine profile in patients with melanoma treated with pazopanib and paclitaxel. Br J Dermatol. 2016 Nov;175(5):966–78.
87. Tsironis G, Liontos M, Kyriazoglou A, Koutsoukos K, Tsiara A, Kaparelou M, et al. Axitinib as a third or further line of treatment in renal cancer: a single institution experience. BMC Urol. 2020 Jun 2;20(1):60.

88. Larkin J, Del Vecchio M, Mandalá M, Gogas H, Arance Fernandez AM, Dalle S, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III/IV Melanoma: 5-Year Efficacy and Biomarker Results from CheckMate 238. Clin Cancer Res. 2023 Sep 1;29(17):3352–61.
89. Motzer RJ, Russo P, Grünwald V, Tomita Y, Zurawski B, Parikh O, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. Lancet. 2023 Mar 11;401(10379):821–32.
90. Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med. 2021 Jun 3;384(22):2102–14.
91. Yau T, Park JW, Finn RS, Cheng AL, Mathurin P, Edeline J, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol. 2022 Jan;23(1):77–90.
92. Rizzetto G, De Simoni E, Molinelli E, Offidani A, Simonetti O. Efficacy of Pembrolizumab in Advanced Melanoma: A Narrative Review. Int J Mol Sci. 2023 Aug 3;24(15):12383.
93. Attieh F, Boutros M, Kourie HR, Mahrous M. Turning the tide: pembrolizumab's triumph in adjuvant RCC therapy. Med Oncol. 2024 Sep 5;41(10):242.
94. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma. N Engl J Med. 2017 Mar 16;376(11):1015–26.
95. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2040–51.
96. Cirillo A, Marinelli D, Romeo U, Messineo D, De Felice F, De Vincentiis M, et al. Pembrolizumab-based first-line treatment for PD-L1-positive, recurrent or metastatic head and neck squamous cell carcinoma: a retrospective analysis. BMC Cancer. 2024 Apr 8;24(1):430.
97. Hahn AW, Chahoud J, Campbell MT, Karp DD, Wang J, Stephen B, et al. Pembrolizumab for advanced penile cancer: a case series from a phase II basket trial. Invest New Drugs. 2021 Oct;39(5):1405–10.
98. Szabados B, Kockx M, Assaf ZJ, van Dam PJ, Rodriguez-Vida A, Duran I, et al. Final Results of Neoadjuvant Atezolizumab in Cisplatin-ineligible Patients with Muscle-invasive Urothelial Cancer of the Bladder. Eur Urol. 2022 Aug;82(2):212–22.
99. Horn L, Mansfield AS, Szczęsna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med. 2018 Dec 6;379(23):2220–9.
100. Reddy SM, Carroll E, Nanda R. Atezolizumab for the treatment of breast cancer. Expert Rev Anticancer Ther. 2020 Mar;20(3):151–8.
101. Oh EL, Redfern A, Hayne D. An evaluation of durvalumab across the spectrum of urothelial carcinoma. Expert Rev Anticancer Ther. 2024 Sep 20;1–15.
102. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017 Nov 16;377(20):1919–29.
103. Rimini M, Fornaro L, Lonardi S, Niger M, Lavacchi D, Pressiani T, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: An early exploratory analysis of real-world data. Liver Int. 2023 Aug;43(8):1803–12.
104. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2017 Oct 5;377(14):1345–56.
105. Motzer RJ, Russo P, Grünwald V, Tomita Y, Zurawski B, Parikh O, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. Lancet. 2023 Mar 11;401(10379):821–32.
106. Kooshkaki O, Derakhshani A, Hosseinkhani N, Torabi M, Safaei S, Brunetti O, et al. Combination of Ipilimumab and Nivolumab in Cancers: From Clinical Practice to Ongoing Clinical Trials. Int J Mol Sci. 2020 Jun 22;21(12):4427.
107. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116–27.
108. van Dijk N, Gil-Jimenez A, Silina K, Hendricksen K, Smit LA, de Feijter JM, et al. Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cancer: the NABUCCO trial. Nat Med. 2020 Dec;26(12):1839–44.
109. Abou-Alfa GK, Lau G, Kudo M, Chan SL, Kelley RK, Furuse J, et al. Tremelimumab plus Durvalumab in Unresectable Hepatocellular Carcinoma. NEJM Evid. 2022 Aug;1(8):EVIDoa2100070.