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Multidisciplinary therapy managements in endometrial and renal cancer patients treated with pembrolizumab and lenvatinib: a virtuous circle between oncologists and organ specialists

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ABSTRACT

A strong rationale supports the combination of an immunocheckpoint inhibitor (ICI) and an antiangiogenic agent in different tumor types such as endometrial cancer (EC) and renal cell carcinoma (RCC). Accordingly, the combination of pembrolizumab plus lenvatinib demonstrated the efficacy in pretreated advanced EC and metastatic RCC, and to optimize drugs administration a more in-depth knowledge of adverse events management for the combination is needed. We analyzed the most common toxicities for appropriate and proactive management to maximize the efficacy of the tyrosine kinase inhibitor (TKI)-ICI combination and a summary of the most relevant recommendations on the management of organ specific disorders was produced. A multidisciplinary approach is suggested, involving collaboration between oncologists and organ specialists to promptly prevent/address possible toxicities associated with the treatment.

1. Introduction

1.1. Endometrial cancer

Endometrial cancer (EC) is the most common gynecological cancer in high income countries with an estimated 66,200 new cases and 13,030 deaths in 2023 in the United States (Crosbie et al., 2022; SEER, 2021). Globally, its incidence rates are increasing in particular in Italy (Gu et al., 2021). At diagnosis, 90% of patients have localised disease, endowed with favorable outcomes and a five-year survival rate of 95%, a figure that dramatically drops to 70% in the case of locally-advanced disease (positive pelvic or para-aortic lymph nodes) and to 18% in the case of metastatic disease (American Cancer Society, 2025). Mortality rates recently increased with an average annual percent change of 1.1–1.87% most rapidly among younger than 50 years old women and non-Hispanic Black/ Hispanic women (Somasegar et al., 2023). Therefore, more efforts are required to manage the disease burden of EC.

Thus, to better guide treatment and discriminate biologic variants, the traditional EC classification has been replaced by the Cancer Genome Atlas (TCGA) project which identified four molecular subgroups based upon shared genomic features that correlated with clinical outcome. The four subgroups were: POLE-ultramutated (POLE), microsatellite instability-hypermutated (MSI), copy number low-microsatellite stable (CNL), and copy number high-serous-like (CNH)

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representing 5%, 25%, 40% and 30% respectively. This molecular classification opens new possibilities for risk stratification, and subgroup-specific therapeutic targets (MacKay et al., 2017).

1.2. Renal cell carcinoma

Renal cell carcinoma (RCC) is the most common malignancy of the kidney (Moch et al., 2016). It has three main pathological subtypes: clear cell RCC (ccRCC), papillary RCC, and chromophobe RCC. Although a number of rarer histotypes have been described over the years, ccRCC accounts for approximately 70–75% of all kidney cancers (Yang et al., 2023). During the last two decades, there has been an annual increase of about 2% in incidence and mortality worldwide with 179,368 deaths in 2022 (Escudier et al., 2019).

Currently, metastatic RCC can be prognostically stratified in three subgroups (good, intermediate, and poor risk) according to the International Metastatic renal cell carcinoma Database Consortium (IMDC) score which defines the prognostic index evaluating six clinical negative prognostic factors: performance status, hemoglobin level, time from diagnosis to start systemic treatment, serum calcium level, neutrophil count and platelet count. Notably these factors reflect a systemic inflammatory state induced by the tumor which leads to a prominent dysfunctional immune cell infiltrate, unable to control tumor growth (Jiang et al., 2015). Overall, patients with a good prognosis may reach a longer survival of approximately 43 months while patients presenting 1 or 2 factors have an intermediate risk of death with a median Overall Survival (mOS) of about 23 months; patients with 3 or more factors have an expected poor risk outcome with mOS of about 8 months (Heng et al., 2013).

1.3. Lenvatinib plus pembrolizumab biological rationale for anti-tumor activity

There is a strong rationale that supports the combination of an immunocheckpoint inhibitor (ICI) and an antiangiogenic agent in different tumor types. In fact, dysfunctional angiogenesis induced by vascular endothelial growth factor (VEGF) and other proangiogenic factors induces an immunosuppressive microenvironment. Thus, angiogenetic drugs could potentially modify the tumor milieu to an immune permissive one and sensitive to ICIs (Song et al., 2020).

Lenvatinib is a tyrosine kinase inhibitor (TKI) that selectively blocks VEGFR, platelet-derived growth factor (PDGFR), RET proto-oncogene, and cKIT, with a higher potency, especially against vascular endothelial growth factor receptor (VEGFR)-2 and VEGFR-3, than other TKIs such as cabozantinib, pazopanib, and sunitinib (Fogli et al., 2020). Lenvatinib enhanced T-cell infiltration, proliferation with a reduction in myeloid derived suppressor cells in the tumor microenvironment (TME) resulting in a long-term antitumor response in vivo (Lu et al., 2021). In fact, through the inhibition of VEGFR and fibroblast growth factor (FGF), lenvatinib reprograms the immunosuppressive TME into an immunostimulatory environment reducing the expression of programmed death receptor-1(PD-1), cytotoxic T-lymphocyte associated protein 4 (CTLA-4), and Tim-3 on T cells and cytotoxicity; the concomitant use of immunotherapy with PD-1/ Programmed Death-Ligand 1 (PD-L1) antibodies further enhances the antitumor activity of T cells (Lorusso et al., 2022).

Pembrolizumab is a well-known ICI humanized monoclonal IgG4 kappa antibody directed against human cell surface PD-1 which are expressed in antigen cells and may be expressed by tumors or other cells in the TME. Pembrolizumab potentiates T-cell responses, generating anti-tumor responses. (Concin et al., 2021).

The anti-angiogenic effect of lenvatinib in combination with the immune-stimulatory effect of pembrolizumab results in a TME with greater T-cell activation to help overcome primary and acquired resistance to immunotherapy and may improve tumor responses compared to either treatment alone. In preclinical murine models, PD-1 plus TKI inhibitors have demonstrated enhanced anti-tumor activity compared to either agent alone (European Medicines Agency, 2025a).

Although lenvatinib plus pembrolizumab has become a standard option in advanced endometrial cancer and first-line clear-cell renal cell carcinoma, clinicians still face day-to-day uncertainty on differentiating and managing overlapping toxicities, and on when to involve organ specialists. Existing reviews often emphasize efficacy and trial safety tables, but provide limited organ-specific, multidisciplinary, management-focused guidance. This review therefore aims to offer a practical, team-based framework ('virtuous circle') for proactive monitoring, early recognition, differential diagnosis, and coordinated management of adverse events (AEs), with the goal of maintaining dose intensity when safe and minimizing unnecessary discontinuations.

2. Methods

This article is a narrative review informed by the authors' clinical and scientific expertise and a selective review of the literature. As no formal systematic review methodology was employed, the selection of studies and the emphasis on specific topics reflect the authors' perspective. The board was led by two oncologists and 6 organ specialists were involved: a gastroenterologist, a cardiologist, a nephrologist, an endocrinologist, a pneumologist.

The board performed a targeted literature review focusing on pivotal trials, post hoc and subgroup analyses, real-world reports, and consensus guidelines on immune-related adverse events and VEGFR-TKI toxicities. In parallel, we reviewed the most recent European Medicines Agency (EMA) product information (SmPC/EPAR) for pembrolizumab (Keytruda; last updated December 2025) and lenvatinib (Lenvima and Kisplyx; last updated April 2025) to align practical recommendations on monitoring, dose interruption, dose reduction, and treatment discontinuation.

3. EC and RCC: current treatments

3.1. Endometrial cancer

The phase III study GOG0209 established platinum-based/taxane chemotherapy (CT) as the gold standard first line treatments for women with advanced EC (Concin et al., 2021). Lately, the results from the two phase III KeyNote 868 and Ruby studies showed that the addition of PD-1 inhibitor to CT led to a favorable OS benefit compared with standard-of-care CT (Eskander et al., 2023; Mirza et al., 2023).

Second-line treatments have been an unmet clinical need for decades until the recent approval of the combination of lenvatinib plus pembrolizumab. According to the benefit obtained in the phase III KeyNote-775 study, the combination is currently indicated for the treatment of advanced or recurrent EC in adults who have disease progression on or following prior treatment with a platinum-containing therapy in any setting and who are not candidates for curative surgery or radiation.

Indeed, in the phase III KeyNote-775 pembrolizumab plus lenvatinib met both primary endpoints showing the superiority of the combination versus standard CT for the median progression-free survival (mPFS) (7.3 vs. 3.8 months; hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.48–0.66; $P < .001$) and for the mOS (18.7 vs. 11.9 months; HR, 0.66; 95% CI, 0.57–0.77; $P < .001$) (Makker et al., 2025, 2022). The 5-y OS rates were 19.9% with pembrolizumab plus lenvatinib vs 7.7% with CT in all-comers; 5-y PFS rates were 9.8% vs 3.2% (Makker et al., 2025). Moreover, the Objective Response Rate (ORR) was twice in comparison with standard CT (33.8% vs 14.7%) with 7.5% and 2.6% of patients had complete responses, respectively. The median duration of response was doubled for lenvatinib plus pembrolizumab 12.9 months vs 5.7 months in the CT arm. Overall, the PFS, OS, and ORR also in the pMMR population and dMMR favoured the ICI-TKI combination. (Table 1) (Makker et al., 2022). Adverse events (AEs) of grade 3 or higher occurred in 78.8% of the patients who received lenvatinib plus pembrolizumab and

Table 1
Summary of lenvatinib plus pembrolizumab clinical efficacy data.

	KeyNote-775 (Makker et al., 2022)	CLEAR (Motzer et al., 2024)
Tumor type	Endometrial cancer	Clear cell Renal cancer
Treatment line	2nd line	1st line
Comparator	Standard CT	Sunitinib
mPFS	7.2 vs 3.8 months* [HR], 0.56	23.9 vs 9.2 months# [HR], 0.47
ORR	33.8% vs 14.7%*	71.3% v 36.7%#
mOS	18.3 vs. 11.4 months*; [HR], 0.62	median not reached for both therapies; [HR], 0.74

* $p < 0.001$; # $p < 0.0001$. CT: chemotherapy; HR: hazard ratio; mPFS: median progression-free survival; ORR: overall response rate; mOS: medial overall survival

in 60.1% of those who received CT; the most common serious adverse events were hypertension. Death due to drug-related AE was inferior for the combination vs CT (6 vs 9 deaths respectively). (Makker et al., 2023, 2022). The percentage of interruption due to treatment emergent adverse events (TEAE) was higher for ICI-TKI combination (71.9% vs 28.4%) with a discontinuation rate of 39.2% vs 8.0% of CT (Makker et al., 2023). Although the percentage of AEs reported, data showed no differences in terms of Quality of Life (QoL) (Lorusso et al., 2023). Clearly, more in-depth knowledge of AEs management for the combination is needed.

3.2. Renal cell carcinoma

Starting in the late 1980s, cytokines were considered the mainstay of treatment for locally advanced or mRCC and two decades ago the advent of VEGF-TKIs revolutioned the treatment paradigm. Then, the introduction of immunotherapy in the form of ICIs showed to improve patient survival vs single-agent TKI therapy. Given enhancement of ICI T-cell mediated effect by VEGF-mediated immunosuppression, the combination of VEGF inhibitors and ICIs in advanced RCC has shown promise (Nizam et al., 2024).

In this scenario, the phase III CLEAR trial demonstrated the efficacy of the lenvatinib plus pembrolizumab combination in patients with advanced ccRCC. The final pre-specified OS analysis recently published confirmed an advantage for lenvatinib plus pembrolizumab (HR 0.79; 95% CI, 0.63–0.99). The mPFS was 23.9 months (95% CI, 20.8–27.7) with the combination and 9.2 months (95% CI, 6.0–11.0) with sunitinib (HR, 0.47; 95% CI, 0.38–0.57); the ORR also favored the combination over sunitinib (71.3% v 36.7%; relative risk 1.94 [95% CI, 1.67–2.26]) (Table 1) (Motzer et al., 2024).

Safety results showed that grade ≥3 TEAs occurred in 84.9% of patients treated with the combination and 74.7% of patients treated with sunitinib. Diarrhea was the most common TEAE, and hypertension was the most common grade ≥3 TEAE across treatment groups (Grünwald et al., 2025; Motzer et al., 2024) (Table 2).

With the support of above-mentioned results, lenvatinib plus pembrolizumab has joined other VEGFR–PD-1 inhibitor-targeted combinations (axitinib–pembrolizumab and cabozantinib-nivolumab) as guidelines-recommended first-line treatment choices for advanced ccRCC irrespective of the IMDC (International Metastatic RCC Database Consortium) risk groups, while Ipilimumab–nivolumab is recommended, together with all the other above combinations, as first-line in IMDC intermediate- and poor-risk patients, with a weaker recommendation in favourable-risk disease. Recent data also support the use of axitinib-toripalimab in intermediate- and poor-risk disease, although OS data are immature (Powles et al., 2024).

The first-line treatment choice could be influenced not only by clinical trials results but also by the sequence that could be used after disease progression and safety profile. The latter should be understood

Table 2
Summary of adverse events of Any Cause with an Incidence of 25% or More among All the Patients treated with lenvatinib plus pembrolizumab.

	KeyNote-775 (Makker et al., 2022)		**CLEAR** (Motzer et al., 2024)	
	Any Grade	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Any adverse event	405 (99.8)	361 (88.9)	351 (99.7)	299 (84.9)
Hypertension	260 (64.0)	154 (37.9)	202 (57.4)	102 (29.0)
Hypothyroidism	233 (57.4)	5 (1.2)	176 (50.0)	5 (1.4)
Diarrhea	220 (54.2)	31 (7.6)	226 (64.2)	39 (11.1)
Nausea	201 (49.5)	14 (3.4)	133 (37.8)	9 (2.6)
Decreased appetite	182 (44.8)	32 (7.9)	144 (40.9)	14 (4.0)
Vomiting	149 (36.7)	11 (2.7)	102 (29.0)	13 (3.7)
Weight decrease	138 (34.0)	42 (10.3)	113 (32.1)	33 (9.4)
Fatigue	134 (33.0)	21 (5.2)	151 (42.9)	19 (5.4)
Arthralgia	124 (30.5)	7 (1.7)	105 (29.8)	5 (1.4)
Proteinuria	117 (28.8)	22 (5.4)	117 (33.2)	35 (9.9)
Anemia	106 (26.1)	25 (6.2)	-	-
Constipation	105 (25.9)	3 (0.7)	96 (27.3)	3 (0.9)
Urinary tract infection	104 (25.6)	16 (3.9)	-	-
Dysphonia	-	-	106 (30.1)	0
Stomatitis	-	-	124 (35.2)	6 (1.7)
Palmar-plantar erythrodysesthesia syndrome	-	-	103 (29.0)	14 (4.0)
Rash	-	-	99 (28.1)	13 (3.7)

to properly manage possible toxicities supporting continuation of treatment, thus affording patients the best opportunity to benefit from the antitumor activity of this important therapeutic option.

4. Management of ICI-TKI combination adverse events

The recent development of combinations between one ICI and one TKI across different tumor types and their safety profile raises the attention to therapy management, i.e. optimization of drugs administration and minimization of their toxicities to help patients to get the most benefit from a given treatment.

Although used in different tumor types and indications, lenvatinib plus pembrolizumab presented a safety profile that was similar in both the CLEAR as well as in the KeyNote-775 study. The latter presented TEAEs of any grade in 99.8% of patients receiving lenvatinib plus pembrolizumab; most common TEAEs were hypertension (65.0%) followed by hypothyroidism (58.9%), diarrhea (55.7%) and nausea (51.7%) (Makker et al., 2022). In the CLEAR trial TEAEs occurred in 99.7% in patients treated with lenvatinib plus pembrolizumab; the most common were diarrhea (64.2%), hypertension (57.4%) and hypothyroidism (50.0%) (Motzer et al., 2024).

The management strategy is to first determine whether the AE is related to lenvatinib or pembrolizumab considering the onset or resolution of the event and in relation to the administration and interruption of the TKI or ICI therapy (Colombo et al., 2024). Grade 2 AEs defined with the CTCAE (Common Terminology Criteria for Adverse Events) classification, generally do not warrant treatment modifications, unless

intolerable to the patient despite optimal management. For any grade 3 or intolerable grade 2 AEs, upon resolution/improvement grade 0–1 or baseline lenvatinib should be resumed at a reduced dose and treatment is to be discontinued for most grade 4 AEs (European Medicines Agency, 2025b). On the contrary, dose reductions of pembrolizumab are not recommended. It should be withheld or discontinued to manage AEs (European Medicines Agency, 2025a). When one component of the combination is withheld, dose-reduced, or discontinued in accordance with the Summary of Product Characteristics (SmPC) due to AE, no dose adjustment is recommended for the other agent (European Medicines Agency, 2025b, 2025c, 2025a).

Limited data are available on the combination in special population including adults ≥ 75 years old, with hepatic or renal impairments and autoimmune diseases (Kato et al., 2025). A recent real-world cohort of older patients with mRCC demonstrated favorable efficacy and manageable safety. For lenvatinib the adjustment of the dose is requested only for severe hepatic or renal impairment while pembrolizumab has not been studied in these patients and clinical data are limited to case reports (Vitorino and Santos, 2022). In patients with pre-existing autoimmune disease (AID), data from observational studies suggest that the risk of immune-mediated AEs following ICI therapy may be increased as compared with the risk in patients without pre-existing AID (European Medicines Agency, 2025a).

An in-depth understanding of AEs and of immune-related adverse events (irAE) in particular, as well as the issue relative to how differentially diagnose, and manage, a given AE, potentially caused by either the TKI or the ICI part of the combination, has gained paramount importance (Cunningham-Bussel et al., 2022; Ramos-Casals et al., 2019). Existing reviews focus on the efficacy of lenvatinib plus pembrolizumab but lack a systematic summary of organ-specific adverse event management; few studies integrate multidisciplinary collaboration strategies, leading to inconsistencies in clinical practice. Thus, this narrative review the most common toxicities were analyzed in order to provide a practical, management-focused framework for the multidisciplinary team maximizing the efficacy of the TKI-ICI combination (Table 3, Table 4).

4.1. Gastrointestinal disorders

Gastrointestinal disorders are common treatment-related adverse events (TRAEs) during TKI or/and ICI therapies and diarrhea/colitis are the most frequent, observed in more than 50% of patients using the combination (Calle Sarmiento, 2023; Shyam Sunder et al., 2023). In fact, diarrhea was the most common treatment-emergent adverse event (TEAE) reported in the CLEAR trial, and the third in the Keynote-775 study; the incidence of grade ≥ 3 diarrhea was equal to 11.1% and 8.1% respectively(Makker et al., 2022; Motzer et al., 2024).

Typically, irAE diarrhea or colitis occurs six to seven weeks after starting treatment, characterized by an acute onset of pronounced symptoms associated with the inflammatory reaction produced by immune system responses against intestinal mucosa (Som et al., 2019). In contrast, VEGFR-TKI associated diarrhea usually has an insidious onset caused by an inhibition of the vascular system of tumors and of the blood supply in the intestinal epithelium (Fan and Iseki, 1998).

Treatment with antidiarrheal drugs may be needed and compensation for electrolyte or fluid losses should be considered, whenever necessary (Leucht et al., 2022); in fact, optimal medical management for diarrhea should be initiated prior to any drug interruption or dose reduction. According to the SmPC for grade 3 diarrhea an interruption is recommended until a resolution to Grade 0–1 or baseline while a discontinuation is necessary for grade 4 (European Medicines Agency, 2025c).

A withhold of ICI therapy is requested for ir-diarrhea/colitis together with symptomatic management and systemic corticosteroids (CS) 40–60 mg/day. For grade 3 i.v. methylprednisolone 1 mg/kg/day should be administered. (Haanen et al., 2022) Recommendations on

Table 3
Recommendations on disorders management of the lenvatinib plus pembrolizumab combination.

Question regarding Gastrointestinal disorders management	
Diarrhea/colitis is a common AE that could be related to both TKI or ICI. How can we do differential diagnosis? Which treatment approaches are mainly recommended?	To differentiate from other causes, starting from grade 2 diarrhea/colitis a stool colture should be examined for bacterial pathogens and clostridioides difficile toxins, faecal calprotectin or lactoferrin; whole blood CRP for CMV, CBC, serum CRP and electrolytes should be tested together with IGRA, hepatitis A, B, C and E and HIV test. Although a biopsy is not decisive for a differential diagnosis an endoscopic evaluation is advisable. Antidiarrheal agents (primarily loperamide but alternatively deodorized tincture of opium, or octreotide) are important to provide supportive care; patients should be encouraged to maintain proper hydration. It is essential to restore gut microbiota, and a personalized diet should be applied (Grünwald et al., 2024). For grade 2–3 ir-diarrhea/colitis, pembrolizumab should be withhold until AEs recover to grade 0–1, while lenvatinib should be interrupted for grade 3 TRAE diarrhea and resumed after its resolution with a proper dose reduction (European Medicines Agency, 2025c, 2025a). In case of recurrent or persistent symptoms of grade 3 and for grade 4 events permanent discontinuation is indicated (Leucht et al., 2022).
Is it reasonable to think on using FMT in cancer patients who receive ICI in the upcoming future?	On November 2022 U.S. Food and Drug Administration approved the first fecal microbiota product for the prevention of recurrence of CDI in adult patients (Food and Drug Administration, 2022). Regulation is handled differently across Europe where FMT centres with high safety standards operate. Promising results indicate that FMT may also be effective in other diseases such as ulcerative colitis, multidrug resistant organism carriage, irritable bowel syndrome and other conditions. More specifically, initial experiences suggest that FMT may be a reliable option to increase the likelihood of response in patient's refractory to ICI (Baruch et al., 2021; Davar et al., 2021).
Questions on Endocrinological Disorders Management	
Thyroid disorders could be caused by both TKI and ICI. When the ICI-TKI combination is used, how can a differential diagnosis be done?	Both classes of drugs induce a similar effect, making differential diagnosis not easy (even with thyroid biopsy). TKIs interact with the thyroid gland through multiple mechanisms, including altered deiodinase activity, decreased iodine uptake, and the development of destructive thyroiditis. The latter is also typically observed during ICI therapy with an initial phase of thyrotoxicosis, caused by the release of preformed thyroid hormones, followed by hypothyroidism. Although it is unnecessary to determine which component of the combination therapy is responsible for this AE, thyroid disorders associated with a proper treatment do not require discontinuation of anticancer therapy.
Fatigue and asthenia are symptoms reported by some patients during	Fatigue could be a clinical manifestation of adrenal insufficiency or hypophysitis,

(*continued on next page*)

Table 3 (*continued*)

Question regarding Gastrointestinal disorders management	
TKI and ICI treatments. Should ACTH and 8 am cortisol levels be tested only in symptomatic patients, or should they be tested routinely for all patients?	which are TRAE that may occur during ICI monotherapy and more "frequently" with combination therapies. Moreover, TKIs may interfere with the hypothalamus-pituitary-thyroid, -adrenal and -gonadal axes. Accordingly, ACTH and 8 am cortisol levels should be tested before starting the TKI and ICI combination treatment and monitored every 4–6 weeks during treatment. ACTH levels may be elevated in asymptomatic patients. In some cases, an ACTH stimulation test can help identify patients who require replacement therapy with cortisone. At the onset of fatigue during lenvatinib and pembrolizumab combination therapy, LH and FSH along with estradiol in women and testosterone in men should also be tested to detect hypophysitis and/or hypogonadism (Castinetti et al., 2018).
Question on Lung Disorders Management	
Which parameters should be assessed for evaluating DIILD?	In DIILD we should evaluate the symptoms, physical examination, the radiological imaging with CT scan (HRCT if it is available) and lung function tests. DLCO and FVC are the two functional tests that could be suggested. While the latter can be an expression of DIILD, DLCO is an aspecific value noticed in other diseases such as emphysema, pulmonary hypertension, or pulmonary embolism. It could be useful to assess DLCO and the FVC at baseline.
Question on Renal Disorders Management	
Some patients with RCC underwent nephrectomy. Does this condition affect renal function?	Cytoreductive nephrectomy is a part of the management of patients with mRCC (Das et al., 2023). Nevertheless, after the CARMENA trial the rate of cytoreductive nephrectomies is decreasing, taking into account that conservative treatments are more and more commonly performed (Méjean et al., 2018; Tsao et al., 2013). In nephrectomized patients with RCC, kidney function could be compromised if an acute stress happens but in normal conditions can maintain its glomerular filtration rate. Accordingly, a good state of hydration, euvolemia, should be suggested to these patients together with a low-sodium diet to maintain a renal function. CT examinations with contrast play a fundamental role throughout the natural history of the oncological disease, being the key to characterizing and staging the pathology correctly, to evaluate the response to oncological treatment, and to monitor disease progression or recurrence during follow-up, and thus, whenever possible, should not be denied to cancer patients (Cosmai et al., 2020).
Which are the kidney-related contraindications for administering contrast-enhanced CT?	According to international and national guidelines prophylaxis with intravenous normal saline is indicated only for patients without contraindication (eg, heart failure) who have AKI or an (eGFR) less than 30 mL/min/1.73 m2, who are not undergoing maintenance dialysis. In individual medium-risk circumstances, prophylaxis may be considered in patients with an eGFR of 30–44 mL/min/1.73 m2 in presence of risk factors such as heart failure, dehydration, concomitant nephrotoxic drugs, hypertension and diabetes. Metformin should be stop only when eGFR is less than 30 mL/min/1.73 m^2. The presence of a solitary kidney should not independently influence decision making regarding the risk of AKI (Davenport et al., 2020). N-Acetylcysteine is not recommended as prophylaxis
Question on Rheumatological disorders management	
Which is the preferred CS dosage and duration to manage arthralgia AE in patients nonresponsive to NSAIDs or analgesics?	Arthralgia is a common symptom for arthritis and ultrasound scan of the joints should be performed for a differential diagnosis. When arthritis is confirmed, CS can be used for 4–6 weeks. Starting with prednisone 10 mg in association with a csDMARD, such as methotrexate and sulfasalazine, could allow a progressive dose reduction of CS therapy.
Can cancer patients with pre-existing immunological rheumatic disease start ICI-TKI combination treatment?	Cancer patients with pre-existing rheumatic conditions were not included in clinical trials evaluating ICI therapies; these data come mainly from real-world and retrospective studies. Flares up are usually mild and manageable and a withdrawal is not requested (Menzies et al., 2017; Pacholczak-Madej et al., 2023). Pre-existing autoimmune rheumatic and/or systemic disease should not preclude the use of cancer ICI-TKI combination, according to EULAR recommendations (Kostine et al., 2021). Rheumatological regular follow-up is always recommended even for patients with rheumatic disease in stable remission Baseline immunosuppressive regimen should be kept at the lowest dose possible (for glucocorticoids, below 10 mg prednisone per day if possible). However, many patients may have a flare of the underlying condition and/or immune-related adverse events, requiring the use of glucocorticoids and/or DMARDs.
Questions regarding Cardiological disorders management	
Which are the baseline cardiological risk assessment tests suggested before starting ICI-TKI combination treatment?	At baseline ECG and TnT test should be performed before starting cancer treatment. In the case of ICI combinations (anti PD-L1 plus anti CTLA4) and ICI plus VEGF-TKI a basal echocardiogram is also suggested. Cardiovascular risk factors (primarily blood pressure, but also dyslipidemia and diabetes) must be treated and targeted according to the directives of international scientific guidelines. The use of ICI plus VEGF-TKI in patients with a high CV risk is not contraindicated; however, a close follow up is recommended and the patient should be instructed to immediately report the onset of new symptoms: chest pain, dyspnea, syncope/fainting (Lyon et al., 2022).
Which is the most appropriate timing for BP measurements at home and how can hypertension be managed during ICI plus VEGF-TKI treatment?	Primarily, BP should be monitored every day or every other day and then every week; it could be useful to provide prompt antihypertensive treatment indications to patients once hypertension appears (Lyon et al., 2022).
What to do if symptoms indicative of cardiovascular disease appears in oncology patients?	Suspicious symptoms indicative of cardiovascular diseases (such as dyspnoea, dizziness, syncope, palpitations, chest pain), particularly

(*continued on next page*)

Table 3 (*continued*)

Question regarding Gastrointestinal disorders management	
	when they occur within the first weeks, require close attention as they may potentially indicate myocarditis. Prompt execution of an ECG, measurement of troponin and CPK levels, and, if indicated, an echocardiogram is essential. In cases of characteristic symptoms and/or abnormal test results, a cardiology consultation, repeated testing in the following hours, and, if necessary, hospitalization should be considered (Lyon et al., 2022).

AE: adverse event; TKI: tyrosine kinase inhibitor; ICI: immune checkpoint inhibitor; CPR: c-reactive protein; CMV: cytomegalovirus; CBC: complete blood count; IGRA: interferon gamma release assay; HIV: human immunodeficiency virus; TRAE: treatment related adverse event; CDI: clostridium difficile infections; FMT: fecal microbiota transplantation; ACTH: adrenocorticotropic hormone; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; DIILD: drug-induced interstitial lung disease; CT: computerized tomography; HRCT: high resolution CT; DLCO: diffusion to carbon monoxide; FVC: forced vital capacity; RCC: renal cell cancer; eGFR: estimated glomerular filtration rate; AKI: acute kidney injury; CS: corticosteroid; NSAID: non-steroidal anti-inflammatory drugs; TnT: troponin T; ECG: electrocardiogram; CTLA4: Cytotoxic T-Lymphocyte Antigen 4; CV: cardiovascular; BP: blood pressure; VEGF: vascular endothelial growth factor; CPK: Creatinine-Phosphokinase

Table 4
Table summarizing baseline assessments and ongoing monitoring.

At baseline	During treatment it is suggested to performed:
- Gastrointestinal assessment: ensure an optimal bowel function, oral intake, and any concerns - Endocrinological assessment: TSH and FT4, blood glucose levels, 8 am cortisol, natremia, and gonadotropic axis evaluation, such as FSH, LH, and estradiol in no menopausal females; FSH in menopausal females; FSH, LH and testosterone in males - Hepatic assessment: liver function - Renal assessment: Urine analysis, creatinine level - Pulmonary assessment: DLCO and FVC - CV assessment: clinical examination, TnT test, BP measurement, a basal ECG and echocardiogram. CV risk factors identification (dyslipidemia and diabetes). Electrolytes (magnesium, potassium and calcium) should be tested	- Assessment related to suspicious symptoms/signs indicative of toxicity - Endocrinological assessments include glycemia, TSH and FT4, natremia, adrenocorticotropic hormone (ACTH) and 8 am cortisol, testosterone (in males), and a full lipidic assessments - Hepatic assessment: liver function during treatment and as indicated based on clinical evaluation - Renal assessment: Urine analysis, creatinine level - CV assessment: BP should be monitored every day or every other day and then every week. Electrolytes (magnesium, potassium and calcium) and ECG should be monitored periodically during treatment

TSH, thyroid-stimulating hormone; FT4, thyroxine; FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; CV, cardiovascular; BP, blood pressure; ECG, electrocardiogram

gastrointestinal disorders management are reported on Table 3.

Recent research suggested the use of fecal microbiota transplantation (FMT) for ir-colitis not responsive to standard treatments, as already shown in TKI-dependent diarrhea (Baunwall et al., 2021; Ianiro et al., 2020). Wang et al. reported the first case series of two patients with irAE diarrhea/colitis successfully treated with FMT, achieving an improvement of endoscopic appearance, a reduction in CD8 and increase in CD4 T cells with reconstitution of the gut microbiome (Food and Drug Administration, 2022; Grünwald et al., 2024; Wang et al., 2018). Indeed, FMT could become a possible treatment for the future in refractory colitis(Baruch et al., 2021; Davar et al., 2021).

4.2. Cardiological disorders

The first European Society of Cardiology (ESC) guideline on cardio-oncology were published in 2022 to help all the healthcare professionals providing care to oncology patients before, during, and after their cancer treatments with respect to their cardiovascular (CV) wellness (Lyon et al., 2022). Recommendations on cardiological disorders management are reported on Table 3.

A baseline cardiological risk assessment before starting a cancer treatment is recommended and according to the risk a different follow-up should be provided (Lyon et al., 2022). For patients reporting a baseline low risk, the follow up should be managed by the oncologist as well as for moderate risk where a closer follow up is recommended, while for patients with a baseline high CV risk the reference expert should be the cardiologist and a discussion of the risk/benefit balance of cardiotoxic anticancer treatment with the oncologist should be proposed (Lyon et al., 2022). Patients reporting baseline hypertension are classified as high-risk patients and the follow up, starting from the baseline assessment, should be managed by the cardiologist. Regarding the pharmacological management, the most European Society of Hypertension Guidelines suggest preferring as antihypertensive class a renin-angiotensin-system (RAS) inhibitor or a dihydropyridinic calcium channel inhibitor (DHP-CCB) for VEGF-induced hypertension. Thiazide/thiazide-like diuretics should be avoided for the increased risk of adverse events as hyponatremia, increased risk of cardiac arrhythmias due to prolonging the QT interval by inducing hypokalemia, and potential worsening of hypovolemic states or dehydration. (Mancia et al., 2023).

TKI CV toxicity differs from ICI CV toxicity; in TKI, it is frequently reported, often predictable and manageable while for ICI is rarely found and probably less predictable. VEGF-TKI use is associated with a wide array of CV complications including hypertension, HF (heart failure), QTc prolongation, and acute vascular events which should be treated according to ESC guidelines. Antihypertensive treatment should be individualised to the patient's clinical circumstances and follow standard medical practice. A baseline CV risk assessment should include clinical examination, blood pressure (BP) measurement, and an electrocardiogram (ECG) with baseline QTcF measurement especially in patients with known hypertension or with impaired left ventricle (LV) function and/or at risk of developing HF (Lyon et al., 2022).

There are intriguing data that VEGF-TKI may lead to hypertension by interfering with different signaling pathways; it reduces Nitric oxide (NO) pathway metabolites and NO-dependent processes causing an impairment in endothelium-dependent vasodilation in the microvasculature increasing endothelin-1 levels which induce vasoconstriction leading to elevated blood pressure (Pandey et al., 2018). TKI-related endothelial dysfunction also promotes abnormal vasoreactivity, atherosclerosis, platelet activation, and coagulation, all in favor of atherothrombotic events observed in this patient population (Touyz et al., 2018). An alternative mechanism for hypertension is microvascular rarefaction; the subsequent diminution of the microvascular surface area leads to an increase in peripheral vascular resistance and resultant increase in blood pressure (Mäki-Petäjä et al., 2021).

In phase III clinical studies evaluating the combination lenvatinib plus pembrolizumab hypertension was the most common CV toxicity noticed in both the CLEAR and Keynote trials with an incidence of 57.4% and 65.0%. (Makker et al., 2022; Motzer et al., 2024) Thus, BP measurements should be performed at baseline and then monitored during VEGF-TKI treatment in order to adequately treat hypertension.

Moreover, following hypertension TKIs increase ventricular wall stress, and alter the coronary microcirculation causing a mismatch between the increase in O2 demands, and the decreased capacity of the coronary circulation to satisfy this increase in demands (Lévy, 2006). The ventricle, instead of undergoing a remodeling in the direction of hypertrophy, tends to dilate. The ventricular dysfunction is also promoted by the reduced contractility of cardiomyocytes caused by

VEGF-TKI (Gao et al., 2020).

Most frequent ICI related CV toxicities are arrhythmias, myocarditis, takotsubo syndrome, pericarditis (Lyon et al., 2022). Myocarditis is a complication of ICI that most frequently develops during the first 12 weeks of treatment; the severity may vary from subclinical that self-resolve to fulminant ones with cardiogenic shock and/or fatal hyperkinetic or hypokinetic. The diagnosis of ICI-associated myocarditis is initially based on the presence of symptoms (dyspnea, dizziness, syncope, palpitations, chest pain), a new increase in troponin (associated with either CV symptoms or non-CV immuno-related adverse events), and new ECG abnormalities (AV or intraventricular conduction disorders, bradycardia, tachyarrhythmias) (Lyon et al., 2022). Transthoracic echocardiographic is recommended in all patients with suspected ICI-associated myocarditis and treatment with CS is recommended as first step (Das et al., 2023; Lyon et al., 2022).

Patients with myositis may show a myasthenia-like syndrome with respiratory failure as concomitant myocarditis could be present and cardiac-specific Troponin T (TnT) together with creatine phosphokinase tests are suggested.

4.3. Endocrinological disorders

Endocrine disorders are commonly reported during TKI and ICI treatments; generally, replacement therapies are recommended for deficiencies (e.g. levothyroxine for hypothyroidism), while symptomatic therapies are used for hyperfunction. Unless severe or life-threatening forms occur, the onset of endocrinopathies does not inherently contraindicate the continuation of anticancer therapies (Castinetti et al., 2018).

Thyroid disorders, particularly hypothyroidism, are the most common irAEs as well as TKI-related endocrine toxicities (De Leo et al., 2023; European Medicines Agency, 2025c). Commonly observed in younger and female patients, particularly after prolonged anti-PD-1/PD-L1 treatment and in those with elevated baseline Thyroid-stimulating hormone (TSH) levels, it could be related also to TKI agents through several mechanisms including destructive thyroiditis, capillary regression in the thyroid gland, thyroperoxidase inactivation, and reduced iodine uptake by thyrocytes (Ahmadieh and Salti, 2013; Chiloiro et al., 2022; Jannin et al., 2019).

In thyroidectomized patients, increased doses of levothyroxine are required because of an alteration in thyroid hormone metabolism. This seems to be mainly caused by type 3 deiodinase induction, which increases the conversion of thyroxine (T4) into reversed triiodothyronine (rT3) (Schlumberger et al., 2017, 2015). Destructive thyroiditis typically presents with an initial phase of thyrotoxicosis, caused by the release of preformed thyroid hormones, followed by hypothyroidism. During the thyrotoxic phase, the use of antithyroid drug is not recommended unless Graves' disease is diagnosed. In the presence of clinical symptoms, non-cardio-selective beta blockers are indicated to manage thyrotoxic symptoms (Drui et al., 2018). Treatment of TKI-induced hypothyroidism is based on levothyroxine, with a starting dosage of 1–1.6 μg/kg/day and is indicated in case of TSH $>$ 10 mIU/L and/or in patients with serum TSH of 5–10 mIU/L, symptomatic, with positive anti-thyroid peroxidase (TPO) antibodies, or with ultrasound signs of autoimmune thyroiditis.

Adrenal toxicities such as cortical congestion or hemorrhage may occur with combination therapies; while ICIs are rarely associated with primary adrenal insufficiency (PAI) it is more frequently reported as a TKI-related AE. Adrenal insufficiency manifests with various nonspecific symptoms (signs of dehydration, hyperkalemia, hyponatremia, hypotension, dizziness, and fatigue) (Colombo et al., 2019; European Medicines Agency, 2025c). It is recommended to test adrenal function especially in patients reporting fatigue, to ensure prompt initiation of replacement therapy; this approach can help prevent treatment discontinuation, dosage reductions, and potentially severe complications associated with PAI.

Hypophysitis is an irAE mostly found in older and male patients under anti-CTLA-4 treatment while TKI may impact the function of pituitary gland, parathyroids or gonads. Type I diabetes mellitus can occur during ICI therapy, typically in patients with a history of autoimmune diseases, which does not contraindicate continuation of treatment (Buffier et al., 2018; Chiloiro et al., 2022).

Thus, according to the French Society of Endocrinology consensus on endocrine toxicity of novel anticancer therapies, the experts suggest, before initiating TKI and ICI therapies, baseline assessments should include TSH and FT4, blood glucose levels, 8 am cortisol, natremia, and gonadotropic axis evaluation, such as Follicle Stimulating Hormone (FSH), Luteinizing Hormone (LH), and estradiol in no menopausal females; FSH in menopausal females; FSH, LH and testosterone in males (Castinetti et al., 2018). During TKI plus ICI treatment, regular monitoring, every 4–6 weeks in the first months of treatment, should include glycemia, TSH and FT4, natremia, adrenocorticotropic hormone (ACTH) and 8 am cortisol, testosterone (in males), and a full lipidic assessments (Castinetti et al., 2018). Recommendations on endocrinological disorders management are reported on Table 3.

4.4. Renal disorders

Adverse renal effects of targeted therapies occur through several complex mechanisms. Wide ranges of toxicities affecting various parts of the nephron have been reported with the novel targeted therapies.

Antiangiogenics used in combination often induce renal toxicities such as hypertension, proteinuria, acute kidney injury (AKI), thrombotic microangiopathy (TMA), electrolytes disturbances, glomerulopathies. Anti-VEGF TKIs activate the endothelin-1 system modulating the renin–angiotensin system, resulting in hypertension and microvascular dysfunction (Cosmai et al., 2021; Porta et al., 2015). In particular, the VEGF inhibition reduces the ability of cell repair, increases apoptosis in vascular endothelial cells, promotes the rarefaction of capillaries and arterioles, and reduces the cellular production of vasodilators such as NO and prostacyclin, favoring vasoconstriction, increasing peripheral resistance, and decreasing sodium renal excretion(Hicklin and Ellis, 2005). This mechanism of action leads to hypertension.

ICI may cause interstitial nephritis, electrolytes disturbances, AKI, glomerulopathies; tubulointerstitial nephritis (TIN) is the most common presenting as reduced renal function, indicated by rising serum creatinine (Cr), low-grade proteinuria, and sterile pyuria in roughly 50% of cases(Cosmai et al., 2021; Sprangers et al., 2022).

Rarely, ICIs lead to the development of glomerular disease. Patients who develop minimal change disease, focal segmental glomerulosclerosis, or membranous nephropathy often present with nephrotic syndrome. Conversely, patients with nephritic lesions (e.g., pauci-immune crescentic glomerulonephritis (GN) due to antineutrophil cytoplasmic antibody [ANCA] associated vasculitis) present with hematuria, subnephrotic proteinuria, and impaired renal function (Porta et al., 2015; Sprangers et al., 2022).

In the phase III Keynote-775 trial during lenvatinib plus pembrolizumab the renal impairment mostly detected was proteinuria (30.5%) followed by urinary tract infection (26.4%); in the CLEAR study proteinuria was found in the 33.2% of patients treated with the TKI-ICI combination (Makker et al., 2022; Motzer et al., 2024).

Proteinuria is an AE related to anti VEGF TKIs and even if no guidelines are available on its treatment, a TKI interruption for a proteinuria $\geq$ 2 g/24 h is requested until resolution (European Medicines Agency, 2025c). In clinical practice it is also reasonable to continue TKIs in presence of proteinuria higher than 2 g/24 h depending on symptoms and on the efficacy of treatment A baseline urine analysis is necessary to detect a first proteinuria that could be related to other causes such as diabetes.

Nephritis, typically related to ICI, may manifest with creatinine level increase defined as grade 2 when a range $>$ 1.5 to $\leq$ 3 times upper limit of normal (ULN) is detected and a withhold until a recover to grade 0–1

is recommended; discontinuation for grade ≥ 3 requires ICI discontinuation (European Medicines Agency, 2025a). Caution should be used with diuretics agents in cancer patients for the risk of dehydration and increased renal toxicity not related to the combination therapy.

Recognition of adverse renal effects of these agents in a timely manner is extremely important for optimal patient care. Accordingly, for the onset of AKI stage ≥ 2 during combination therapies with ICI and VEGFR-TKI serum creatinine, urea, uric acid electrophoresis, electrolytes, blood count, urinalysis should be performed. Recommendations on renal disorders management are reported on Table 3.

4.5. Rheumatological disorders

Rheumatic irAEs could be related to both ICI and TKI and during a combination treatment the identification of the causative agent would be important to establish a better therapeutic strategy (Makker et al., 2021).

Arthralgia is the most common rheumatological symptom reported in patients subjected to lenvatinib plus pembrolizumab; rarely myasthenia gravis (detected with acetylcholine receptor antibodies lab test), myocarditis, vasculitides or sarcoidosis/sarcoid-like reactions may be found (Kostine et al., 2018). Median onset is usually within 2–16 weeks, equally distributed between different age and sex, many patients simultaneously have more than one irAE.

Arthralgia could dissimulate rheumatoid arthritis (RA) presenting with symmetrical small joint arthritis, predominantly in the hands; rheumatic polymyalgia-like presentation would see the involvement of scapular and pelvic waist; a further manifestation is the spondylarthritis (Makker et al., 2022; Motzer et al., 2024). While the latter is more likely associated to CTLA4 inhibitor therapy, patients on PD-1/PD-L1 inhibitor therapy are more likely to experience RA-like arthritis.

The wide spectrum of clinical presentations of rheumatic and/or systemic irAEs that often do not fulfil traditional classification criteria of rheumatic and musculoskeletal diseases requires cooperation between rheumatologists and oncologists to provide the best treatment for the patient. (Kostine et al., 2018) The rheumatologist should play an active role in the differential diagnosis of these manifestations, which may also be paraneoplastic or unrelated to the ICI mechanism and should offer adequate management and treatment participating in the choices of therapeutic strategy. Ideally, in case of a suspicion of rheumatic irAE without an improvement after analgesic therapies and a pre-existing rheumatic disease the rheumatologist should be approached (Haanen et al., 2022).

Initial therapy should include Nonsteroidal anti-inflammatory drugs (NSAIDs) and/or other analgesics (Kostine et al., 2021). Corticosteroids (CS) is an aspecific treatment for irAE that should be tapered to the lowest effective dose to control the symptoms while a conventional synthetic disease modifying antirheumatic drugs (csDMARD) should be considered in patients with insufficient response to acceptable dose of glucocorticoids or requiring glucocorticoid-sparing (Kostine et al., 2021). bDMARDs such as tumor necrosis factor (TNF), Interleukin 6 (IL6) inhibitor are possible options in case of severe irAEs with insufficient response to csDMARDs (Kostine et al., 2021). Recommendations on rheumatological disorders management are reported on Table 3.

Before starting ICI therapy patients with thymoma should be tested for an anti-acetylcholine receptor given the high risk to develop myositis / myasthenia gravis with poor prognosis; no indication to test every patient for the presence of autoantibodies is recommended. Nevertheless, their presence in patients who develop rheumatic irAEs could predict their progression to difficult-to-treat clinical manifestations. Such predictors could greatly impact clinical practice as it could prompt the early start of add-on therapies, thus possibly preventing the accrual of organ damage (Campochiaro et al., 2022; Ramos-Casals et al., 2019).

Cancer patients with pre-existing rheumatic conditions were not included in clinical trials evaluating ICI therapies; these data come mainly from real-world and retrospective studies. In patients observed in those studies, flares up are usually mild and manageable and a withdrawal is not usually requested(Menzies et al., 2017; Pacholczak--Madej et al., 2023). However, according to EULAR recommendations, the decision-making about immunotherapy (to hold or to continue) should be based on the severity of rheumatic irAE (Kostine et al., 2021).

4.6. Lung disorders

The occurrence of lung disorders such as pneumonitis or interstitial lung disease were first described in clinical trials and case reports, which included also fatal cases of pneumonia in patients treated both with TKI and ICIs (Delaunay et al., 2019; Gupta et al., 2021; Picard et al., 2021).

Generally, Drug Induced Interstitial Lung Disease (DIILD) diagnosis in patients treated with both these classes of drugs show exertional dyspnea and abnormal gas exchange until manifestation of acute respiratory failure. The radiological presentation can be heterogeneous with various radiological patterns, including usual interstitial pneumonia (UIP), non-specific interstitial pneumonia (NSIP), diffuse alveolar damage, organizing pneumonia (OP), hypersensitivity pneumonitis (HP) and acute interstitial pneumonia detected by high-resolution computed tomography (HRCT) of the chest (Skeoch et al., 2018). Although OP appears to be the most frequent radiological pattern, the clinical non-specificity and the radiological heterogeneity, diagnosis of DIILD may be very challenging, and a detailed collection of medical history and of the timeline of patient's drug exposition is crucial for an optimal diagnostic assessment, as stated by the international guidelines for diagnosis of idiopathic pulmonary fibrosis (IPF) (Raghu et al., 2022).

In a multicentre retrospective study from 6 Italian centres of patients receiving ICIs, who developed lung toxicity, radiological imaging showed a ground glass opacities in 56% of patients, followed by emphysema (34.1%) and organizing pneumonia (14.6%) (Cameli et al., 2022). Nevertheless, DIILD is also an AE found in patients treated with different TKIs, with both ground glass opacities or organizing pneumonia (Kataoka et al., 2025).

The rate of lung toxicities using the combination of both TKI and ICI in comparison with TKI (osimertinib, afatinib, erlotinib, and gefitinib) was analyzed in the FAERS database study conducted with 20,516 patients; the rate of DIILD was 25.7% for the combination treatment versus 4.59% for TKI monotherapy (Oshima et al., 2018). This could indicate that there is a higher probability of DIILD occurring with combination therapy (Oshima et al., 2018). Recommendations on lung disorders management are reported on Table 3.

Suspected pneumonitis should be confirmed by imaging and for grade ≥ 2 an initial dose of 1–2 mg/kg/day prednisone is recommended for irAE; for grade 3, grade 4 or recurrent grade 2 pneumonitis pembrolizumab should be permanently discontinued (European Medicines Agency, 2025a).

5. Conclusions

The combination of lenvatinib and pembrolizumab has demonstrated its efficacy in two common malignancies, RCC and EC. Specifically, the ICI-TKI combination improved the PFS, OS, and ORR in the pMMR and all-comer populations in pretreated advanced EC while in metastatic RCC an advantage in terms of mOS, mPFS and ORR was demonstrated (Makker et al., 2022; Motzer et al., 2024).

Along with efficacy, understanding the safety profile is crucial for managing TRAEs, which is fundamental for ensuring good treatment tolerance and compliance. The combination of targeted therapies and immunotherapies showed a changing spectrum of AEs that may affect various organs with differing times of onset.

Management of AEs associated with ICI–TKI combinations encompasses education of patients, families, caregivers, and the treatment team, including other specialists, to enable prompt implementation of mitigation strategies, close monitoring, dose modification, and appropriate use of concomitant medications. Accordingly, a multidisciplinary

approach is suggested, involving collaboration between oncologists and organ specialists to promptly prevent/address possible toxicities associated with the treatment. Future insights should explore strategies for implementing this model in clinical practice, providing useful tools such as standardized baseline checklists and patient-reported symptom monitoring and shared, multidisciplinary rechallenge decisions captured in a standardized format to enable continuous improvement of prompt adverse event management

CRediT authorship contribution statement

Roberto Sabbatini: Conceptualization, Methodology, Writing – review & editing. Camillo Porta: Conceptualization, Methodology, Writing – review & editing. Simone De Leo: Writing – review & editing endocrinology section; Laura Cosmai: Writing – review & editing nephrology section. Gianluca Ianiro: Writing – review & editing gastroenterology section. Caterina Vacchi: Writing – review & editing rheumatology section. Fabrizio Luppi: review & editing pulmonology section. Paolo: Spallarossa: Writing – review & editing cardiology section.

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This manuscript did not generate any new dataset. All data analyzed are from publicly available sources, as cited in the manuscript.

References

Ahmadieh, H., Salti, I., 2013. Tyrosine kinase inhibitors induced thyroid dysfunction: a review of its incidence, pathophysiology, clinical relevance, and treatment. BioMed. Res. Int. 2013, 1–9. https://doi.org/10.1155/2013/725410.

American Cancer Society, 2025. Uterine Cancer Survival Rate | Survival Rates for Endometrial Cancer.

Baruch, E.N., Youngster, I., Ben-Betzalel, G., Ortenberg, R., Lahat, A., Katz, L., et al., 2021. Fecal microbiota transplant promotes response in immunotherapy-refractory melanoma patients. Science 371, 602–609. https://doi.org/10.1126/science.abb5920.

Baunwall, S.M.D., Terveer, E.M., Dahlerup, J.F., Erikstrup, C., Arkkila, P., Vehreschild, M.J., 2021. The use of faecal microbiota transplantation (FMT) in Europe: a Europe-wide survey (Iaet al.). Lancet Reg. Health Eur. 9, 100181. https://doi.org/10.1016/j.lanepe.2021.100181.

Buffier, P., Bouillet, B., Smati, S., Archambeaud, F., Cariou, B., Verges, B., 2018. Expert opinion on the metabolic complications of new anticancer therapies: Tyrosine kinase inhibitors. Ann. Endocrinol. 79, 574–582. https://doi.org/10.1016/j.ando.2018.07.011.

Calle Sarmiento, P.M., 2023. Immune checkpoint inhibitor-induced colitis: how long does the threat last? Cureus. https://doi.org/10.7759/cureus.40627.

Cameli, P., Faverio, P., Ferrari, K., Bonti, V., Marsili, S., Mazzei, M.A., et al., 2022. Immune-checkpoint-inhibitor-related lung toxicity: a multicentre real-life retrospective portrait from six Italian centres. Life 12, 1149. https://doi.org/10.3390/life12081149.

Campochiaro, C., Farina, N., Tomelleri, A., Ferrara, R., Viola, S., Lazzari, C., et al., 2022. Autoantibody positivity predicts severity of rheumatic immune-related adverse events to immune-checkpoint inhibitors. Eur. J. Intern. Med. 103, 95–99. https://doi.org/10.1016/j.ejim.2022.07.005.

Castinetti, F., Albarel, F., Archambeaud, F., Bertherat, J., Bouillet, B., Buffier, P., et al., 2018. Endocrine side-effects of new anticancer therapies: Overall monitoring and conclusions. Ann. Endocrinol. 79, 591–595. https://doi.org/10.1016/j.ando.2018.07.005.

Chiloiro, S., Bianchi, A., Giampietro, A., Milardi, D., De Marinis, L., Pontecorvi, A., 2022. The changing clinical spectrum of endocrine adverse events in cancer immunotherapy. Trends Endocrinol. Metab. 33, 87–104. https://doi.org/10.1016/j.tem.2021.10.009.

Colombo, C., De Leo, S., Di Stefano, M., Vannucchi, G., Persani, L., Fugazzola, L., 2019. Primary Adrenal Insufficiency During Lenvatinib or Vandetanib and Improvement of Fatigue After Cortisone Acetate Therapy. J. Clin. Endocrinol. Metab. 104, 779–784. https://doi.org/10.1210/jc.2018-01836.

Colombo, N., Lorusso, D., Monk, B.J., Slomovitz, B., Hasegawa, K., Nogueira-Rodrigues, A., et al., 2024. Characterization and Management of Adverse Reactions in Patients With Advanced Endometrial Cancer Receiving Lenvatinib Plus Pembrolizumab. The Oncologist 29, 25–35. https://doi.org/10.1093/oncolo/oyad201.

Concin, N., Matias-Guiu, X., Vergote, I., Cibula, D., Mirza, M.R., Marnitz, S., et al., 2021. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int. J. Gynecol. Cancer 31, 12–39. https://doi.org/10.1136/ijgc-2020-002230.

Cosmai, L., Porta, C., Foramitti, M., Perrone, V., Mollica, L., Gallieni, M., Capasso, G., 2021. Preventive strategies for acute kidney injury in cancer patients. Clin. Kidney J. 14, 70–83. https://doi.org/10.1093/ckj/sfaa127.

Cosmai, L., Porta, C., Privitera, C., Gesualdo, L., Procopio, G., Gori, S., Laghi, A., 2020. Acute kidney injury from contrast-enhanced CT procedures in patients with cancer: white paper to highlight its clinical relevance and discuss applicable preventive strategies. ESMO Open 5, e000618. https://doi.org/10.1136/esmoopen-2019-000618.

Crosbie, E.J., Kitson, S.J., McAlpine, J.N., Mukhopadhyay, A., Powell, M.E., Singh, N., 2022. Endometrial cancer. Lancet 399, 1412–1428. https://doi.org/10.1016/S0140-6736(22)00323-3.

Cunningham-Bussel, A., Wang, J., Prisco, L.C., Martin, L.W., Vanni, K.M.M., Zaccardelli, A., et al., 2022. Predictors of Rheumatic Immune-Related Adverse Events and De Novo Inflammatory Arthritis After Immune Checkpoint Inhibitor Treatment for Cancer. Arthritis Rheuma 74, 527–540. https://doi.org/10.1002/art.41949.

Das, A., Shapiro, D.D., Craig, J.K., Abel, E.J., 2023. Understanding and integrating cytoreductive nephrectomy with immune checkpoint inhibitors in the management of metastatic RCC. Nat. Rev. Urol. 20, 654–668. https://doi.org/10.1038/s41585-023-00776-5.

Davar, D., Dzutsev, A.K., McCulloch, J.A., et al., 2021. Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients. Science 371, 595–602. https://doi.org/10.1126/science.abf3363.

Davenport, M.S., Perazella, M.A., Yee, J., Dillman, J.R., Fine, D., McDonald, R.J., et al., 2020. Use of intravenous iodinated contrast media in patients with kidney disease: consensus statements from the American college of radiology and the national kidney foundation. Radiology 294, 660–668. https://doi.org/10.1148/radiol.2019192094.

De Leo, S., Trevisan, M., Moneta, C., Colombo, C., 2023. Endocrine-related adverse conditions induced by tyrosine kinase inhibitors. Ann. Endocrinol. 84, 374–381. https://doi.org/10.1016/j.ando.2023.03.009.

Delaunay, M., Prévot, G., Collot, S., Guilleminault, L., Didier, A., Mazières, J., 2019. Management of pulmonary toxicity associated with immune checkpoint inhibitors. Eur. Respir. Rev. 28, 190012. https://doi.org/10.1183/16000617.0012-2019.

Drui, D., Illouz, F., Do Cao, C., Caron, P., 2018. Expert opinion on thyroid complications of new anti-cancer therapies: Tyrosine kinase inhibitors. Ann. Endocrinol. 79, 569–573. https://doi.org/10.1016/j.ando.2018.07.003.

Escudier, B., Porta, C., Schmidinger, M., Rioux-Leclercq, N., Bex, A., Khoo, V., et al., 2019. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann. Oncol. 30, 706–720. https://doi.org/10.1093/annonc/mdz056.

Eskander, R.N., Sill, M.W., Beffa, L., Moore, R.G., Hope, J.M., Musa, F.B., et al., 2023. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. N. Engl. J. Med. 388, 2159–2170. https://doi.org/10.1056/NEJMoa2302312.

European Medicines Agency, 2025a. Keytruda - Summary of Product Characteristics.

European Medicines Agency, 2025b. Lenvima - Summary of Product Characteristics.

European Medicines Agency, 2025c. Kisplyx - Summary of Product Characteristics.

Fan, L., Iseki, S., 1998. Immunohistochemical Localization of Vascular Endothelial Growth Factor in the Endocrine Glands of the Rat. Arch. Histol. Cytol. 61, 17–28. https://doi.org/10.1679/aohc.61.17.

Fogli, S., Porta, C., Del Re, M., Crucitta, S., Gianfilippo, G., Danesi, R., et al., 2020. Optimizing treatment of renal cell carcinoma with VEGFR-TKIs: a comparison of clinical pharmacology and drug-drug interactions of anti-angiogenic drugs. Cancer Treat. Rev. 84, 101966. https://doi.org/10.1016/j.ctrv.2020.101966.

Food and Drug Administration, 2022. Commissioner O of the FDA Approves First Fecal Microbiota Product.

Gao, X., Zhang, J., Dai, Z., Luo, D., He, R., Li, M., 2020. Anti-tumor drug lenvatinib induced cardiotoxicity via mitochondrial oxidative stress and apoptosis. J. Mol. Cell. Cardiol. 140, 25. https://doi.org/10.1016/j.yjmcc.2019.11.058.

Grünwald, V., Larkin, J., Puente, J., Bedke, J., Porta, C., 2024. Management of Adverse Reactions Related to Lenvatinib Plus Pembrolizumab Treatment Among Patients With Renal Cell Carcinoma. Clin. Genitourin. Cancer 22, 394–401. https://doi.org/10.1016/j.clgc.2023.12.010.

Grünwald, V., McKay, R.R., Buchler, T., Eto, M., Park, S.H., Takagi, T., et al., 2025. Clinical outcomes by baseline metastases in patients with renal cell carcinoma treated with lenvatinib plus pembrolizumab versus sunitinib: Post hoc analysis of the CLEAR trial. Int. J. Cancer 156, 1326–1335. https://doi.org/10.1002/ijc.35288.

Gu, B., Shang, X., Yan, M., Li, X., Wang, W., Wang, Q., Zhang, C., 2021. Variations in incidence and mortality rates of endometrial cancer at the global, regional, and national levels, 1990–2019. Gynecol. Oncol. 161, 573–580. https://doi.org/10.1016/j.ygyno.2021.01.036.

Gupta, K., Uchel, T., Karamian, G., Loschner, A., 2021. Pulmonary complications of tyrosine kinase inhibitors and immune checkpoint inhibitors in patients with non-small cell lung cancer. Cancer Treat. Res. Commun. 28, 100439. https://doi.org/10.1016/j.ctarc.2021.100439.

Haanen, J., Obeid, M., Spain, L., Carbonnel, F., Wang, Y., Robert, C., et al., 2022. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann. Oncol. 33, 1217–1238. https://doi.org/10.1016/j.annonc.2022.10.001.

Heng, D.Y., Xie, W., Regan, M.M., Harshman, L.C., Bjarnason, G.A., Vaishampayan, U.N., et al., 2013. External validation and comparison with other models of the International Metastatic Renal-Cell Carcinoma Database Consortium prognostic model: a population-based study. Lancet Oncol. 14, 141–148. https://doi.org/10.1016/S1470-2045(12)70559-4.

Hicklin, D.J., Ellis, L.M., 2005. Role of the Vascular Endothelial Growth Factor Pathway in Tumor Growth and Angiogenesis. J. Clin. Oncol. 23, 1011–1027. https://doi.org/10.1200/JCO.2005.06.081.

Ianiro, G., Rossi, E., Thomas, A.M., Schinzari, G., Masucci, L., Quaranta, G., et al., 2020. Faecal microbiota transplantation for the treatment of diarrhoea induced by tyrosine-kinase inhibitors in patients with metastatic renal cell carcinoma. Nat. Commun. 11, 4333. https://doi.org/10.1038/s41467-020-18127-y.

Jannin, A., Penel, N., Ladsous, M., Vantyghem, M.C., Do Cao, C., 2019. Tyrosine kinase inhibitors and immune checkpoint inhibitors-induced thyroid disorders. Crit. Rev. Oncol. Hematol. 141, 23–35. https://doi.org/10.1016/j.critrevonc.2019.05.015.

Jiang, Y., Li, Y., Zhu, B., 2015. T-cell exhaustion in the tumor microenvironment. e1792–e1792 Cell Death Dis. 6. https://doi.org/10.1038/cddis.2015.162.

Kataoka, K., Taniguchi, H., Hasegawa, Y., et al., 2025. Real-world efficacy and safety of pembrolizumab plus lenvatinib in patients with metastatic renal cell carcinoma: a multi-institutional retrospective study. Sci. Rep. 15, 43676. https://doi.org/10.1038/s41598-025-27578-6.

Kato, T., Nakai, Sato, M., Takao, T., Iwanishi, T., Toyoda, S., et al., 2025. Real-world efficacy and safety of pembrolizumab plus lenvatinib in patients with metastatic renal cell carcinoma: a multi-institutional retrospective study. Sci. Rep. 15, 43676. https://doi.org/10.1038/s41598-025-27578.

Kostine, M., Finckh, A., Bingham, C.O., Visser, K., Leipe, J., Schulze-Koops, H., et al., 2021. EULAR points to consider for the diagnosis and management of rheumatic immune-related adverse events due to cancer immunotherapy with checkpoint inhibitors. Ann. Rheum. Dis. 80, 36–48. https://doi.org/10.1136/annrheumdis-2020-217139.

Kostine, M., Rouxel, L., Barnetche, T., Veillon, R., Martin, F., Dutriaux, C., et al., 2018. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—clinical aspects and relationship with tumour response: a single-centre prospective cohort study. Ann. Rheum. Dis. 77, 393–398. https://doi.org/10.1136/annrheumdis-2017-212257.

Leucht, K., Ali, N., Foller, S., Grimm, M.-O., 2022. Management of Immune-Related Adverse Events from Immune-Checkpoint Inhibitors in Advanced or Metastatic Renal Cell Carcinoma. Cancers 14, 4369. https://doi.org/10.3390/cancers14184369.

Lévy, B.I., 2006. Microvascular Plasticity and Experimental Heart Failure. Hypertension 47, 827–829. https://doi.org/10.1161/01.HYP.0000215283.53943.39.

Lorusso, D., Colombo, N., Herraez, A.C., Santin, A.D., Colomba, E., Miller, D.S., et al., 2023. Health-Related Quality of Life in Patients With Advanced Endometrial Cancer Treated With Lenvatinib Plus Pembrolizumab or Treatment of Physician's Choice. Eur. J. Cancer 186, 172–184. https://doi.org/10.1016/j.ejca.2023.03.015.

Lorusso, D., Danesi, R., Locati, L.D., Masi, G., De Giorgi, U., Gadducci, A., et al., 2022. Optimizing the use of lenvatinib in combination with pembrolizumab in patients with advanced endometrial carcinoma. Front. Oncol. 12, 979519. https://doi.org/10.3389/fonc.2022.979519.

Lu, M., Zhang, X., Gao, X., Sun, S., Wei, X., Hu, X., et al., 2021. Lenvatinib enhances T cell immunity and the efficacy of adoptive chimeric antigen receptor-modified T cells by decreasing myeloid-derived suppressor cells in cancer. Pharmacol. Res. 174, 105829. https://doi.org/10.1016/j.phrs.2021.105829.

Lyon, A.R., López-Fernández, T., Couch, L.S., Asteggiano, R., Aznar, M.C., Bergler-Klein, J., et al., 2022. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur. Heart J. 43, 4229–4361. https://doi.org/10.1093/eurheartj/ehac244.

MacKay, H.J., Levine, D.A., Bae-Jump, V.L., Bell, D.W., McAlpine, J.N., Santin, A., et al., 2017. Moving forward with actionable therapeutic targets and opportunities in endometrial cancer: NCI clinical trials planning meeting report on identifying key genes and molecular pathways for targeted endometrial cancer trials. Oncotarget 8, 84579–84594. https://doi.org/10.18632/oncotarget.19961.

Mäki-Petäjä, K.M., McGeoch, A., Yang, L.L., Hubsch, A., McEniery, C.M., Meyer, P.A.R., et al., 2021. Mechanisms Underlying Vascular Endothelial Growth Factor Receptor Inhibition–Induced Hypertension: The HYPAZ Trial. Hypertension 77, 1591–1599. https://doi.org/10.1161/HYPERTENSIONAHA.120.16454.

Makker, V., Colombo, N., Casado Herráez, A., Santin, A.D., Colomba, E., Miller, D.S., et al., 2022. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N. Engl. J. Med. 386, 437–448. https://doi.org/10.1056/NEJMoa2108330.

Makker, V., Colombo, N., Herráez, A.C., Monk, B.J., Mackay, H., Santin, A.D., et al., 2023. Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775. J. Clin. Oncol. 41, 2904–2910. https://doi.org/10.1200/JCO.22.02152.

Makker, V., Colombo, N., Herraez, A.C., Santin, A.D., Colomba, E., Miller, D.S., 2025. 1119P Lenvatinib plus pembrolizumab (L + P) vs treatment of physician's choice (TPC) for advanced endometrial cancer (EC): 5-year outcomes from study 309/KEYNOTE-775 (Fet al.). Ann. Oncol. 36, S699–S700. https://doi.org/10.1016/j.annonc.2025.08.1756.

Makker, V., Taylor, M.H., Oaknin, A., Casado Herraez, A., Orlowski, R., Dutta, L., 2021. Characterization and Management of Adverse Reactions in Patients with Advanced Endometrial Carcinoma Treated with Lenvatinib Plus Pembrolizumab (Ret al.). Oncologist 26, e1599–e1608. https://doi.org/10.1002/onco.13883.

Mancia, G., Kreutz, R., Brunström, M., Burnier, M., Grassi, G., Januszewicz, A., et al., 2023. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J. Hypertens. 41, 1874–2071. https://doi.org/10.1097/HJH.0000000000003480.

Méjean, A., Ravaud, A., Thezenas, S., Colas, S., Beauval, J.-B., Bensalah, K., et al., 2018. Sunitinib Alone or after Nephrectomy in Metastatic Renal-Cell Carcinoma. N. Engl. J. Med. 379, 417–427. https://doi.org/10.1056/NEJMoa1803675.

Menzies, A.M., Johnson, D.B., Ramanujam, S., Atkinson, V.G., Wong, A.N.M., Park, J.J., et al., 2017. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann. Oncol. 28, 368–376. https://doi.org/10.1093/annonc/mdw443.

Mirza, M.R., Chase, D.M., Slomovitz, B.M., dePont Christensen, R., Novák, Z., Black, D., 2023. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer (Get al.). N. Engl. J. Med. 388, 2145–2158. https://doi.org/10.1056/NEJMoa2216334.

Moch, H., Cubilla, A.L., Humphrey, P.A., Reuter, V.E., Ulbright, T.M., 2016. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs—Part A: Renal, Penile, and Testicular Tumours. Eur. Urol. 70, 93–105. https://doi.org/10.1016/j.eururo.2016.02.029.

Motzer, R.J., Porta, C., Eto, M., Powles, T., Grünwald, V., Hutson, T.E., et al., 2024. Lenvatinib Plus Pembrolizumab Versus Sunitinib in First-Line Treatment of Advanced Renal Cell Carcinoma: Final Prespecified Overall Survival Analysis of CLEAR, a Phase III Study. J. Clin. Oncol. 42, 1222–1228. https://doi.org/10.1200/JCO.23.01569.

Nizam, A., Rader, R.K., Tzeng, A., Wei, W., Sheng, I.Y.-F., Martin, A., et al., 2024. Safety and Efficacy Outcomes in Immune Checkpoint Inhibitor-Treated Patients With Metastatic Urothelial Carcinoma Requiring Treatment Interruption or Discontinuation Due to Immune-Related Adverse Events. Clin. Genitourin. Cancer 22, 368–379. https://doi.org/10.1016/j.clgc.2023.12.007.

Oshima, Y., Tanimoto, T., Yuji, K., Tojo, A., 2018. EGFR–TKI-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients With Non–Small Cell Lung Cancer. JAMA Oncol. 4, 1112. https://doi.org/10.1001/jamaoncol.2017.4526.

Pacholczak-Madej, R., Kosałka-Węgiel, J., Kuszmiersz, P., Mituś, J.W., Püsküllüoğlu, M., Grela-Wojewoda, A., et al., 2023. Immune Checkpoint Inhibitor Related Rheumatological Complications: Cooperation between Rheumatologists and Oncologists. Int. J. Environ. Res. Public. Health 20, 4926. https://doi.org/10.3390/ijerph20064926.

Pandey, A.K., Singhi, E.K., Arroyo, J.P., Ikizler, T.A., Gould, E.R., Brown, J., et al., 2018. Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor–Associated Hypertension and Vascular Disease. Hypertension 71. https://doi.org/10.1161/HYPERTENSIONAHA.117.10271.

Picard, S., Goh, D., Tan, A., Sikotra, N., Gabbay, E., Clay, T., 2021. Patterns of immunotherapy-induced pneumonitis in patients with non-small-cell lung cancer: a case series. J. Med. Case Rep. 15, 332. https://doi.org/10.1186/s13256-021-02926-y.

Porta, C, Cosmai, L, Gallieni, M, Pedrazzoli, P, Malberti, F, 2015. Renal effects of targeted anticancer therapies. Nat Rev Nephrol 11 (6), 354–370. https://doi.org/10.1038/nrneph.2015.15.

Powles, T., Albiges, L., Bex, A., Comperat, E., Grünwald, V., Kanesvaran, R., et al., 2024. Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann. Oncol. 35, 692–706. https://doi.org/10.1016/j.annonc.2024.05.537.

Raghu, G., Remy-Jardin, M., Richeldi, L., Thomson, C.C., Inoue, Y., Johkoh, T., et al., 2022. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am. J. Respir. Crit. Care Med. 205, e18–e47. https://doi.org/10.1164/rccm.202202-0399ST.

Ramos-Casals, M., Lambotte, O., Kostine, M., Calabrese, L., Suarez-Almazor, M., Bingham, C., et al., 2019. THU0649 Phenotypic clusters of rheumatic/systemic immune-related adverse events induced by cancer immunotherapies (immunocancer international registry). Ann. Rheum. Dis. 78, 620–621. https://doi.org/10.1136/annrheumdis-2019-eular.2870.

Schlumberger, M., Elisei, R., Müller, S., Schöffski, P., Brose, M., Shah, M., 2017. Overall survival analysis of EXAM, a phase III trial of cabozantinib in patients with radiographically progressive medullary thyroid carcinoma (Let al.). Ann. Oncol. 28, 2813–2819. https://doi.org/10.1093/annonc/mdx479.

Schlumberger, M., Tahara, M., Wirth, L.J., Robinson, B., Brose, M.S., Elisei, R., et al., 2015. Lenvatinib versus Placebo in Radioiodine-Refractory Thyroid Cancer. N. Engl. J. Med. 372, 621–630. https://doi.org/10.1056/NEJMoa1406470.
SEER, 2021. Cancer of the Endometrium - Cancer Stat Facts.
Shyam Sunder, S., Sharma, U.C., Pokharel, S., 2023. Adverse effects of tyrosine kinase inhibitors in cancer therapy: pathophysiology, mechanisms and clinical management. Signal Transduct. Target. Ther. 8, 262. https://doi.org/10.1038/s41392-023-01469-6.
Skeoch, S., Weatherley, N., Swift, A.J., Oldroyd, A., Johns, C., Hayton, C., et al., 2018. Drug-Induced Interstitial Lung Disease: A Systematic Review. J. Clin. Med. 7, 356. https://doi.org/10.3390/jcm7100356.
Som, A., Mandaliya, R., Alsaadi, D., Farshidpour, M., Charabaty, A., Malhotra, N., et al., 2019. Immune checkpoint inhibitor-induced colitis: A comprehensive review. World J. Clin. Cases 7, 405–418. https://doi.org/10.12998/wjcc.v7.i4.405.
Somasegar, S., Bashi, A., Lang, S.M., Liao, C.-I., Johnson, C., Darcy, K.M., et al., 2023. Trends in Uterine Cancer Mortality in the United States: A 50-Year Population-Based Analysis. Obstet. Gynecol. 142, 978–986. https://doi.org/10.1097/AOG.0000000000005321.
Song, Y., Fu, Y., Xie, Q., Zhu, B., Wang, J., Zhang, B., 2020. Anti-angiogenic agents in combination with immune checkpoint inhibitors: a promising strategy for cancer treatment. Front. Immunol. 11, 1956. https://doi.org/10.3389/fimmu.2020.01956.
Sprangers, B., Leaf, D.E., Porta, C., Soler, M.J., Perazella, M.A., 2022. Diagnosis and management of immune checkpoint inhibitor-associated acute kidney injury. Nat. Rev. Nephrol. 18, 794–805. https://doi.org/10.1038/s41581-022-00630-8.
Touyz, R.M., Herrmann, S.M.S., Herrmann, J., 2018. Vascular toxicities with VEGF inhibitor therapies–focus on hypertension and arterial thrombotic events. J. Am. Soc. Hypertens. 12, 409–425. https://doi.org/10.1016/j.jash.2018.03.008.
Tsao, C., Small, A.C., Kates, M., Moshier, E.L., Wisnivesky, J.P., Gartrell, B.A., et al., 2013. Cytoreductive nephrectomy for metastatic renal cell carcinoma in the era of targeted therapy in the United States: a SEER analysis. World J. Urol. 31, 1535–1539. https://doi.org/10.1007/s00345-012-1001-3.
Vitorino, M., Santos, C., 2022. Use of pembrolizumab in end-stage renal disease: a case report with complete response. Case Rep. Oncol. 15, 187–190. https://doi.org/10.1159/000521979.
Wang, Y., Wiesnoski, D.H., Helmink, B.A., Gopalakrishnan, V., Choi, K., DuPont, H.L., et al., 2018. Fecal microbiota transplantation for refractory immune checkpoint inhibitor-associated colitis. Nat. Med. 24, 1804–1808. https://doi.org/10.1038/s41591-018-0238-9.
Yang, J., Wang, K., Yang, Z., 2023. Treatment strategies for clear cell renal cell carcinoma: past, present and future. Front. Oncol. 13, 1133832. https://doi.org/10.3389/fonc.2023.1133832.

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