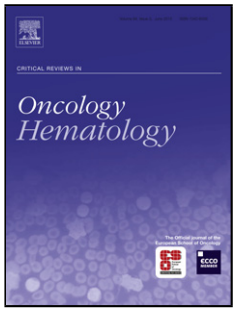


Managing side effects of immune checkpoint inhibitors in breast cancer

Carmen Criscitiello, Chiara Corti, Gabriella Pravettoni, Giuseppe Curigliano

PII: S1040-8428(21)00142-6

DOI: https://doi.org/10.1016/j.critrevonc.2021.103354

Reference: ONCH 103354

To appear in: *Critical Reviews in Oncology / Hematology*

Received Date: 8 February 2021

Revised Date: 13 May 2021

Accepted Date: 14 May 2021

Please cite this article as: Criscitiello C, Corti C, Pravettoni G, Curigliano G, Managing side effects of immune checkpoint inhibitors in breast cancer, *Critical Reviews in Oncology / Hematology* (2021), doi: https://doi.org/10.1016/j.critrevonc.2021.103354

Article title: Managing side effects of immune checkpoint inhibitors in breast cancer

Author names: Carmen Criscitiello[1,2], Chiara Corti[1,2], Gabriella Pravettoni[2,3], Giuseppe Curigliano[1,2]

Author affiliations:

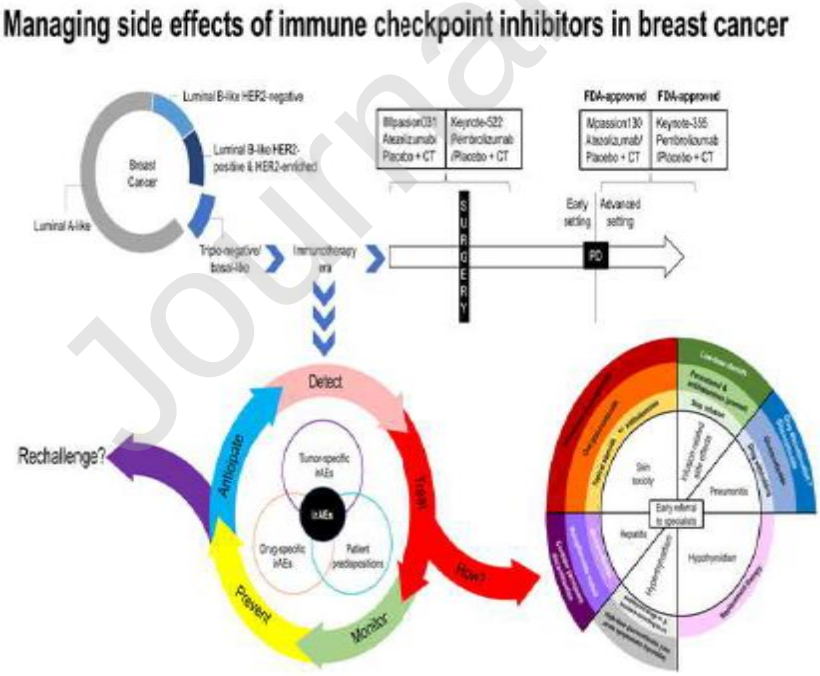
[1] Division of Early Drug Development for Innovative Therapy, European Institute of Oncology, IRCCS, Milan, Italy

[2] Department of Oncology and Haematology (DIPO), University of Milan, Milan, Italy

[3] Applied Research Division for Cognitive and Psychological Science, European Institute of Oncology, IRCCS, Milan, Italy

Corresponding author: Carmen Criscitiello, MD, PhD, Division of Early Drug Development for Innovative Therapy, European Institute of Oncology, IRCCS, Via Ripamonti 435, 20141 Milan, Italy. E-mail: carmen.criscitiello@ieo.it. Phone number: +39 0257489599.

Graphical abstract



Highlights:

- Immune-checkpoint inhibitors (ICIs), represent a major development in cancer therapy. (**85**/85)
- For years breast cancer (BC) has been considered somewhat immunologically quiescent. (**84**/85)
- Recent findings paved the way for landmark approvals of immunotherapy in BC. (**76**/85)
- As ICI-treated BC patients increase, so does the incidence of immune-related AEs. (**81**/85)
- Taking into account BC patients characteristics may improve the management of irAEs. (**85**/85)

Abstract (146/150): Immune-checkpoint inhibitors (ICIs) represent a major development in cancer therapy. The indications for these agents continue to expand across malignancies and disease settings. For years breast cancer (BC) has been considered immunologically quiescent compared with other tumor types. However, recent findings highlighted the immunogenicity of some BCs and paved the way for clinical trials of immunotherapy in BC that led to recent landmark approvals. As a drawback, the safety profile of ICIs is shaped by a specific spectrum of immune-related adverse events (irAEs) that can vary according to ICI class and tumor histology. This review will discuss the epidemiology of these adverse events, their kinetics, risk factors and the most important aspects in their management. A particular focus will be put on BC as the current landscape of immunotherapy for this disease is rapidly increasing the number of people treated with ICIs, thus susceptible to irAEs.

Word count: 4148
Figure number: 4
Table number: 4

Keywords: immunotherapy, adverse events, management, immune checkpoint inhibitors, breast cancer.

Review

Introduction (4148 words)

Immunotherapy relies on a cytotoxic immune response against a tumor and requires a multifaceted interaction between different immune cells in the adaptive and innate immune system (1). In particular, T lymphocytes recognize self- and non-self-antigens, which are presented by antigen-presenting cells (APCs) (1). For activation of a naïve T cell, its T cell receptor (TCR) binds to a processed tumor neoantigen presented by the major histocompatibility complex (MHC). In the absence of a mandatory co-stimulatory signal, such as CD28, Inducible T-cell COStimulator (ICOS) and CD137, or in the presence of a co-inhibitory signal, for example programmed cell death receptor 1 (PD1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), Lymphocyte-activation gene 3 (LAG-3) and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), a state of anergy develops (2).

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies (mAbs) able to unleash the immune system by preventing the co-inhibitory signal from being sent (**Figure 1**) (3). The primary targets for ICIs include PD-1 with nivolumab, pembrolizumab, and cemiplimab; programmed cell death ligand 1 (PD-L1) with atezolizumab, avelumab, and durvalumab; CTLA-4 with ipilimumab and tremelimumab.

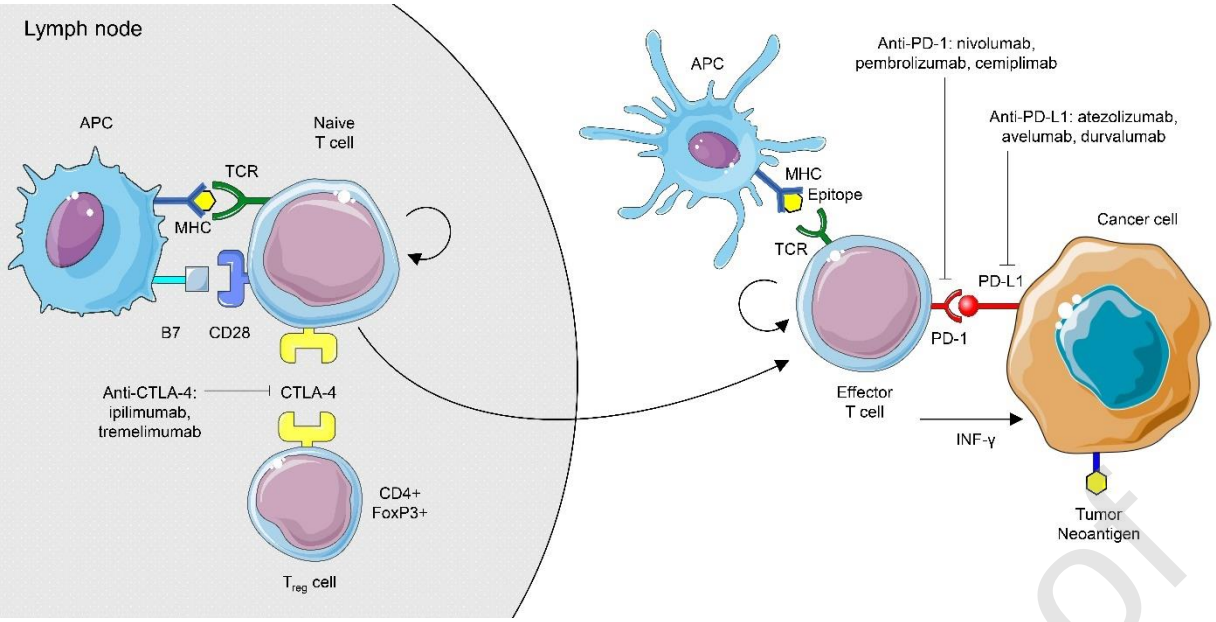


Figure 1. **CTLA-4 and PD-1 checkpoint blockade affects T cells at different stages of differentiation and at different anatomical locations**. Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen 4; APC, antigen-presenting cell; TCR, T-cell receptor; FoxP3, forkhead box P3; CD4, cluster of differentiation 4; Treg, regulatory T cell; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; INF-γ, interferon gamma; CD28, Cluster of Differentiation 28.

For years breast cancer (BC) has been considered immunologically quiescent compared with other tumor types (4). This is partially because of its lower somatic mutational burden and consequent lower neoantigen load (4, 5). However, recent findings highlighted the immunogenicity of some BCs and paved the way for clinical trials of immunotherapy in BC that led to recent landmark approvals (5, 6).

The growing interest in immunotherapy for BC, with the consequent increasing number of people treated with ICIs, demands to focus the attention on the immune-related adverse events (irAEs) that may affect a subset of patients (7, 8). This review will focus on the most frequent toxicities associated with ICI immunotherapy and their management, with a particular insight on the current landscape of immunotherapy, especially in TNBC, for which ICIs in combination with chemotherapy are currently approved.

Current landscape of immunotherapy in breast cancer

Since the somatic mutational burden in BC is lower in comparison with other tumor types, breast tumors have been considered immunologically quiescent in the past few years (4). However, human epidermal growth factor receptor 2 (HER2)-positive and basal-like BCs show a higher mutational burden than hormone receptor (HR)-positive BC (9, 10). Consistently, tumor-infiltrating lymphocyte (TIL) rates are higher in HER2-positive and triple-negative breast cancer (TNBC) in comparison with HR-positive BCs (6, 11-15). Moreover, higher TIL levels are associated with improved prognosis in HER2-positive BC and TNBC, with a 10% increase in TILs associated with a 15-25% decrease in risk of relapse and death (4, 16, 17). Finally, several chemotherapeutic agents commonly used in BC are known to promote immunogenic cell death, resulting in release of neoantigens and potential recruitment of APCs (4, 18, 19). Hence, great interest surrounds combination treatment with chemotherapy (CT) and immune checkpoint blockade (4, 20). On these bases, in 2018 IMpassion130 trial paved the way for the entrance of immunotherapy, in combination with nab-paclitaxel, as a new first-line treatment option for patients with metastatic TNBC displaying PD-L1-stained tumor-infiltrating immune cells of any intensity covering ≥ 1% of the tumor area (21). This phase III trial randomized 902 patients with previously untreated metastatic TNBC to receive nab-paclitaxel combined with either atezolizumab or placebo (18). At a median follow-up of 13 months, a statistically significant difference in progression-free survival (PFS, 7.2 versus 5.5 months, HR 0.80, 95% CI, 0.69-0.92) in favor of the combo with atezolizumab was demonstrated. However, in a prospectively planned subset analysis of outcomes according to PD-L1-expressing immune effector cells within the tumors, atezolizumab improved both PFS (7.5 versus 5 months, HR 0.62, 95% CI 0.49-0.78), and, importantly, overall survival (OS, 25 versus 15.5 months; HR 0.62, 95% CI, 0.45-0.86). Interestingly, the mature OS analysis presented at ESMO 2020 after 3-year follow-up confirmed the benefit of atezolizumab plus nab-paclitaxel in patients with PD-L1-positive disease, reducing the risk of deaths by 33% in this subgroup, when compared with placebo (22). On the other hand, in KEYNOTE-355 trial, 847 patients with locally recurrent, inoperable, or metastatic TNBC, all of whom had a disease-free interval of ≥ 6 months,

were randomly assigned to CT (nabpaclitaxel, paclitaxel, or gemcitabine/carboplatin), with or without pembrolizumab (23). Overall, a modest improvement in median PFS with the addition of pembrolizumab (7.5 versus 5.6 months; HR 0.82, 95% CI 0.69-0.97) was observed. Remarkably, the benefit seemed to be limited to those with combined positive score (CPS) ≥10, in whom the addition of pembrolizumab to CT improved median PFS (9.7 versus 5.6 months; HR 0.65, 95% CI 0.49-0.86). As a result of these trials, the checkpoint inhibitor atezolizumab received the Food and Drug Administration (FDA) approval in combination with nabpaclitaxel for patients with advanced PD-L1 ≥ 1% TNBC (24). Similarly, on 13 November 2020 FDA granted accelerated approval to pembrolizumab in combination with chemotherapy (CT) for patients with locally recurrent unresectable or metastatic TNBC, whose tumors express PD-L1 with CPS ≥ 10 (25).

As for the early setting, CT is often administered as neoadjuvant treatment in TNBC, in order to downsize the tumor, as well as to assess the prognosis of the patient (26). Indeed, patients who achieve pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) exhibit a significantly lower risk of relapse and death compared with patients with residual disease (27). To understand if ICI addition could be beneficial in the early setting as well, randomized trials of neoadjuvant chemo-immunotherapy have been initiated in early TNBC, though with conflicting results (28). In this context, increased TILs have shown to predict pathologic response to neoadjuvant therapy (6, 29).

As for HER2-positive BC, a T-helper 1 (Th1)-adaptive immune response against the tumor-associate antigen HER2 has been described (30-32). Thus far, early phase clinical trials of new immune agents for the treatment of patients with HER2-positive BC have shown modest results (33). In this context, the phase 1b/2 KEYNOTE-014/PANACEA clinical trial, investigated the safety and efficacy of pembrolizumab combined with trastuzumab for the treatment of HER2-positive metastatic BC (31). In the PD-L1-positive population, only 15% of patients achieved a partial response, without evidence of response in the PD-L1-negative cohort (31). Collectively, the results of the clinical trial investigating ICIs in HER2-positive BC published to date suggest that the antitumor efficacy is low in unselected and/or heavily pretreated patients (34, 35).

Spectrum of toxicity in the general ICI-treated population

In the general ICI-treated population, T-cell hyperactivity is associated with autoimmune events, such as colitis, hepatitis, nephritis, pneumonitis, endocrinopathies, skin toxicities, fatigue and uncommon events, such as heart or central nervous system (CNS) involvement (**Figure 2**) (3, 36-39). Importantly, any grade infusion-related side effects - including fever, chills, headaches and nausea - have been reported in up to 25% of patients treated with ICIs (40, 41). Most reactions result from antibody-antigen interactions causing cytokine release, from type I-like hypersensitivity and from mixed responses (42). However, the incidence of life-threatening infusion-related reactions, such as throat tightness or shortness of breath, is less than 2% and desensitization attempts have been proposed (42, 43).

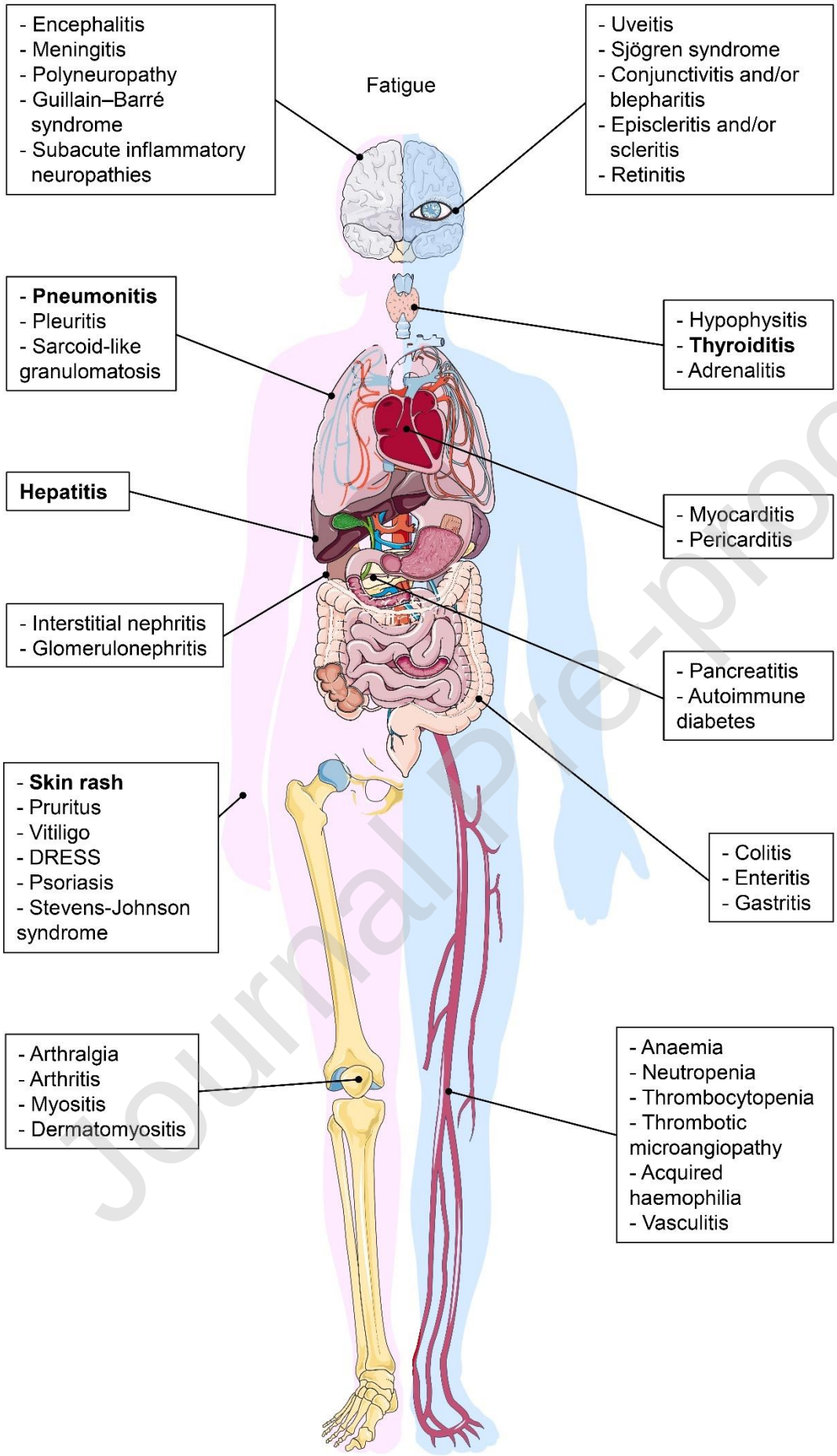


Figure 2.**The spectrum of irAEs by affected organs**. ICIs can cause a wide range of irAEs, and these can potentially affect any organ. The most frequently affected organs and the most common specific irAEs in breast cancer are reported in bold (42). Abbreviations: DRESS, Drug rash with eosinophilia and systemic symptoms.

Incidence of irAEs can vary according to ICI class and to tumor histology (44). For example, colitis, hypophysitis and skin toxicities appear as more frequent with anti-CTLA-4 mAbs, whereas pneumonitis, thyroid impairment, arthralgia and vitiligo are more common with anti-PD-1/PD-L1 mAbs (44). Combination therapy of nivolumab plus ipilimumab displays diarrhea as the most frequent irAE of any grade (44.7% of melanoma patients), followed by dermatological events (41.5%), hepatic events (22.3%) and endocrine disturbances (16%) (42, 45).

As for tumor histology, melanoma patients experience a higher frequency of gastrointestinal (GI) and skin toxicities, with lower incidence of pneumonitis in comparison with non-small-cell lung cancer (NSCLC) patients (44). Conversely, arthritis and myalgia are more common in melanoma patients than in renal cell carcinoma (RCC) patients. The latter exhibits pneumonitis and dyspnea at a higher rate (44). The reasons for such histology-dependent and patient-specific irAE profile are not clear, although few hypotheses have been proposed (**Figure 3**) (3, 39, 44, 46-51).

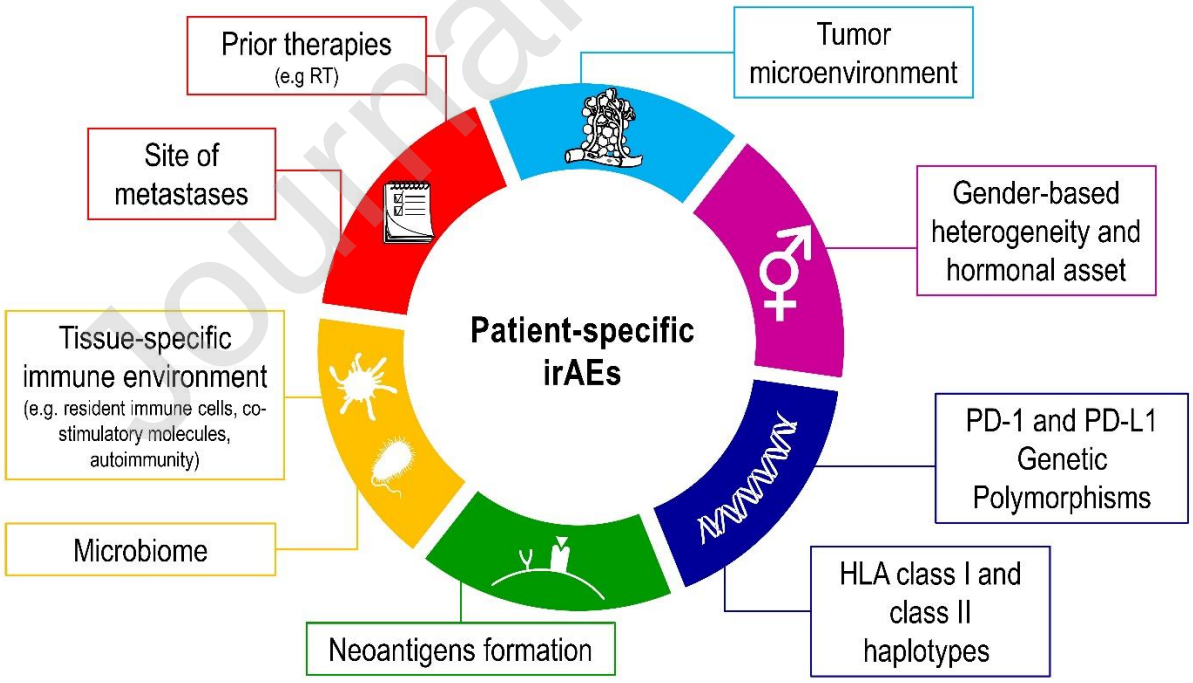


Figure 3. Patients with different tumor histologies show different irAE profile when treated with the same ICI. Currently the reasons for this observation are not clear. Few hypotheses and mechanisms have been proposed. The most important are tumor microenvironment and tissue-specific immune environment, medical history, genetics and type of neoantigens (5, 19, 39, 44, 46, 49-54). Abbreviations: irAEs, immune-related adverse events; RT, radiotherapy; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; HLA, human leukocyte antigen.

Spectrum of toxicity in breast cancer patients treated with ICIs

The variable incidence of irAEs according to ICI class and to tumor histology would allow for a more accurate assessment of susceptibility to develop irAEs. For BC, in clinical trials investigating the role of ICI monotherapy in both the early and advanced setting, the most common irAEs observed were arthralgia and fatigue (15-25%), thyroid impairment (up to 11.8% for hypothyroidism and up to 5.3% for hyperthyroidism), transaminitis (up to 6-10%), skin toxicities (1-2%) and pneumonitis (up to 2.4%), as shown in **Table 1**.

Trial	Setting	N. of pts	Any t-r AEs	G≥3 t-r AEs	Any irAEs	G≥3 irAEs	Fatal AEs	Fatal irAEs
Phase 1; KEYNOTE012; pembrolizumab (NCT01848834)	MBC	32	56.3% (18.8%, arthralgia, 18.8% fatigue, 18.8% myalgia)	15.6% (anemia, aseptic meningitis, ↓lympho, headache)	15.6% (3.1% hypothyr, 3.1% colitis, 3.1% hepatitis)	9.3% (1 colitis, 1 hepatitis)	3.1% (1 due to DIC)	0
Phase 1; atezolizumab (NCT01375842)	MBC	116	63% (16% pyrexia, 13% fatigue, 11% nausea)	11%	rash, adrenal insuff, pneumonitis	NR	0.86 % (NR)	0.86% (1 due to pulmunary HTN)
Phase 1b; JAVELIN; avelumab (NCT01772004)	MBC	168	68.5% (fatigue 19%, inf-rel 14.3%, nausea 13.1%)	13.7% (1.8% fatigue, 1.8% hepatitis, 1.2% ↑GGT)	10.1%	2.4% (1.8% hepatitis, 0.6% pneumonitis, 0.6% ITP)	1.2%	0
Phase 1; KEYNOTE028;	MBC	25	64% (20% nausea, 12%	20% (4% hepatitis, 4% nausea, 4% ↑GGT)	20% (thyroid impairment,	4% (1, hepatitis)	0	0

pembrolizumab (NCT02054806)			fatigue, 8% arthralgia)		hepatitis, pneumonitis, inf-rel)			
Phase 2; KEYNOTE086-cohort A; pembrolizumab (NCT02447003)	MBC	170	60.6% (20.6% fatigue, 11.2% nausea)	12.9% (1.8% diarrhea)	26.4% (11.8% hypothyr, 5.3% hyperthyr)	1.2% (0.6% type I DM, 0.6% pneumonitis)	0	0
Phase 2; KEYNOTE086-cohort B; pembrolizumab (NCT02447003)	MBC	84	63.1% (26.2% fatigue, 13.1% nausea, 11.9% diarrhea)	9.5% (1.2% fatigue, 1.2% diarrhea, 1-2% anemia)	22.6% (9.5%, hypothyr, 4.8% hyperthyr, 2.4% pneumonitis, 1.2 inf-rel)	1.2% (rash)	0	0
Phase 2; SAFIR02-BREAST IMMUNO; durvalumab	MBC	131	82.2%	13.2%	NR	NR (1.6% hypothyr; 0.8% rash, 0.8% dyspnoea, 0.8% hepatitis)	0	0
Phase 3; KEYNOTE119; pembrolizumab (NCT02555657)	MBC	309	80.9% (17.4% fatigue, 16.2% constipation, 16.5% cough)	14% (0.97% fatigue, 0.65% anemia,0.32% diarrhea)	21.5% (9.06% diarrhea, 7.77% hypothyr, transaminitis 10.36%)	3.2%	0.3% (1 death)	0
Phase 3; A-BRAVE; avelumab (NCT02926196)	early	349 (before randomization)	NR	NR	NR	NR	NR	NR
Phase 3; KN-242; SWOG S1418/NRG BR006 (NCT02954874)	Early (residual disease)	NR	NR	NR	NR	NR	NR	NR

Table 1. Breast cancer trials with anti-PD-1/PD-L1 monotherapy, with data about immune-related adverse events as of 27 January 2021. Abbreviations: N, number; pts, patients; G, grade; **MBC,** metastatic breast cancer; AEs, adverse events; t-r, treatment-related; irAEs, immune-related adverse events; DIC, disseminated intravascular coagulation; inf-rel, infusion-related; insuff, insufficiency; ↓lympho, lymphopenia; DM, diabetes mellitus; GGT, γ-

Glutamyltransferase; ITP, immune thrombocytopenia; ↑, increase; hypothyr, hypothyroidism; HTN, hypertension; NR, not reported.

Similarly, for BC clinical trials investigating the role of ICIs combined with chemotherapy in both the early and advanced setting, the most common AEs observed were arthralgia and fatigue (24-43%, up to 87%), thyroid impairment (up to 18% for hypothyroidism and up to 5.1% for hyperthyroidism), transaminitis (up to 0.7-19%), skin toxicities (1-14%), pneumonitis (~1-3%) and colitis (up to 3%), as presented in **Table 2**.

Trial	setting	N. of pts	Any t-r AEs	G≥3 t-r AEs	Any irAEs	G≥3 irAEs	Fatal AEs	Fatal irAEs
Phase 1b; KN-173 pembrolizumab + CT (55) (NCT02622074)	early	60 (10 pts per cohort))	100%	90%	30%	10%	0	0
Phase 1b; atezolizumab + CT (56) (NCT01633970)	MBC	33	100% (70% ↓N, 39% Diarrhea, 30 % neuropathy)	73% (46% ↓N, 9% ↓PLT, 6% Diarrhea)	91% (72% transaminitis, 9% pneumonitis, 3% colitis)	21% (12% hepatitis, 3% pneumonitis, 3% colitis)	0	0
Phase 1b/2; ENHANCE-1; pembrolizumab + CT (57) (NCT02513472)	MBC	167	99%	50.3%	71%	14%	0	0
Phase 2; I-SPY2 pembrolizumab + CT (58) (NCT01042379)	early	69	Fatigue 87%; nausea 79.7%	Feb ↓N 8.7%	thyroid dysfunction 13.0%; AI 8.7%	AI 7.2%	0	0
Phase 2; GeparNuevo; durvalumab + CT (59) (NCT02685059)	early	88 (92 safety pop)	NR	34%	thyroid dysfunction 50%; dermatitis 14.1%	3.3% neuro-pathy	0	0
Phase 2b; ALICE; atezolizumab + CT (60) (NCT03164993)	MBC	75	NR	NR	NR	NR	NR	NR
Phase 2b; ICON; ipilimumab + nivolumab + CT (61) (NCT03409198)	MBC	75	NR	NR	NR	NR	NR	NR
Phase 2; pembrolizumab + CT (NCT03095352)	MBC (chest wall disease)	84	NR	NR	NR	NR	NR	NR
Phase 2;	MBC	68	28% (24% fatigue, 19%	12% ↑GGT, 10%	81% (19% hepatitis, 18%	19% (4.4% ↑GGT, 1.5% ↑ALP, 1% ↑AST)	0	0

TONIC; nivolumab + CT; (62) (NCT02499367)			hepatitis, 18% hypothyr)	↑ALP, 4% ↑lipase	hypothyr, 13% diarrhea)			
Phase 2; KN-756; pembrolizumab + CT (NCT03725059)	early	NR	NR	NR	NR	NR	NR	NR
Phase 3; IMpassion130; atezolizumab + CT (18) (NCT02425891)	MBC	453	97% (45% nausea, 43% fatigue, 31% diarrhea)	48.7% (8% ↓N, 6% periferal neuropathy, 4% fatigue)	58% (18% hypothyr, 5% hyperthyr, 4% pneumonitis)	8% (2% hepatitis, <1% rash, <1% pneumonitis, <1% colitis)	<1%	1% (<1% pneumonitis)
Phase 3; IMpassion131; atezolizumab + CT (63)(NCT03125902)	MBC	431	97%	49%	31.8% rash, 12.8% hypothyr, 5.1% hyperthyr	1.4% pancreatitis, rash 0.9%, pneumonitis 0.7%	0.9 %	0.2%
Phase 3; KN-355; pembrolizumab + CT (23) (NCT02819518)	MBC	562	96% (49% anemia, 41%↓N, 39% nausea)	68% (30% ↓N, 16% anemia, 6% ↑ALT)	26% (15% hypothyr, 5% hyperthyr, 2% rash)	5% (2% rash, 1% pneumonitis, <1% hypothyr)	<1% (2)	0
Phase 3; KN-522; pembrolizumab + CT (combined phases) (64) (NCT03036488)	early	781	99% (62.7% nausea, 60.3% alopecia, 55.1% anemia, 46.7% ↓N)	76.8% (34.6% ↓N, 18.2% anemia, 5.2 ↑ALT)	38.9% (16.9% inf react, 13.7% hypothyr, 4.6% hyperthyr, 4.4% rash)	12.9% (3.8% rash, 2.6% inf react, 1.3% AI, 0.4% hypothyr)	<1% (2)	0.1% (1 due to pneumonitis)
Phase 3; Impassion031 atezolizumab + CT (65) (NCT03197935)	early	165	99%	30% (Feb ↓N 10%)	70% (rash 49%, hypothyr 7%)	15%	0	0
Phase 3; NeoTRIPaPDL1 atezolizumab + CT (NCT02620280)	early	138	97.8%	77.5%	Inf react 8%, hypothyr 5.8%, hepatitis 0.7%	Inf react 1.4%, pancreatitis 1.5%	0.7 %	NR

Table 2. Selected breast cancer trials with anti-PD-1/PD-L1 combined with chemotherapy, with data about immune-related adverse events as of 27 January 2021. Abbreviations: N, number; pts, patients; G, grade; AEs, adverse events; MBC, metastatic breast cancer; irAEs, immune-related adverse events; NR, not reported; ↑, increased; CT, chemotherapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AI, adrenal insufficiency; ↓N, decreased neutrophil count; GGT, γ-Glutamyltransferase; Feb ↓N, febrile neutropenia; pop, population; ↓PLT, decreased platelets count; hypothyr, hypothyroidism; inf react, infusion reaction.

Besides a general higher incidence of treatment-related AEs (trAEs) of any grade compared with ICI monotherapy, combination strategies with nab-paclitaxel/paclitaxel chemotherapy had the highest rate of trAEs (66). Interestingly, a recent pooled analysis found that irAEs tend to occur with lower frequency (~28%) in patients treated with PD-1 inhibitors compared with those treated with anti-PD-L1 molecules (~53%). Specifically, pembrolizumab (~18%) and avelumab (~10%) had a significantly lower rate of irAEs than atezolizumab (~74%) and nivolumab (~81%) (66). Finally, irAEs directly affecting the female reproductive system (e.g. hypophysitis and oophoritis) do not seem to be frequent in current immunotherapy BC trials (**Table 1** and **Table 2**). However, concern about the potential detrimental effects of ICIs on fertility and subsequent pregnancies should be raised, especially for young women receiving treatment in the early setting. First, because other irAEs, such as dysthyroidism, can indirectly affect fertility and child-bearing potential; second, because higher rates of endocrine irAEs adverse events have been reported specifically in premenopausal women, placing them at risk for infertility after receiving neoadjuvant or adjuvant anti-PD-1 and anti-PD-L1 agents (67); third, because there is lack of concrete long-term data about the direct effects on ICIs on conception (68).

Grade of toxicity

In the general ICI-treated population, toxicities with anti-PD-1/PD-L1 mAbs are typically less severe than those with anti-CTLA-4 mAbs (10% of patients experiencing grade ≥ 3 irAEs) (42, 44, 52-54, 69). Indeed, irAEs of any grade can occur in up to 60% of patients treated with ipilimumab, and 10-30% of these are typically considered serious adverse events (SAE), defined as grade 3-4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (42). In this context, toxicity especially from CTLA-4 inhibition shows a dose-dependent profile (70). Hence, lower doses and scheduling modifications of ICIs have been investigated over time (71, 72). Besides, a higher rate of grade 3-4 toxicities (up to 35%) is documented for patients treated with ipilimumab administered after an anti-PD-1 mAb (73, 74). Conversely, patients with a grade 3-4 toxicity on ipilimumab followed by an anti-PD-1 mAb is reported in > 20% of cases (74,

75). Consistently, patients receiving a combination of anti-PD-1/PD-L1 and anti-CTLA4 mAbs have the highest incidence of immune-related SAEs (up to 33-55% vs 24-27% for melanoma and NSCLC patients treated with combination therapy versus monotherapy, respectively) (42, 45, 76-78).

Though CT plus ICI has shown promising efficacy (4), its toxicity profile is less favorable compared to ICI monotherapy (79). Indeed, combination treatment leads more often to grade 3-4 AEs and discontinuations, especially with anti-CTLA4 mAbs (79). However, no differences in mortality have been shown between combination treatment and ICI monotherapy (79).

Fatal irAEs have been reported in literature with a prevalence between 0.3-1.3% (80-86). Ipilimumab-based therapy showed the highest mortality rates, whereas fatalities with anti-PD-1/PD-L1-based therapies are recorded in less than 0.4% of cases (80-86). Anti-CTLA4-related fatalities are dominated by colitis, whereas anti-PD-1 deaths revealed a wider spectrum of events, i.e. pneumonitis, infectious causes and cardiac events (86). Accordingly, deaths occurring during combination therapy often display a multiorgan involvement, with myocarditis, myositis, hepatitis and neurologic events representing one third of deaths (86).

As for selected trials (**Table 1**) that enrolled BC patients treated with ICI monotherapy, any-grade irAEs showed a mean prevalence of 19.3%, with grade ≥ 3 irAEs ranging from 1.2% to 9.3%. Conversely, as for selected trials (**Table 2**) including BC patients treated with a combination of CT plus ICI, the average prevalence of any-grade irAEs is 58.2%, with grade ≥ 3 irAEs ranging from 5% to 21%.

Consistently, a recent pooled analysis of 21 clinical trials focused only on metastatic BC, including both trAEs and irAEs, displayed a relatively high frequency of trAEs of any grade (70%, 95% CI = 58–82%) and of trAEs of grade ≥ 3 (25%, 95% CI = 16–34%) (66). Of note, combination of ICI treatment with systematic therapy (91%, 95% CI = 85–97%) showed a higher incidence of trAEs of any grade compared with monotherapy (64%, 95% CI = 64% to 68%) (66).

Kinetics of main irAEs

Although data about incidence of irAEs are traditionally mentioned in clinical trial reports about BC, data on time to onset are often lacking (66). In the general ICI-treated population, IrAEs typically occur within the first three months of therapy, though they can develop at any time (**Figure 4**) (42).

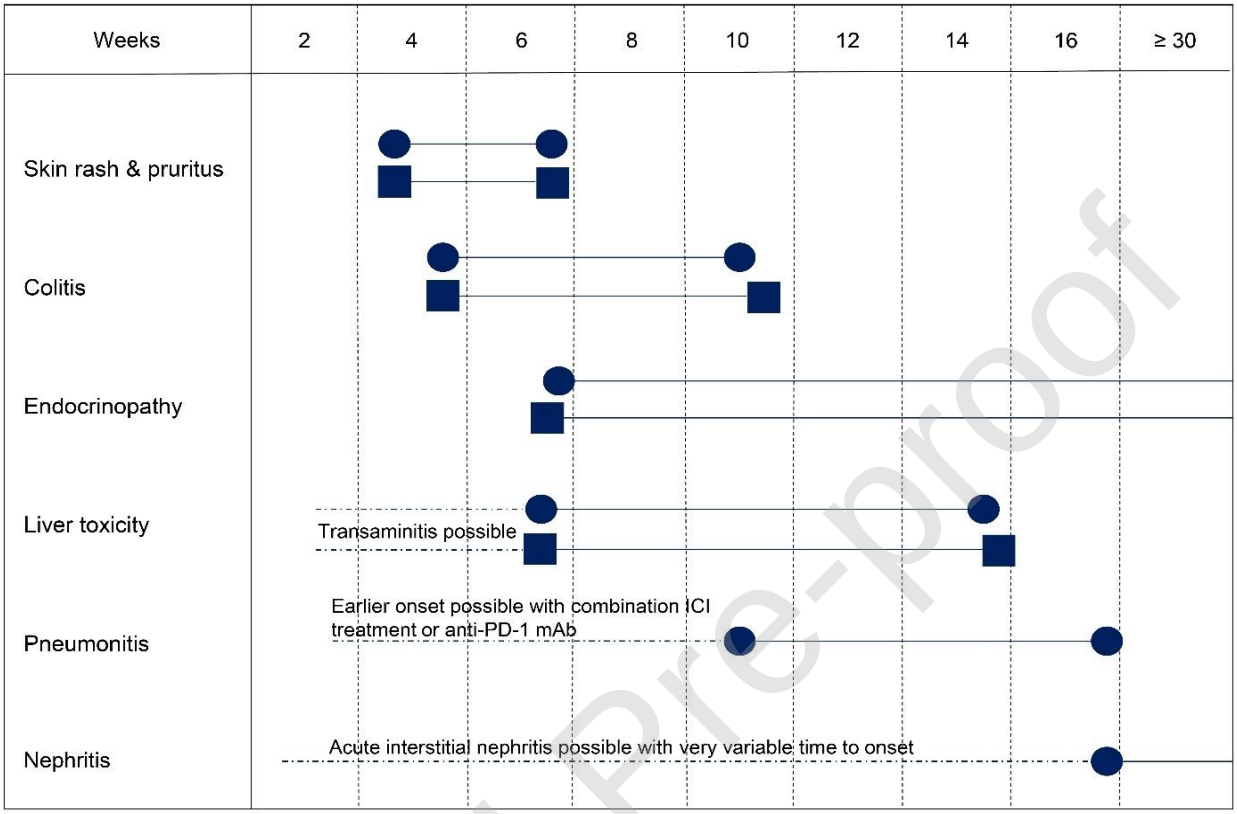


Figure 4. Kinetics of main irAEs in patients receiving anti-CTLA4 monoclonal antibody ipilimumab (square), anti-PD-1 or anti-PD-L1 monoclonal antibodies (circle) (42). Abbreviations: irAE, immune-related adverse event; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

Mild fatigue typically shows an early onset (54, 87). Although rare, severe fatigue can underlie endocrine disorders (e.g. hypothyroidism, adrenal insufficiency, hypophysitis) (73). These abnormalities, such as those in thyroid function, tend to arise in 4-14 weeks after start of treatment (88-90). Skin toxicities are commonly found within the first 4-6 weeks of treatment (42). Time to onset of colitis ranges between 4 and 8 weeks after the first infusion and it is rare after more than two months (91-93). Hepatitis shows a variable onset time, with asymptomatic transaminitis

possible even after the first two weeks of treatment (94, 95). Though uncommon, neurological irAEs are reported to occur after 1-7 weeks of treatment, especially in patients receiving ipilimumab, with a slightly earlier onset for anti-PD-1 mAbs and for myasthenia gravis (96, 97). Acute interstitial nephritis (AIN) is documented after 2-12 weeks of ICI administration, with a longer delay of onset reported for an anti-PD-1/PD-L1-treated patient population (42, 98, 99). Rheumatic complications exhibit a wide dispersion of onset times, with events described after more than 50 weeks of ICI administration (100). Finally, pneumonitis displays a median time to onset of 2.5 months with ICI monotherapy, whereas a shorter time to onset, as early as 9 days from first infusion, is reported for anti-PD-1 mAbs and for combination therapy (81, 86, 101). Fatal events occur with a median time to onset of 40 days with ICI monotherapy and of 14.5 days with ICI combination therapy (86). Notably, no major differences in kinetics have been highlighted for BC patients receiving ICIs (4).

Management of most common irAEs in breast cancer

Even though consensus guidelines have been published for the management of irAEs, none of these are based on outcomes of RCTs (7, 8, 73, 102). Therefore, clinical judgement, irrespectively of the grade-related management suggestions discussed below, is a caveat that should always be remembered.

Before starting treatment, patients should be assessed in terms of susceptibility to develop irAEs (73). Accordingly, signs and symptoms of autoimmunity should be assessed before each immunotherapy treatment (73). Patients with a history of autoimmune disease are at risk for worsening of their pre-existing condition while on ICI (74). In this regard, as patients with active preexisting autoimmune disease have been systematically excluded from clinical trials with ICIs, and because ICIs could be beneficial in such patients as well, prospective clinical trials focused on this subpopulation are warranted (103). From this perspective, a personalized risk-based prevention approach with a tailored immunosuppressive strategy has been proposed as one of the most promising future directions (103).

In general, a prompt and up-to-date patient education is critical, so that a more active role of patients may help managing ICI toxicity profile in a timely manner (73). In general, steroids and other immunosuppressants may be given to manage most irAEs, though dose reduction is not a recommended strategy (8, 73). Simplified key points in the initial management of irAEs are shown in **Table 3**.

	ICI therapy	**irAE treatment**	**Exception**
Grade 1	Continue with close monitoring		Some neurologic, hematologic, and cardiac toxicities
Grade 2	Held until toxicity reverts to G1 or less	Corticosteroids	
Grade 3	Held. When irAE reverts to G1 or less, re-challenging may be considered, with caution. Dose adjustments not recommended	High-dose corticosteroids, to be tapered (over at least 2-4 weeks) once irAE resolves to G1 or less. If no improvement in 1-3 days, consider other immunosuppressant agents	
Grade 4	Permanently discontinued		Endocrinopathies controlled by hormone replacement

Table 3. Simplified key points in the management of irAEs. Note that clinical judgement and an organ-specific system-based approach to toxicity management is always recommended (8). Abbreviations: irAE, immune-related adverse event; G, grade.

Infusion-related side effects – Reducing the rate of infusion, temporarily suspending the infusion, administering premedication consisting of paracetamol and antihistamines or, if required, administering low-dose steroids are all effective methods of managing this type of adverse event (73). As for avelumab, premedication with acetaminophen and an antihistamine is recommended prior to the first four infusions and subsequently as needed (41).

Dermatologic and mucosal toxicity – Most ICI-related rashes can be treated with topical emollients and steroids (104). If pruritus is prominent, oral antihistamines may be useful (e.g. hydroxyzine, diphenhydramine) (104). For grade 2 irAE, ICI should be discontinued and possibly reinitiated when the toxicity is back to grade 1. Severe rashes (grade 3-4) should be managed with oral glucocorticoids, and treatment with ICIs should be held as per consensus guidelines (73).

Although rare, Stevens-Johnson syndrome/toxic epidermal necrolysis require hospitalization, intravenous glucocorticoids, dermatologic evaluation, and close monitoring, especially to supervise imbalances in fluids and electrolytes (73). If recovering from a treated skin toxicity does not occur or if blistering develops, a specialized dermatologist should be consulted and a biopsy considered (102).

Thyroid abnormalities – Thyroid function should be monitored every 4-6 weeks (8). Autoimmune thyroid disease can occur as primary hypothyroidism secondary to a destructive thyroiditis or as hyperthyroidism associated with Graves' disease (105). Hypothyroidism can present with nonspecific symptoms such as fatigue (105). Hence, differentiating primary thyroid disorders from secondary hypothyroidism, typically due to hypophysitis, is a critical differential diagnosis (73). Replacement therapy with levothyroxine and endocrinology consultation are the cornerstone of clinical management for primary hypothyroidism (73). Hyperthyroidism is less frequent and should be treated similarly to primary hyperthyroidism (105). For rare acute symptomatic thyroiditis, a short period of high-dose glucocorticoids may be helpful (105).

Hepatitis – Routine monitoring of liver functions is the standard of care. In most cases, only asymptomatic laboratory abnormalities are found, although patients can rarely develop fever (106). Infrequently, elevation in total bilirubin are recorded, especially when associated with a prolonged increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (106). For grade 2 hepatitis, ICIs should be withheld with close AST/ALT monitoring. If no other etiology is discovered and no improvement is witnessed over 1 week, prompt treatment with glucocorticoids should be started according to guidelines (73). For grade 3 hepatitis, ICIs should be discontinued and prednisone 1–2 mg/kg immediately started. If there is no improvement in 2–3 days, addition of mycophenolate mofetil (MMF) should be contemplated. Importantly, hepatitis may require prolonged glucocorticoid tapering, with a suggested minimum of three weeks of treatment (8). Prompt admission to hospital, high-dose steroids and permanent discontinuation of treatment should be considered for grade 4 hepatic toxicity (102). If no improvement in 2-3 days, MMF can be added. Hepatologist consultation is strongly recommended if the patient does not recover under double immunosuppression. Alternative immunosuppressive drugs to consider are anti-thymocyte

globulin and tacrolimus. Of note, infliximab should not be given to this subset of patients, since it carries an additional risk of drug-induced liver injury (DILI) (73).

Pneumonitis - Though uncommon, it is a potentially severe or fatal irAE and, importantly, a diagnosis of exclusion (48, 81, 107-109). The most common symptoms are dyspnea and cough, albeit one-third of patients are asymptomatic and no radiographic or pathologic features are pathognomonic (81). Also, pulmonary toxicity may rarely manifest as a radiation recall pneumonitis, involving previously irradiated fields of the lung, even years after radiation therapy (RT) (110).

For asymptomatic (grade 1) pneumonitis, drug withholding for 2-4 weeks, close monitoring and exclusion of possible underlying infection is a favored strategy (8). If symptoms arise (grade 2) or radiographic progression is documented, glucocorticoids are appropriate (prednisone 1–2 mg/kg orally) and taper over 4-6 weeks (8). Grade ≥ 3 pneumonitis dictates admission to hospital, even intensive care unit (ICU), prompt drug permanent discontinuation, treatment with glucocorticoids, e.g. (methyl)prednisone 2–4 mg/kg, and vigilant monitoring (8). Additional immunosuppression (MMF or cyclophosphamide) is possible if further worsening is witnessed, although the benefit of this approach is uncertain (8, 81). In case of long lasting or refractory immune toxicities, case-specific escalation of immunosuppression is recommended (38, 111).

Colitis - In patients with grade 1 diarrhea (increase <4 stools per day over baseline), ICIs can be continued. Treatment with antidiarrheal medication (e.g. loperamide) should be prescribed. ICIs should be interrupted, and the patient should start with corticosteroids depending on the severity and other symptoms (either budesonide or oral corticosteroids 1 mg/kg) for grade 2 irAE (increase of 4-6 stools per day over baseline; increase in ostomy output over baseline; limiting instrumental activities of daily living). In the case of no improvement within 3–5 days, colonoscopy should be carried out and, in the case of colitis, infliximab 5 mg/kg should be administered. If diarrhea is severe (grade 3-4), ICIs should be permanently discontinued. Patient admission to the hospital is required with the administration of intravenous methylprednisolone 2 mg/kg. Addition of MMF can be pondered, according to evolution of the condition. If no improvement observed under double immunosuppression, a hepatologist should be consulted. Other immunosuppressive drugs to

consider are anti-thymocyte globulin and tacrolimus. Tapering is suggested over 6 weeks, under close monitoring of liver tests (73).

Rheumatological toxicity - In case of mild arthralgia, nonsteroidal anti-inflammatory drugs (NSAIDs) could be considered as first strategy. In the case of no improvement, low dose steroids (10–20 mg prednisone) represent a second valid choice. If severe polyarthritis develops, prednisone 1 mg/kg could be considered, with prompt patient referral to a rheumatologist. Infliximab or another anti-TNFα drug may be required for further improvement of the arthritis (73).

Adrenal insufficiency – Although infrequent in BC patients, dehydration, hypotension, and electrolyte imbalances (hyperkalemia, hyponatremia) are common findings and may constitute an emergency. If adrenal crisis is suspected, intravenous glucocorticoids and immediate hospitalization is warranted. Consultation with an endocrinologist, aggressive hydration, and evaluation for sepsis are also critical. However, in most patients long-term hormone supplementation is necessary (73).

Hypophysitis - Fatigue and headache should promptly raise suspicion. Laboratory findings differentiate hypophysitis from primary adrenal insufficiency (manifested by low cortisol or inappropriate cortisol stimulation test and high adrenocorticotropic hormone) and primary hypothyroidism (manifested by low free thyroxine and high thyroid-stimulating hormone, TSH). The diagnosis of hypophysitis is also supported by the possible enhancement and swelling of the pituitary gland on imaging (73). For hypophysitis, a course of high-dose glucocorticoids given during the acute phase may result in reversal of the inflammatory process in some cases and prevent the need for longer term hormone replacement. However, in most patients long-term supplementation of the affected hormones is necessary (73).

Neurological toxicity - Although infrequent in BC patients, withholding ICIs and performing an accurate work-up is the first strategy to adopt (magnetic resonance imaging, lumbar puncture) to define the nature of neurotoxicity. In the case of deterioration or severe neurological symptoms, patient should be admitted to hospital and promptly treated with prednisone 1–2 mg/kg. In the case of Guillain-Barré or myasthenia-like symptoms, consider adding plasmapheresis or intravenous immunoglobulin (102).

Cardiac toxicity - If myocarditis is suspected, admission of patient and immediate start of high-dose steroids are the cornerstone of management. In case of deterioration, consider adding another immunosuppressive drug (MMF or tacrolimus) (73).

Renal toxicity – Although infrequent in BC patients, the onset of renal failure can underlie an immune-related nephritis. Certainly, other causes of kidney injury must be ruled out in first place. ICIs should be interrupted or permanently discontinued, depending on the severity of the renal insufficiency. Alongside, concomitant nephrotoxic drugs should be discontinued and prednisone 1–2 mg/kg can be considered. A renal biopsy may be proposed to confirm diagnosis (73).

Rechallenge after prior toxicity

The choice to retreat depends on multiple factors, such as the severity and nature of the initial irAE, its responsiveness to immunosuppression and the availability of alternative options (8). Data about the patient populations who should not be offered retreatment are limited, thus careful clinical judgment is mandatory (112).

When rechallenge with ICI is tempted, the rate of recurrent irAEs ranges between 18% and 88%, with 28.8% of recurrences regarding the same irAE that prompted discontinuation of ICI (112, 113). The highest rates of recurrent irAEs are recorded among patients receiving CTLA-4 blockade after discontinuation of anti-PD-1/PD-L1 mAbs due to prior toxicity (74, 114, 115). A summary of the conditions in which retreatment after prior toxicity could be appropriate is provided in **Table 4**. However, if rechallenge is not possible, ICI definitive interruption should not be stigmatized, as growing evidence shows that patients who discontinued ICIs due to treatment limiting toxicity still experienced durable responses (112).

Organ	**Rechallenge**	**Do NOT Rechallenge**
Skin	Grade ≤ 1 rash, pruritus	Grade 3/4 severe, life-threatening bullous disease
GI	Grade 2/3 PD-1/PD-L1–associated colitis*	Grade 3 CTLA-4–associated colitis; grade 4 colitis
Liver	Grade 2 transaminitis without elevated bilirubin*	Grade 3/4 hepatitis
Pancreatitis	Symptomatic grade 2	Grade 3/4 pancreatitis
Endocrine	After hormone repletion	Symptomatic pituitary inflammation

Lung	Grade 1/2, off steroids	Grade 3/4 pneumonitis
Renal	Grade 1/2*	Grade 3/4 proteinuria
Ocular	Grade 2	Grade 3/4 uveitis, episcleritis
Neurologic	Grade 1/2 peripheral neuropathy	GBS, encephalitis, transverse myelitis, grade 2-4 myasthenia gravis
Cardiovascular	Grade 1 myocarditis	Grade 2-4 myocarditis
Musculoskeletal	Resume after stabilization, adequate management	Severe inflammatory arthritis that impairs ADLs

Table 4. Key points in the rechallenge of ICIs after an irAE (8, 112). Note that clinical judgement and an organ-specific system-based approach to toxicity management is always recommended. *May resume once prednisone < 10 mg/day. Abbreviations: GI, gastrointestinal; CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; ADLs, activities of daily life; GBS, Guillain-Barré syndrome.

Conclusion and future perspectives

Before starting treatment, patients should be assessed in terms of susceptibility to develop irAEs, considering that patients with a history of autoimmune disease are at risk for worsening of their pre-existing condition while on ICI (74). However, a recent personalized risk-based prevention approach with a tailored immunosuppressive strategy has been proposed (103).

The development of irAEs in patients treated with anti-PD-1/PD-L1 mAbs has been suggested as a positive predictive factor for tumor response in melanoma and NSCLC (53, 54, 74-77). However, other findings did not support such an association (78, 79). Rates of irAEs in BC patients treated with PD-1/PD-L1 blockade are lower than rates reported for other tumor types (4). Although this low incidence of irAEs benefits the safety profile, the chance to adopt irAEs as a predictive biomarker for immunotherapy efficacy in BC is smaller (113, 116). In BC, other factors seem to help predicting response to ICI therapy, such as PD-L1-positive status, first-line treatment setting, the absence of liver metastases, high TILs, and high CD8+ T-cell infiltrating levels, but further research is warranted (66).

In conclusion, cancer immunotherapy will continue to shape the therapeutic landscape for BC in the coming years, as new agents continue to enter the clinic. Hence, improving awareness, training a new generation of physicians with specific skills in the diagnosis and management of irAEs and encouraging multidisciplinary approaches are essential strategies. In fact, no consensus guidelines are based on outcomes of RCTs (7, 8, 73, 102). Therefore, clinical judgement, irrespectively of the grade-related management suggestions discussed, is a caveat that should always be recalled.

- **Competing Interests:** CCr has received honoraria for consultancy/advisory role/speaker bureau from Pfizer, Lilly, Novartis, Roche, and MSD all outside the submitted work. CCo has no potential conflicts of interest to disclose. GP has no potential conflict of interest to disclose. GC served as consultant or advisor for Roche, Lilly, and Bristol-Myers Squibb, served on the speaker's bureau for Roche, Pfizer, and Lilly, received travel funding from Pfizer and Roche, and received honoraria from Roche, Pfizer, Lilly, Novartis, and SEAGEN, all outside the submitted work.

References

1. Hennecke J, Wiley DC. T cell receptor-MHC interactions up close. Cell. 2001;104(1):1-4.

2. Schwartz RH. A cell culture model for T lymphocyte clonal anergy. Science. 1990;248(4961):1349-56.

3. June CH, Warshauer JT, Bluestone JA. Is autoimmunity the Achilles' heel of cancer immunotherapy? Nat Med. 2017;23(5):540-7.

4. Adams S, Gatti-Mays ME, Kalinsky K, Korde LA, Sharon E, Amiri-Kordestani L, et al. Current Landscape of Immunotherapy in Breast Cancer: A Review. JAMA Oncol. 2019.

5. Lawrence MS, Stojanov P, Polak P, Kryukov GV, Cibulskis K, Sivachenko A, et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature. 2013;499(7457):214-8.

6. Criscitiello C, Vingiani A, Maisonneuve P, Viale G, Curigliano G. Tumor-infiltrating lymphocytes (TILs) in ER+/HER2- breast cancer. Breast Cancer Res Treat. 2020;183(2):347-54.

7. Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):95.

8. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018;36(17):1714-68.

9. Budczies J, Bockmayr M, Denkert C, Klauschen F, Lennerz JK, Györffy B, et al. Classical pathology and mutational load of breast cancer - integration of two worlds. J Pathol Clin Res. 2015;1(4):225-38.

10. Luen S, Virassamy B, Savas P, Salgado R, Loi S. The genomic landscape of breast cancer and its interaction with host immunity. Breast. 2016;29:241-50.

11. Stanton SE, Adams S, Disis ML. Variation in the Incidence and Magnitude of Tumor-Infiltrating Lymphocytes in Breast Cancer Subtypes: A Systematic Review. JAMA Oncol. 2016;2(10):1354-60.

12. Loi S, Sirtaine N, Piette F, Salgado R, Viale G, Van Eenoo F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol. 2013;31(7):860-7.

13. Dieci MV, Mathieu MC, Guarneri V, Conte P, Delaloge S, Andre F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in two phase III randomized adjuvant breast cancer trials. Ann Oncol. 2015;26(8):1698-704.

14. Loi S, Michiels S, Salgado R, Sirtaine N, Jose V, Fumagalli D, et al. Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: results from the FinHER trial. Ann Oncol. 2014;25(8):1544-50.

15. Denkert C, von Minckwitz G, Darb-Esfahani S, Lederer B, Heppner BI, Weber KE, et al. Tumour-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol. 2018;19(1):40-50.

16. Adams S, Gray RJ, Demaria S, Goldstein L, Perez EA, Shulman LN, et al. Prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancers from two phase III randomized adjuvant breast cancer trials: ECOG 2197 and ECOG 1199. J Clin Oncol. 2014;32(27):2959-66.

17. Ibrahim EM, Al-Foheidi ME, Al-Mansour MM, Kazkaz GA. The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis. Breast Cancer Res Treat. 2014;148(3):467-76.

18. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(1):44-59.

19. Garg AD, More S, Rufo N, Mece O, Sassano ML, Agostinis P, et al. Trial watch: Immunogenic cell death induction by anticancer chemotherapeutics. Oncoimmunology. 2017;6(12):e1386829.

20. Galluzzi L, Buqué A, Kepp O, Zitvogel L, Kroemer G. Immunogenic cell death in cancer and infectious disease. Nat Rev Immunol. 2017;17(2):97-111.

21. FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer March 8, 2019 [Available from: https://bit.ly/39Slkl5.

22. Emens LA, Adams S, Barrios CH, Dieras VC, Iwata H, Loi S, et al. LBA16 - IMpassion130: Final OS analysis from the pivotal phase III study of atezolizumab + nab-paclitaxel vs placebo + nab-paclitaxel in previously untreated locally advanced or metastatic triple-negative breast cancer. Annals of Oncology 31.

23. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet. 2020;396(10265):1817-28.

24. FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer March 8, 2019 [Available from: https://bit.ly/3sK4zAY.

25. FDA grants accelerated approval to pembrolizumab for locally recurrent unresectable or metastatic triple negative breast cancer November 13, 2020 [Available from: https://bit.ly/3bWSsdW.

26. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. Ann Oncol. 2019;30(8):1194-220.

27. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384(9938):164-72.

28. Tarantino P, Gandini S, Trapani D, Criscitiello C, Curigliano G. Immunotherapy addition to neoadjuvant chemotherapy for early triple negative breast cancer: A systematic review and meta-analysis of randomized clinical trials. Crit Rev Oncol Hematol. 2021;159:103223.

29. Salgado R, Denkert C, Campbell C, Savas P, Nuciforo P, Nucifero P, et al. Tumor-Infiltrating Lymphocytes and Associations With Pathological Complete Response and Event-Free Survival in HER2-Positive Early-Stage Breast Cancer Treated With Lapatinib and Trastuzumab: A Secondary Analysis of the NeoALTTO Trial. JAMA Oncol. 2015;1(4):448-54.

30. Datta J, Fracol M, McMillan MT, Berk E, Xu S, Goodman N, et al. Association of Depressed Anti-HER2 T-Helper Type 1 Response With Recurrence in Patients With Completely Treated HER2-Positive Breast Cancer: Role for Immune Monitoring. JAMA Oncol. 2016;2(2):242-6.

31. Loi S, Giobbie-Hurder A, Gombos A, Bachelot T, Hui R, Curigliano G, et al. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial. Lancet Oncol. 2019;20(3):371-82.

32. Park S, Jiang Z, Mortenson ED, Deng L, Radkevich-Brown O, Yang X, et al. The therapeutic effect of anti-HER2/neu antibody depends on both innate and adaptive immunity. Cancer Cell. 2010;18(2):160-70.

33. Costa RLB, Czerniecki BJ. Clinical development of immunotherapies for HER2. NPJ Breast Cancer. 2020;6:10.

34. Emens L, Esteva F, Beresford M, Saura C, Laurentiis MD, Kim S-B, et al., editors. Abstract PD3-01: Results from KATE2, a randomized phase 2 study of atezolizumab (atezo)+trastuzumab emtansine (T-DM1) vs placebo (pbo)+T-DM1 in previously treated HER2+ advanced breast cancer (BC). San Antonio Breast Cancer Symposium; December 4-8, 2018; San Antonio, Texas.

35. Chia SKL, Bedard PL, Hilton J, Amir E, Gelmon KA, Goodwin RA, et al. A phase I study of a PD-L1 antibody (Durvalumab) in combination with trastuzumab in HER-2 positive metastatic breast cancer (MBC) progressing on prior anti HER-2 therapies (CCTG IND.229). Journal of Clinical Oncology. June 01, 2018;36:1029-.

36. Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. Ann Oncol. 2016;27(4):559-74.

37. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med. 2018;378(2):158-68.

38. Hassel JC, Heinzerling L, Aberle J, Bähr O, Eigentler TK, Grimm MO, et al. Combined immune checkpoint blockade (anti-PD-1/anti-CTLA-4): Evaluation and management of adverse drug reactions. Cancer Treat Rev. 2017;57:36-49.

39. Conforti F, Pala L, Bagnardi V, Viale G, De Pas T, Pagan E, et al. Sex-Based Heterogeneity in Response to Lung Cancer Immunotherapy: A Systematic Review and Meta-Analysis. J Natl Cancer Inst. 2019;111(8):772-81.

40. D'Angelo SP, Bhatia S, Brohl AS, Hamid O, Mehnert JM, Terheyden P, et al. Avelumab in patients with previously treated metastatic Merkel cell carcinoma: long-term data and biomarker analyses from the single-arm phase 2 JAVELIN Merkel 200 trial. J Immunother Cancer. 2020;8(1).

41. Avelumab injection. United States Prescribing Information. US National Library of Medicine. [Available from: https://bit.ly/39XCMVe.

42. Martins F, Sofiya L, Sykiotis GP, Lamine F, Maillard M, Fraga M, et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol. 2019;16(9):563-80.

43. Galvão VR, Castells MC. Hypersensitivity to biological agents-updated diagnosis, management, and treatment. J Allergy Clin Immunol Pract. 2015;3(2):175-85; quiz 86.

44. Khoja L, Day D, Wei-Wu Chen T, Siu LL, Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Ann Oncol. 2017;28(10):2377-85.

45. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006-17.

46. Tumeh PC, Rosenblum M, Handley N, Tsai K, Rodriguez RRS, Khurana N, et al. Abstract 2857: Metastatic site and response to pembrolizumab (anti-PD1 antibody) in melanoma. Cancer Res August 1 (75) (15 Supplement) 2857, 2015.

47. Khoja L, Kibiro M, Metser U, Gedye C, Hogg D, Butler MO, et al. Patterns of response to anti-PD-1 treatment: an exploratory comparison of four radiological response criteria and associations with overall survival in metastatic melanoma patients. Br J Cancer. 2016;115(10):1186-92.

48. Nishino M, Giobbie-Hurder A, Hatabu H, Ramaiya NH, Hodi FS. Incidence of Programmed Cell Death 1 Inhibitor-Related Pneumonitis in Patients With Advanced Cancer: A Systematic Review and Meta-analysis. JAMA Oncol. 2016;2(12):1607-16.

49. Prokunina L, Padyukov L, Bennet A, de Faire U, Wiman B, Prince J, et al. Association of the PD-1.3A allele of the PDCD1 gene in patients with rheumatoid arthritis negative for rheumatoid factor and the shared epitope. Arthritis Rheum. 2004;50(6):1770-3.

50. Mitchem JB, Brennan DJ, Knolhoff BL, Belt BA, Zhu Y, Sanford DE, et al. Targeting tumor-infiltrating macrophages decreases tumor-initiating cells, relieves immunosuppression, and improves chemotherapeutic responses. Cancer Res. 2013;73(3):1128-41.

51. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med. 2014;6(230):230ra45.

52. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-32.

53. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2015;16(4):375-84.

54. Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol. 2015;26(12):2375-91.

55. Schmid P, Salgado R, Park YH, Muñoz-Couselo E, Kim SB, Sohn J, et al. Pembrolizumab plus chemotherapy as neoadjuvant treatment of high-risk, early-stage triple-negative breast cancer: results from the phase 1b open-label, multicohort KEYNOTE-173 study. Ann Oncol. 2020;31(5):569-81.

56. Adams S, Diamond JR, Hamilton E, Pohlmann PR, Tolaney SM, Chang CW, et al. Atezolizumab Plus nab-Paclitaxel in the Treatment of Metastatic Triple-Negative Breast Cancer With 2-Year Survival Follow-up: A Phase 1b Clinical Trial. JAMA Oncol. 2019;5(3):334-42.

57. Tolaney S, Kalinsky K, Kaklamani V, D'Adamo D, Aktan G, Tsai M, et al. A phase Ib/II study of eribulin (ERI) plus pembrolizumab (PEMBRO) in metastatic triple-negative breast cancer (mTNBC) (ENHANCE 1). Journal of Clinical Oncology. 2020, May 20;38:1015-.

58. Nanda R, Liu MC, Yau C, Shatsky R, Pusztai L, Wallace A, et al. Effect of Pembrolizumab Plus Neoadjuvant Chemotherapy on Pathologic Complete Response in Women With Early-Stage Breast Cancer: An Analysis of the Ongoing Phase 2 Adaptively Randomized I-SPY2 Trial. JAMA Oncol. 2020;6(5):676-84.

59. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, Blohmer JU, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;30(8):1279-88.

60. Kyte JA, Røssevold A, Falk RS, Naume B. ALICE: a randomized placebo-controlled phase II study evaluating atezolizumab combined with immunogenic chemotherapy in patients with metastatic triple-negative breast cancer. J Transl Med. 2020;18(1):252.

61. Kyte JA, Andresen NK, Russnes HG, Fretland S, Falk RS, Lingjærde OC, et al. ICON: a randomized phase IIb study evaluating immunogenic chemotherapy combined with ipilimumab and nivolumab in patients with metastatic hormone receptor positive breast cancer. J Transl Med. 2020;18(1):269.

62. Voorwerk L, Slagter M, Horlings HM, Sikorska K, van de Vijver KK, de Maaker M, et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. Nat Med. 2019;25(6):920-8.

63. Miles DW, Gligorov J, André F, Cameron D, Schneeweiss A, Barrios CH, et al. LBA15 - Primary results from IMpassion131, a double-blind placebo-controlled randomised phase III trial of first-line paclitaxel (PAC) ± atezolizumab (atezo) for unresectable locally advanced/metastatic triple-negative breast cancer (mTNBC). ESMO Virtual Congress 202019 Sep 2020.

64. Schmid P, Cortes J, Pusztai L, McArthur H, Kümmel S, Bergh J, et al. Pembrolizumab for Early Triple-Negative Breast Cancer. N Engl J Med. 2020;382(9):810-21.

65. Mittendorf EA, Zhang H, Barrios CH, Saji S, Jung KH, Hegg R, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020;396(10257):1090-100.

66. Zou Y, Zou X, Zheng S, Tang H, Zhang L, Liu P, et al. Efficacy and predictive factors of immune checkpoint inhibitors in metastatic breast cancer: a systematic review and meta-analysis. Ther Adv Med Oncol. 2020;12:1758835920940928.

67. Duma N, Abdel-Ghani A, Yadav S, Hoversten KP, Reed CT, Sitek AN, et al. Sex Differences in Tolerability to Anti-Programmed Cell Death Protein 1 Therapy in Patients with Metastatic Melanoma and Non-Small Cell Lung Cancer: Are We All Equal? Oncologist. 2019;24(11):e1148-e55.

68. Duma N, Lambertini M. It Is Time to Talk About Fertility and Immunotherapy. Oncologist. 2020;25(4):277-8.

69. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv119-iv42.

70. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122-33.

71. Lebbé C, Meyer N, Mortier L, Marquez-Rodas I, Robert C, Rutkowski P, et al. Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced

Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. J Clin Oncol. 2019;37(11):867-75.

72. Ascierto PA, Del Vecchio M, Robert C, Mackiewicz A, Chiarion-Sileni V, Arance A, et al. Ipilimumab 10 mg/kg versus ipilimumab 3 mg/kg in patients with unresectable or metastatic melanoma: a randomised, double-blind, multicentre, phase 3 trial. Lancet Oncol. 2017;18(5):611-22.

73. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28 Suppl 4:iv119-iv42.

74. Menzies AM, Johnson DB, Ramanujam S, Atkinson VG, Wong ANM, Park JJ, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. Ann Oncol. 2017;28(2):368-76.

75. Bowyer S, Prithviraj P, Lorigan P, Larkin J, McArthur G, Atkinson V, et al. Efficacy and toxicity of treatment with the anti-CTLA-4 antibody ipilimumab in patients with metastatic melanoma after prior anti-PD-1 therapy. Br J Cancer. 2016;114(10):1084-9.

76. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019;381(16):1535-46.

77. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015;33(17):1889-94.

78. Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31-41.

79. Carretero-González A, Lora D, Ghanem I, Otero I, López F, Castellano D, et al. Comparative safety analysis of immunotherapy combined with chemotherapy versus monotherapy in solid tumors: a meta-analysis of randomized clinical trials. Oncotarget. 2019;10(35):3294-301.

80. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis with Combination Immune Checkpoint Blockade. N Engl J Med. 2016;375(18):1749-55.

81. Naidoo J, Wang X, Woo KM, Iyriboz T, Halpenny D, Cunningham J, et al. Pneumonitis in Patients Treated With Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy. J Clin Oncol. 2017;35(7):709-17.

82. Koelzer VH, Rothschild SI, Zihler D, Wicki A, Willi B, Willi N, et al. Systemic inflammation in a melanoma patient treated with immune checkpoint inhibitors-an autopsy study. J Immunother Cancer. 2016;4:13.

83. Wang DY, Ye F, Zhao S, Johnson DB. Incidence of immune checkpoint inhibitor-related colitis in solid tumor patients: A systematic review and meta-analysis. Oncoimmunology. 2017;6(10):e1344805.

84. Hottinger AF. Neurologic complications of immune checkpoint inhibitors. Curr Opin Neurol. 2016;29(6):806-12.

85. Moslehi JJ, Salem JE, Sosman JA, Lebrun-Vignes B, Johnson DB. Increased reporting of fatal immune checkpoint inhibitor-associated myocarditis. Lancet. 2018;391(10124):933.

86. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol. 2018;4(12):1721-8.

87. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711-23.

88. Patel NS, Oury A, Daniels GA, Bazhenova L, Patel SP. Incidence of Thyroid Function Test Abnormalities in Patients Receiving Immune-Checkpoint Inhibitors for Cancer Treatment. Oncologist. 2018;23(10):1236-41.

89. Girotra M, Hansen A, Farooki A, Byun DJ, Min L, Creelan BC, et al. The Current Understanding of the Endocrine Effects From Immune Checkpoint Inhibitors and Recommendations for Management. JNCI Cancer Spectr. 2018;2(3):pky021.

90. Faje AT, Sullivan R, Lawrence D, Tritos NA, Fadden R, Klibanski A, et al. Ipilimumab-induced hypophysitis: a detailed longitudinal analysis in a large cohort of patients with metastatic melanoma. J Clin Endocrinol Metab. 2014;99(11):4078-85.

91. Soularue E, Lepage P, Colombel JF, Coutzac C, Faleck D, Marthey L, et al. Enterocolitis due to immune checkpoint inhibitors: a systematic review. Gut. 2018;67(11):2056-67.

92. Beck KE, Blansfield JA, Tran KQ, Feldman AL, Hughes MS, Royal RE, et al. Enterocolitis in patients with cancer after antibody blockade of cytotoxic T-lymphocyte-associated antigen 4. J Clin Oncol. 2006;24(15):2283-9.

93. Gupta A, De Felice KM, Loftus EV, Khanna S. Systematic review: colitis associated with anti-CTLA-4 therapy. Aliment Pharmacol Ther. 2015;42(4):406-17.

94. De Martin E, Michot JM, Papouin B, Champiat S, Mateus C, Lambotte O, et al. Characterization of liver injury induced by cancer immunotherapy using immune checkpoint inhibitors. J Hepatol. 2018;68(6):1181-90.

95. Gauci ML, Baroudjian B, Zeboulon C, Pages C, Poté N, Roux O, et al. Immune-related hepatitis with immunotherapy: Are corticosteroids always needed? J Hepatol. 2018;69(2):548-50.

96. Cuzzubbo S, Javeri F, Tissier M, Roumi A, Barlog C, Doridam J, et al. Neurological adverse events associated with immune checkpoint inhibitors: Review of the literature. Eur J Cancer. 2017;73:1-8.

97. Touat M, Talmasov D, Ricard D, Psimaras D. Neurological toxicities associated with immune-checkpoint inhibitors. Curr Opin Neurol. 2017;30(6):659-68.

98. Shirali AC, Perazella MA, Gettinger S. Association of Acute Interstitial Nephritis With Programmed Cell Death 1 Inhibitor Therapy in Lung Cancer Patients. Am J Kidney Dis. 2016;68(2):287-91.

99. Wanchoo R, Karam S, Uppal NN, Barta VS, Deray G, Devoe C, et al. Adverse Renal Effects of Immune Checkpoint Inhibitors: A Narrative Review. Am J Nephrol. 2017;45(2):160-9.

100. Calabrese C, Kirchner E, Kontzias A, Velcheti V, Calabrese LH. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. RMD Open. 2017;3(1):e000412.

101. Chuzi S, Tavora F, Cruz M, Costa R, Chae YK, Carneiro BA, et al. Clinical features, diagnostic challenges, and management strategies in checkpoint inhibitor-related pneumonitis. Cancer Manag Res. 2017;9:207-13.

102. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Management of Immunotherapy-Related Toxicities, Version 1.2019. J Natl Compr Canc Netw. 2019;17(3):255-89.

103. Haanen J, Ernstoff MS, Wang Y, Menzies AM, Puzanov I, Grivas P, et al. Autoimmune diseases and immune-checkpoint inhibitors for cancer therapy: review of the literature and personalized risk-based prevention strategy. Ann Oncol. 2020;31(6):724-44.

104. Phillips GS, Wu J, Hellmann MD, Postow MA, Rizvi NA, Freites-Martinez A, et al. Treatment Outcomes of Immune-Related Cutaneous Adverse Events. J Clin Oncol. 2019;37(30):2746-58.

105. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of Endocrine Dysfunction Following the Use of Different Immune Checkpoint Inhibitor Regimens: A Systematic Review and Meta-analysis. JAMA Oncol. 2018;4(2):173-82.

106. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012;30(21):2691-7.

107. Khunger M, Rakshit S, Pasupuleti V, Hernandez AV, Mazzone P, Stevenson J, et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest. 2017;152(2):271-81.

108. Nishino M, Ramaiya NH, Awad MM, Sholl LM, Maattala JA, Taibi M, et al. PD-1 Inhibitor-Related Pneumonitis in Advanced Cancer Patients: Radiographic Patterns and Clinical Course. Clin Cancer Res. 2016;22(24):6051-60.

109. Delaunay M, Cadranel J, Lusque A, Meyer N, Gounant V, Moro-Sibilot D, et al. Immune-checkpoint inhibitors associated with interstitial lung disease in cancer patients. Eur Respir J. 2017;50(2).

110. Shibaki R, Akamatsu H, Fujimoto M, Koh Y, Yamamoto N. Nivolumab induced radiation recall pneumonitis after two years of radiotherapy. Ann Oncol. 2017;28(6):1404-5.

111. Shoushtari AN, Friedman CF, Navid-Azarbaijani P, Postow MA, Callahan MK, Momtaz P, et al. Measuring Toxic Effects and Time to Treatment Failure for Nivolumab Plus Ipilimumab in Melanoma. JAMA Oncol. 2018;4(1):98-101.

112. Dolladille C, Ederhy S, Sassier M, Cautela J, Thuny F, Cohen AA, et al. Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events in Patients With Cancer. JAMA Oncol. 2020.

113. Emens LA, Cruz C, Eder JP, Braiteh F, Chung C, Tolaney SM, et al. Long-term Clinical Outcomes and Biomarker Analyses of Atezolizumab Therapy for Patients With Metastatic Triple-Negative Breast Cancer: A Phase 1 Study. JAMA Oncol. 2019;5(1):74-82.

114. Simonaggio A, Michot JM, Voisin AL, Le Pavec J, Collins M, Lallart A, et al. Evaluation of Readministration of Immune Checkpoint Inhibitors After Immune-Related Adverse Events in Patients With Cancer. JAMA Oncol. 2019.

115. Pollack MH, Betof A, Dearden H, Rapazzo K, Valentine I, Brohl AS, et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. Ann Oncol. 2018;29(1):250-5.

116. Haratani K, Hayashi H, Chiba Y, Kudo K, Yonesaka K, Kato R, et al. Association of Immune-Related Adverse Events With Nivolumab Efficacy in Non-Small-Cell Lung Cancer. JAMA Oncol. 2018;4(3):374-8.

Authors' Biographies:

Dr. Carmen Criscitiello: Medical Oncologist with High Specialization at the Division of New Drugs and Early Drug Development of the European Institute of Oncology IRCCS, Assistant Professor at the Department of Hematology and Oncology of the University of Milan.

Dr. Chiara Corti: Medical Doctor at the Division of New Drugs and Early Drug Development of the European Institute of Oncology IRCCS, Medical Oncology Resident of the Department of Hematology and Oncology of the University of Milan.

Prof. Gabriella Pravettoni: Full Professor of Psychology of Decision-Making at the University of Milan, Director of the Psycho-Oncology Division at the European Institute of Oncology IRCCS.

Prof. Giuseppe Curigliano: Clinical Director of the Division of New Drugs and Early Drug Development of the European Institute of Oncology IRCCS, Associate Professor of the Department of Hematology and Oncology at the University of Milan.