

SPECIAL ARTICLE

ESMO—ESTRO consensus statements on the safety of combining radiotherapy with immune checkpoint inhibitors, VEGF(R) inhibitors, or multitargeted tyrosine kinase inhibitors

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Background: The combination of radiotherapy (RT) with targeted agents or immunotherapy may result in improved outcomes, but it can also increase toxicity. However, there is a paucity of high-quality toxicity data, leading to an absence of evidence-based guidelines.

Design: To address this, European Society for Medical Oncology (ESMO) and European Society for Radiotherapy and Oncology (ESTRO) initiated a series of systematic reviews followed by a Delphi consensus process to develop multidisciplinary, evidence-based consensus statements regarding the safety of combining RT with such agents. The current publication describes the combination of RT with immune checkpoint inhibitors (ICIs), vascular endothelial growth factor (receptor) [VEGF(R)] inhibitors, or multitargeted tyrosine kinase inhibitors (TKIs). By systematically covering different drug classes and irradiated areas, 76 clinical scenarios were evaluated during two Delphi rounds

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with 20 international experts. Safety statements were developed for each scenario, based on the systematic literature reviews.

Results: A total of 5921 records were screened during the systematic literature review process for ICIs, VEGF(R) inhibitors, and multitargeted TKIs, and 159 reports were selected for inclusion in the final literature reviews and the database. During the two Delphi rounds, agreement was reached regarding the safety statements for 74 clinical scenarios.

Conclusions: Generally, the expected toxicity of combining RT with ICIs is low, particularly for programmed death (-ligand) 1 inhibitors. For most combinations with VEGF(R) inhibitors and multitargeted TKIs, exercising caution is recommended. The evidence-based safety statements developed during this comprehensive project provide practical guidance on combining RT with targeted cancer therapies and immunotherapy.

Key words: radiotherapy, tyrosine kinase inhibitors, immune checkpoint inhibitors, toxicity, systematic review, consensus statements

INTRODUCTION

Systemic therapy is a crucial pillar in the treatment of cancer, along with surgery and radiotherapy (RT). Recently, the number of systemic treatment options has increased considerably, due to the introduction of immune checkpoint inhibitors (ICIs) and a wide array of targeted agents. This has led to improved treatment outcomes across nearly all cancer types and various disease settings.¹

Approximately 50% of cancer patients will receive RT at some point during their treatment.²⁻⁴ Consequently, patients already receiving targeted agents or ICIs are frequently referred for RT, mostly for oligometastases, oligoprogression, or local palliative treatment.⁵⁻⁸ Although concurrently combining these agents with RT may improve tumor control, increased toxicity is a potential threat.⁸ Unfortunately, there is a very limited amount of high-quality evidence about toxicity when combining RT with the latest systemic agents. For several targeted drug–RT combinations, unexpected clinically relevant toxicity has been reported, including mucositis, ulceration, pulmonary toxicity, and dermatitis, raising safety concerns for some combinations.⁹⁻¹⁵

This lack of evidence causes clinical dilemmas for oncologists. On the one hand, disproportionate adverse effects of combined-modality treatment should be avoided. On the other hand, drug interruption or dosage reduction may affect disease control, leading to tumor progression or flare,¹⁶⁻¹⁸ while RT avoidance or dose reduction can result in reduced tumor or symptom control. Therefore, unnecessary treatment deintensification or interruption should be avoided. We face a significant knowledge gap and a lack of consensus regarding this issue. Moreover, there are no evidence-based, multidisciplinary protocols or guidelines for most targeted/immunotherapy drug–RT combinations.^{8,19,20} Depending on the specific drug–RT combination, site of irradiation, and the treatment decision, this lack of knowledge can lead to suboptimal treatment or unexpected increased toxicity for these patients.

Therefore, the European Society for Medical Oncology (ESMO) and the European Society for Radiotherapy and Oncology (ESTRO) jointly initiated an elaborate and comprehensive series of drug class-specific and irradiated area-specific systematic literature reviews and Delphi consensus

statements regarding the safety of combining RT with targeted agents or ICIs. For each drug class, irradiated area-specific systematic literature reviews and Delphi consensus statements were developed. A complementing paper provides a framework of the most important (radio)biological and pharmacological factors, along with general clinical considerations.²¹ The goal of the current publication within this series is to provide clinicians with systematic reviews and consensus statements regarding the safety of combining RT with ICIs, vascular endothelial growth factor (receptor) [VEGF (R)] inhibitors, or multitargeted tyrosine kinase inhibitors (TKIs).

METHODS

Project governance

This project was carried out in close collaboration with ESMO and ESTRO. Permission was granted by both the ESMO board and the ESTRO guidelines committee. The project was overseen by a coordinating committee, consisting of representatives and experts from both ESMO and ESTRO, who convened monthly. Daily project coordination was managed by researchers from the Netherlands Cancer Institute. The project received financial support from the KWF Dutch Cancer Society [grant number: 12702]. Production costs have been covered by ESMO and ESTRO from central funds.

Systematic literature reviews

The coordinating committee evaluated the clinical relevance and emerging evidence of novel anticancer treatments to cluster the research into 10 different drug classes, namely ICIs and different classes of targeted agents. Antibody–drug conjugates were not included in the current project.

For each drug class, a systematic literature search was carried out in the Medline, Embase, and SCOPUS databases on 21 December 2020. The search strategy and key words are provided in [Supplementary Tables S1-S3](#), available at <https://doi.org/10.1016/j.annonc.2025.09.008>. Studies were only included if RT and the targeted agents were combined concurrently, which was defined as a maximum time gap between drug administration and RT of 5 drug half-lives

before RT,^{21–26} or 2 weeks after RT. A description of treatment-related toxicity was required as well. Further inclusion and exclusion criteria can be found in [Supplementary Table S4](https://doi.org/10.1016/j.annonc.2025.09.008), available at <https://doi.org/10.1016/j.annonc.2025.09.008>. Initially, double-blind title-abstract screening was carried out by two researchers (EA and PB, with a consulting role by MJ), followed by full-text screening of the selected reports. For multitargeted TKIs, full-text screening and review was carried out by the same researchers. For ICIs and VEGF(R) inhibitors, representatives from ESMO (AG, AP, BD, JB, LCB, SOC) assisted during the full-text screening and review. The quality of the literature screening and review process was ensured through regular meetings and discussions with the screening researchers. Due to the high number of reports included in the ICI and VEGF(R) literature searches, an additional selection step was added to select the largest studies with the highest levels of evidence for each drug–RT scenario ([Supplementary Figure S1](https://doi.org/10.1016/j.annonc.2025.09.008), available at <https://doi.org/10.1016/j.annonc.2025.09.008>).

In order to provide the evidence for drug-specific and irradiated area-specific safety recommendations, each drug target-specific systematic literature review was divided into six irradiated area-specific literature reviews: for irradiation of the skin, brain, head and neck, thorax, abdomen/pelvis, and musculoskeletal tissues ([Supplementary Material](https://doi.org/10.1016/j.annonc.2025.09.008), pages 2–41, available at <https://doi.org/10.1016/j.annonc.2025.09.008>). Summaries were written for each drug class and irradiated area. Additionally, information about commonly used drugs, their mechanisms, and the pathways involved was provided.

Literature database

All included reports were added to a searchable literature database in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), available at <https://doi.org/10.1016/j.annonc.2025.09.008>, enabling selection of publications based on a specific drug target, irradiated area, and/or study type. Additional relevant information from each publication was recorded in this database, including the study type, number of patients, primary tumor, drug name, drug dose, drug scheduling relative to RT, RT technique, RT dose, RT fractionation scheme, tumor response, acute toxicity, late toxicity, and toxicity comparisons with monotherapy.

Safety recommendations

The project coordinators and coordinating committee members defined three safety measure options for each drug–RT scenario: not combining both treatments, a major treatment adaptation, or a minor/no treatment adaptation ([Figure 1](#)). Based on the systematic literature reviews, scenario-specific safety recommendations were written per drug class, specifically for each of the six irradiated areas and for three RT scenarios ([Table 1](#)). This resulted in at least 18 scenario-specific safety recommendations per drug class. Based on the systematic literature reviews, EA

selected one of the three predefined safety measure options for each safety recommendation.

The levels of evidence are derived from the ESMO Clinical Practice Guidelines Standard Operating Procedures (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System) ([Supplementary Table S5](https://doi.org/10.1016/j.annonc.2025.09.008), available at <https://doi.org/10.1016/j.annonc.2025.09.008>).^{27,28}

Modified Delphi process

A total of 20 experts, equally divided between ESMO and ESTRO representatives, were invited to participate in a modified Delphi process.²⁹ This Delphi process took place between 19 September 2023 and 7 February 2024. All participating Delphi experts were requested to read a briefing document summarizing general information, to read the systematic literature reviews ([Supplementary Material](https://doi.org/10.1016/j.annonc.2025.09.008), pages 2–41, available at <https://doi.org/10.1016/j.annonc.2025.09.008>), to use the literature database provided, to consider any other evidence that they might be aware of (e.g. published after our literature review time point), and to vote whether they agreed or disagreed with the proposed safety measure statement for each drug–RT scenario. If they disagreed, they were requested to explain their decision, preferably with supporting (new) literature references.

Two digital Delphi voting rounds were carried out. During round 1, statements with an agreement rate of $\geq 90\%$ were immediately regarded as consensus. During round 2, statements with $\geq 75\%$ agreement were accepted.³⁰ Statements with $\geq 90\%$ agreement are more strongly recommended than statements with 75%–89% agreement. For statements that were voted on in both Delphi rounds, the round 2 agreement rates were decisive.

Between round 1 and round 2, statements were reviewed by EA and selected experts (AP, CM, DDR, DP, KH). Delphi expert feedback was analyzed and statements were added, removed, or adapted, if necessary. The Delphi process was coordinated by the project coordinators and the ESMO office. Microsoft Excel 2016 was used for questionnaire development and analysis of the Delphi results.

RESULTS

Immune checkpoint inhibitors

Systematic literature review process results. After screening 3251 unique records for ICIs, 46 reports were included in the literature review and database. The PRISMA flow diagram³¹ ([Supplementary Figure S2](https://doi.org/10.1016/j.annonc.2025.09.008)) and the full systematic literature review are shown in [Supplementary Material](https://doi.org/10.1016/j.annonc.2025.09.008), pages 2–14, available at <https://doi.org/10.1016/j.annonc.2025.09.008>.

Drug class and systematic literature review summary.

Commonly used ICIs are monoclonal antibodies targeted against programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4). PD-1 and CTLA-4 are immune

Expected risk of combined therapy and corresponding safety measures			
Expected risk:	Strongly increased toxicity	No/marginally increased toxicity	
Consider:	Not combining	Major adaptation	Minor/no adaptation
Safety measure definitions			
Not combining	Consider protracted drug interruption or no radiotherapy, to avoid a drug–radiotherapy interaction. If omitting radiotherapy is undesirable, it is important to reach an estimated drug ^a concentration unlikely to cause severe synergistic toxicity, before the start of radiotherapy. In this safety category, a time interval of at least 5 drug ^a elimination half-lives between drug interruption and the start of radiotherapy is proposed. This time interval can be individually adapted, based on clinical and pharmacological factors. Consider restarting the drug 1 week or later after radiotherapy completion.		
	Major adaptation	Consider a clinically relevant drug interruption/dosage reduction or a major radiotherapy adaptation. A major radiotherapy adaptation is defined as a ≥20% lower prescribed dose to the PTV and/or underdosing ≥20% of the PTV volume, compared with local standard therapy. When applying a drug interruption/dosage reduction, it is important to reach an estimated drug ^a concentration unlikely to cause severe synergistic toxicity, before the start of radiotherapy. In this safety category, this will usually concern a time interval of <5 drug ^a elimination half-lives between drug interruption/dosage reduction and the start of radiotherapy. When implemented, the drug dosage reduction should be clinically relevant with a perceived impact on the likelihood of efficacy. The time interval and/or drug dosage reduction can be individually adapted, based on clinical and pharmacological factors. Consider restarting the drug (or the original drug dosage) up to 1 week after radiotherapy completion, or later in case of persistent or severe acute radiotherapy toxicity.	
Minor/no adaptation		Consider a clinically insignificant drug interruption/dosage reduction, a minor radiotherapy adaptation, or no adaptations. For minor radiotherapy adaptations, the BED/EQD ₂ to the target volume should not change. The following adaptations can be considered: - More fractionated radiotherapy. - More advanced radiotherapy techniques than standard practice (e.g. IMRT, VMAT, IGRT), to reduce the normal tissue dose. A clinically insignificant drug interruption/dosage reduction may be applied when it is unlikely to reduce drug efficacy.	

Figure 1. Predefined safety measure definitions for combining targeted agents with radiotherapy, based on the expected risk.

BED, biologically equivalent dose; EQD₂, equivalent dose in 2 Gy fractions; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; VMAT, volumetric-modulated arc therapy.

^aDrug or active drug metabolites.

checkpoint receptors located on the membrane of T (and other) cells.^{32,33} In lymph nodes, upon T-cell activation by recognition of an antigen-presenting cell in a lymph node,

CTLA-4 is expressed on the cell surface of the T cell. Binding of CTLA-4 to B7 ligands on the antigen-presenting cell inhibits T-cell activation. CTLA-4 inhibitors prevent this CTLA-4-mediated suppression of T-cell activation, thereby enhancing the immune response.^{32,33} In the tumor micro-environment, PD-1 is expressed on the cell membrane of activated T cells, B cells, and natural killer cells.³²⁻³⁴ Engaging with (e.g. tumor) cells expressing PD-L1 or PD-L2 leads to inhibition of T-cell activation. PD-1 and PD-L1 inhibitors enhance the immune response by preventing this interaction.^{32,33} While the enhanced immune response by ICIs is favorable for suppressing tumor growth, it can cause various autoimmune, inflammatory adverse events, including rash, thyroid disorders, hypophysitis, hepatitis, diabetes mellitus, enterocolitis, and pneumonitis.³⁵

Despite a hypothetically increased risk of inflammation in the irradiated field when combining RT with ICIs, most clinical studies do not report a markedly increased risk of RT toxicity. However, there might be a higher risk of brain radionecrosis and pneumonitis. For RT with CTLA-4 inhibitors, less high-quality data are available than for RT with PD-(L)1 inhibitors. Also, combining RT with CTLA-4 inhibitors [$\pm$ PD-(L)1 inhibitors] possibly leads to more

Table 1. Radiotherapy scenario examples	
RT scenario	Example
Low-dose palliative RT	Examples: 1×8 , 2×8 , 5×4 , 10×3 Gy. Often used in patients with metastases and for palliation of symptoms. It generally has a lower risk of RT-induced toxicity. However, low-dose whole-brain RT is relatively toxic compared with local high-dose stereotactic RT for brain metastases.
High-dose conventionally fractionated RT	Examples: 33×2 Gy (5 times per week), 5×5 Gy (daily) or similar. Often used in treatments with curative/radical (or) (neo) adjuvant intent.
High-dose stereotactic RT	Examples: ≥ 14 Gy in 1 fraction, 60 Gy in 5-8 fractions, or similar. Often used in treatments with curative/radical intent. Radical, high-dose stereotactic RT is also increasingly used in the oligometastatic or oligoprogressive setting or to treat brain metastases.

RT, radiotherapy.

toxicity than combining RT with PD-(L)1 inhibitors alone. In smaller studies with increased toxicity, it is difficult to distinguish if this is merely due to additive toxicity, or due to synergistic/supra-additive toxicity caused by an interaction between ICIs and RT. It remains important to consider the toxicity profiles of both individual treatments.

For the different irradiated areas, the following data were found:

- Skin³⁶⁻⁴⁴: apart from the skin toxicities typically associated with RT and ICIs alone, no increased risk of skin toxicity is observed when RT is combined with ICIs.
- Brain^{22,45-57}: the combination of brain RT concurrently with ICIs appears generally safe. However, some studies report an (often not statistically significant) increased risk of radionecrosis.
- Head and neck^{37,46,58-62}: generally, the concurrent combination of head and neck RT with ICIs does not markedly increase RT toxicity. For CTLA-4 inhibitors, high-quality data are very limited.
- Thorax^{39-43,46-48,59-70}: there are no serious safety concerns when combining thoracic RT with ICIs. However, it may slightly increase the risk of pneumonitis. Based on the mentioned studies, combining PD-(L)1 inhibitors with thoracic RT leads to a grade (G) ≥ 3 pneumonitis risk of 5.9% (95% confidence interval 2.6% to 12.8%) (Supplementary Figure S3, available at <https://doi.org/10.1016/j.annonc.2025.09.008>). For CTLA-4 inhibitors, high-quality data are limited.
- Abdomen/pelvis^{38,42,43,46,48,59,61,65,67,68,71-76}: despite a hypothetically increased risk of gastrointestinal toxicity (colitis or diarrhea) when combining abdominal/pelvic RT with ICIs, these combinations are generally manageable with no clear trend toward increased severe toxicities. For CTLA-4 inhibitors, high-quality data are limited.

- Musculoskeletal tissues^{22,38,47,48,59,67,74,75,77-80}: there are no serious safety concerns based on the available data.

Delphi process results. All 20 Delphi experts completed both Delphi questionnaires, resulting in a response rate of 100%. For certain scenarios, one expert deliberately refrained from making a decision during round 1, but no answers were missing. The Delphi statement flow diagram, the first Delphi round, and the second Delphi round agreement rates are provided in Supplementary Figure S4, and Tables S6-S9, respectively, available at <https://doi.org/10.1016/j.annonc.2025.09.008>. The final Delphi results for PD-(L)1 and CTLA-4 inhibitors are shown in Tables 2 and 3, respectively.

Delphi consensus statements. Considering a minor/no adaptation is recommended for all RT combinations with PD-(L)1 inhibitors (Table 2). For CTLA-4 inhibitors, we recommend considering a major adaptation with some high-dose RT schedules (Table 3). For CTLA-4 inhibitors combined with high-dose conventionally fractionated RT to the head and neck, no consensus was reached (70%). We did not develop separate statements for RT combined with both PD-(L)1 inhibitors and CTLA-4 inhibitors. Although the ICI toxicity is increased, the added toxicity of RT is expected to be comparable to the combination of RT with CTLA-4 inhibitors alone or slightly increased.

For patients and treatments with a high risk of brain radionecrosis or pneumonitis, it is relevant to take into account that ICIs could potentially increase the risk of these inflammatory toxicities. When applying treatment adaptations, it is essential to be aware of the long drug elimination half-lives of most ICIs (Supplementary Material, page 2, available at <https://doi.org/>

Table 2. PD-(L)1 inhibitor consensus statements

For the combination of PD-(L)1 inhibitors with radiotherapy to the:			Agreement rate ^a	Level of evidence
Irradiated area	Radiotherapy scenario	Recommendation		
Skin	Low-dose palliative	Minor/no adaptation	100%	I ^b
	High-dose conventionally fractionated	Minor/no adaptation	100%	I
	High-dose stereotactic	Minor/no adaptation	100%	III
Brain	Low-dose palliative	Minor/no adaptation	100%	III ^b
	High-dose conventionally fractionated	Minor/no adaptation	100%	V
	High-dose stereotactic	Minor/no adaptation	100%	III
Head and neck	Low-dose palliative	Minor/no adaptation	100%	II ^b
	High-dose conventionally fractionated	Minor/no adaptation	95%	II
	High-dose stereotactic	Minor/no adaptation	95%	V
Thorax	Low-dose palliative	Minor/no adaptation	100%	I ^b
	High-dose conventionally fractionated	Minor/no adaptation	100%	I
	High-dose stereotactic	Minor/no adaptation	100%	II
Abdomen/pelvis	Low-dose palliative	Minor/no adaptation	100%	III ^b
	High-dose conventionally fractionated	Minor/no adaptation	100%	III
	High-dose stereotactic	Minor/no adaptation	100%	III
Musculoskeletal tissues	Low-dose palliative	Minor/no adaptation	100%	I ^b
	High-dose conventionally fractionated	Minor/no adaptation	100%	I
	High-dose stereotactic	Minor/no adaptation	100%	III

Drug examples: nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab. The recommendation color codes reflect the corresponding safety levels and their associated toxicity risks, as shown in Figure 1.

PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1.

^aAgreement rates $\geq 90\%$: strongly recommended.

^bLevel of evidence based on data from high radiotherapy dose scenarios.

Table 3. CTLA-4 inhibitor consensus statements

For the combination of CTLA-4 inhibitors with radiotherapy to the:			Agreement rate ^a	Level of evidence
Irradiated area	Radiotherapy scenario	Recommendation		
Skin	Low-dose palliative	Minor/no adaptation	100%	I
	High-dose conventionally fractionated	Minor/no adaptation	100%	III
	High-dose stereotactic	Minor/no adaptation	100%	III
Brain	Low-dose palliative	Minor/no adaptation	100%	III
	High-dose conventionally fractionated	Minor/no adaptation	95%	V
	High-dose stereotactic	Minor/no adaptation	95%	III
Head and neck	Low-dose palliative	Minor/no adaptation	90%	III ^b
	High-dose conventionally fractionated	Major adaptation (no consensus)	70%	III
	High-dose stereotactic	Major adaptation	85%	V
Thorax	Low-dose palliative	Minor/no adaptation	100%	III ^b
	High-dose conventionally fractionated	Major adaptation	90%	III
	High-dose stereotactic	Major adaptation	85%	III
Abdomen/pelvis	Low-dose palliative	Minor/no adaptation	95%	I
	High-dose conventionally fractionated	Major adaptation	90%	V
	High-dose stereotactic	Major adaptation	100%	III
Musculoskeletal tissues	Low-dose palliative	Minor/no adaptation	100%	I
	High-dose conventionally fractionated	Minor/no adaptation	95%	III
	High-dose stereotactic	Minor/no adaptation	95%	III

Drug examples: ipilimumab, tremelimumab.

CTLA-4, cytotoxic T lymphocyte antigen 4.

^aAgreement rates $\geq 90\%$: strongly recommended.

^bLevel of evidence based on data from high radiotherapy dose scenarios.

10.1016/j.annonc.2025.09.008), as well as their prolonged immunological effects after drug discontinuation. This limits the applicability of the drug adaptation options, which increases the relevance of considering RT adaptations for this drug category.

VEGF(R) inhibitors

Systematic literature review process results. After screening 2113 unique records for VEGF(R) inhibitors, 31 reports were included in the literature review and database. The PRISMA flow diagram³¹ (Supplementary Figure S5, available at <https://doi.org/10.1016/j.annonc.2025.09.008>) and the full systematic literature review are shown in Supplementary Material, pages 15-24, available at <https://doi.org/10.1016/j.annonc.2025.09.008>.

Drug class and systematic literature review summary.

There are five types of VEGF glycoproteins, VEGFA-VEGFD and placental growth factor (PlGF).^{81,82} Upon binding to one of the three VEGF receptors (I-III), downstream cascades are activated, leading to endothelial cell proliferation, migration and invasion, increased blood vessel permeability, and recruitment of bone marrow-derived vascular precursor cells.⁸¹⁻⁸⁴ This ultimately leads to (tumor) angiogenesis and vasculogenesis, resulting in increased blood flow and increased tumor oxygenation.⁸¹ VEGF(R) inhibition aims to disrupt blood vessel formation and, consequently, tumor growth and development, while normalizing existing tumor vasculature, thereby possibly optimizing tumor oxygenation and susceptibility to antineoplastic agents.^{81,85} Additional effects of VEGF(R) inhibition may be direct tumor cell growth inhibition, restoration of dendritic cell function (and, hence, a potentially increased antitumor immune response), and vasoconstriction, leading to hypertension, a well-known adverse effect of VEGF(R) inhibitors.^{81,86}

Other adverse events of VEGF(R) inhibitors include diarrhea, fatigue, hemorrhage, thrombosis, proteinuria, and gastrointestinal perforation.⁸⁶

The available evidence indicates that concurrent VEGF axis inhibition can increase the risk of RT-related toxicity. In particular, mucosal and other gastrointestinal toxicity may increase. Hemorrhages and fistulae, well-known risks of VEGF(R) inhibitors, should be carefully considered as these events are also observed when these agents are combined with RT. Skin toxicity may also moderately increase. With regard to brain RT, data on radiation necrosis/pseudoprogression are conflicting.

For the different irradiated areas, the following data were found:

- Skin⁸⁷⁻⁹⁷: the risk of skin toxicity appears moderately increased when RT is combined with bevacizumab.
- Brain^{87,88,97-108}: most of the selected prospective studies focus on high-grade gliomas. The observed safety profile of adding VEGF(R) inhibitors aligns with the expected outcomes from standard-of-care adjuvant RT and temozolomide (TMZ) in patients with newly diagnosed glioblastoma (GBM), combined with the well-known toxicities of VEGF(R) inhibitors. The toxicity of combined treatment was often manageable. The most common toxicities of combined therapy are hematological or extracranial, indicating that there is no absolute contraindication to combining VEGF(R) inhibition with brain RT. However, data on radiation necrosis/pseudoprogression are conflicting. Intracranial and extracranial bleeding risk may increase upon use of VEGF(R) inhibitors. Furthermore, data regarding cognitive function and late toxicity are often limited.
- Head and neck^{90,109,110}: there are limited data available, but the combination of VEGF(R) inhibitors (bevacizumab) with concurrent cisplatin and cetuximab-based RT may

result in increased toxicity, including hemorrhage, lymphopenia, mucositis, and dermatitis.

- Thorax^{89,96,111-114}: the selected studies indicate that RT-related toxicities, like esophagitis, may increase with concurrent VEGF(R) inhibition. It is relevant to note that for lung tumors, both bevacizumab¹¹⁵ and ultracentral stereotactic RT¹¹⁶ may increase the risk of G5 hemorrhage, both individually and when combined.¹¹⁷
- Abdomen/pelvis^{91-95,118,119}: the available studies combining VEGF(R) inhibitors with RT suggest that there may be an increased risk of wound complications, gastrointestinal toxicities, and vascular toxicities with the addition of bevacizumab to RT. Less high-quality clinical data are available for other VEGF(R) inhibitors, such as aflibercept.
- Musculoskeletal tissues¹²⁰⁻¹²²: most studies do not indicate an evidently increased risk of RT-related toxicities, although VEGF(R) inhibitor therapy might increase the risk of myositis.

Delphi consensus statements. All 20 Delphi experts completed both Delphi questionnaires, resulting in a response rate of 100%. For one scenario, one expert deliberately refrained from making a decision during round 1, but no answers were missing. The Delphi statement flow diagram, the first Delphi round, and the second Delphi round agreement rates are provided in [Supplementary Figure S6](#), and [Tables S10](#) and [S11](#), respectively, available at <https://doi.org/10.1016/j.annonc.2025.09.008>. The final Delphi results for VEGF(R) inhibitors are shown in [Table 4](#).

These Delphi statements were primarily developed for anti-VEGF(R) antibodies (e.g. bevacizumab and ramucirumab) and VEGFR fusion proteins (e.g. aflibercept). Due to the risk of increased toxicity, we recommend considering a major adaptation for most RT combinations with VEGF(R) inhibitors. For low-dose palliative skin RT and for all musculoskeletal RT, considering a minor/no adaptation is recommended. For low-dose palliative brain RT, no consensus was reached (60%) for the proposed major adaptation.

Our recommendation is to consider not combining these treatments in case of (ultra)central lung stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), when large blood vessels, main bronchi, or the esophagus are included in the high-dose region. This exception was based on studies indicating that both bevacizumab and (ultra)central lung SBRT can individually increase the risk of G5 hemorrhage and a study indicating an increased risk of fatal pulmonary hemorrhage when ultracentral SBRT was combined with anti-angiogenic agents.¹¹⁵⁻¹¹⁷

Multitargeted TKIs

Systematic literature review process results.

After screening 557 unique records for multitargeted TKIs, focusing on cabozantinib, lapatinib, pazopanib, sorafenib,

sunitinib, and vandetanib, 82 reports were included in the literature review and database. The PRISMA flow diagram³¹ ([Supplementary Figure S7](#), available at <https://doi.org/10.1016/j.annonc.2025.09.008>) and the full, drug-specific systematic literature review are shown in [Supplementary Material](#), pages 25-41, available at <https://doi.org/10.1016/j.annonc.2025.09.008>.

Drug class and systematic literature review summary.

It is important to realize that many multitargeted TKIs not only bind to VEGF(R), their presumed primary mode of action, but also bind to tyrosine kinase domains of other (partly 'non-target') receptors.⁸² While these broad (partly 'off-target') effects of some VEGF(R) TKIs may increase efficacy, they may also negatively influence their toxicity profile. The only multitargeted TKI analyzed in this systematic review that does not target VEGF(R) is lapatinib. Common toxicities of VEGF(R) TKIs include hematological toxicity, hypertension, proteinuria, fatigue, hand-foot skin reaction, diarrhea, and hypothyroidism.¹²³

The toxicity data are limited for the combination of RT with this heterogeneous drug class. Combined treatment can result in increased RT toxicity, but this is often manageable. Increased hematological toxicity is a concern, which should be taken into account when irradiating larger (bone marrow) volumes. Furthermore, some studies indicate increased risks of gastrointestinal toxicity, hepatotoxicity, or mucosal toxicity. Particularly for cabozantinib, pazopanib, and vandetanib, toxicity data are scarce, warranting more caution with these combinations.

For the different irradiated areas, the following data were found:

- Skin¹²⁴⁻¹⁷⁴: generally, no increased radiation-induced toxicity rates are observed.
- Brain^{125,129-131,140,150,151,158,160,161,163,166,168,169,171,172,175-182}: most studies do not report increased radiation-induced toxicity rates, but hematological toxicities are common. However, late toxicity data are not always available, which warrants caution.
- Head and neck^{124,127,133,134,167,183,184}: generally, toxicity data are scarce, warranting caution. Lapatinib may increase the risk of G 3-4 mucositis.
- Thorax^{126,132,135,137,139,140,142,157,158,170,185-192}: most studies do not report increased radiation-induced toxicity rates. However, toxicity data are scarce for some drugs.
- Abdomen/pelvis^{14,135,139-143,148,153,154,157-159,162,164,165,185,188-191,193-207}: for most drugs, toxicity data are scarce or not available, warranting caution. Most toxicity data were derived from sorafenib and sunitinib studies. Combining sorafenib with liver RT may lead to excessive hepatotoxicity, particularly with larger irradiated liver volumes. Gastrointestinal toxicity may be increased with the sorafenib-RT combination as well. For the combination with sunitinib, primarily hematological toxicity should be taken into account, as well as possible gastrointestinal toxicity.

Table 4. VEGF(R) inhibitor consensus statements

For the combination of anti-VEGF(R) antibodies (or VEGFR fusion proteins) with radiotherapy to the:			Agreement rate ^a	Level of evidence
Irradiated area	Radiotherapy scenario	Recommendation		
Skin	Low-dose palliative	Minor/no adaptation	95%	I ^b
	High-dose conventionally fractionated	Major adaptation	85%	I
	High-dose stereotactic	Major adaptation	85%	V
Brain	Low-dose palliative	Major adaptation (no consensus)	60%	I ^b
	High-dose conventionally fractionated	Major adaptation	95%	I
	High-dose stereotactic	Major adaptation	95%	IV
Head and neck	Low-dose palliative	Major adaptation	95%	III ^b
	High-dose conventionally fractionated	Major adaptation	95%	III
	High-dose stereotactic	Major adaptation	95%	V
Thorax	Low-dose palliative	Major adaptation	90%	II ^b
	High-dose conventionally fractionated	Major adaptation	95%	II
	High-dose stereotactic	Major adaptation	95%	V
Abdomen/pelvis	Low-dose palliative	Major adaptation	95%	III ^b
	High-dose conventionally fractionated	Major adaptation	100%	III
	High-dose stereotactic	Major adaptation	100%	V
Musculoskeletal tissues	Low-dose palliative	Minor/no adaptation	100%	II ^b
	High-dose conventionally fractionated	Minor/no adaptation	95%	II
	High-dose stereotactic	Minor/no adaptation	90%	V
Exception: in case of (ultra)central lung SBRT/SABR (when large blood vessels, main bronchi or the esophagus are included in the high-dose region):				
Thorax	High-dose stereotactic	Not combining	100%	IV

Drug examples: bevacizumab, ramucirumab, aflibercept. The recommendation color codes reflect the corresponding safety levels and their associated toxicity risks, as shown in Figure 1.

SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy; VEGF(R), vascular endothelial growth factor (receptor).

^aAgreement rates $\geq 90\%$: strongly recommended.

^bLevel of evidence based on data from high radiotherapy dose scenarios.

- Musculoskeletal tissues^{135,136,138,139,147,149,152,164,165,202,203,206,208}: the available data primarily indicate a possible increased risk of hematological toxicities. For some drugs, toxicity data are not available, warranting caution.

Delphi consensus statements. All 20 Delphi experts completed both Delphi questionnaires, resulting in a response rate of 100%. For one scenario, one expert deliberately refrained from making a decision, but no answers were missing. The Delphi statement flow diagram, the first Delphi round, and the second Delphi round agreement rates are provided in [Supplementary Figure S8](#), and [Tables S12](#) and [S13](#), respectively, available at <https://doi.org/10.1016/j.annonc.2025.09.008>. The final Delphi results for multitargeted TKIs are shown in [Table 5](#).

Due to the lack of high-quality toxicity data, the potential for increased toxicity, and the previously described toxicities when RT is combined with VEGF(R) inhibitors, we recommend considering a major adaptation for most RT combinations with multitargeted TKIs ([Table 5](#)). For low-dose palliative RT to the skin and musculoskeletal tissues, considering a minor/no adaptation is recommended. Similar to VEGF(R) inhibitors, our recommendation is to consider not combining multitargeted TKIs with RT in case of (ultra)central lung SBRT/SABR, when large blood vessels, main bronchi, or the esophagus are included in the high-dose region. Due to the excessive hepatotoxicity observed when sorafenib was combined with liver RT, it is recommended to consider not combining sorafenib with high-dose RT to the liver.

DISCUSSION

These are the first, evidence-based ESMO–ESTRO consensus statements to provide guidance on combining RT with targeted cancer therapies and immunotherapy. To the best of our knowledge, this is the most complete exercise coupling systematic reviews with experts' opinion consensus to increase the level of evidence in this field.

In the current publication, we systematically review and provide recommendations regarding the safety of combining RT with ICIs, VEGF(R) inhibitors, and multitargeted TKIs. Generally, the expected synergistic or additive toxicity of combining RT with ICIs is low, particularly for PD-(L)1 inhibitors. For most combinations with VEGF(R) inhibitors and multitargeted TKIs, we recommend exercising caution, while considering the irradiated site and the clinical goals (e.g. palliative versus curative intention).

These multidisciplinary and scenario-specific ESMO–ESTRO consensus statements were developed through intensive interdisciplinary collaboration and by developing systematic reviews for each drug–RT scenario. The purpose of these statements is to provide evidence-based safety recommendations for real-world clinical practice. They are not intended to serve as strict guidelines, nor as guidance or substitute for high-quality registries or clinical trials evaluating the combination of RT with targeted agents or immunotherapy. The anticipated toxicity should always be weighed against the expected treatment efficacy.

This project has some limitations. Due to the large scale of the systematic literature reviews and Delphi process in this project, there is a considerable time gap between the

Table 5. Multitargeted TKI consensus statements

For the combination of multitargeted TKIs with radiotherapy to the:			Agreement rate ^a	Level of evidence
Irradiated area	Radiotherapy scenario	Recommendation		
Skin	Low-dose palliative	Minor/no adaptation	90%	II ^b
	High-dose conventionally fractionated	Major adaptation	90%	II
	High-dose stereotactic	Major adaptation	90%	V
Brain	Low-dose palliative	Major adaptation	75%	III
	High-dose conventionally fractionated	Major adaptation	80%	III
	High-dose stereotactic	Major adaptation	85%	V
Head and neck	Low-dose palliative	Major adaptation	90%	III ^b
	High-dose conventionally fractionated	Major adaptation	95%	III
	High-dose stereotactic	Major adaptation	95%	V
Thorax	Low-dose palliative	Major adaptation	85%	III
	High-dose conventionally fractionated	Major adaptation	100%	III
	High-dose stereotactic	Major adaptation	95%	III
Abdomen/pelvis	Low-dose palliative	Major adaptation	95%	III
	High-dose conventionally fractionated	Major adaptation	90%	III
	High-dose stereotactic	Major adaptation	90%	III
Musculoskeletal tissues	Low-dose palliative	Minor/no adaptation	95%	II ^b
	High-dose conventionally fractionated	Major adaptation	90%	II
	High-dose stereotactic	Major adaptation	85%	III
Exceptions: For the combination of 'sorafenib' with radiotherapy to the:				
Liver	High-dose conventionally fractionated	Not combining	100%	III
	High-dose stereotactic	Not combining	95%	III
Exception: In case of (ultra)central lung SBRT/SABR (when large blood vessels, main bronchi or the esophagus are included in the high-dose region):				
Thorax	High-dose stereotactic	Not combining	90%	IV

Drug examples: cabozantinib, lapatinib, pazopanib, sorafenib, sunitinib, vandetanib. The recommendation color codes reflect the corresponding safety levels and their associated toxicity risks, as shown in Figure 1.

SABR, stereotactic ablative radiotherapy; SBRT, stereotactic body radiotherapy; TKI, tyrosine kinase inhibitor.

^aAgreement rates $\geq 90\%$: strongly recommended.

^bLevel of evidence based on data from high radiotherapy dose scenarios.

original literature searches and the Delphi process. Furthermore, the levels of evidence are low for the toxicity of many RT–drug combinations, particularly regarding late toxicity. To mitigate this, we further developed the Delphi process and experts were requested to consider and mention (new) literature references if they disagreed with a statement. The amount of suggested new literature was low, and the agreement rates were high, indicating the relevance and validity of the consensus statements.

The clinical challenges arising from the rapid introduction of new systemic agents, without toxicity data regarding the combination with RT, underscore the need for strategies to acquire these data. This could be achieved by raising awareness among pharmaceutical companies, practitioners, and regulators for optimal pharmacovigilance, and by collaborative efforts to develop clinical trials, prospective cohort studies and registries, real-world studies, or preclinical models (e.g. organoids) that capture the effects of these agents combined with RT.^{8,209,210}

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DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used ChatGPT (OpenAI) and DeepL (DeepL SE) in order to improve language and readability. After using these tools/services, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication. These AI tools were not used in the systematic review process, nor to generate content.

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