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REVIEW

ESMO-ESTRO consensus statements on the safety of combining radiotherapy with EGFR, ALK, or BRAF/MEK inhibitors

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Background: Combining radiotherapy (RT) with targeted agents may lead to improved treatment outcomes across various tumor types. However, there is a risk of increased toxicity. Unfortunately, high-quality toxicity data are scarce, contributing to a lack of evidence-based guidelines.

Design: ESMO and ESTRO launched a series of systematic literature reviews and evidence-based, multidisciplinary Delphi consensus recommendations on the safety of combining RT with targeted agents. The current paper addresses the safety of combining EGFR, ALK, and BRAF/MEK inhibitors with RT, regardless of (solid) tumor histology. During the two Delphi consensus rounds with 19 international experts, 57 clinical scenarios were evaluated by systematically covering different drug classes and irradiated areas. Based on the systematic literature reviews, safety statements were developed for all scenarios.

Results: During the systematic literature review process for EGFR, ALK, and BRAF/MEK inhibitors, 2745 records were screened, and 110 reports were included in the final literature reviews and the database. Over the course of the subsequent Delphi consensus rounds, agreement was reached on all 57 scenario-specific safety statements.

Conclusions: For most scenarios, concurrently combining RT with targeted agents may lead to increased toxicity. Therefore, we recommend a drug interruption, a drug dosage reduction, or a major RT adaptation in various scenarios.

Key words: radiotherapy, targeted therapy, toxicity, systematic review, consensus statements

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INTRODUCTION

Systemic therapy, along with surgery and radiotherapy (RT), is a fundamental component of cancer treatment. The introduction of targeted agents and immune checkpoint inhibitors (ICIs) has caused a considerable increase in the number of systemic treatment options, and improved treatment outcomes across nearly all cancer types.[1]

Fifty percent of cancer patients receive RT at a certain stage in their treatment, with curative, radical, or palliative intent.[2-4] Accordingly, patients on targeted agents are regularly referred for RT, mainly due to oligometastases, oligoprogression, or for palliative treatment.[5-8] The combination of RT with targeted agents may enhance tumor control but can also cause increased toxicity.[9] Therefore, it is important to determine the safety of RT for patients on these targeted agents.[8] There is a lack of high-quality toxicity data regarding the combination of RT with various targeted agents. Safety concerns have emerged for several combinations, due to reports of unexpected toxicity.[10-16]

Thus, oncologists are faced with a clinical dilemma when combining RT with targeted agents. Excessive toxicity should be avoided; however, interrupting the drug or reducing the drug dosage may cause tumor progression or tumor flare, [17-19] and reducing the RT dose may lead to impaired tumor or symptom control. We are confronted with a serious lack of data, knowledge, and consensus on this topic, and evidence-based, multidisciplinary guidelines are missing for most combinations.[8,20,21] Depending on the drug—RT combination and treatment approach, this knowledge gap may lead to suboptimal treatment decisions (including both over- and undertreatment) or unanticipated toxicity in these patients.

Hence, the European Society for Medical Oncology (ESMO) and the European SocieTy for Radiotherapy and Oncology (ESTRO) launched a series of drug class-specific and irradiated area-specific systematic literature reviews and evidence-based, multidisciplinary Delphi consensus recommendations on the safety of combining RT with 10 classes of targeted agents and ICIs.[22] Additionally, a framework paper complements this series by outlining the key (radio)biological processes, pharmacological aspects, and general clinical considerations.[9] The current publication features the systematic reviews and Delphi consensus recommendations regarding the safety of combining RT with the following targeted agents, irrespective of tumor type: epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and B-rapidly accelerated fibrosarcoma (BRAF)/mitogen-activated protein kinase (MEK) inhibitors.

METHODS

Project governance

This project was a collaboration with ESMO and ESTRO. Both the ESMO board and the ESTRO guidelines committee granted permission. A coordinating committee of ESMO and ESTRO representatives and experts met monthly and managed the project. Researchers at the Netherlands Cancer Institute carried out the daily operational coordination of the project.

Systematic literature reviews

Systematic searches of the Medline, Embase, and SCOPUS databases were carried out on 21 December 2020 (ALK and BRAF/MEK), and 26 March 2021 (EGFR). For the search strategy and keywords, please refer to Supplementary Tables S1-S4, available at https://doi.org/10.1016/j.esmoop.2026.106076. Only studies describing treatment-related toxicity on concurrent treatment of RT and targeted agents were included, with a maximum drug—RT time interval of five drug half-lives before RT, or 2 weeks after RT. Full inclusion and exclusion criteria are provided in Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2026.106076. Title and abstract screening was conducted using a double-blind approach by EA and PB, with a consulting role by MJ. Subsequently, full-text screening was conducted by the same researchers for ALK and BRAF/MEK inhibitors. For EGFR inhibitors, representatives from ESMO (AKG, AP, BD, JB, LCB, SOC) contributed to the full-text screening and review (Supplementary Figures S1-S3, available at https://doi.org/10.1016/j.esmoop.2026.106076). The uniformity and quality of the review process were ensured via ongoing meetings and discussions. For EGFR inhibitors, an additional selection step was introduced to identify the highest-quality trials, to reduce the high number of included reports (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2026.106076).

To offer drug class-specific and irradiated area-specific toxicity data, the drug-specific systematic literature reviews were separated into six irradiated area-specific reviews: for irradiation of the skin, brain, head and neck, thorax, abdomen/pelvis, and musculoskeletal tissues. Each section contained a summary, providing an accessible overview of the data. General information on frequently used drugs and the biological pathways involved was given as well (Supplementary Material, pages 2-26, available at https://doi.org/10.1016/j.esmoop.2026.106076).

Literature database

All included reports were incorporated into a literature database built in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA), with search functionality to select publications with a specific drug target, irradiated area and/or study type. For all included publications, we registered all relevant data in the database, including the number of patients, drug name, drug dose, RT dose, RT fractionation scheme, RT technique, drug and RT timing, primary tumor type, tumor response, acute toxicity, late toxicity, and comparisons with drug and RT monotherapy toxicity.

Safety recommendations

The daily operational coordinators and the coordinating committee developed three safety measure options as defined in Figure 1: (i) not combining both treatments, (ii) a major treatment adaptation, or (iii) a minor/no treatment adaptation. For each drug class, at least 18 irradiated area-specific and RT scenario-specific (Table 1) safety recommendations were developed. Guided by the systematic literature reviews, EA proposed the most appropriate safety measure option 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 S6, available at https://doi.org/10.1016/j.esmoop.2026.106076).[23,24]

Modified Delphi process

Ten ESMO experts and 10 ESTRO experts were solicited to participate in a modified Delphi process.[25] After receiving the systematic literature reviews and the literature database, they were requested to vote whether they agreed or disagreed with the proposed safety measure for each scenario. Upon disagreement, experts were asked to explain their choice and to add supporting (new) literature references, if applicable.

Two Delphi rounds were organized with a digital voting process. During the first Delphi round, ≥90% agreement was required to accept a statement without further voting in the second Delphi round. During the second Delphi round, ≥75% agreement was required to accept a statement.[26] Statements with ≥90% agreement led to a stronger recommendation than statements with 75%-89% agreement. For statements evaluated in both Delphi rounds, the agreement rates from the second round were leading.

The voting results and expert comments from Delphi round one were evaluated by EA and selected experts (JB, PMP, SOC, UR). If applicable, statements were added, removed, or adapted, before starting Delphi round two. The daily operational coordinators and the ESMO office organized the Delphi process. Microsoft Excel 2016 was used for both developing the questionnaires and analyzing the voting results.

RESULTS

EGFR inhibitors

Systematic literature review process results. For EGFR inhibitors, 2384 unique records were screened, and 54 reports were included in the literature review and the database. The PRISMA flow diagram[27] and the full systematic literature review are provided (Supplementary Figure S1, and Supplementary Material, pages 2-13, available at https://doi.org/10.1016/j.esmoop.2026.106076).

Drug class and systematic literature review summary. Binding of a ligand to the EGFR leads to structural changes, promoting receptor dimerization and subsequently

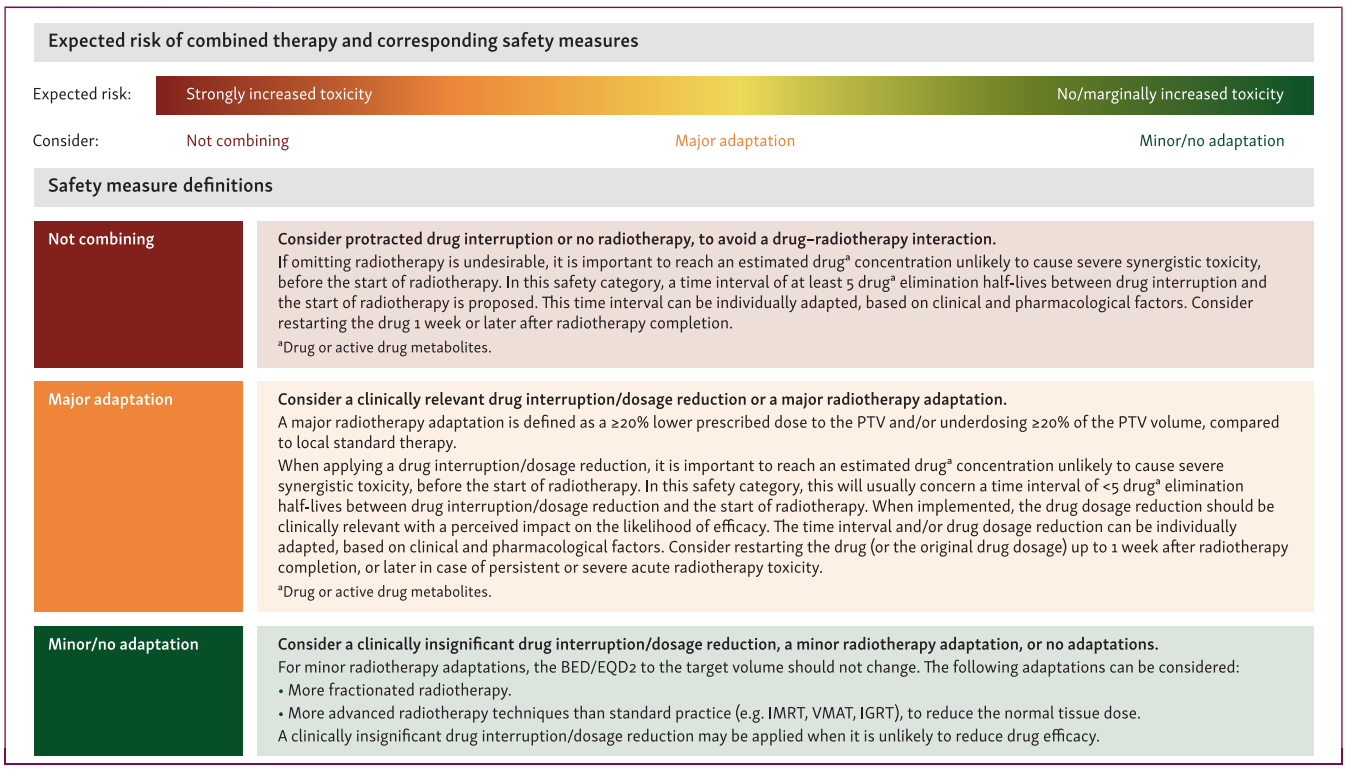

Figure 1. Predefined safety measure definitions for combining targeted agents with radiotherapy, based on the expected risk.
BED, biologically equivalent dose; EQD_2, equivalent dose in 2 Gy fractions; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, planning target volume; VMAT, volumetric-modulated arc therapy.

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.

activation by phosphorylation of the cytoplasmic tail of the receptor.[28] EGFR activation leads to downstream upregulation of several signaling pathways that are involved in cell survival and proliferation, including the MAPK and phosphatidylinositol 3-kinase (PI3K) pathways.[28,29] Upregulated EGFR signaling is a common feature of many tumors, making the inhibition of EGFRs an effective target in several tumor types, including head and neck cancer (also in combination with RT[30]), colorectal cancer and lung cancer.[29] EGFR inhibition influences DNA repair and cell cycle arrest and can increase radiosensitivity to some extent.[29,31-35] Blood—brain barrier penetration of many EGFR inhibitors is generally poor, but significantly better for osimertinib and afatinib.[36-39]

Data regarding the combination of RT and EGFR inhibitors clearly demonstrate an increased risk of dermatitis, skin rash, and mucositis. In addition, EGFR inhibitors possibly increase the risk of pneumonitis, and they may modestly increase (lower) gastrointestinal (GI)-related and brain-related toxicity, when combined with RT. However, results from most studies suggest that these combinations are feasible.

The data identified for each irradiated area (Supplementary Material, pages 2-13, available at https://doi.org/10.1016/j.esmoop.2026.106076) are summarized here:

- *Skin*[40-48]: a large number of high-quality data show a markedly increased risk of high-grade dermatitis and skin rash when RT is combined with EGFR inhibitors. Most data are derived from head and neck cancer trials.
- *Brain*[46-62]: most studies describe the addition of EGFR tyrosine kinase inhibitors (TKIs) (and not monoclonal antibodies) to brain RT. Several studies suggest an increased risk of toxicity when EGFR inhibitors are combined with RT, but most RT-related toxicities are moderately or insignificantly increased.
- *Head and neck*[40,42-44,63-69]: a reasonable number of randomized studies and meta-analyses show that combining EGFR antibodies (particularly cetuximab) with head and neck RT significantly increases the risk of grade ≥3 mucositis. Fewer data are available about EGFR TKI combinations, but some show increased grade ≥3 mucositis risks as well.
- *Thorax*[41,59,61,62,70-86]: EGFR inhibitors may modestly increase the risk of RT toxicities, primarily radiation pneumonitis, when combined with thoracic RT. One retrospective study shows a high radiation pneumonitis risk when RT is combined with osimertinib. The effect of EGFR inhibitors on RT-related esophageal toxicity appears limited.
- *Abdomen/pelvis*[45,87-96]: the reported evidence on toxicity of anti-EGFR drugs in combination with RT was mainly derived from studies involving pancreatic or rectal cancer. Toxicity is slightly increased, but considered acceptable, when these drugs are combined with RT or chemoradiotherapy (CRT). Most studies lack a (C)RT-only control arm, but the available data indicate a modestly increased toxicity risk, particularly GI-related.
- Musculoskeletal tissues: no publications were identified that are specific for this RT area, but in the other studies, musculoskeletal toxicity was not a main concern.

Delphi process results. The Delphi process was conducted between 18 September 2023 and 14 February 2024. Among the Delphi experts, 95% (19/20) completed both Delphi rounds. There were no other missing answers. The full results from Delphi round one, Delphi round two, and the Delphi statement flow diagram are provided (Supplementary Tables S7, S8 and Supplementary Figure S5, respectively, available at https://doi.org/10.1016/j.esmoop.2026.106076). The final Delphi outcomes for EGFR inhibitors are presented in Table 2.

Delphi consensus recommendations

For most scenarios with EGFR inhibitors, we recommend considering a major adaptation (Table 2). For low-dose palliative RT to the skin, brain, abdomen/pelvis, and musculoskeletal tissues, we recommend considering a minor or no adaptation. Due to data from one retrospective study indicating a high risk of radiation pneumonitis, it is recommended to consider not combining osimertinib and high-dose RT to the thorax.

ALK inhibitors

Systematic literature review process results. For ALK inhibitors, 54 unique records were screened, and 15 reports were included in the literature review and the database. For

Table 2. EGFR inhibitor consensus statements

For the combination of EGFR inhibitors with radiotherapy to the:				
Irradiated area	Radiotherapy scenario	Recommendation	Agreement rate[a]	Level of evidence
Skin	Low-dose palliative	Minor/no adaptation	89%	I[b]
	High-dose conventionally fractionated	Major adaptation	95%	I
	High-dose stereotactic	Major adaptation	100%	II
Brain	Low-dose palliative	Minor/no adaptation	89%	II
	High-dose conventionally fractionated	Major adaptation	95%	III
	High-dose stereotactic	Major adaptation	100%	II
Head & neck	Low-dose palliative	Major adaptation	100%	I[b]
	High-dose conventionally fractionated	Major adaptation[c]	100%	I
	High-dose stereotactic	Major adaptation	95%	V
Thorax	Low-dose palliative	Major adaptation	89%	I[b]
	High-dose conventionally fractionated	Major adaptation	95%	I
	High-dose stereotactic	Major adaptation	95%	III
Abdomen/pelvis	Low-dose palliative	Minor/no adaptation	95%	II[b]
	High-dose conventionally fractionated	Major adaptation	100%	II
	High-dose stereotactic	Major adaptation	100%	V
Musculoskeletal tissues	Low-dose palliative	Minor/no adaptation	95%	I[b]
	High-dose conventionally fractionated	Major adaptation	100%	I
	High-dose stereotactic	Major adaptation	100%	V
EXCEPTIONS: for the combination of osimertinib with radiotherapy to the:				
Thorax	High-dose conventionally fractionated	Not combining	95%	V
	High-dose stereotactic	Not combining	95%	V

EGFR, epidermal growth factor receptor.
[a]Agreement rates ≥90%: strongly recommended.
[b]Level of evidence based on data from high radiotherapy dose scenarios.
[c]This does not apply to intentional concurrent radiotherapy with cetuximab.

the PRISMA flow diagram[27] and the full systematic literature review please refer to Supplementary Figure S2, and Supplementary Material, pages 14-18, respectively, available at https://doi.org/10.1016/j.esmoop.2026.106076.

Drug class and systematic literature review summary. ALK signaling influences several major oncogenic pathways that contribute to cell survival and proliferation, including RAS, phospholipase C-γ, signal transducer and activator of transcription 3 (STAT3) and PI3K.[97,98] Increased ALK activation is primarily caused by chromosomal translocations or inversions, leading to fusion proteins (e.g. EML4-ALK in non-small-cell lung cancer) that lead to ligand-independent activation of the ALK protein kinase domains.[98,99] In addition, mutations or ALK amplification can play a role in certain cancer types.[98,99]

Inhibition of ALK (e.g. alectinib, brigatinib, ceritinib, crizotinib, lorlatinib), IGF1R (brigatinib), MET (crizotinib), RET (alectinib), ROS1 (brigatinib, crizotinib, and lorlatinib) receptor tyrosine kinases downregulates RAS PI3K and STAT3 signaling,[100] leading to inhibition of growth/proliferation, fewer cells in the radioresistant S-phase,[101] and inhibition of anti-apoptotic signals, possibly leading to radiosensitization of (mostly rapidly proliferating) normal tissue and tumor cells. So in general, reduced cell survival and repopulation by ALK inhibitors may lead to an increased risk of RT toxicity, whereas inhibition of growth/proliferation could lead to a decreased number of cells in the radiosensitive M-phase,[101] leading to more radioresistance.

Information on the combination of ALK inhibitors and RT is scarce and consists of case reports and small retrospective series. Most data available are about RT to the central nervous system (CNS). Based on available biological/pharmacological data, it can be hypothesized that survival and repopulation of (particularly fast dividing) normal tissues could be reduced by ALK inhibitors after RT, thus increasing the toxicity of RT. Most interactions could be expected in days-to-weeks after RT (acute phase). However, evidence is scarce and what is available, primarily applies to crizotinib. A case of severe (grade 4) esophagitis has been reported with crizotinib and 10 × 3 Gy on the cervical spine. Gamma Knife RT for brain metastases seemed safe during crizotinib therapy. However, it should be noted that crizotinib is the only ALK inhibitor reported to not cross the blood—brain barrier, whereas CNS-penetrant ALK inhibitors may have a greater potential for side effects when combined with CNS-directed RT.

The data identified for each irradiated area (Supplementary Material, pages 14-18, available at https://doi.org/10.1016/j.esmoop.2026.106076) are summarized here:

- *Skin*[102]: no severe skin toxicity is reported, but the available safety data are very limited.
- *Brain*[103-118]: in general, no high rates of grade ≥3 toxicity are reported. Most data concern crizotinib use during RT, which has a limited blood—brain barrier penetration.[103,104] These results should therefore not be extrapolated to newer TKIs with a higher brain penetration rate. Furthermore, some relatively larger studies combine data from patients using ALK and EGFR inhibitors,[105-109] which complicates interpretation of the ALK-specific results. A possibly increased risk of

ototoxicity (with whole brain RT) should be considered as well.

- *Head and neck*[102,108,119]: with only case reports, the available safety data are limited. One case report shows grade 4 ulceration of the hypopharynx with the combination of crizotinib and low-dose palliative RT. Ototoxicity was already described in the brain section.
- *Thorax*[105,109,119,120]: with only retrospective studies and a case report, often with different drug types and timing schedules, the available safety data are limited. The case report showing grade 4 ulceration of the hypopharynx also describes ulceration of the upper esophagus.
- *Abdomen/pelvis*[109,120]: the available safety data are limited. Two studies interrupting ALK (or EGFR) inhibitors during RT, include abdominal RT and do not describe increased toxicity.[109,120]
- *Musculoskeletal tissues*[105,106,109]: the available safety data are limited, but do not indicate increased toxicity risks.

Delphi consensus recommendations. The Delphi process was conducted between 18 September 2023 and 14 February 2024. Among the Delphi experts, 95% (19/20) completed both Delphi rounds. During round one, one expert deliberately refrained from making a decision for two scenarios. In round two, one expert answer was missing for one statement. There were no other missing answers. The full results from Delphi round one, Delphi round two, and the Delphi statement flow diagram are provided (Supplementary Tables S9, S10 and Supplementary Figure S6, respectively, available at https://doi.org/10.1016/j.esmoop.2026.106076). The final Delphi outcomes for ALK inhibitors are presented in Table 3.

For most scenarios with ALK inhibitors, we recommend considering a major adaptation (Table 3). Only for low-dose palliative skin and musculoskeletal RT, do we recommend considering a minor/no adaptation. It should be noted that the level of evidence for these scenarios is low.

BRAF/MEK inhibitors

Systematic literature review process results. For BRAF/MEK inhibitors, 307 unique records were screened, and 41 reports were included in the literature review and the database. The PRISMA flow diagram[27] and the full systematic literature review (Supplementary Figure S3, and Supplementary Material, pages 19-26, respectively) are available at https://doi.org/10.1016/j.esmoop.2026.106076).

Drug class and systematic literature review summary. BRAF is part of the RAS-RAF-MEK-ERK signaling pathway. In BRAF-mutated tumors (most frequent mutation: BRAFV600E), activation of BRAF can cause cell proliferation, independently from upstream signaling.[121] Inhibition of BRAF protein kinases downregulates RAF signaling, leading to inhibition of growth/proliferation in BRAF-mutated cells.[121] Inhibition of BRAF can also lead to paradoxical MAPK signaling in RAS-mutant and RAS/RAF wild-type cells, leading to fast division of these cells.[122,123] Additionally, increased vascular endothelial growth factor production has been described when BRAF is inhibited.[124] Faster proliferation of keratinocytes can lead to more cells in M-phase and consequently increased skin radiosensitivity. Alternatively, inhibition of proliferation could lead to less repopulation after RT.

MEK inhibitors (MEKi) inhibit activation of MEK, downstream of RAF. The combination with BRAF inhibitors (BRAFi) can increase progression-free and overall survival in patients with BRAF V600-mutated melanoma. Additionally, this combination probably reduces the risk of paradoxical MAPK signaling-induced hyperkeratosis and cutaneous squamous-cell carcinoma.[125,126]

The data identified for each irradiated area (Supplementary Material, pages 19-26, available at https://doi.org/10.1016/j.esmoop.2026.106076) are summarized here:

Table 3. ALK inhibitor consensus statements

For the combination of ALK inhibitors with radiotherapy to the:

Irradiated area	Radiotherapy scenario	Recommendation	Agreement rate[a]	Level of evidence
Skin	Low-dose palliative	Minor/no adaptation	95%	V
	High-dose conventionally fractionated	Major adaptation	95%	V
	High-dose stereotactic	Major adaptation	95%	V
Brain	Low-dose palliative	Major adaptation	100%	V
	High-dose conventionally fractionated	Major adaptation	100%	V
	High-dose stereotactic	Major adaptation	95%	IV
Head & neck	Low-dose palliative	Major adaptation	84%	V
	High-dose conventionally fractionated	Major adaptation	95%	V
	High-dose stereotactic	Major adaptation	95%	V
Thorax	Low-dose palliative	Major adaptation	89%	V
	High-dose conventionally fractionated	Major adaptation	95%	V
	High-dose stereotactic	Major adaptation	94%	V
Abdomen/pelvis	Low-dose palliative	Major adaptation	84%	V
	High-dose conventionally fractionated	Major adaptation	95%	V
	High-dose stereotactic	Major adaptation	95%	V
Musculoskeletal tissues	Low-dose palliative	Minor/no adaptation	95%	V
	High-dose conventionally fractionated	Major adaptation	100%	V
	High-dose stereotactic	Major adaptation	100%	V

ALK, anaplastic lymphoma kinase.
[a]Agreement rates ≥90%: strongly recommended.

- *Skin*[12,13,16,127-156]: the literature data clearly indicate an increased risk of skin toxicity when RT is given concurrently or in close proximity to BRAFi ± MEKi, particularly in combination with vemurafenib. Stereotactic RT may be combined without increased skin toxicity when the dose to the skin is low. Reducing the skin dose and temporary drug interruption probably reduces the risk of an interaction but does not exclude this possibility. MEKi-specific data are scarce, but the addition of MEKi to BRAFi does not clearly increase skin toxicity, compared with BRAFi alone.
- *Brain*[12,16,135,136,138,145-151,157-167]: a number of retrospective studies and case reports have been published with varying methodologies, toxicity analyses, and time intervals between BRAFi ± MEKi and RT. In many studies, BRAFi/MEKi are temporarily paused. Although some studies show higher neurological toxicity rates when BRAFi/MEKi are combined with RT (concurrently or within a certain time interval), several other studies do not report increased toxicity. Combined therapy should therefore not be considered an absolute contra-indication regarding neurological toxicity, but due to the low quality and heterogeneity of the data, increased neurological toxicity cannot be ruled out. We found no studies investigating brain RT combined with a MEKi without a BRAFi.
- *Head and neck*: apart from two case reports concerning increased skin toxicity,[131,142] we identified no studies concerning head and neck RT combined with BRAFi/MEKi. Hecht et al. (2015 and 2018) report hearing disorder in 0%-7%, which might also be related to whole brain RT.[12,146]
- *Thorax*[12,127,129,130,134,136,140,142,146,168]: very limited data are available regarding thoracic RT combined with BRAFi/MEKi. Two case reports show increased toxicity, but the other studies do not clearly indicate increased non-skin-related thoracic RT toxicity. Nevertheless, caution is needed when combining these therapies due to the low number of toxicity data.
- *Abdomen/pelvis*[128,130,132,135,136,140,142,152-154]: although some increased toxicity is reported, very limited data are available regarding abdominal/pelvic RT combined with BRAFi/MEKi. Caution is needed when combining these therapies.
- *Musculoskeletal tissues*[12,132,139,140,142-146]: no increased musculoskeletal-specific toxicity is reported.

Delphi consensus recommendations. The Delphi process was conducted between 18 September 2023 and 14 February 2024. Among the Delphi experts, 95% (19/20) completed both Delphi rounds. There were no other missing answers. The full results from Delphi round one, Delphi round two, and the Delphi statement flow diagram (Supplementary Tables S11, S12, and Supplementary Figure S7, respectively, available at https://doi.org/10.1016/j.esmoop.2026.106076), are provided. The final Delphi outcomes for BRAF/MEK inhibitors are presented in Table 4.

Due to the lack of high-quality toxicity data and the possible increased toxicity, we recommend considering a major adaptation for most RT combinations with BRAF/MEK inhibitors. As the data clearly indicate increased skin toxicity, it is recommended to consider not combining BRAF/MEK inhibitors and RT in cases of high-dose skin RT. For vemurafenib, it is recommended to consider not combining this with skin RT, not even with low-dose palliative RT.

Table 4. BRAF/MEK inhibitor consensus statements

For the combination of BRAF/MEK inhibitors with radiotherapy to the:				
Irradiated area	Radiotherapy scenario	Recommendation	Agreement rate[a]	Level of evidence
Skin	Low-dose palliative	Major adaptation	100%	IV
	High-dose conventionally fractionated	Not combining	100%	IV
	High-dose stereotactic	Not combining	95%	IV
Brain	Low-dose palliative	Major adaptation	100%	IV
	High-dose conventionally fractionated	Major adaptation	100%	IV
	High-dose stereotactic	Major adaptation	100%	IV
Head & neck	Low-dose palliative	Major adaptation	100%	V
	High-dose conventionally fractionated	Major adaptation	100%	V
	High-dose stereotactic	Major adaptation	100%	V
Thorax	Low-dose palliative	Major adaptation	100%	V
	High-dose conventionally fractionated	Major adaptation	100%	V
	High-dose stereotactic	Major adaptation	100%	V
Abdomen/pelvis	Low-dose palliative	Major adaptation	100%	V
	High-dose conventionally fractionated	Major adaptation	100%	III
	High-dose stereotactic	Major adaptation	100%	V
Musculoskeletal tissues	Low-dose palliative	Major adaptation	95%	IV
	High-dose conventionally fractionated	Major adaptation	100%	V
	High-dose stereotactic	Major adaptation	100%	V
EXCEPTION: for the combination of vemurafenib with radiotherapy to the:				
Skin	Low-dose palliative	Not combining	100%	IV

BRAF, B-rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase.
[a]Agreement rates ≥90%: strongly recommended.

DISCUSSION

These ESMO-ESTRO consensus recommendations provide evidence-based guidance on the safety of combining RT with targeted cancer therapies. In the current publication, we provide the systematic literature reviews and recommendations on the safety of combining RT with EGFR, ALK, or BRAF/MEK inhibitors. For most combination scenarios with these drugs and RT, we recommend exercising caution.

The development of these scenario-specific and multidisciplinary ESMO-ESTRO consensus recommendations required an intensive interdisciplinary collaboration and the development of drug class-specific and RT scenario-specific systematic reviews. With these statements, we aim to provide pragmatic and evidence-based safety recommendations for clinical practice, based on the current best available evidence and supported by expert validation. These recommendations are not intended to serve as strict guidelines, nor to substitute high-quality registries or clinical trials that combine these drugs with RT. During decision making, various patient and treatment characteristics (including previous RT) should be evaluated, as described in more detail in the complementary ESMO-ESTRO framework paper.[9] Furthermore, the expected toxicity should always be considered in light of the anticipated or ongoing treatment efficacy.

This comprehensive project comprising multiple papers has some limitations. The extensive size of the systematic literature reviews and the Delphi processes in this project resulted in relevant time intervals between the original literature searches, the Delphi consensus processes, and publication of the manuscripts. To mitigate the effects as far as possible, we invited the experts to provide (new) literature references if they did not agree with a proposed safety recommendation. The high agreement rates and the limited amount of suggested new literature indicate the relevance and the validity of the consensus recommendations. However, the published recommendations should always be evaluated in consideration of any new data that may enhance our knowledge of combined treatment toxicity.

The lack of high-quality evidence for many drug—RT combination scenarios remains a concerning reality for clinicians, particularly in the context of ALK and BRAF/MEK inhibitors. This is reflected in the evidence levels assigned to each recommendation. Major limitations of many reviewed studies are their retrospective design and low patient numbers. Other important limitations include the absence of RT-only or drug-only control groups, limited RT dose and fractionation details, varying intervals between drug administration and RT, pooled results of different targeted agents, concurrent use of chemotherapy, heterogeneous toxicity reporting, and limited follow-up. We carefully addressed these limitations in the literature database and full systematic literature reviews (Supplementary Material, pages 2-26, available at https://doi.org/10.1016/j.esmoop.2026.106076).

Introducing new targeted agents without first acquiring toxicity data for their combination with RT causes challenging clinical dilemmas, emphasizing the critical need for strategies to be developed to collect these data. To accomplish this, it is essential to increase awareness within the pharmaceutical industry and academic collaborative groups. Cross-disciplinary collaborations, aimed at collecting these data by developing preclinical studies, clinical trials, and prospective data registries combining targeted agents with RT should be initiated.[8,169,170] However, the results from this comprehensive project provide valuable guidance for clinicians facing the dilemma of combining RT with targeted agents.

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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) 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.

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