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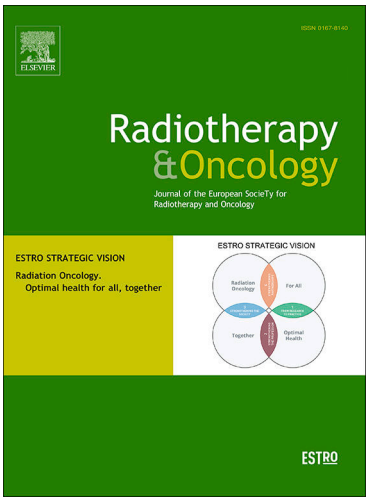

Guidelines

ESMO-ESTRO consensus statements on the safety of combining radiotherapy with CDK4/6, HER2, PARP, or mTOR inhibitors

Evert S.M. van Aken, Ajeet Kumar Gandhi, Sean M. O'Cathail, Gerben Borst, Jorge Barriuso, Emmanouil Fokas, Luis Castelo-Branco, Anne Hansen Ree, Evandro de Azambuja, Stephanie Kroeze, Ilaria Colombo, Antonin Levy, Carmen Criscitiello, Maximilian Niyazi, Nadia Harbeck, Ewa Szutowicz, Gabor Liposits, Marcel Verheij, Isabelle Ray-Coquard, Paolo Tarantino, Dario Trapani, Paulien Boot, Claus Belka, Dirk De Ruysscher, George Pentheroudakis, Corrie A.M. Marijnen, Florian Lordick, Umberto Ricardi, Diogo Martins-Branco, Arsela Prelaj, Monique C. de Jong, Bharti Devnani

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ESMO-ESTRO consensus statements on the safety of combining radiotherapy with CDK4/6, HER2, PARP, or mTOR inhibitors

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Abstract

Background

While combining radiotherapy (RT) with targeted agents or immunotherapy may improve outcomes, it may also increase toxicity. High-quality toxicity data and multidisciplinary, evidence-based guidelines on the combination of these treatment modalities are scarce.

Design

The European Society for Medical Oncology (ESMO) and the European SocieTy for Radiotherapy and Oncology (ESTRO) developed a series of systematic reviews with multidisciplinary, tumor-agnostic, evidence-based Delphi consensus statements regarding the safety of combining RT with targeted agents or immunotherapy. The current study addresses the safety of combining RT with CDK4/6 inhibitors, anti-HER2 monoclonal antibodies, PARP inhibitors, or mTOR-inhibitors. During the modified Delphi process, two digital voting rounds were organized with 18 international experts. By systematically evaluating the different drug classes and irradiated areas, 74 clinical scenarios were assessed. Safety statements were formulated for all scenarios, based on the evidence from the systematic literature reviews.

Results

A total of 1,341 records were screened during the systematic literature reviews, of which 107 studies were ultimately included in the final reviews and the literature database. After two Delphi voting rounds, agreement was reached on all 74 scenario-specific safety statements.

Conclusions

The expected combined toxicity is often low for anti-HER2 monoclonal antibodies. For most scenarios with CDK4/6, PARP, or mTOR inhibitors, exercising caution is recommended.

Keywords

Radiotherapy; targeted therapy; toxicity; systematic review; consensus statements

Introduction

Systemic therapies are an essential part of treatment for many cancer types, together with surgery and radiotherapy (RT). The range of systemic treatment options has expanded substantially with the introduction of targeted agents and immune checkpoint inhibitors (ICIs). In most cancer types, this has contributed to improved treatment outcomes and survival [1].

Half of all cancer patients receive RT at some point during the continuum of care [2-4]. RT is used in curative, radical, and palliative treatment settings [2-4]. As a result, patients are often referred for RT while being treated with targeted agents, either for palliation, for oligometastases, or due to oligoprogression [5-8]. Combining RT and targeted agents could enhance tumor control but may also increase toxicity. It is, therefore, crucial to determine whether RT can be safely applied be given while patients receive targeted agents [8]. However, the amount of high-quality toxicity data when combining RT and targeted agents is very limited [9]. Moreover, reports of unexpected and serious toxicity have raised safety concerns about various RT and targeted agent combinations [10-16].

This is a dilemma for clinicians. Disproportionate toxicity of combined-modality treatment should be avoided. However, drug interruption or dosage reduction can cause tumor progression or tumor flare [17-19], while RT dose reduction may result in suboptimal tumor or symptom control [20, 21]. There is a substantial knowledge gap regarding the toxicity of combined treatment and a lack of consensus on this increasingly relevant clinical issue. For most RT and targeted agent combinations, no multidisciplinary evidence-based protocols or guidelines are available [8, 22, 23].

The European Society for Medical Oncology (ESMO) and the European SocieTy for Radiotherapy and Oncology (ESTRO) therefore initiated a series of systematic literature reviews and Delphi consensus statements regarding the safety of combining RT with ten classes of targeted agents or ICIs, divided into three studies. This series provides drug class-specific and irradiated area-specific systematic reviews and multidisciplinary, evidence-based consensus statements [24]. A complementing framework paper describes the central (radio)biological processes and pharmacological factors, as well as general clinical considerations [9].

In the current paper, we provide the systematic reviews and Delphi consensus statements on the safety of combining RT with several drug classes that are commonly used for the treatment of patients with breast cancer: cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibodies, poly (ADP-ribose) polymerase (PARP) inhibitors, and mammalian target of rapamycin (mTOR) inhibitors. These drug type-specific and irradiated area-specific recommendations were defined for all irradiated areas, regardless of tumor type, and are

therefore not limited to breast cancer. Hence, these recommendations are applicable to other tumor types as well.

Methods

Project governance

This is a collaborative project between ESMO and ESTRO. Permission was granted by both the ESMO board and the ESTRO guidelines committee. A coordinating committee consisting of nine experts and representatives from both ESMO and ESTRO convened monthly and led the project. Researchers from the Netherlands Cancer Institute carried out the daily project coordination.

Systematic literature reviews

Drug class-specific systematic literature searches were performed in the Medline, Embase, and SCOPUS database on the 21st of December 2020. If deemed relevant, new studies could be added during the systematic literature reviews and Delphi process. The keywords and search strategies are provided in the Supplementary Tables S1-S4. Studies were included when RT and the targeted agents were administered concurrently. This was defined as a maximum time gap between drug administration and RT of up to five drug half-lives before RT, or two weeks after RT. Treatment-related toxicity needed to be documented. Supplementary Table S5 provides the full inclusion and exclusion criteria. Two researchers (EA and PB, with a consulting role by MJ) performed double-blind title-abstract screening, as well as full-text screening of the selected reports. Regular meetings and discussions were organized to ensure the quality of the process.

To provide drug class-specific and irradiated area-specific toxicity data, all drug class-specific systematic literature reviews were split into six irradiated area-specific literature reviews: for irradiation of the skin, brain, head and neck, thorax, abdomen/pelvis, and musculoskeletal tissues (Supplementary Material, page 2-23). Toxicity data were summarized for each drug class and irradiated area. Furthermore, we included information on commonly used drugs and the relevant biological pathways.

Literature database

A literature database was developed in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA), enabling users to filter publications for a specific drug class, irradiated area and/or study type. Of each included publication, relevant data were registered in this database, including the study type, primary tumor, number of patients, drug name, drug dose, RT technique, RT dose, RT fractionation

scheme, RT and drug timing, tumor response, acute toxicity, late toxicity, and toxicity comparisons with drug or RT monotherapy.

Safety statements

The daily project coordinators and the coordinating committee developed three safety measure options: (1) not combining targeted therapy and RT, (2) a major treatment adaptation, or (3) a minor/no treatment adaptation (Figure 1). After the systematic literature reviews, scenario-specific statements were developed for each drug class, for each irradiated area, and for three different RT scenarios (Table 1). Informed by the systematic literature reviews, EA proposed the most suitable safety measure for each scenario. This resulted in at least 18 scenario-specific recommendations per drug class.

For each statement, scientific levels of evidence were determined based on 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) [25, 26].

Table 1. Radiotherapy scenario examples

Abbreviation: RT, radiotherapy.
RT doses were defined as follows: (number of fractions) x (dose per fraction).

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

Modified Delphi process

Twenty experts from ESMO or ESTRO (equally divided) were requested to participate in a modified Delphi process [27]. This Delphi process was organized between 18 September 2023 and 5 March 2024. All participating experts were requested to read a briefing document, to read the systematic literature reviews (Supplementary Material, page 2-23), and to use the literature database. Based on this information and their expertise, the experts were requested to vote whether they agreed or disagreed with the proposed safety measure statement for each drug class-RT scenario. If the experts disagreed, they were asked to provide an explanation, preferably with supporting literature that they might be aware of (e.g. published after our literature review time point).

We organized two digital Delphi voting rounds with predefined agreement cutoffs for the acceptance of statements. In round one, statements with ≥90% agreement were immediately regarded as consensus. In round two, ≥75% agreement was sufficient to accept a statement [28]. Statements with ≥90% agreement imply a stronger recommendation than those with 75-89% agreement. If a statement

was assessed in both Delphi rounds, the second-round agreement rate determined its acceptance. The flow diagram of the Delphi voting rounds is shown in Supplementary Figure S1.

After the first Delphi round, EA and selected experts (CB, DMB, DT, EdA, GB, MV) reviewed the statements. Based on the agreement rates and feedback from the Delphi experts, statements could be added, removed, or adapted, if necessary. The daily project coordinators and the ESMO office coordinated the Delphi process. The Delphi questionnaires were built and analyzed with Microsoft Excel 2016.

Results

CDK4/6 inhibitors

Systematic literature review process results

We screened 47 unique studies for CDK4/6 inhibitors (palbociclib, abemaciclib, ribociclib) and included 18 reports in the literature review and database. In Supplementary Material, the full systematic literature review (Supplementary Material, page 2-6) and the PRISMA flow diagram [29] (Supplementary Figure S2) are provided.

Drug class and systematic literature review summary

CDK4/6 inhibitors interfere with cell division by causing a block during the G1 phase of the cell cycle, which inhibits cell cycle progression [30], leading to the elimination of fast-dividing cancer cells. However, cell division is also important for repopulation of normal tissues. Therefore, CDK4/6 inhibitors possibly cause increased and prolonged normal tissue damage after RT. Although the main mechanism is cell cycle inhibition, radiosensitization by other (off-target) mechanisms may occur as well. For example, radiosensitization by inhibition of the DNA damage response has been reported [10, 31]. The main adverse events related to this drug class are well-known and include hematologic toxicity (particularly palbociclib and ribociclib) and mucosal/gastrointestinal (GI) toxicity (particularly abemaciclib) [32].

High-quality clinical data are scarce, but in several retrospective studies and case reports, CDK4/6 inhibitors are combined with RT. Most retrospective studies conclude that there is no clearly increased toxicity, particularly with palliative RT doses [33-42]. However, some case reports indicate that higher, unexpected RT toxicity may occur, especially when the gastrointestinal tract is within the irradiated field. Based on these data, combining RT with CDK4/6 inhibitors can be considered, although caution is needed, particularly regarding mucosal/GI toxicity.

For the different irradiated areas, the following data were identified (full systematic literature review in Supplementary Material, page 2-6):

- *Skin [10, 33, 36, 38, 40, 42-45]:* A slightly increased risk of dermatological toxicity may be expected, particularly for higher RT doses or larger volumes.
- *Brain [33-35, 38, 41-44]:* Limited data are available regarding brain RT. No notable neurological toxicities are observed. Of note, low patient numbers, the inclusion of patients receiving RT to other tissues and the inclusion of non-concurrently treated patients limit the possibility to draw brain-RT specific conclusions from the studies.
- *Head and neck [40, 45, 46]:* Limited data are available regarding head and neck RT. Apart from one case report with grade 3 esophagitis and dermatitis, the reported toxicity is not severe.
- *Thorax [10, 33, 38, 40, 42, 43, 45, 47]:* The limited data suggest that increased toxicity (particularly GI) might occur.
- *Abdomen/pelvis [10, 37, 38, 40, 42, 43, 46, 48, 49]:* Although case studies and selected cases from retrospective cohorts may lead to a negative bias [50], the high number of similar cases with grade 3 GI toxicity after low-dose RT is striking and warrants caution when combining abdominal/pelvic RT with concurrent CDK4/6 inhibitors.
- *Musculoskeletal tissues [10, 40]:* Generally, musculoskeletal toxicity does not appear increased. An increase in acute hematologic toxicity should be considered.

Delphi process results

Both Delphi questionnaires were completed by 18/20 experts, which resulted in a response rate of 90%. Among these replies, no answers were missing. In Supplementary Material, we provide the first (Supplementary Table S7) and second Delphi round agreement rates (Supplementary Table S8), as well as the Delphi statement flow diagram (Supplementary Figure S3). Table 2 shows the final Delphi results for CDK4/6 inhibitors.

Delphi consensus statements

For most scenarios with CDK4/6 inhibitors, considering a major adaptation is recommended (Table 2). Due to the reports of increased GI toxicity, combined with the low amount of high-quality toxicity data, our recommendation is to consider not combining these treatments in case of high-dose RT to the head and neck, thorax, and abdomen/pelvis. For low-dose palliative RT to the skin and musculoskeletal tissues, we recommend considering a minor/no adaptation. All statements are strongly recommended with agreement rates ≥90%.

Table 2. CDK4/6 inhibitor consensus statements.

[a] Agreement rates ≥90%: strongly recommended.

Anti-HER2 monoclonal antibodies

Systematic literature review process results

We screened 516 unique studies for anti-HER2 monoclonal antibodies (trastuzumab and pertuzumab; lapatinib is assessed separately in the multi-targeted tyrosine kinase inhibitors systematic review), and included 37 reports in the literature review and database. In Supplementary Material, the full systematic literature review (Supplementary Material, page 7-12) and the PRISMA flow diagram [29] (Supplementary Figure S4) are provided.

Drug class and systematic literature review summary

The HER2 receptor can be overexpressed in cancer cells, and is associated with a more aggressive tumor biology and worse survival [51]. The HER2 receptor is part of the HER family, including the epidermal growth factor receptor (EGFR, HER1) [52]. Downstream, it influences the mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) pathways leading to cell survival and proliferation [52]. While the mechanism of trastuzumab is not completely elucidated, possible mechanisms include inhibition of HER2 dimerization, cleavage inhibition, HER2 downregulation, antibody-dependent cytotoxicity, internalization and degradation of HER2, inhibition of angiogenesis, p27 induction and PI3K inhibition [51, 52]. Pertuzumab inhibits downstream signaling by binding to a different HER2 domain, leading to the inhibition of dimerization with HER3 [52]. Antibody-drug conjugates targeting HER2, like trastuzumab-emtansine and trastuzumab-deruxtecan, are not reviewed here due to their different mechanism of action [52, 53].

In general, no severe toxicities are expected when anti-HER2 monoclonal antibodies are combined with RT, although caution is needed, particularly regarding cardiotoxicity. As most studies only describe the combination of trastuzumab and breast RT, data for other RT locations and pertuzumab are very limited.

For the different irradiated areas, the following data were identified (full systematic literature review in Supplementary Material, page 7-12):

- *Skin [54-67]:* Several studies report skin toxicity rates when RT is combined with anti-HER2 monoclonal antibodies (often trastuzumab). The skin toxicity rates do not exceed the expected rates without anti-HER2 monoclonal antibodies. Therefore, no increased skin toxicity is expected.

- *Brain [58, 68, 69]:* The data considering brain RT combined with anti-HER2 monoclonal antibodies are limited, and do not indicate increased toxicity.
- *Head and neck:* No studies were identified concerning the combination of head and neck RT with anti-HER2 monoclonal antibodies.
- *Thorax [54-57, 59, 70-72]:* A considerable amount of data is available for combined trastuzumab and thoracic RT, given its wide application in the clinic. Regarding non-cardiac toxicities, most data do not indicate unacceptable safety risks, although in one trial a borderline significant association was seen between cumulative trastuzumab dose before RT and esophagitis risk [57].
- *Cardiac toxicity:* anti-HER2 monoclonal antibodies (particularly trastuzumab) and RT are both individually capable of inducing cardiac toxicity [73-76]. The largest concurrent trials for breast cancer show grade ≥2 left ventricular ejection fraction (LVEF) dysfunction in 3-18% [55-57, 64, 77]. The phase III N9831 trial indicates a larger role for trastuzumab than for RT [54]. Although a smaller study from Cao et al. suggests a higher risk when trastuzumab is started during RT (compared to started before RT) [78], most clinical data do not indicate that concurrent administration leads to more cardiac toxicity than expected from both individual modalities.
- *Abdomen/pelvis [79]:* Based on one phase I/II trial, mildly increased toxicity cannot be ruled out.
- *Musculoskeletal tissues:* No relevant specific musculoskeletal RT data were identified. Based on the previously shown data, a substantial increase in musculoskeletal RT toxicity is not expected. Also, no increase in chest wall RT toxicity was reported for the combination of trastuzumab with thoracic RT.

Delphi consensus statements

Both Delphi questionnaires were completed by 18/20 experts, which resulted in a response rate of 90%. Among these replies, only one expert answer was missing for two statements in the second Delphi round. In Supplementary Material, we provide the first (Supplementary Table S9) and second Delphi round agreement rates (Supplementary Table S10), as well as the Delphi statement flow diagram (Supplementary Figure S5). Table 3 shows the final Delphi results for HER2 antibodies.

The toxicity of combining anti-HER2 monoclonal antibodies with RT is usually mild. For most scenarios with anti-HER2 monoclonal antibodies, we recommend considering a minor/no adaptation (Table 3). Due to a lack of high-quality data and some studies suggesting slightly increased toxicity risks, considering a major adaptation is recommended for high-dose stereotactic head and neck RT, high-dose RT to the abdomen/pelvis, and high-dose esophageal RT. If treatment adaptations are applied, RT adaptations may be more feasible than drug adaptations, due to the long drug elimination half-lives of anti-HER2 monoclonal antibodies (shown in Supplementary Material, page 7).

Table 3. Anti-HER2 monoclonal antibody consensus statements.

[a] Agreement rates ≥90%: strongly recommended.
[b] Level of evidence based on data from high radiotherapy dose scenarios.

PARP inhibitors

Systematic literature review process results

We screened 301 unique studies for PARP inhibitors (olaparib, niraparib, veliparib, talazoparib, rucaparib) and included 17 reports in the literature review and database. In Supplementary Material the full systematic literature review (Supplementary Material, page 13-17) and the PRISMA flow diagram [29] (Supplementary Figure S6) are provided.

Drug class and systematic literature review summary

PARP molecules play an important role in the repair of single-strand and double-strand DNA breaks [80]. Some major proposed mechanisms of PARP inhibitors are trapping of PARP on the DNA and suppression of the repair process. Consequently, DNA replication with unrepaired single-strand breaks and PARP trapping can lead to double-strand breaks. Particularly cells with homologous recombination deficiencies (such as *BRCA*-mutated cancer cells) are affected by this process, a concept called synthetic lethality [80, 81]. It is important to note that veliparib has a much weaker PARP-trapping ability than other PARP inhibitors [82, 83].

PARP inhibitors are able to radiosensitize cells, probably by inhibiting the repair of the numerous single-strand breaks caused by irradiation, ultimately leading to double-strand breaks and cell death [81, 84]. The safety profile of PARP inhibitors is well-known and common drug class acute adverse events include nausea, fatigue, and anemia, with specific variations between agents [85].

The limited toxicity data are mostly based on phase I and II studies combining olaparib or veliparib with high-dose (chemo-)RT. Combining PARP inhibitors with RT appears feasible with varying PARP inhibitor doses, but increased RT toxicity is regularly reported. Particularly hematologic, pulmonary, and esophageal toxicity risks may be increased. The data indicate that low PARP inhibitor doses can already cause radiosensitization.

For the different irradiated areas, the following data were identified (full systematic literature review in Supplementary Material, page 13-17):

- *Skin [11, 86, 87]:* While a few studies suggest increased skin toxicity, it is not a major concern in general.
- *Brain [88-95]:* Combining PARP inhibitors with brain RT appears feasible up to certain PARP inhibitor doses. The most common reported toxicities are hematologic and are probably primarily drug-related. However, long-term safety data, as well as possible effects on cognitive functioning, are lacking.

- *Head and neck [87, 96]:* The amount of data for head and neck RT is limited. In one phase I trial combining olaparib and cetuximab with RT, a phase II dose of 25 mg twice daily for olaparib is recommended. Another phase I trial combining olaparib with RT, shows a maximum tolerated dose of 25 mg once daily (with conventional high-dose RT), as 25 mg twice daily (with accelerated RT, n=4) led to laryngeal stenosis requiring tracheotomy in two patients, and osteoradionecrosis in one patient.
- *Thorax [11, 86, 97-101]:* There are some phase I trials and a phase I/II trial available showing mixed results, but combining PARP inhibitors with RT probably creates a risk of increased toxicity. For lung cancer, veliparib combined with chemo-RT (carboplatin and paclitaxel) was considered mostly safe in two studies. However, low-dose olaparib combined with RT may already lead to increased esophageal, hematologic, and (high-grade) late pulmonary toxicity. For breast cancer, tolerated olaparib doses appear higher, but tolerated veliparib doses appear lower due to late toxicity.
- *Abdomen/pelvis [102-104]:* Three phase I trials examined the combination of (chemo-)RT with veliparib. This combination appears relatively well-tolerated, although the MTDs of veliparib varied from 40 mg to 400 mg b.i.d. Hematologic toxicity may be the major concern.
- *Musculoskeletal tissues:* No articles were identified.

Delphi consensus statements

Both Delphi questionnaires were completed by 18/20 experts, which resulted in a response rate of 90%. For one scenario, one expert deliberately refrained from deciding during round one; no other answers were missing. In Supplementary Material, we provide the first (Supplementary Table S11) and second Delphi round agreement rates (Supplementary Table S12), as well as the Delphi statement flow diagram (Supplementary Figure S7). Table 4 shows the final Delphi results for PARP inhibitors.

For all scenarios with PARP inhibitors in combination with RT, we recommend considering a major adaptation (Table 4). Particularly a drug interruption or drug dosage reduction should be considered, as several studies showed radiosensitization with PARP inhibitor dosages that are far below common monotherapy dosages. Depending on the drug dosage, even after interrupting the drug five half-lives, the remaining drug concentration can still lead to radiosensitization.

Table 4. PARP inhibitor consensus statements.

[a] Agreement rates ≥90%: strongly recommended.
[b] Level of evidence based on data from high radiotherapy dose scenarios.

mTOR inhibitors

Systematic literature review process results

We screened 477 unique studies for mTOR inhibitors (e.g., sirolimus, temsirolimus, everolimus), and included 35 reports in the literature review and database. In Supplementary Material, the full systematic literature review (Supplementary Material, page 18-23) and the PRISMA flow diagram [29] (Supplementary Figure S8) are provided.

Drug class and systematic literature review summary

The PI3K/AKT/mTOR pathway is frequently hyperactivated in cancer cells [105]. This pathway is one of the central pathways in a cell, like MAPK signaling and Ca^{2+} signaling, and is influenced by multiple receptor tyrosine kinases, like EGFR and vascular endothelial growth factor receptor (VEGFR) [106]. This pathway is involved in several processes, such as cell survival, growth, and proliferation. By inhibiting these processes, mTOR inhibitors may be able to increase radiosensitivity [105]. Preclinical data support a possible radiosensitization, for example by an antiangiogenic effect and by inhibition of DNA double-strand break repair [107-109]. Mucositis and rash are the most common adverse events of this class, but metabolic, hematologic, and pulmonary toxicities may also occur [110].

Several phase II trials (primarily for glioblastoma), phase I(/II) trials, and case series provide the currently available toxicity data for the combination of mTOR inhibition and RT. For the doses applied in these studies (often lower than monotherapy doses), no severely increased toxicity was observed, with the exception of hematologic toxicity. However, mucosal and pulmonary toxicity should also be considered.

For the different irradiated areas, the following data were identified (full systematic literature review in Supplementary Material, page 18-23):

- *Skin [111-121]*: Most studies combining RT with mTOR inhibitors do not report increased skin toxicity.
- *Brain [116, 122-131]:* Hematologic toxicity and infection risk (probably primarily drug-related) may be most concerning when (chemo-)RT to the brain is combined with mTOR inhibitors. For stereotactic RT and radionecrosis risk, data are scarce: one retrospective study shows a non-

significant increase of radionecrosis (HR 1.92, p = 0.24, multivariate analysis) with mTOR inhibitors within 30 days of stereotactic RT [131].

- *Head and neck [121, 132-135]:* The available toxicity data are very limited. An increased risk of common RT-related toxicities exists.
- *Thorax [111, 136-142]:* The available toxicity data are limited. An increased risk of the most common RT-related toxicities exists, particularly esophagitis, even with drug doses lower than the approved monotherapy doses. Pneumonitis risk should also be considered, as this can also be caused by mTOR inhibitors alone [111].
- *Abdomen/pelvis [112, 115, 117-119, 143-146]:* The available toxicity data are very limited. Increased toxicity is possible, but with a low mTOR inhibitor dose and/or RT dose, the toxicity risk does not appear high. The risk of surgical complications may be increased when surgery is performed within a short time interval after RT combined with mTOR inhibitors.
- *Musculoskeletal tissues [147-150]:* In 4 small studies, total body irradiation or total marrow irradiation was performed concurrently or within a couple of days from sirolimus administration, without increased toxicity.

Delphi consensus statements

Both Delphi round questionnaires were completed by 18/20 experts, which resulted in a response rate of 90%. Among these replies, no answers were missing. In Supplementary Material, we provide the first (Supplementary Table S13) and second Delphi round agreement rates (Supplementary Table S14), as well as the Delphi statement flow diagram (Supplementary Figure S9). Table 5 shows the final Delphi results for mTOR inhibitors.

For RT to the skin, for low-dose palliative brain RT, and for low-dose palliative musculoskeletal RT, a minor/no adaptation is recommended (Table 5). For high-dose conventionally fractionated thoracic RT, our recommendation is to consider not combining both treatments, due to the potentially increased pneumonitis risk, which is already associated with mTOR inhibitors. For all other scenarios, we recommend considering a major adaptation.

Table 5. mTOR inhibitor consensus statements.

[a] Agreement rates ≥90%: strongly recommended.
[b] Level of evidence based on data from high radiotherapy dose scenarios.

Discussion

With these first, evidence-based, joint ESMO-ESTRO consensus statements, we provide guidance regarding the combination of RT with targeted cancer therapies. The current publication covers systematic literature reviews and statements on the safety of combining RT with CDK4/6 inhibitors, anti-HER2 monoclonal antibodies, PARP inhibitors, and mTOR inhibitors. While the expected combined toxicity is often low for anti-HER2 monoclonal antibodies, we recommend caution for most scenarios with CDK4/6, PARP, or mTOR inhibitors.

To develop these multidisciplinary, scenario-specific ESMO-ESTRO consensus statements, extensive interdisciplinary collaboration and drug class-RT scenario-specific systematic reviews were essential. With these statements, we provide pragmatic and evidence-based safety recommendations for real-world, clinical practice. These statements should not be used as strict guidelines, nor should they guide or replace high-quality registries and clinical trials combining targeted agents with RT. Furthermore, the anticipated treatment toxicity should always be evaluated against the expected efficacy.

The extensive nature of the systematic literature reviews and Delphi process in this project has resulted in a relevant time gap between the initial literature searches and the Delphi process. Furthermore, the levels of evidence for toxicity data are frequently low for various drug class-RT scenarios, with particularly limited data on late toxicity. In addition, case studies and series may contain a higher risk of bias [50]. Experts were, therefore, invited to provide (new) literature references if they disagreed with a proposed statement. The comprehensive approach of the systematic literature reviews, the high agreement rates, and the low amount of suggested new literature by the participating experts emphasize the validity and relevance of the consensus statements.

Recently, Meattini et al. developed ESTRO-endorsed recommendations for combining targeted agents with RT for patients with breast cancer. They evaluated the same drug classes, but their recommendations are more context-driven, emphasizing in which clinical or research context these combinations should or should not be used. In contrast, we provide pragmatic statements for RT-specific scenarios that reflect daily clinical practice. Furthermore, their review was solely focused on breast cancer studies, whereas our review encompasses studies across all cancer types. Nevertheless, similar trends can be observed in both studies [151]. Additionally, Kroeze et al. published EORTC-ESTRO consensus recommendations regarding the combination of specifically stereotactic body RT combined with several targeted agents or immunotherapy, showing similar trends for anti-HER2 antibodies compared to those observed in our study. For CDK4/6 inhibitors, no consensus was reached in their study [152].

The increasing introduction of targeted agents without toxicity data on their combination with RT causes various clinical challenges, which underlines the urgency of developing strategies to collect

these data. In order to achieve this, it remains crucial to increase awareness among pharmaceutical companies, to promote interdisciplinary collaboration, and to initiate new clinical trials, prospective cohort studies, registries, real-world studies, and preclinical studies that evaluate the combination of RT with targeted agents [8, 153, 154]. Furthermore, comprehensive reporting of combined treatment details and associated toxicities is essential [9, 155].

Disclaimer

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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.

Conflict of Interest Statement

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

PTV, planning target volume; BED, biologically equivalent dose; EQD_2, equivalent dose in 2 Gy fractions; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; IGRT, image-guided radiotherapy.

Figure 1

Click here to access/download;Figure;Figure 1 - ESMO-ESTRO Consensus - CDK46 HER2 PARP mTOR.xlsx

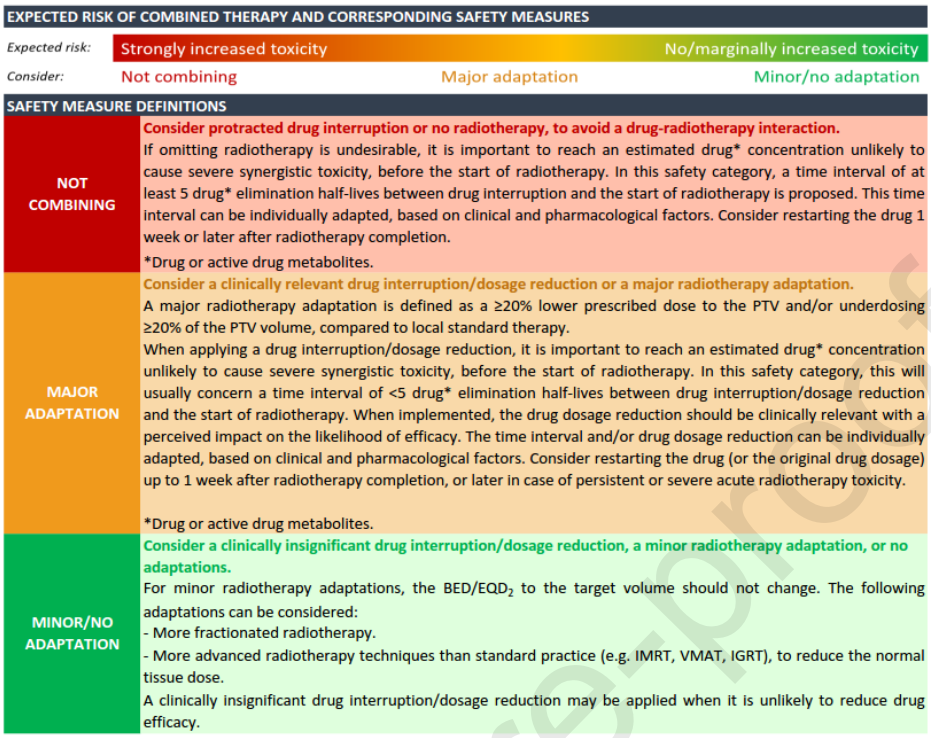

Table 1. Radiotherapy scenario examples

Abbreviation: RT, radiotherapy.
RT doses were defined as follows: (number of fractions) x (dose per fraction).

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

PTV, planning target volume; BED, biologically equivalent dose; EQD_2, equivalent dose in 2 Gy fractions; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy; IGRT, image-guided radiotherapy.

Table 2. CDK4/6 inhibitor consensus statements.

[a] Agreement rates ≥90%: strongly recommended.

Table 3. Anti-HER2 monoclonal antibody consensus statements.

[a] Agreement rates ≥90%: strongly recommended.
[b] Level of evidence based on data from high radiotherapy dose scenarios.

Table 4. PARP inhibitor consensus statements.

[a] Agreement rates ≥90%: strongly recommended.
[b] Level of evidence based on data from high radiotherapy dose scenarios.

Table 5. mTOR inhibitor consensus statements.

[a] Agreement rates ≥90%: strongly recommended.
[b] Level of evidence based on data from high radiotherapy dose scenarios.

RT scenario	Example
Low-dose palliative RT	*Examples:* 1x8, 2x8, 5x4, 10x3 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 to local high-dose stereotactic RT for brain metastases.
High-dose conventionally fractionated RT	*Examples:* 33x2 Gy (5 times per week), 5x5 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.

For the combination of CDK4/6 inhibitors with radiotherapy to the:				
Irradiated area	**Radiotherapy scenario**	**Recommendation**	**Agreement rate[a]**	**Level of evidence**
Skin	Low-dose palliative	**Minor/no adaptation**	100%	IV

	High-dose conventionally fractionated	**Major adaptation**	100%	IV
	High-dose stereotactic	**Major adaptation**	100%	IV
Brain	Low-dose palliative	**Major adaptation**	100%	V
	High-dose conventionally fractionated	**Major adaptation**	100%	V
	High-dose stereotactic	**Major adaptation**	94%	V
Head & neck	Low-dose palliative	**Major adaptation**	100%	V
	High-dose conventionally fractionated	**Not combining**	94%	V
	High-dose stereotactic	**Not combining**	94%	V
Thorax	Low-dose palliative	**Major adaptation**	94%	IV
	High-dose conventionally fractionated	**Not combining**	94%	IV
	High-dose stereotactic	**Not combining**	94%	IV
Abdomen/pelvis	Low-dose palliative	**Major adaptation**	94%	IV
	High-dose conventionally fractionated	**Not combining**	94%	IV
	High-dose stereotactic	**Not combining**	94%	IV
Musculoskeletal tissues	Low-dose palliative	**Minor/no adaptation**	100%	IV
	High-dose conventionally fractionated	**Major adaptation**	94%	IV
	High-dose stereotactic	**Major adaptation**	100%	IV

For the combination of anti-HER2 monoclonal antibodies (trastuzumab and/or pertuzumab) with radiotherapy to the:

Irradiated area	Radiotherapy scenario	Recommendation	Agreement rate[a]	Level of evidence
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%	V
Brain	Low-dose palliative	**Minor/no adaptation**	100%	II
	High-dose conventionally fractionated	**Minor/no adaptation**	94%	V
	High-dose stereotactic	**Minor/no adaptation**	94%	IV
Head & neck	Low-dose palliative	**Minor/no adaptation**	100%	V
	High-dose conventionally fractionated	**Minor/no adaptation**	89%	V

	High-dose stereotactic	**Major adaptation**	83%	V
Thorax	Low-dose palliative	**Minor/no adaptation**	94%	I[b]
	High-dose conventionally fractionated	**Minor/no adaptation**	94%	I
	High-dose stereotactic	**Minor/no adaptation**	94%	V
Abdomen/pelvis	Low-dose palliative	**Minor/no adaptation**	94%	III[b]
	High-dose conventionally fractionated	**Major adaptation**	94%	III
	High-dose stereotactic	**Major adaptation**	94%	V
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%	V
EXCEPTIONS: For the combination of anti-HER2 monoclonal antibodies (trastuzumab and/or pertuzumab) with radiotherapy to the:				
Esophagus	High-dose conventionally fractionated	**Major adaptation**	88%	III
	High-dose stereotactic	**Major adaptation**	94%	V

For the combination of PARP inhibitors with radiotherapy to the:

Irradiated area	Radiotherapy scenario	Recommendation	Agreement rate[a]	Level of evidence
Skin	Low-dose palliative	**Major adaptation**	89%	II
	High-dose conventionally fractionated	**Major adaptation**	94%	III
	High-dose stereotactic	**Major adaptation**	94%	V
Brain	Low-dose palliative	**Major adaptation**	94%	II
	High-dose conventionally fractionated	**Major adaptation**	94%	II
	High-dose stereotactic	**Major adaptation**	94%	V
Head & neck	Low-dose palliative	**Major adaptation**	94%	V
	High-dose conventionally fractionated	**Major adaptation**	94%	III
	High-dose stereotactic	**Major adaptation**	94%	V
Thorax	Low-dose palliative	**Major adaptation**	94%	III[b]
	High-dose conventionally fractionated	**Major adaptation**	100%	III
	High-dose stereotactic	**Major adaptation**	94%	V
Abdomen/pelvis	Low-dose palliative	**Major adaptation**	94%	III

	High-dose conventionally fractionated	**Major adaptation**	94%	III
	High-dose stereotactic	**Major adaptation**	94%	V
Musculoskeletal tissues	Low-dose palliative	**Major adaptation**	83%	III
	High-dose conventionally fractionated	**Major adaptation**	94%	III
	High-dose stereotactic	**Major adaptation**	100%	V

For the combination of mTOR inhibitors with radiotherapy to the:

Irradiated area	Radiotherapy scenario	Recommendation	Agreement rate[a]	Level of evidence
Skin	Low-dose palliative	**Minor/no adaptation**	100%	III
	High-dose conventionally fractionated	**Minor/no adaptation**	100%	III
	High-dose stereotactic	**Minor/no adaptation**	94%	III
Brain	Low-dose palliative	**Minor/no adaptation**	100%	II[b]
	High-dose conventionally fractionated	**Major adaptation**	100%	II
	High-dose stereotactic	**Major adaptation**	100%	III
Head & neck	Low-dose palliative	**Major adaptation**	100%	III[b]
	High-dose conventionally fractionated	**Major adaptation**	94%	III
	High-dose stereotactic	**Major adaptation**	100%	V
Thorax	Low-dose palliative	**Major adaptation**	94%	III
	High-dose conventionally fractionated	**Not combining**	100%	III
	High-dose stereotactic	**Major adaptation**	89%	V
Abdomen/pelvis	Low-dose palliative	**Major adaptation**	94%	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%	III
	High-dose conventionally fractionated	**Major adaptation**	100%	III
	High-dose stereotactic	**Major adaptation**	94%	V

Highlights

1. This is an ESMO-ESTRO initiative on the safety of drug-radiotherapy combinations.

2. Combining radiotherapy with anti-HER2 monoclonal antibodies is generally safe.
3. Combining radiotherapy with CDK4/6, PARP, or mTOR inhibitors warrants caution.
4. Consensus was reached for all 74 clinical scenarios.

Declaration of Interest Statement

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