



Combining radiotherapy with targeted therapies in non-small cell lung cancer: focus on anti-EGFR, anti-ALK and anti-angiogenic agents

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Abstract: The combination of radiotherapy (RT) with targeted agents in non-small cell lung cancer (NSCLC) has been expected to improve the therapeutic ratio and tumor control. The EGFR blockade enhances the antitumor effect of RT. The ALK inhibition elicits anti-proliferative, pro-apoptotic and antiangiogenic effects in *ALK*-positive NSCLC cell lines, enhanced by the exposure to RT. The antiangiogenic agents normalize pathological tumor vessels, thus decrease tumor cell hypoxia and improve radiosensitivity. To date, however, none of the targeted agents combined with RT has shown proven clinical benefit over standard chemoradiation (CRT) in locally advanced NSCLC. The risk of potential excessive toxicity related to the therapeutic combination of RT and targeted agents cannot be ignored. Well-designed clinical trials may allow development of more effective combination strategies. Another potential application of combined RT and targeted therapies in oncogene-driven NSCLC is metastatic oligoprogressive or oligopersistent disease. The use of RT in oligoprogressive oncogene-driven NSCLC, while continuing first line targeted therapy, can potentially eradicate resistant cell clones and provide survival benefit. Likewise, the consolidation of oligopersistent foci (molecularly resistant to first line targeted therapy) may potentially interfere with the natural course of the disease by avoiding or delaying progression. We discuss here the molecular and radiobiological mechanisms of combining RT and targeted agents, and summarize current clinical experience.

Keywords: Non-small cell lung cancer (NSCLC); radiotherapy; targeted therapy, tyrosine kinase inhibitors (TKI); monoclonal antibodies

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Introduction

Radiotherapy (RT) in non-small cell lung cancer (NSCLC) is an undeniable backbone of curative treatment for early and locally advanced disease, as well as palliation of symptoms in advanced disease.

Decoding of lung cancer genome and identification of driving molecular aberrations causing carcinogenesis stimulated the design of molecularly targeted therapies.

These include monoclonal antibodies targeting specific antigens on the tumor cell surface, and small molecule tyrosine kinase inhibitors (TKI) acting intracellularly. Both groups of compounds interfere with crucial cellular signaling pathways involved in tumor cell growth and cancer progression. Activating epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements (occurring almost exclusively in lung

adenocarcinomas) represent the most common druggable molecular events in NSCLC. Randomized clinical trials showed that in advanced NSCLC harboring specific molecular aberrations, EGFR and ALK TKIs provide superior response rate and progression-free survival (PFS), as well as lower toxicity compared to chemotherapy (1,2).

Within the past few decades therapeutic progress in lung cancer has mainly been accomplished by the rational combination of various modalities. For example, sequential chemoradiotherapy (CRT) has been found to be more effective than RT alone and concurrent use of both modalities provides longer survival compared to their sequential administration (3). The pivotal RTOG 0617 trial showed that escalation of RT dose from 60 to 74 Gy did not translate into survival benefit (4).

Likewise, no benefit was demonstrated from maintenance or consolidation chemotherapy (5). In turn, the recent PACIFIC trial demonstrated survival benefit from 12-month consolidation immunotherapy with durvalumab, an anti-PD-L1 antibody, in locally advanced NSCLC patients who responded to concurrent CRT, making this approach the new therapeutic standard (6,7).

The combination of molecularly targeted agents with RT has been expected to substantially improve the therapeutic ratio and tumor control. Indeed, preclinical models suggested that these agents may enhance tumor response to RT and elicit radioprotection of normal tissues (8). Whereas many of these models indicate synergistic interactions with exclusive RT, preclinical evidence on combination of targeted agents with CRT is relatively scarce.

Another promising strategy addressed in this review is adding consolidative RT to targeted systemic treatment in metastatic oligoproggressive or oligopersistent NSCLC harboring defined molecular aberration.

The scientific rationale for combining radiotherapy with targeted agents

Bentzen *et al.* (8) named five exploitable mechanisms describing the radiobiological basis by which a specific agent may interact with RT to improve the clinical outcome. The first mechanism, spatial cooperation, refers to the use of RT to target locoregional disease and systemic therapy for micrometastatic or occult systemic disease. The modalities are typically applied here sequentially to reduce toxicity, as spatial cooperation does not necessitate an interaction at the cellular level. Three other mechanisms require concomitant administration of drugs and RT. The strategy of cytotoxic

enhancement is aimed at cell killing intensification by modulating the induction or repair of cellular DNA damage. Biological cooperation of drugs and RT exploits distinct sensitivity of particular cell populations within a heterogeneous tumor, or employs diverse mechanisms of cell killing. The rationale behind temporal modulation is to enhance the tumor response to fractionated RT, as the drug affects DNA damage repair, cellular repopulation, proliferation, reoxygenation and redistribution. The last mechanism, normal tissue protection, refers to substances which show cytoprotection of normal cells.

EGFR signaling pathway and radiation

The *EGFR* is frequently over-expressed or mutated in cancer cells, including NSCLC (9-12). NSCLC cell lines harboring somatic *EGFR* mutations on the intracellular domain exhibit increased radiosensitivity (13,14). Overexpression of EGFR protein promotes unregulated growth and likely contributes to RT resistance of NSCLC (12).

EGFR signaling pathway is involved in cell proliferation, apoptosis inhibition and accelerated DNA double-strand breaks (DSB) repair, and is related to downstream survival pathways upregulated by exposure to radiation (15-17). The two important signaling pathways, phosphoinositide 3-kinase/AKT (inhibiting apoptosis) and RAS/RAF/MEK/ERK (stimulating proliferation) induce radioresistance when activated, and their suppression is expected to radiosensitize tumor cells (18). The temporal modulation mechanism represents the scientific background of combining RT with EGFR inhibitors, and explains that expected benefit may not be restricted to *EGFR*-positive cancers. The EGFR blockade enhances the antitumor effect of RT (19,20). EGFR inhibition, by suppressing cellular DNA repair capacity and prolonging the presence of DSB, may render tumor cells more vulnerable to radiation-induced apoptosis. While reaching cell surface, radiation causes EGFR internalization. The receptor is captured by binding proteins Ku70/Ku80 and DNA-PKcs and translocated into the nucleus, activating there damage repair. If EGFR is blocked, the complex does not reach the nucleus, resulting in the inhibition of DNA repair. Additionally, both RT and EGFR inhibition increase apoptosis, as determined by caspase activity. When a TKI is combined with RT, poly(ADP-ribose) polymerase (PARP - an enzyme involved in DNA damage repair) cleavage increases, resulting in its reduced activity and suppressed DNA repair (17). Finally, EGFR inhibition by inducing G1- and G2-arrest reduces the rate of lung cancer cells in the

radioresistant S-phase of cell cycle (21).

Clinical data on anti-EGFR antibodies and radiotherapy combinations in locally advanced NSCLC

Cetuximab is a human-murine chimeric IgG1 monoclonal antibody that binds to the extracellular region of the EGFR, and acts as a competitive antagonist. It stimulates EGFR internalization and can promote antibody-dependent cellular cytotoxicity (ADCC). The idea of combining RT and cetuximab has been considered promising on the basis of proven radiosensitizing effect and frequent overexpression of EGFR in NSCLC. Indeed, compared to RT alone, concomitant administration of cetuximab and RT improves local control and survival in head and neck cancer (22,23). Preclinical models using NSCLC cell lines revealed similar efficacy of cetuximab and cisplatin in combination with RT (24). The pilot SCRATCH study proved that in stage III NSCLC cetuximab can be safely combined with RT following induction chemotherapy (25). In a phase II study including elderly and/or poor performance status (PS) stage III NSCLC patients not eligible to concomitant CRT, addition of cetuximab to definitive RT provided median overall survival (OS) of 15.1 months, without excessive toxicity (26). Similar results (median survival of 19.6 months) were obtained in the prospective phase II NEAR trial using intensity modulated RT (IMRT) and weekly cetuximab followed by a maintenance period (27). The toxicity was mild: 3.3% of patients experienced grade 3 pneumonitis and 37% any grade 3 toxicity. In the phase II Satellite SWOG study induction chemotherapy followed by concurrent cetuximab and definitive RT provided median OS of 17 months, with acceptable toxicity profile (28). Grade 3 diarrhea and skin toxicity occurred in 11.3% and 4.2% of patients, respectively, and grade ≥ 3 RT-induced esophagitis and pneumonitis in 1.4% and 5.6% patients, respectively (seemingly less compared to schedules using concurrent CRT). Similar results (median OS of 19.4 months) and acceptable toxicity (no grade 3-4 esophagitis) were seen in another phase II study of cetuximab combined with RT and continued with chemotherapy as consolidation (29). *EGFR* gene copy number assessed by fluorescence *in situ* hybridization (FISH) was not predictive of efficacy outcomes. In a phase II study, consolidation with docetaxel and cetuximab after concurrent RT with cetuximab was associated with unacceptable pulmonary toxicity: 19% of patients developed severe pneumonitis and there were eight treatment-related deaths among 27 evaluable patients (30). The phase II RTOG 0324 trial showed feasibility

and median OS of 22.7 months with the combination of cetuximab with CRT, followed by consolidative chemotherapy in stage IIIA/B NSCLC (31). Adverse events included 20% grade 4 hematologic toxicities, 60% grade ≥ 3 non-hematologic toxicities (similar to historic CRT control seen in the LAMP/ACR427 trial), 8% grade 3 esophagitis (compared to 28% in the LAMP/ACR427 trial), 7% grade 3-4 pneumonitis, and 2% fatal pulmonary events. The Cancer and Leukemia Group B phase II trial 30407 confirmed feasibility of a therapeutic combination consisting of cetuximab, RT and pemetrexed/carboplatin chemotherapy in stage III NSCLC (32). The 18-month OS rate was 54% in the CRT/cetuximab arm, compared to 58% in the CRT arm, with no apparent differences in toxicity. No significant OS difference was noted between squamous and non-squamous NSCLC patients (median 22.2 *vs.* 22.4 months, respectively). Another phase I/II study demonstrated safety and efficacy (median OS of 26.7 months) of induction cetuximab combined with chemotherapy, followed by concurrent cetuximab and CRT in stage III NSCLC (33). Treatment efficacy was not correlated with the *EGFR* status, and the survival data numerically exceeded those reported in similarly designed trials without cetuximab (34). Grade 2 pneumonitis occurred in 21% of patients, and grade 3 esophagitis in 13%. In a randomized phase II study using daily cisplatin (6 mg/m² iv) combined with concurrent hypofractionated RT (66 Gy/24 fx) in stage III NSCLC, the addition of weekly cetuximab to CRT did not improve disease control (35). More patients in the cetuximab arm experienced grade ≥ 3 toxicity (65% *vs.* 45%, $P=0.03$), which included: dysphagia (23%), pneumonia (6%), late esophageal toxicity (8%) and late pulmonary toxicity (4%). *EGFR* status showed neither prognostic nor predictive value. Median OS for the entire group was remarkably high—31.5 months, and was not significantly different between the study arms (36). The authors concluded that hypofractionation rather than addition of cetuximab, might have contributed to impressive OS in this trial. Finally, the pivotal randomized phase III RTOG 0617 study with factorial design evaluated standard (60 Gy/30 fx) *vs.* high dose (74 Gy/37 fx) RT with concurrent and consolidation carboplatin/paclitaxel regimen with or without cetuximab in stage III NSCLC (4). Median OS in the cetuximab and no-cetuximab arms was 25 months and 24 months, respectively ($P=0.29$). The addition of cetuximab was associated with a higher rate of grade ≥ 3 toxicity (86% *vs.* 70%, $P=0.0001$), with explicitly increased acute pulmonary toxicity. G3 pneumonitis occurred in

7% and 4% of patients receiving 60 Gy with and without cetuximab, respectively. G3 pneumonitis was experienced by 5% and 0% of patients receiving 74 Gy with and without cetuximab, respectively. The preplanned retrospective analysis showed no difference in outcomes between low (EGFR H score <200) and high (EGFR H score \geq 200) EGFR expressing tumors. Cetuximab might have had a detrimental effect in the cohort with EGFR H score <200, and a benefit in those with a H score \geq 200. In the former group median OS in patients who did and did not receive cetuximab was 19.5 and 29.6 months, respectively ($P=0.056$), whereas in the latter—42 months and 21.2 months, respectively ($P=0.032$). Intriguingly, RT dose of 74 Gy was associated with shorter OS compared to standard dose 60 Gy (median 20.3 *vs.* 28.7 months, $P=0.004$).

Panitumumab, a fully human anti-EGFR IgG2 monoclonal antibody, can augment radiation response in NSCLC cell lines (37). A phase II RTOG 0839 randomized study evaluated preoperative CRT with or without panitumumab, followed by consolidation chemotherapy in potentially operable stage IIIA, N2 NSCLC patients (38). As expected, panitumumab exerted high incidence of rash (grade 2–3 in 29% *vs.* 0% in the CRT alone arm), but esophageal toxicity was similar in both arms. The addition of panitumumab did not improve PFS and OS. Mortality rate in the panitumumab arm was unexpectedly high (14%), although its relationship with this compound is not fully understood.

Nimotuzumab, a humanized anti-EGFR IgG1 monoclonal antibody, has a lower incidence of skin toxicity compared to other drugs in this class (39). Two phase I studies showed efficacy and acceptable toxicity of nimotuzumab combined with palliative RT in advanced NSCLC (40,41). Preliminary results of the phase II study in stage III NSCLC confirmed the efficacy and safety of RT in this combination (42).

The results of studies using definitive CRT combined with anti-EGFR antibodies are disappointing. Importantly, in contrast to combining anti-EGFR antibodies with RT, their combinations with CRT have not been subjected to thorough preclinical studies, and there is no strong evidence of synergistic effect from this approach.

Table 1 summarizes the key studies of anti-EGFR antibodies in combination with radiotherapy.

Clinical data on EGFR tyrosine kinase inhibitors and radiotherapy combinations in locally advanced NSCLC

A phase I study showed safety of oral gefitinib 250 mg (with no dose limiting toxicity) administered concurrently with

full dose CRT in stage III NSCLC (43). Another phase I study revealed moderate esophageal and pulmonary toxicity (grade 3–4 in 27% and 20% of patients, respectively) of weekly docetaxel and daily gefitinib concurrently with RT in stage III NSCLC (44). Dose-limiting esophagitis and pulmonary toxicity occurred at a weekly docetaxel dose of 25 mg/m², setting down the maximum tolerated dose at the level of 20 mg/m²/week. Induction chemotherapy followed by concurrent CRT with gefitinib demonstrated acceptable toxicity profile, however OS was disappointing (median 16 months) (45). The phase III SWOG S0023 study using gefitinib maintenance therapy *vs.* placebo after CRT and consolidative docetaxel in molecularly unselected stage III NSCLC showed favorable safety profile, but potential detrimental effect of gefitinib (median OS of 23 *vs.* 35 months in the placebo arm) (46). The Cancer and Leukemia Group B (CALGB) 30106 phase II trial showed promising OS (median 19 months) in poor risk patients (PS 2 and/or weight loss \geq 5%) with wild type or *EGFR* mutated stage III NSCLC receiving induction chemotherapy, definitive RT with concurrent gefitinib, followed by gefitinib in consolidation (47). The median OS of good risk patients receiving concurrent CRT with gefitinib was dismal (median 13 months). OS was not related to *EGFR* status, but the trial was underpowered to draw any firm conclusions. Acute in-field toxicities (dermatitis, esophagitis, pneumonitis) were not increased with gefitinib, and there was no case of interstitial lung disease. Another Asian feasibility study demonstrated efficacy (median OS of 28.5 months) and acceptable toxicity (grade 1–2 rash in 71% of patients, grade 2–3 pneumonitis in 5.8%) of induction chemotherapy followed by RT plus gefitinib in stage III molecularly unselected NSCLC patients (48). Currently, ongoing trials (LOGIK0902/OLCSG0905 and WJOG6911L) assess the therapeutic ratio of RT combined with EGFR TKIs in *EGFR*-mutated NSCLC (49,50).

Erlotinib, another EGFR TKI, showed acceptable tolerance at a dose of 150 mg daily given concurrently with CRT in a phase I study in stage III NSCLC (51). The rate of in-field dermatitis or radiation pneumonitis was not increased. Another prospective study demonstrated acceptable toxicity (4% grade 3 pneumonitis, 4% grade 3–4 esophagitis, no fatal events) and promising outcomes of concurrent EGFR TKIs (gefitinib or erlotinib) and RT in stage III–IV NSCLC (52). The safety and relative efficacy (median OS of 17 months) of induction chemotherapy followed by RT combined with erlotinib in poor risk stage III NSCLC patients was also demonstrated in the CALGB

Table 1 Selected trials of radio(chemo)therapy combined with anti-EGFR antibodies in NSCLC

Therapy	Trial ID, ref.	Phase	No pts/stage	Induction	Concurrent	Consolidation/ maintenance	RT	Median OS (months)	Toxicity
Cet	SCRATCH, Hughes <i>et al.</i> , (25)	I	12/III	Pt-based CHT	Cet	–	64 Gy/32 fx	NA	G3 fatigue 8%; G3 pneumonia 8%, G5 bronchopneumonia 1 pt
Cet	N0422, Jatoi <i>et al.</i> , (26)	II	57/III	–	Cet	–	60 Gy/30 fx ENI 44 Gy	15.1	G _{≥3} dyspnea 9%, dysphagia 7%
Cet	NEAR, Jenson <i>et al.</i> , (27)	II	30/III	–	Cet	Cet	66 Gy/3 3fx IMRT ENI	19.5	G2 pneumonitis 20%; G3 pneumonitis 3.3%
Cet	Satellite, Hallqvist <i>et al.</i> , (28)	II	75/III	Cis/Doc	Cet	–	68 Gy/34 fx 3D RT	17	G3: skin reactions 11.3%, diarrhea 5.6%, hypersensitivity 5.6%, esophagitis 1.4%, G _{≥3} pneumonitis 4.2%
Cet	Ramalingam <i>et al.</i> , (29)	II	38/III	–	Cet	Car/Pac/Cet	73.5 Gy/35 fx		G3: rash 8%, G3/4: pulmonary embolism 1.1%, G5: pneumonitis - 1 pt, no G _{≥3} esophagitis
Cet	RTOG 0324, Blumenschien <i>et al.</i> , (31)	II	87/III	–	Car/Pac/Cet	Cet→Cet/Car/ Pac	63 Gy/35 fx, ENI 45 Gy	22.7	G3 esophagitis 8%, G _{≥3} pneumonitis 7%, G4 hematologic 20%
Cet	CALGB 30407, Govindan <i>et al.</i> , (32)	II, R	Arm A: 48/III Arm B: 53/III	–	Arm A: Car/Pem Arm B: Car/Pem/Cet	Both arms: Pem	Both arms: 70 Gy/35 fx 3D RT	Arm A: 21.2 Arm B: 25.2	Arm A: G3/4 hematologic: 70%, G _{≥3} pneumonitis: 12%; esophagitis 16%, G5 AE: 2 pts pulmonary hemorrhage, pneumonitis Arm B: G3/4 hematologic: 70%; G _{≥3} pneumonitis: 11%, esophagitis 13%; G5 AE 3 pts (pneumonitis)
Cet	RADITUX, Van den Heuvel <i>et al.</i> , (35,36)	I/II	110/III	–	RT + Cis (6 mg/m ² daily) +/-Cet	–	66 Gy/24 fx	CRT+ Cet: 33 CRT: 30	Acute G _{≥3} : dysphagia 23%, pneumonitis 6%; Late G _{≥3} : esophagitis 8%, pulmonary fibrosis 4%
Cet	RTOG0617, Bradley <i>et al.</i> , (4)	III	544/III	–	Arm I: CRT 60 Gy; Arm II: CRT 74 Gy; Arm III: CRT 60 Gy + Cet; Arm IV: CRT 74 Gy + Cet; CHT: Car/Pac	–	Arm I + III: 60 Gy/30 fx; Arm II + IV: 74 Gy/37 fx	With/without Cet: 25/24; RT 60 Gy: 28.7; RT 74 Gy: 20.3	≥3 AE 60 Gy-arms: 76%, G _{≥3} AE 74 Gy-arms: 79%; G _{≥3} AE Cet-arms: 86%, G _{≥3} AE no Cet-arms: 70%; G _{≥3} radiation pneumonitis 60 Gy-arms: 7%; G _{≥3} radiation pneumonitis 74 Gy-arms: 4%; G _{≥3} radiation esophagitis 60 Gy-arms: 7%; G _{≥3} radiation esophagitis 74 Gy-arms: 21%
Nim	Bebb <i>et al.</i> , (40)	I	18/IV	–	Nim	Nim	30 Gy/10 fx or 36 Gy/12 fx	15	G3/4 AE: neutropenia 5.6%, pneumonia 5.6%; radiation pneumonitis 5.6%, no G3/4 skin toxicity
Nim	Choi <i>et al.</i> , (41)	I	15/IV	–	Nim	Nim	30 Gy/10 fx or 36 Gy/12 fx	9.8	G4 pneumonia with neutropenia 1 pt, at 200 mg Nim (DLT)
Nim	Zhou <i>et al.</i> , (42)	II	11/III	–	Doc/Car/Nim	Doc/Car	50-66 Gy/25-30 fx	Not reached	G4 neutropenia 36.4%, G4 thrombocytopenia 18.2%, G3 radiation pneumonitis 18.2%, G3 esophagitis 18.2%

Ref, reference; RT, radiotherapy; OS, overall survival; NA, not available; IMRT, intensity modulated radiotherapy; 3D RT; 3-dimensional radiotherapy; CRT, chemoradiotherapy; DLT, dose limiting toxicity; Cet, Cetuximab; Nim, Nimotuzumab; Pt, Platinum; Cis, Cisplatin; Car, Carboplatin; Doc, Docetaxel; CHT, Chemotherapy; Pac, Paclitaxel; Pem, Pemetrexed; ENI, Elective nodal irradiation; pt, patient.

30605/RTOG 0972 phase II study (53). A randomized phase II study demonstrated that combining erlotinib with RT in molecularly unselected poor risk stage III NSCLC patients increases complete response rates compared to RT alone, however without OS benefit (54). Adverse events, with the dominant skin toxicity, were significantly more common in the erlotinib arm, but there was no increase of esophageal and pulmonary toxicity. A single-arm prospective phase II trial using erlotinib in combination with CRT in stage III NSCLC showed impressive OS (median 36.5 months) with low toxicity (55). This trial represents the first study to analyze the data considering *EGFR* status. The activating *EGFR* mutation was detected in 10% of tumors and did not impact OS and toxicity. This study suggests that erlotinib can be safely combined with CRT, with the caveat that it was not administered on the same days as chemotherapy because of overlapping toxicity concerns.

Table 2 summarizes the key studies of anti-*EGFR* TKIs in combination with radiotherapy in NSCLC.

ALK signaling pathway and radiation

c-MET represents an upstream activator of AKT and its activity is associated with radioresistance (56,57). Recent studies revealed that *EML4-ALK* fusion protein may network with similar signaling pathways, such as c-MET (58,59). Crizotinib was designed as the first generation *ALK*, *ROS1* and *MET* inhibitor. The preclinical model using a panel of NSCLC cell lines with varying expression levels of c-MET and *EML4-ALK* showed that crizotinib did not affect cellular radiosensitivity (60). It was hypothesized that crizotinib may by-pass the radiosensitizing effect of c-MET inhibition by activating the AKT pathway. Subsequent preclinical studies demonstrated a radiosensitizing potential of crizotinib in *ALK*-positive NSCLC cell lines (61,62). Crizotinib in combination with RT was also shown to inhibit *ALK* autophosphorylation and phosphorylation of its downstream effectors: AKT, STAT3 and ERK1/2, leading to radiosensitization of cells harboring the *EML4-ALK* rearrangement (61). In another preclinical model crizotinib exerted potent and selective anti-proliferative, pro-apoptotic and antiangiogenic radiation-enhancing effects in *ALK*-positive NSCLC cell lines (62). In the *ALK*-positive xenografts the combination of crizotinib and RT was most effective in reducing tumor proliferation and perfusion. In contrast, in tumors that lack *ALK* rearrangement dual combination was inferior compared to RT alone.

Clinical data on *ALK* inhibitors and radiotherapy combinations in locally advanced NSCLC

The NRG/RTOG1306 trial evaluated erlotinib and crizotinib as a 3-month induction preceding standard CRT in stage III *EGFR*-positive or *ALK*-positive NSCLC (63). The study stopped early with only 59 patients enrolled out of 234 planned and the results were disappointing. The median loco-regional PFS was 25.7 months in *EGFR*-positive NSCLC patients treated with induction erlotinib, and 14.7 months in *ALK*-positive NSCLC patients treated with induction crizotinib. The median OS (39.5 months) was reached only for the *EGFR*-positive NSCLC patients who did not receive erlotinib. Serious adverse events occurred in 7% of *EGFR*-positive patients receiving induction erlotinib (one patient developed esophageal fistula), 35% of *EGFR*-positive patients receiving CRT alone (vomiting and pneumonia being the most common), in 44% of *ALK*-positive patients receiving induction crizotinib (pneumonitis, thromboembolic event and esophagitis was experienced by one patient each) and in 29% of *ALK*-positive patients receiving CRT alone (one patient experienced pneumonia and another atrial fibrillation).

With the absence of firm data for concurrent *ALK* TKIs and RT, there is a concern that this strategy may increase radiotoxicity due to radiosensitizing effect in normal tissues. Indeed, the clinical case reports using RT combined with next-generation *ALK* TKIs (alectinib, lorlatinib) showed radiation-induced central nervous system (CNS) necrosis (64,65). One crizotinib-refractory *ALK*-positive NSCLC patient developed radiation necrosis in a CNS metastatic site after 12 months of alectinib treatment and over 7 years from the completion of RT (whole brain radiotherapy, followed by radiosurgery) (64). As pointed out by the authors, the risk of this sequelae remains long after RT.

Angiogenesis inhibition and radiation

The antiangiogenic agents, through neutralization of vascular endothelial growth factor A (VEGF-A), lead to the normalization of pathological tumor vessels, decrease hypoxia of cancer cells and increase their radiosensitivity through the mechanism of biological cooperation (66). Bevacizumab, an anti-VEGF antibody, was also shown to enhance radiosensitivity by inhibiting DSB repair in endothelial cells via direct suppression of the PIK3/AKT/DNA-PK α s signaling pathway (67). Preclinical models

Table 2 Selected trials of radio(chemo)therapy combined with EGFR tyrosine kinase inhibitors in NSCLC

Therapy	Trial ID, ref.	Phase	No pts/stage	Induction	Concurrent	Consolidation/maintenance	RT	Median OS (months)	Toxicity
G	CRITICAL, Ball <i>et al.</i> , (43)	I	28	–	Car/Pac + G	+/- surgery	60 Gy/3 0fx	Not reached, 2Y OS 60%	No DLTs
G	Center <i>et al.</i> , (44)	I	16	–	Do c + G	Doc	70 Gy/35 fx Elective nodal irradiation 40 Gy	21	G3/4 hematologic 27%, G3/4 esophagitis 27%, G3-5 pulmonary toxicity 20%
G	Stinchcombe <i>et al.</i> , (45)	I	23	Car + Irinotecan + Pac + Pegfilgrastim	Car/Pac + G	–	74 Gy/37 fx	16	G3 esophagitis 19.5%, G3 cardiac arrhythmia 9.5%, anterior spinal cord syndrome 1 patient
G	Kelly <i>et al.</i> , (46)	III		+/- G	Eto +/- Cis/	Doc	61 Gy/33 fx	G arm: 23 No G arm: 35	G3/4 pneumonitis 3%, G3 diarrhea 7%, G3 rash 7% G3/4 neutropenia 43%, G \geq 3 esophagitis 13%
G	Ready <i>et al.</i> , (47)	II	Stratum 1: poor risk: 21 Stratum 2: good risk: 39	Car/Pac Car/Pac/irinotecan	G Car/Pac + G	G G	66 Gy/33 fx Elective nodal irradiation 44 Gy	19 13	Stratum 1: G \geq 3 esophagitis 19%, pneumonitis 15%, diarrhea 10% Stratum 2: G \geq 3 esophagitis 31%, diarrhea 18%, pneumonitis 16%, no increased acute radiation-induced toxicity
E	Choong <i>et al.</i> , (51)	I	Arm A: 17 Arm B: 17	– Car/Pac	Cis/Eto + E Ca/Pac + E	Doc –	66 Gy/33 fx, ENI 44 Gy	Arm A: 10.2 Arm B: 13.7	Arm A: G3/4 neutropenia 8 pts, esophagitis 3 pts, diarrhea 2 pts, pneumonitis 1 pt Arm B: G3/4, esophagitis 6 pts, neutropenia 3 pts
E	Wang <i>et al.</i> , (52)	II	G:19, E:7	–	G, E	G, E	Median 70 y	21.8	G3: acne-like rash 8%, esophagitis 4%, pneumonitis 4%, diarrhea 4% G4: symptomatic pulmonary fibrosis 14%, neutropenia 4%
E	Martinez <i>et al.</i> , (54)	II	Arm A: 10 Arm B: 13	– –	Arm A: No E Arm B: E	Arm A: No E Arm B: E	66 Gy/33 fx	Not reached	Arm A: G3: pneumonitis 1 pt Arm B: G3 radiodermatitis 1 pt
E	Komaki <i>et al.</i> , (55)	II	48	–	Pac/Car + E (daily, except days of chemotherapy)	Pac	63 Gy/35 fx	25.8	G3: acne 2 pts, esophagitis 1 pt, pneumonitis 3 pts

ref, reference; RT, radiotherapy; OS, overall survival; DLT, dose limiting toxicity; gefitinib, G; Erlotinib, E; Paclitaxel, Pac; Docetaxel, Doc; Car, Carboplatin; Eto, Etoposide; ENI, elective nodal irradiation; pt, patient.

demonstrated that the combination of bevacizumab with RT markedly inhibits tumor growth and promotes radiation-induced ceramide-dependent apoptosis of endothelial cells (68).

Clinical data on antiangiogenic agents and radiotherapy combinations in locally advanced NSCLC

The randomized phase III ECOG 3598 study demonstrated increased toxicity and no survival benefit (median OS 16 *vs.* 15.3 months) from the addition of thalidomide (an antiangiogenic agent, originally introduced as a sedative and antiemetic compound) to CRT in stage III NSCLC (69). Grade 3 adverse events were more common in the thalidomide arm (53% *vs.* 44%, $P=0.004$). Importantly, 11% of patients in the thalidomide group developed grade ≥ 3 thromboembolic events, compared to 3% in the CRT alone group ($P<0.001$).

A phase I study of bevacizumab in escalating dose combined with RT preceded by chemotherapy in stage III NSCLC was terminated early due to high rates of radiation pneumonitis (70). Bevacizumab was also evaluated in two phase II trials including, respectively, stage III non-squamous NSCLC (71) and limited stage small cell lung cancer (72). In both studies, bevacizumab was administered concurrently with CRT and alone as maintenance therapy. These studies were closed prematurely due to high incidence of tracheoesophageal fistulae (TEF) (5 of 34 patients) (71). This serious toxicity was the result of post-radiation esophageal injury followed by impaired neovascularization and wound healing caused by bevacizumab. The phase I/II trial evaluated bevacizumab administered concurrently with CRT and erlotinib, following induction chemotherapy in stage III NSCLC (72). The main non-hematological grade ≥ 3 toxicity was prolonged esophagitis (39%, one case of tracheoesophageal fistula). The median OS of 18.4 months was disappointing, and the authors did not recommend the use of this combination. The SWOG S0533 pilot trial investigated the addition of bevacizumab to CRT followed by consolidation docetaxel in stage III NSCLC, in two risk strata: high risk—squamous histology, hemoptysis, tumor cavitation and/or proximity to major vessels; low risk—none of these features) (73). Median OS was 46 months and 17 months for the low-risk and high-risk strata, respectively, with two cases of fatal pulmonary hemorrhage. The authors stated that it is not possible to successfully integrate bevacizumab to CRT in stage III NSCLC, particularly in patients with high risk of pulmonary hemorrhage.

The clinical data on multi-targeted antiangiogenic TKIs

(sunitinib, vandetanib) or recombinant human endostatin in combination with RT in NSCLC are also disappointing (74,75).

Table 3 highlights the key studies of antiangiogenic agents in combination with radiotherapy in NSCLC.

The concept of combining targeted therapies with radiotherapy in oligoprogressive and oligopersistent NSCLC

Molecularly targeted therapies represent the standard of care in oncogene-addicted advanced NSCLC. Despite initial response, virtually all patients will develop drug resistance and disease progression (on average after 10–14 months). Around a half of relapses present as oligoprogression, *i.e.*, progression in just a few metastases with otherwise optimal control in the other sites (76). This phenomenon is explained by primary intratumor heterogeneity, where targeted therapies selectively favor intrinsically resistant tumor cell clones. Prolonged administration of a targeted agent may induce acquired resistance development through emergence of secondary mutations, activation of by-pass signaling pathways or phenotypic transformation (77). Oligoprogressive oncogene-addicted advanced NSCLC may be managed by changing systemic therapy, continuation of the same systemic therapy beyond progression, but also by incorporating local therapy, preferentially stereotactic body RT (SBRT), into primary systemic therapy. The idea behind using SBRT, novel RT technique delivering focused high ablative dose of radiation to the target, is to eradicate resistant clones while continuing first line systemic therapy.

The term oligopersistence refers to an oncogene-addicted NSCLC diagnosed at onset as oligometastatic. In this setting, local therapy is used as consolidation to combat oligometastatic lesions. At the development of acquired drug resistance 50–60% of the patients will recur in the original tumor sites (78). The repopulation of TKI-resistant clones present in the residual disease foci explains the biological phenomenon of oligopersistence. In most cases new distant metastases arise from these resistant clones of cancer cells. RT targeting oligopersistent tumor sites may potentially depopulate these clones and defer progression.

Clinical data on targeted agents and radiotherapy combinations in oligoprogressive oncogene-addicted NSCLC

Clinical experience with the use of SBRT in addition to EGFR and ALK TKIs in oligoprogressive NSCLC is

mainly based on small retrospective series. The combination of SBRT and EGFR TKIs was initially evaluated in the context of advanced molecularly unselected oligoprogressive NSCLC. SBRT to the sites of disease progression in NSCLC patients treated with gefitinib, after first line chemotherapy failure, offered median PFS and OS of 7 and 19 months, respectively (79). In another retrospective series of unselected NSCLC patients experiencing oligoprogression while on erlotinib, and salvaged with SBRT to the sites of extracranial progression, median PFS and OS were 14.7 and 20.4 months, respectively (80). The survival parameters were substantially improved compared to historical outcomes of patients who only received systemic therapy. With SBRT, most new distant progressions occurred in new sites (only 6% of recurrences in the irradiation field). The treatment was well tolerated.

In the first small study evaluating oligoprogression in oncogene-addicted NSCLC adding local therapy (RT, surgery or radiofrequency ablation) to EGFR TKIs in patients experiencing oligoprogression provided median time to progression after local therapy, median time to switch to subsequent systemic therapy and median OS from local therapy of 10, 22 and 41 months, respectively (81). In other series using local therapy in addition to EGFR and ALK TKIs, median time to next progression from local therapy ranged between 6 and 11 months (76,82). Administering SBRT during crizotinib treatment in *ALK*-positive oligoprogressive NSCLC resulted in 86% of one-year local control in the irradiated foci, allowing longer crizotinib exposure and providing OS benefit (83). Patients who underwent SBRT continued crizotinib for 28 *vs.* 10 months in patients not offered local therapy. One-year local control rate with single-fraction equivalent dose of >25 Gy and ≤25 Gy was 100% and 60%, respectively (P=0.01). No acute or late >G2 radiation-related toxicity was reported. In a retrospective match cohort of *EGFR*-positive NSCLC patients with oligoprogression during TKI therapy, the median OS in those who did and did not receive additional SBRT was 28.2 and 14.7 months, respectively (P=0.026) (84). Undergoing SBRT was an independent predictor of OS and PFS in the multivariate analysis. In the largest retrospective series of *EGFR*-positive NSCLC patients experiencing oligoprogression during first line EGFR TKI therapy, median PFS1 (calculated from time of initiation of TKI to first progression), PFS2 (calculated from time of initiation of TKI therapy to off-TKI disease progression) and OS were 10.7, 18.3 and 37.4 months, respectively (85). No unexpected toxicities were observed. A large retrospective series using TKIs with RT in oligoprogressive *ALK*-positive

and *EGFR*-positive NSCLC showed impressive two-year OS of 62% (86).

In the clinic, targeted agents are usually withheld 1–3 days before SBRT, reasoning on the half-life time of 36 hours for erlotinib and 40–42 hours for gefitinib and crizotinib, or up to five treatment half-lives (allowing theoretical elimination of 95% of the drug). The drug is usually re-started when the acute radiation-induced toxicity grade ≥2 has disappeared (often the following day after RT if no toxicity is observed).

Table 4 summarizes key clinical trials addressing the role of radiotherapy in advanced oligoprogressive oncogene-addicted NSCLC.

Clinical data on targeted agents and radiotherapy combinations in oligopersistent oncogene-addicted NSCLC

Two randomized phase II trials on systemic therapy with or without local ablative therapy (mostly SBRT) to all oligometastatic NSCLC sites were prematurely stopped after interim analyses found a significant PFS improvement in the experimental arms (87,88). In the first of these trials median OS in the local consolidation therapy arm was 41.2 months, compared to 17 months in the observation arm (87). These data support the concept of using local ablative therapies at the best response to systemic treatment, without waiting for inevitable progression, also in oncogene-addicted oligometastatic NSCLC patients.

In the retrospective analysis including NSCLC patients (<20% with targetable molecular aberrations) treated with SBRT for oligometastases, oligoprogression or the dominant primary tumor, median OS in patients receiving early RT to oligometastases and irradiated only at oligoprogression was 39.3 *vs.* 21.1 months, respectively (89). In a retrospective analysis including *EGFR*-positive NSCLC patients treated with first line EGFR TKIs, PFS in a subset of patients who underwent additional local treatment (hypofractionated RT, SBRT or surgery) was 36 months, compared to 14 months with TKI alone (P=0.0024) (90). The largest retrospective series included 145 *EGFR*-positive NSCLC patients with oligoprogressive disease during first line EGFR TKIs (91). Of those, 35% received additionally ablative therapy (RT, surgery or both) targeting all residual disease sites, 38% targeting the primary tumor or oligometastases, and 27% received no local treatment. The median PFS was 20.6, 15.6 and 13.9 months, respectively, and the median OS was 40.9, 34.1 and 30.8 months, respectively. Importantly, the OS benefit from local therapy was significant only for patients treated to all sites of residual disease, and not for those who

received a partial local treatment. Grade ≥ 3 adverse events included pneumonitis (7.7%) and esophagitis (16.9%). The recently published ATOM phase II trial evaluated the use of SBRT to residual oligopersistent disease after EGFR TKI. The study was closed early due to slow accrual. One-year PFS was 68.8% and median OS reached 43.3 months. No ≥ 3 grade SBRT related toxicities occurred (92).

Table 5 highlights key clinical trials addressing the role of radiotherapy in oligopersistent oncogene-addicted NSCLC.

Summary

Considering the biological rationale supported by preclinical data, combining targeted therapies with RT has long been considered a promising approach in NSCLC. However, none of the targeted therapies so far have demonstrated their added value to CRT, a standard treatment in locally advanced NSCLC. The main reason of these disappointing outcomes is likely due to using TKIs-RT combinations in molecularly unselected patients. The only phase III trial in the field that included molecularly selected (ALK-positive and EGFR-positive) NSCLC patients (RTOG 1306) was prematurely closed due to poor accrual, resulting in the lack of statistical power of the analysis. Another possible explanation of unsuccessful TKIs-RT combination in LA-NSCLC is the hypothetical lack of true synergism between TKIs and chemotherapy if both are combined with concurrent RT, and—potentially—even inhibitory effect of such a trimodality treatment. Indeed, the preclinical data on this strategy has been scarce. Importantly, all available data in this field come from the pre-PACIFIC era, and should be viewed in the context of the new standard of care in locally advanced NSCLC, i.e., CRT followed by consolidation durvalumab.

The side effects of particular targeted therapies while combined with RT are generally specific for their classes. However, since these substances are expected to own radiosensitizing potential, their concomitant use with RT may increase both acute and late thoracic radiation toxicity, such as pulmonary, esophageal, cardiac and skin toxicity.

Combining RT with targeted agents in locally advanced NSCLC still raises questions concerning optimal patient selection, RT timing, duration and fractionation, to mention only a few. These issues can only be answered by large, well-designed multi-center clinical trials dedicated to molecularly-selected populations, with careful long-term safety analyses, and using best available agents in particular classes (e.g., osimertinib for EGFR-positive tumours and

alectinib for ALK-positive tumours. Future studies should also be based on more robust data from preclinical research.

The heterogeneity of oligoprogression definitions and limited clinical experience do not allow for firm conclusions regarding the role of RT in oligoprogressive oncogene-driven NSCLC patients managed with targeted therapy. Nonetheless, this strategy is already considered a standard clinical practice, supported by European Society of Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines. The use of consolidation RT in advanced oligopersistent oncogene-driven NSCLC creates the possibility to interfere with the natural course of the disease, resulting in progression delay. However, the real benefit from combining targeted agents with RT in oligoprogressive or oligopersistent oncogene-driven NSCLC still warrants confirmation in well-designed trials. These trials will necessitate advanced functional imaging (to confirm real oligoprogression and rule out polyprogression) and biomarker analysis of material obtained through tissue or liquid biopsy. Careful patient selection and the identification of reliable factors that predict a biologically favorable oligometastatic disease seem crucial. A few trials with the focus on oligoprogressive or oligopersistent oncogene-driven NSCLC are currently ongoing. The Canadian STOP-NSCLC (NCT02756793) phase II trial enrolls NSCLC patients with up to five progressing metastases during TKI or maintenance chemotherapy. Patients are randomized to SBRT to progressing sites while continuing primary systemic therapy, or systemic therapy alone (continuing the same drug beyond progression, switching to another agent, or observation). In the European HALT trial, EGFR-positive or ALK-positive NSCLC patients undergoing TKI treatment are randomized to TKI continuation with or without SBRT. In both studies the primary end point is PFS. In the ongoing NCT02314364 phase II trial, EGFR-positive, ALK-positive or ROS1-positive NSCLC patients after 6 months on TKIs without disease progression receive SBRT to residual extracranial (up to five) disease sites. The primary end point is frequency of distant failure. The ongoing US NCT02759835 trial, with PFS as the primary endpoint, includes oligoprogressive EGFR-positive NSCLC patients treated with a third generation EGFR TKI osimertinib.

Combining SBRT with targeted therapies in oligometastatic oncogene-driven NSCLC holds great promise for prolonging PFS and OS, at least in some subsets of patients. While waiting for the results of trials, physicians are encouraged to offer SBRT with risk-adapted

Table 3 Selected trials of radio(chemo)therapy combined with antiangiogenic agents in NSCLC

Therapy	Trial ID, ref.	Phase	No pts/stage	Induction	Concurrent	Consolidative/ maintenance	RT	Median OS (months)	Toxicity
Tha	ECOG 3598, Hoang <i>et al.</i> , (69)	III	546/III	Arm A: Pac + Car Arm B: Pac + Car + Thalidomide	Arm A: Pac/Car Arm B: Pac/Car + Tha	Arm A: – Arm B: thalidomide	60 Gy/30 fx	Arm A: 15.3 Arm B: 16	Arm A: G \geq 3 thromboembolic events 3%, fatigue 6%, sensory neuropathy 6%, dizziness 1%, decreased consciousness 1% Arm B: G \geq 3 thromboembolic events 11%, fatigue 11%, sensory neuropathy 11%, dizziness 6%, decreased consciousness 5%, no increased radiation-related toxicities
Bev	Lind <i>et al.</i> , (70)	I	6/III	Cis-based	Bev 7.5 mg/kg, 15 mg/kg	–	66 Gy/33 fx	N/A	G3 pneumonia 2 pts, G2 pneumonia 2 pts
Bev	Socinski <i>et al.</i> , (72)	II	45/III	Pac + Car + Bev	Pac/Car + Bev +/- erlotinib	Bev +/- erlotinib	74 Gy/37 fx	18.4	G3/4 esophagitis 29%, G \geq 3 esophagitis 54%, tracheoesophageal fistula 1 pt
Bev	SWOG S0533, Wozniak <i>et al.</i> , (73)		Low risk strata: 16 High risk strata: 12/III	–	Eto/Cis+ Cohort 1: no Bev Cohort 2: Bev d. 15,36,57 Cohort 3: Bev d. 1,22,43	Doc+ Bev	64.8 Gy/36 fx	46 17	Low risk strata—CRT. G3/4 neutropenia 4 pts, esophagitis 1 pt, Consolidation phase: G3 pneumonitis 1 pt High risk strata—CRT. G3/4 neutropenia 6 pts, G3 pneumonitis 1 pt, esophagitis 1 pt, Consolidation phase: G5 hemorrhage 2 pts, G3 hemorrhage 1 pt, G3 pneumonitis 1 pt

Ref, reference; Tha, Thalidomide; Bev, bevacizumab; pt, patient; Pac, Paclitaxel; Cis, Cisplatin; Car, Carboplatin; Doc, Docetaxel; Eto, Etoposide.

Table 4 Selected trials of radiotherapy combined with tyrosine kinase inhibitors in oligoprogressive oncogene-driven NSCLC

Author, ref.	No pts	Molecular status	Therapy	Median PFS	Median OS	Toxicity
Wang <i>et al.</i> , (79)	14	UNK	G, SBRT	7	19	G3 pneumonitis 7%, esophagitis 7%, rash 7%, no G4/5
Iyengar <i>et al.</i> , (80)	24	0/13 EGFR+, other UNK	E, SBRT	14.7	20.4	G5 1 pt
Yu <i>et al.</i> , (81)	18	EGFR+	E, G, SBRT	10	41	G4 SBRT-related 1 pt, G4 TKI-related 4 pts
Weickhardt <i>et al.</i> , (76)	25	EGFR+, ALK+	E, C, SBRT	PFS 2–6.2 (from progression on TKIs)	NR	G1/2 fatigue 16%, G1/2 nausea 5%, no G3/4 toxicity
Conforti <i>et al.</i> , (82)	15	EGFR+	E, G, SBRT	10.9	39	No G3/4 toxicity
Gan <i>et al.</i> , (83)	14	ALK+	C, SBRT	9.1	39	No >G2 toxicity
Borghetti <i>et al.</i> , (86)	50	EGFR +, ALK+	E, G; C; SBRT, HRT	5.5	19.3	G3 neurologic: 2 pts

ref, reference; pt, patient; UNK, unknown; SBRT, stereotactic body radiotherapy; PFS, progression free survival; OS, overall survival; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; G, Gefitinib; E, Erlotinib; C, crizotinib; HRT, hyperfractionated radiotherapy.

Table 5 Selected trials of radiotherapy combined with tyrosine kinase inhibitors in oligopersistent oncogene-driven NSCLC

Author, ref.	No pts	Molecular status	Therapy	Median PFS (months)	Median OS (months)	Toxicity
Gomez <i>et al.</i> , (87)	49	EGFR+ 6 ALK+ 2 No aberration 41	Systemic therapy + local consolidative therapy	14.2	41.2	G3 in local consolidative therapy group: esophagitis 2 patients, anaemia 1 patient, pneumothorax 1 patient, abdominal pain 1 patient, No G4-5 toxicities
Elamin <i>et al.</i> , (90)	12	EGFR+	EGFR TKI + SBRT, HRT or surgery	36	NR	No G4 toxicities
Xu <i>et al.</i> , (91)	51	EGFR+	EGFR TKI + Arm A: SBRT to all residual metastatic sites Arm B: SBRT to primary tumor and oligometastatic sites Arm C: no SBRT	20.6 15.6 13.9	40.9 34.1 30.8	G \geq 3, esophagitis 16.9%, pneumonitis 7.7%

ref, reference; pt, patient; PFS, progression free survival; OS, overall survival; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; SBRT, stereotactic body radiotherapy; NR, not reached; HRT, hypofractionated radiotherapy.

dose fractionation to carefully selected oncogene-addicted oligoprogressive/oligopersistent NSCLC patients in the course of targeted therapy.

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Footnote

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