Chapter 9
Locally Advanced Non-small Cell Lung Cancer and Targeted Therapy

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Abstract Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB diseases, has been treated with concurrent chemoradiotherapy using a platinum doublet, but the effect of this conventional therapy has reached a plateau. Current research focuses on molecular targeted agents, especially epidermal growth factor receptor (EGFR)-directed agents and angiogenesis inhibitors. Although many preclinical experiments showed promising synergistic effects of EGFR-directed agents and radiation, no clinical trials have yet demonstrated the reproducibility of the preclinical results. Numerous preclinical models also showed synergistic effects of angiogenesis inhibitors and radiation without excessive toxicity. However, early clinical investigations of bevacizumab and chemoradiotherapy were closed early due to serious and unacceptable toxicities such as tracheoesophageal fistula and potentially fatal pneumonitis. The current review disclosed and discussed many issues on incorporation of molecular targeted agents into the treatment of unresectable stage III NSCLC.

Keywords Chemoradiotherapy • Epidermal growth factor receptor • Angiogenesis inhibitors • Tracheoesophageal fistula

9.1 Standard Treatment of Locally Advanced Unresectable Non-small Cell Lung Cancer

Locally advanced unresectable non-small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB diseases, accounts for approximately one fourth of all patients with NSCLC [1, 2]. The disease of this stage is characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes as well as occult systemic micrometastases in the majority of patients. The standard treatment for patients with a good performance status has been concurrent

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chemoradiotherapy [3, 4]. A platinum doublet using a third-generation anticancer agent combined with thoracic radiotherapy has yielded a median overall survival time of 22–30 months and long-term survivors of about 20 % [5], but the effect of platinum-based chemotherapy has reached a plateau [6–8]. Since about one third of patients had a relapse within a radiation field, enhanced local treatment may improve survival of these patients. However, a phase III trial of high-dose versus standard-dose thoracic radiotherapy using three-dimensional conformal radiotherapy or IMRT concurrently combined with chemotherapy (RTOG0617) showed poorer survival in the high-dose arm probably due to excessive toxicity to normal tissues [9]. Thus, new types of agents are needed for patients with locally advanced NSCLC to lead a longer and fuller life. Current research focuses on molecular targeted agents, especially epidermal growth factor receptor (EGFR)-directed agents and angiogenesis inhibitors.

9.2 Monoclonal Antibodies Against EGFR

In tumor cells, EGFR has an important role in cellular proliferation, inhibition of apoptosis, migration and invasion, and angiogenesis through activation of many signaling pathways including the RAS-mitogen-activated protein kinase pathway and phosphatidylinositol-3-kinase-AKT pathway [10]. Activation of EGFR signaling can be mediated by ionizing radiation as well as oncogenic EGFR. The activated EGFR signaling leads to radioresistance by inducing cell proliferation and apoptosis inhibition and enhancing DNA repair [11, 12]. The relationship between EGFR expression and radioresistance was shown among several murine carcinoma cell lines [13, 14], and a transfection study confirmed this relationship [15]. Several in vitro and in vivo studies showed synergistic effect of anti-EGFR antibody cetuximab and radiation [13, 16, 17]. This synergistic activity was obtained only in cetuximab-sensitive cell lines [17].

A benefit of the cetuximab and radiation combination was also demonstrated in a clinical setting; a combination of cetuximab and radiotherapy resulted in a significant improvement in 5-year overall over radiotherapy alone (45.6 % vs. 36.4 %) in a randomized phase III trial of locally advanced head and neck cancer [18]. However, the addition of cetuximab to chemoradiotherapy failed to show any survival benefits in either head and neck cancer (RTOG 0522) [19] or esophageal cancer (RTOG 0436) [20].

Safety of cetuximab combined with thoracic radiotherapy was firstly evaluated in SCRATCH study ($n = 12$), showing that the early and late toxicities of concurrent cetuximab and thoracic radiotherapy were acceptable, although one patient died of bronchopneumonia [21]. The following phase II trials of concurrent cetuximab and thoracic radiation with induction or consolidation platinum-doublet chemotherapy showed a median OS of 17.0 months or 19.4 months, respectively, with one death of pneumonitis in each study [22, 23]. A phase I trial of cetuximab in addition to chemoradiotherapy with cisplatin and vinorelbine showed that cetuximab could be

safely added to chemoradiotherapy with grade 3–4 toxicity in 12 of 25 patients and one treatment-related death of hemoptysis 4 months after radiotherapy [24]. Phase II trials confirmed the toxicity profile of cetuximab combined with chemoradiotherapy, but median overall survival times seemed no improvement when compared with chemoradiotherapy without cetuximab (Table 9.1) [22, 23, 25–28]. A randomized phase II trial of carboplatin, pemetrexed, and thoracic radiotherapy with or without cetuximab (CALGB30407) showed no difference in failure-free survival, overall survival, or grade 3 or severe toxicity except for skin rash between the arms [27]. A landmark phase III trial of paclitaxel and carboplatin chemotherapy combined with thoracic radiotherapy of 60 Gy (n = 151), 74 Gy (n = 107), 60 Gy with cetuximab (n = 137), or 74 Gy with cetuximab (n = 100) (RTOG0617) showed an identical median overall survival of 25.0 months in patients receiving cetuximab and 24.0 months in patients who did not (HR 1.07, 95 % CI 0.84–1.35; p = 0.29). The overall incidence of grade 3 or worse toxicity for patients receiving chemoradiotherapy with cetuximab and chemoradiotherapy alone was 86 % and 70 %, respectively ($P < 0.0001$).

9.3 EGFR Tyrosine Kinase Inhibitors

EGFR tyrosine kinase inhibitors (TKIs) are another class of agents that inhibit EGFR, especially EGFR with somatic mutations in its tyrosine kinase domain [29, 30]. The EGFR mutations sensitize tumor cells to ionizing radiation by 500- to 1000-fold through the delayed repair of DNA double-strand breaks when compared with EGFR wild-type tumor cells [31, 32]. Several lines of studies showed that gefitinib and erlotinib potentiated radiation effects in NSCLC with EGFR wild type in vitro and in vivo by suppressing cellular DNA repair capacity and G2/M phase cell cycle arrest [33–38]. For EGFR-mutated cells, there are no experimental studies that tried to investigate the interaction between EGFR-TKIs and radiation.

There are several feasibility and phase II trials of EGFR-TKIs combined with thoracic radiotherapy or chemoradiotherapy in patients with unresectable stage III NSCLC (Table 9.2) [39–45]. These studies showed that these attempts were all feasible with acceptable toxicity, but the efficacy was disappointing in all but one trial. Komaki R et al. reported a phase II trial of erlotinib concurrently with weekly carboplatin and paclitaxel chemotherapy and thoracic intensity-modulated radiation therapy at a total dose of 63 Gy in 35 fractions followed by carboplatin and paclitaxel chemotherapy in 46 patients with previously untreated unresectable stage III NSCLC [45]. In the amended protocol, the primary endpoint of this study was time to progression, and the authors hypothesized that combining erlotinib and chemoradiation would increase the median time to progression from 15 to 25 months. The survival results looked promising at a glance; the median OS in this study was 36.5 months, and 2- and 5-year OS rates were 67.4 % and 35.9 %, respectively. None of these survival parameters differed by EGFR mutation status. The time to progression, however, was only 14 months with a distant failure noted in 59 % of

Table 9.1 Phase II trials of cetuximab and thoracic radiotherapy or chemoradiotherapy in patients with non-small cell lung cancer

Author (study name)	Year	Radiation (Gy/fractions)	Chemotherapy			N of patients	Overall survival		Grade 3–4 pneumonitis (%)	Treatment-related death (%)
			Induction	Concurrent	Consolidation		Median (month)	2y rate (%)		
Hallqvist A (SATELLITE)	2011	68/34	CDDP+DTX	Cetuximab	None	75	17.0	37.0	4.2	1.4
Ramalingam SS	2013	73.5/35	None	Cetuximab	CBDCA + PTX	38	19.4	25.0	0	2.6
van den Heuvel MM	2014	66/24	None	Daily cisplatin	None	51	NR	58.0	0	0
		66/24	None	Daily cisplatin + cetuximab	None	51	NR	62.0	11.8	3.9
Blumenschein GR (RTOG 0324)	2011	63/35	None	CBDCA + PTX + cetuximab	CBDCA + PTX + cetuximab	93	22.7	49.3	16.1	6.5
Govindan R (CALGB 30407)	2011	70/35	None	CBDCA + PEM	PEM	48	21.2	48.0	12.0	4.0
		70/35	None	CBDCA + PEM + cetuximab	PEM	53	25.2	50.0	11.3	5.7
Liu D	2015	60–66/30–33	CDDP + DTX + cetuximab	CDDP + DTX + cetuximab	None	27	26.7	51.9	0	0

CBDCA carboplatin, *CDDP* cisplatin, *DTX* docetaxel, *NR* not reported, *PEM* pemetrexed, *PTX* paclitaxel

Table 9.2 Epidermal growth factor receptor-tyrosine kinase inhibitors: feasibility and phase II trials

Author (study name)	Year	Radiation (Gy/fractions)	Chemotherapy			N of patients	Mutated EGFR (%)	Overall survival		Grade 3–4 pneumonitis (%)	Treatment-related death (%)
			Induction	Concurrent	Consolidation			Median (month)	2y rate (%)		
Feasibility trials											
Stinchcombe TE	2008	74/37	CBDCA + PTX + CPT	CBDCA + PTX + gefitinib	Gefitinib	23	NR	16.0	20.0	4.8	0
Okamoto I	2011	60/30	Gefitinib	Gefitinib	Gefitinib	9	25	6.3	33.0	11.1	0
Rothschild S	2011	63/34	CDDP + GEM or CBDCA +PTX	Gefitinib	Gefitinib	5	NR	12.6	NR	0.0	0
				CDDP + gefitinib	Gefitinib	9	NR			11.1	0
Choong NW	2008	66/33	None	CDDP + ETP + erlotinib	DTX	17	NR	10.2	25.0	5.9	0
			CBDCA + PTX	CBDCA + PTX + erlotinib	none	17	NR	13.7	20.0	0.0	0
Phase II trials											
Ready N (CALGB30106)	2010	66/33	CBDCA + PTX	Gefitinib	Gefitinib	(Poor risk) 21	28.9	19.0	32.0	9.5	4.8
		66/33	CBDCA + PTX	CBDCA + PTX + gefitinib	Gefitinib	(Good risk) 39		13.0	26.0	10.3	5.1
Niho S (JCOG0402)	2012	60/30	CDDP + VNR	Gefitinib	Gefitinib	38	NR	28.1	65.4	3.0	0
Komaki R	2015	63/32	None	CBDCA + PTX + erlotinib	CBDCA + PTX	48	9.8	36.6	67.4	8.3	0

CBDCA carboplatin, *CDDP* cisplatin, *CPT* irinotecan, *DTX* docetaxel, *EGFR* epidermal growth factor receptor, *ETP* etoposide, *GEM* gemcitabine, *NR* not reported, *PEM* pemetrexed, *PTX* paclitaxel, *VNR* vinorelbine

patients. They concluded that the time to progression did not meet the assumption and more effective systemic therapy was needed.

Another approach to unresectable stage III NSCLC is to add an EGFR-TKI as a maintenance therapy after completion of a standard chemoradiotherapy. A phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in unresectable stage III NSCLC showed that the gefitinib arm was inferior in overall survival to the placebo arm (median survival: 23 months versus 35 months, $p = 0.013$) [46]. This unexpected outcome could not be explained by excessive toxicity in the gefitinib arm, because grade 4 toxicity was noted only 2 % of patients and no toxic death in the gefitinib arm. One possible explanation was an imbalance in prognostic factors including smoking history, tumor EGFR mutation status, and K-ras mutation status, which might have contribution in poorer outcome in the gefitinib arm. Finally, the possibility that gefitinib somehow stimulated tumor growth either directly or indirectly cannot be excluded [47]. Erlotinib as maintenance treatment after concurrent chemoradiotherapy seemed also not promising in patients with stage III NSCLC not selected by EGFR mutations [48].

9.4 Angiogenesis Inhibitors

Angiogenesis is the essential process for further growth after tumors reach a diameter of 1–2 mm to maintain blood supply to the tumors. Angiogenesis is also critical for the efficacy of radiotherapy through several mechanisms. Tumor vascular bed is abnormal and irregular in its structure and function with the incomplete and heterogeneous oxygen supply. This leads to hypoxic radioresistance of tumor cells through lack of oxygen to facilitate DNA damage by radiation-induced free radicals and upregulation of hypoxia-inducible factor-1α (HIF-1α) [49]. In addition, radiation directly induces HIF-1α expression in tumor cells. The HIF-1α renders tumor cell phenotype suitable for proliferation by transcriptionally activating several genes, as well as induces tumor cells to secrete vascular endothelial growth factor (VEGF) [50], which serves to enhance endothelial cell radioresistance and angiogenesis after radiation [51, 52]. It was shown that tumor response to radiotherapy was closely related to endothelial cell apoptosis [53].

The rationale of combining angiogenesis inhibitors and radiation is vascular normalization, the remodeling of a dysfunctional tumor vasculature to a normal phenotype to restore tumor perfusion and oxygenation, and inhibition of radiation-induced angiogenesis signaling for repopulation of tumor cells after radiation [54]. Numerous preclinical models showed synergistic effects of the two modalities in a dose- and schedule-dependent manner, probably because disruption of tumor vessels hampers proper perfusion and aggravates tumor tissue hypoxia [55–58]. Thus, the vascular normalization window, the transient period of vessel normalization during anti-angiogenesis therapy, is important for the clinical application of angiogenesis inhibitors during radiotherapy, but it is difficult to determine when the normalization window occurs in patients, because the tumor growth kinetics in patients differ from those in animal models [54].

Early clinical investigations of bevacizumab and chemoradiotherapy were closed early due to severe toxicity. A phase II trial of carboplatin, pemetrexed, and bevacizumab induction for two cycles followed by thoracic radiotherapy at a dose of 61.2 Gy in 34 fractions concurrently combined with the same chemotherapy in patients with stage III NSCLC showed that of five patients enrolled, two developed tracheoesophageal fistula, and one died of bilateral pulmonary hemorrhage, left ventricular dysfunction, and subsequent pneumonia [59]. Socinski et al. reported a phase I/II trial of carboplatin, paclitaxel, and bevacizumab for two cycles followed by chemoradiotherapy with weekly carboplatin, paclitaxel and biweekly bevacizumab, and thoracic radiotherapy at a dose of 74 Gy in 37 fractions. Patients in cohort 1 received no erlotinib, whereas patients in cohorts 2 and 3 also received erlotinib at 100 and 150 mg, respectively. Of 45 patients enrolled, one developed grade 3 pulmonary hemorrhage and another developed tracheoesophageal fistula [60]. A phase I trial of induction cisplatin-based doublet chemotherapy and subsequent thoracic radiotherapy to a total dose of 66 Gy in 33 fractions concurrently combined with escalating doses of bevacizumab showed that four of six patients developed pneumonitis [61]. These trials clearly showed that concurrent bevacizumab and thoracic radiotherapy was too toxic. Another feasibility trial of chemoradiotherapy followed by consolidation docetaxel and bevacizumab resulted in two grade 3 pneumonitis and two fatal pulmonary hemoptysis among 21 patients assessable for safety [62]. Thus, even after completion of chemoradiotherapy, bevacizumab develops serious toxicity.

9.5 The Current Issues and Future Directions

The current review disclosed many issues on incorporation of molecular-targeted agents into the treatment of unresectable stage III NSCLC. One strategy for the treatment of stage III disease has been selecting a drug with a survival benefit demonstrated in patients with stage IV NSCLC. In addition, special importance has been placed on synergistic effects shown by preclinical studies. However, these strategies used for conventional cytotoxic chemotherapy require amendment because little is known about combined effects and optimal schedule of molecular-targeted agents and radiation. Identification of patient populations most likely to benefit is also an important subject for both clinical and basic researchers. The EGFR mutation status is crucial when selecting treatment for patients with stage IV NSCLC, but its significance in the treatment of stage III NSCLC remains unknown, because no preclinical or clinical studies showed combined effects of EGFR-TKIs and radiation on EGFR-mutated tumors. Toxicity enhancement by the combination of molecular-targeted agents and radiation also requires further investigation. Observation of tumor-bearing mice treated with a molecular-targeted agent and radiation to the tumor is not enough to evaluate toxicity. Precise experiments focused on toxicity may be more helpful to predict toxicity of the combination in humans.

References

1. Goldstraw P, Crowley J, Chansky K et al (2007) The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2:706–714
2. Groome PA, Bolejack V, Crowley JJ et al (2007) The IASLC Lung Cancer Staging Project: validation of the proposals for revision of the T, N, and M descriptors and consequent stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2:694–705
3. Furuse K, Fukuoka M, Kawahara M et al (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 17:2692–2699
4. Curran WJ Jr, Paulus R, Langer CJ et al (2011) Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 103:1452–1460
5. Horinouchi H, Sekine I, Sumi M et al (2013) Long-term results of concurrent chemoradiotherapy using cisplatin and vinorelbine for stage III non-small-cell lung cancer. Cancer Sci 104:93–97
6. Segawa Y, Kiura K, Takigawa N et al (2010) Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. J Clin Oncol 28:3299–3306
7. Yamamoto N, Nakagawa K, Nishimura Y et al (2010) Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. J Clin Oncol 28:3739–3745
8. Senan S, Brade A, Wang LH et al (2016) PROCLAIM: randomized Phase III trial of Pemetrexed-Cisplatin or Etoposide-Cisplatin Plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 34:953–962
9. Bradley JD, Paulus R, Komaki R et al (2015) Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 16:187–199
10. Roskoski R Jr (2014) The ErbB/HER family of protein-tyrosine kinases and cancer. Pharmacol Res 79:34–74
11. Nyati MK, Morgan MA, Feng FY, Lawrence TS (2006) Integration of EGFR inhibitors with radiochemotherapy. Nat Rev Cancer 6:876–885
12. Baumann M, Krause M, Dikomey E et al (2007) EGFR-targeted anti-cancer drugs in radiotherapy: preclinical evaluation of mechanisms. Radiother Oncol 83:238–248
13. Milas L, Fan Z, Andratschke NH, Ang KK (2004) Epidermal growth factor receptor and tumor response to radiation: in vivo preclinical studies. Int J Radiat Oncol Biol Phys 58:966–971
14. Akimoto T, Hunter NR, Buchmiller L et al (1999) Inverse relationship between epidermal growth factor receptor expression and radiocurability of murine carcinomas. Clin Cancer Res 5:2884–2890
15. Liang K, Ang KK, Milas L et al (2003) The epidermal growth factor receptor mediates radioresistance. Int J Radiat Oncol Biol Phys 57:246–254
16. Huang SM, Harari PM (2000) Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. Clin Cancer Res 6:2166–2174
17. Raben D, Helfrich B, Chan DC et al (2005) The effects of cetuximab alone and in combination with radiation and/or chemotherapy in lung cancer. Clin Cancer Res 11:795–805

18. Bonner JA, Harari PM, Giralt J et al (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354:567–578
19. Ang KK, Zhang Q, Rosenthal DI et al (2014) Randomized phase III trial of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III to IV head and neck carcinoma: RTOG 0522. J Clin Oncol 32:2940–2950
20. Suntharalingam M, Winter K, Ilson D et al (2014) The initial report of RTOG 0436: a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer treated without surgery. J Clin Oncol 32:(suppl 3; abstr LBA6)
21. Hughes S, Liong J, Miah A et al (2008) A brief report on the safety study of induction chemotherapy followed by synchronous radiotherapy and cetuximab in stage III non-small cell lung cancer (NSCLC): SCRATCH study. J Thorac Oncol 3:648–651
22. Hallqvist A, Wagenius G, Rylander H et al (2011) Concurrent cetuximab and radiotherapy after docetaxel-cisplatin induction chemotherapy in stage III NSCLC: satellite—a phase II study from the Swedish Lung Cancer Study Group. Lung Cancer 71:166–172
23. Ramalingam SS, Kotsakis A, Tarhini AA et al (2013) A multicenter phase II study of cetuximab in combination with chest radiotherapy and consolidation chemotherapy in patients with stage III non-small cell lung cancer. Lung Cancer 81:416–421
24. Dingemans AM, Bootsma G, van Baardwijk A et al (2014) A phase I study of concurrent individualized, isotoxic accelerated radiotherapy and cisplatin-vinorelbine-cetuximab in patients with stage III non-small-cell lung cancer. J Thorac Oncol 9:710–716
25. van den Heuvel MM, Uyterlinde W, Vincent AD et al (2014) Additional weekly Cetuximab to concurrent chemoradiotherapy in locally advanced non-small cell lung carcinoma: efficacy and safety outcomes of a randomized, multi-center phase II study investigating. Radiother Oncol 110:126–131
26. Blumenschein GR Jr, Paulus R, Curran WJ et al (2011) Phase II study of cetuximab in combination with chemoradiation in patients with stage IIIA/B non-small-cell lung cancer: RTOG 0324. J Clin Oncol 29:2312–2318
27. Govindan R, Bogart J, Stinchcombe T et al (2011) Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol 29:3120–3125
28. Liu D, Zheng X, Chen J et al (2015) Induction chemotherapy with cetuximab, vinorelbine-cisplatin followed by thoracic radiotherapy and concurrent cetuximab, vinorelbine-cisplatin in patients with unresectable stage III non-small cell lung cancer. Lung Cancer 89:249–254
29. Lynch TJ, Bell DW, Sordella R et al (2004) Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129–2139
30. Paez JG, Janne PA, Lee JC et al (2004) EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 304:1497–1500
31. Das AK, Sato M, Story MD et al (2006) Non-small-cell lung cancers with kinase domain mutations in the epidermal growth factor receptor are sensitive to ionizing radiation. Cancer Res 66:9601–9608
32. Das AK, Chen BP, Story MD et al (2007) Somatic mutations in the tyrosine kinase domain of epidermal growth factor receptor (EGFR) abrogate EGFR-mediated radioprotection in non-small cell lung carcinoma. Cancer Res 67:5267–5274
33. Bianco C, Tortora G, Bianco R et al (2002) Enhancement of antitumor activity of ionizing radiation by combined treatment with the selective epidermal growth factor receptor-tyrosine kinase inhibitor ZD1839 (Iressa). Clin Cancer Res 8:3250–3258
34. She Y, Lee F, Chen J et al (2003) The epidermal growth factor receptor tyrosine kinase inhibitor ZD1839 selectively potentiates radiation response of human tumors in nude mice, with a marked improvement in therapeutic index. Clin Cancer Res 9:3773–3778
35. Tanaka T, Munshi A, Brooks C et al (2008) Gefitinib radiosensitizes non-small cell lung cancer cells by suppressing cellular DNA repair capacity. Clin Cancer Res 14:1266–1273

36. Zhuang HQ, Sun J, Yuan ZY et al (2009) Radiosensitizing effects of gefitinib at different administration times in vitro. Cancer Sci 100:1520–1525
37. Park SY, Kim YM, Pyo H (2010) Gefitinib radiosensitizes non-small cell lung cancer cells through inhibition of ataxia telangiectasia mutated. Mol Cancer 9:222
38. Chinnaiyan P, Huang S, Vallabhaneni G et al (2005) Mechanisms of enhanced radiation response following epidermal growth factor receptor signaling inhibition by erlotinib (Tarceva). Cancer Res 65:3328–3335
39. Stinchcombe TE, Morris DE, Lee CB et al (2008) Induction chemotherapy with carboplatin, irinotecan, and paclitaxel followed by high dose three-dimension conformal thoracic radiotherapy (74 Gy) with concurrent carboplatin, paclitaxel, and gefitinib in unresectable stage IIIA and stage IIIB non-small cell lung cancer. J Thorac Oncol 3:250–257
40. Okamoto I, Takahashi T, Okamoto H et al (2011) Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor. Lung Cancer 72:199–204
41. Rothschild S, Bucher SE, Bernier J et al (2011) Gefitinib in combination with irradiation with or without cisplatin in patients with inoperable stage III non-small cell lung cancer: a phase I trial. Int J Radiat Oncol Biol Phys 80:126–132
42. Choong NW, Mauer AM, Haraf DJ et al (2008) Phase I trial of erlotinib-based multimodality therapy for inoperable stage III non-small cell lung cancer. J Thorac Oncol 3:1003–1011
43. Ready N, Janne PA, Bogart J et al (2010) Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial. J Thorac Oncol 5:1382–1390
44. Niho S, Ohe Y, Ishikura S et al (2012) Induction chemotherapy followed by gefitinib and concurrent thoracic radiotherapy for unresectable locally advanced adenocarcinoma of the lung: a multicenter feasibility study (JCOG 0402). Ann Oncol 23:2253–2258
45. Komaki R, Allen PK, Wei X et al (2015) Adding erlotinib to chemoradiation improves overall survival but not progression-free survival in Stage III non-small cell lung cancer. Int J Radiat Oncol Biol Phys 92:317–324
46. Kelly K, Chansky K, Gaspar LE et al (2008) Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non-small-cell lung cancer: SWOG S0023. J Clin Oncol 26:2450–2456
47. Keedy VL, Arteaga CL, Johnson DH (2008) Does gefitinib shorten lung cancer survival? Chaos redux. J Clin Oncol 26:2428–2430
48. Casal Rubio J, Firvida-Perez JL, Lazaro-Quintela M et al (2014) A phase II trial of erlotinib as maintenance treatment after concurrent chemoradiotherapy in stage III non-small-cell lung cancer (NSCLC): a Galician Lung Cancer Group (GGCP) study. Cancer Chemother Pharmacol 73:451–457
49. Wachsberger P, Burd R, Dicker AP (2003) Tumor response to ionizing radiation combined with antiangiogenesis or vascular targeting agents: exploring mechanisms of interaction. Clin Cancer Res 9:1957–1971
50. Semenza GL (2003) Targeting HIF-1 for cancer therapy. Nat Rev Cancer 3:721–732
51. Moeller BJ, Cao Y, Li CY, Dewhirst MW (2004) Radiation activates HIF-1 to regulate vascular radiosensitivity in tumors: role of reoxygenation, free radicals, and stress granules. Cancer Cell 5:429–441
52. Moeller BJ, Dreher MR, Rabbani ZN et al (2005) Pleiotropic effects of HIF-1 blockade on tumor radiosensitivity. Cancer Cell 8:99–110
53. Garcia-Barros M, Paris F, Cordon-Cardo C et al (2003) Tumor response to radiotherapy regulated by endothelial cell apoptosis. Science 300:1155–1159
54. Kleibeuker EA, Griffioen AW, Verheul HM et al (2012) Combining angiogenesis inhibition and radiotherapy: a double-edged sword. Drug Resist Updat 15:173–182

55. Winkler F, Kozin SV, Tong RT et al (2004) Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. Cancer Cell 6:553–563
56. Dings RP, Loren M, Heun H et al (2007) Scheduling of radiation with angiogenesis inhibitors anginex and Avastin improves therapeutic outcome via vessel normalization. Clin Cancer Res 13:3395–3402
57. Cao C, Albert JM, Geng L et al (2006) Vascular endothelial growth factor tyrosine kinase inhibitor AZD2171 and fractionated radiotherapy in mouse models of lung cancer. Cancer Res 66:11409–11415
58. Geng L, Donnelly E, McMahon G et al (2001) Inhibition of vascular endothelial growth factor receptor signaling leads to reversal of tumor resistance to radiotherapy. Cancer Res 61:2413–2419
59. Spigel DR, Hainsworth JD, Yardley DA et al (2010) Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. J Clin Oncol 28:43–48
60. Socinski MA, Stinchcombe TE, Moore DT et al (2012) Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non-small-cell lung cancer: results of a phase I/II trial. J Clin Oncol 30:3953–3959
61. Lind JS, Senan S, Smit EF (2012) Pulmonary toxicity after bevacizumab and concurrent thoracic radiotherapy observed in a phase I study for inoperable stage III non-small-cell lung cancer. J Clin Oncol 30:e104–e108
62. Wozniak AJ, Moon J, Thomas CR Jr et al (2015) A pilot trial of cisplatin/etoposide/radiotherapy followed by consolidation docetaxel and the combination of bevacizumab (NSC-704865) in patients with inoperable locally advanced stage III non-small-cell lung cancer: SWOG S0533. Clin Lung Cancer 16:340–347