Supplemental Data

Legend

Supplemental Table. Inhibitors of homologous recombination combined with radiation therapy in clinical studies. (A) c-Abl kinase inhibitors, (B) tyrosine kinase inhibitors, (C) proteasome inhibitors, (D) histone deacetylase inhibitors that have been combined with radiation therapy in clinical studies. Radiation therapy delivered with conventional fractionation, unless otherwise noted. Patients in the trials are adults, unless otherwise noted. RT, fractionated external beam radiation therapy; MTD, maximum tolerated dose; OS, overall survival; SRS, stereotactic radiosurgery; DLT, dose limiting toxicity; EIAED, hepatic enzyme inducing anti-epileptic drug; WBRT, whole brain radiation therapy; SBRT, stereotactic body radiation therapy; bRFS, biochemical relapse free survival.

Supplemental Tables

A

Drug	Study design	Cancer(s)	Concurrent RT (dose) + other chemotherapy	Outcome	Trial identifier, Reference
imatinib	Phase I/II	high grade glioma	RT (55.8 Gy in 22 fractions, delivered 4 days/week)	patients received 600 mg 3 days per week; toxicity not reported; median OS: 4 months, PFS: 4 months	Scheda
imatinib	Phase I	pediatric brainstem glioma	RT (55.8 Gy in 31 fractions)	50% DLT rate (intratumoral hemorrhage) at 150 mg/m2 twice daily, therefore concurrent administration was discontinued (26% of patients experienced this complication with sequential therapy)	NCT00021229, Pollack
imatinib	case report	rectal gastointestinal stromal tumor	RT (37.8 Gy in 21 fractions)	patient received 400 mg daily starting one week prior to RT, and continuing during RT; achieved partial clinical response, followed by complete pathologic response at surgery	Ciresa

imatinib	case report	metastatic gastrointestinal stromal tumor	RT (54 Gy in 27 fractions)	patient received 400 mg daily during RT; durable (>37 months) clinical complete response in regions also treated with RT	Boruban

B

erlotinib	Phase II	glioblastoma multiforme	RT (59.4 - 60 Gy in 30 - 33 fractions) + temozolomide	patients received 200 mg daily (on EIAED), 100 mg daily (if not on EIAED) during RT; ≥3.1% grade 4 (neutropenia) toxicity; median OS: 19.3 months	Prados
erlotinib	Phase II	glioblastoma multiforme	RT (60 Gy in 30 fractions) + temozolomide	MTD: 50-150 mg daily (escalated dose in each patient); 11% grade 5 toxicity rate; median OS: 8.3 months	Peereboom
erlotinib	Phase I/II	glioblastoma multiforme	RT (60 Gy in 30 fractions) + temozolomide	patients received 150 mg daily 1 week prior to, and during RT; 2.5% grade 5 (pneumonia) and ≥7.3% grade 4 (leukopenia) toxicity; median OS: 15.7 months	Brown
erlotinib	Phase I	locally advanced pancreatic cancer	RT (50.4 Gy in 28 fractions) + gemcitabine/paclitaxel	MTD: 50 mg daily; 6 of 13 patients had partial response; median OS: 14 months	Ianitti
erlotinib	Phase I	locally advanced pancreatic cancer	RT (50.4 Gy in 28 fractions) + gemcitabine	MTD: 100 mg daily; 6 of 17 patients had partial response; median OS: 18.7 months	Duffy
erlotinib	Phase I	locally advanced pancreatic cancer	RT (30 - 38 Gy in 15 - 19 fractions) + gemcitabine	patients received 100 mg daily; MTD of RT was 30 Gy in 15 fractions; efficacy not reported	Robertson
erlotinib	Phase I	locally advanced non-small cell lung cancer	RT (50.4 Gy in 28 fractions) + cisplatin/5-fluorouracil	MTD: 150 mg daily; no response data reported	Dobelbower
erlotinib	Phase I	locally advanced non-small cell lung cancer	RT (45 - 60 Gy in 15 - 30 fractions)	MTD: 100 mg daily; 20% rate of grade 5 toxicity (pneumonitis) at 150 mg daily; 62.5% clinical partial response	Wan
erlotinib	Phase I	glioblastoma multiforme	RT (60 Gy in 30 fractions)	MTD: ≥200 mg daily (on EIAED), ≥150 mg daily (if no EIAED); median OS: 11.7 months (on EIAED), 15.1 months (if no EIAED)	Krishnan
erlotinib	Phase I	pediatric high grade glioma	RT (54 - 59.4 Gy in 30 - 33 fractions)	MTD: 120 mg daily; median OS: ~24 months	Broniscer

erlotinib	Phase I	brain metastasis from non-small cell lung cancer	WBRT (30 Gy in 10 fractions)	MTD: 150 mg daily; median OS: 4.4 months	NCT00536861, Lind
erlotinib	Phase I	locally advanced non-small cell lung cancer	RT (66 Gy in 33 fractions) + cisplatin/etoposide or carboplatin/paclitaxel	MTD: 150 mg daily; median OS: 11 months	Choong
erlotinib	Phase I	uterine cervix cancer	RT (45 Gy in 25 fractions + 24 Gy in 4 insertions) + cisplatin	MTD: 150 mg daily; 91.7% clinical complete response rate	Nogueira-Rodgrigues
erlotinib	case report	metastatic non-small cell lung cancer	RT (16 Gy in 2 fractions), once weekly	patient receiving 150 mg daily experienced fatal diarrhea	Silvano
erlotinib	case report	2nd primary non-small cell lung cancer	RT (50 Gy in 25 fractions)	patient receiving erlotinib for initial primary non-small cell lung cancer experienced complete clinical response at 28 Gy; grade 3 pneumonitis developed 10 weeks after RT	Nanda
gefitinib	Phase II	brain metastases from non-small cell lung cancer	WBRT (40 Gy in 20 fractions)	patients received 250 mg daily during RT; no grade ≥4 toxicity; median OS: 13.0 months	Ma
gefitinib	Phase II	locally advanced head and neck cancer	RT (68.4 Gy in 38 fractions) +/- docetaxel	MTD: 250 mg daily; 3 year OS: 54%	Hainsworth
gefitinib	Phase II	locally advanced pancreatic cancer	RT (50.4 Gy in 28 fractions) + paclitaxel	patients received 250 mg daily 7-10 days before, and during RT; no grade ≥4 toxicity; median OS: 8 months	Olsen
gefitinib	Phase II	locally advanced esophageal cancer	RT (1.5 Gy in 20 fractions) twice daily + cisplatin/5-fluorouracil	patients received 250 mg daily during RT; 5% grade 3-4 toxicity; median OS: 24 months	NCT00258323, Rodriguez
gefitinib	Phase II	locally advanced non-small cell lung cancer	RT (66 Gy in 33 fractions) + carboplatin/paclitaxel (if good risk)	patients received 250 mg daily; toxicity not reported; median OS: 19.0 months (poor risk), 12.0 months (good risk)	NCT00040794, Ready
gefitinib	Phase I/II	localized prostate cancer	RT (72.4 Gy in 29 fractions)	patients treated with 250 mg daily 7 days before, and during RT; 38.1% of patients experienced DLTs; 5 year bRFS: 97%	NCT00239291, Joensuu
gefitinib	Phase I/II	glioblastoma multiforme	RT	MTD: 500 mg daily (if not on EIAED); median OS: 11 months	NCT00052208, Chakravarti

gefitinib	Phase I/II	locally advanced esophageal cancer	RT (50.4 Gy in 28 fractions) + oxaliplatin	patients received 150 mg daily during RT; no grade ≥4 toxicity; median OS: 10.8 months	NCT00093652, Javle
gefitinib	Phase I/II	locally advanced head and neck cancer	RT (50 - 104 Gy in 25 - 52 fractions)	MTD: 250 mg daily; median OS: 8.5 months	NCT00233636, Caponigro
gefitinib	Phase I	locally advanced head and neck cancer	RT (70 Gy) +/- cisplatin	MTD: 500 mg daily; 3 year OS: 74%	NCT00033449, Chen
gefitinib	Phase I	locally advanced head and neck cancer	RT (70 - 76 Gy in 35 - 38 fractions) + paclitaxel	MTD: 250 mg daily (with paclitaxel 36 mg/m2 weekly); 50% complete pathologic response rate	NCT00083057, Van Waes
gefitinib	Phase I	locally advanced non-small cell lung cancer	RT (74 Gy in 37 fractions + carboplatin/paclitaxel	patients received 250 mg daily during RT; 4.8% grade 4 toxicity (embolism and thrombocytopenia); median OS: 16 months	NCT00280787, Stinchcombe
gefitinib	Phase I	locally advanced non-small cell lung cancer	RT (70 Gy in 35 fractions) + docetaxel	patients received 250 mg daily; MTD of docetaxel: 20 mg/m2; median OS: 21 months	NCT00310154, Center
gefitinib	Phase I	rectal and pancreatic cancer	RT (50.4 Gy in 28 fractions) + capecitabine	MTD: <250 mg daily (50% of patients experienced DLTs at initial dose level); all patients that underwent resection experienced partial pathologic response	Czito
gefitinib	Phase I	locally advanced pancreatic cancer	RT (45 Gy in 25 fractions) + gemcitabine	MTD: 250 mg daily (with gemcitabine 200 mg/m2); median OS: 7.5 months	Maurel
gefitinib	Phase I	recurrent malignant glioma	SRS (18 - 36 Gy in 3 fractions)	patients received 250 mg daily, 7 days before, and during SRS; no toxicity reported; median OS: 10 months	Schwer

C

bortezomib	Phase I	recurrent or metastatic head and neck cancer	RT (50 - 70 Gy in 25 - 35 fractions)	MTD: <0.6 mg/m2 (40% of patients experienced DLTs at initial dose level); median OS: 6 months	NCT00016003, Van Waes
bortezomib	Phase I	primary and recurrent central nervous system	RT (30 - 66 Gy in 10 - 35 fractions) + temozolomide	MTD: 1.3 mg/m2; median OS: 17.4 months (all diseases), 16.9 months (newly diagnosed high grade gliomas)	Kubicek

		cancers			
bortezomib	Phase I	relapsed/refractory multiple myeloma	^{153}Sm-lexidronam pentasodium (0.5 - 1.0 mCi/kg)	MTD: 1.3 mg/m2 (for 0.5 mCi/kg), ≥1.0 mg/m2 (for 1.0 mCi/kg); overall response rate: 21%	NCT00316940, Berenson
nelfinavir	Phase I	locally advanced pancreatic cancer	RT (59.4 Gy in 33 fractions) + cisplatin/gemcitabine	patient received 1.25 mg twice daily; 10% rate of DLTs (gastrointestinal); median OS: ≥9.5 months	Brunner
nelfinavir	case report	locally advanced non-small cell lung cancer	RT (20 Gy in 10 fractions)	patient taking 3.75 mg twice daily experienced rapid clinical complete response, then died of hemoptysis	Chapman

D

valproic acid	Phase I/II	high grade glioma	RT + temozolomide	preliminary MTD: 25 mg/kg twice daily; efficacy not reported	NCT00313664, Kamrava
vorinostat	Phase I	pelvic malignancies	RT	preliminary MTD: ≥300 mg once daily	NCT00455351, Ree
valproic acid	retrospective cohort	pediatric high grade glioma	RT +/- various chemotherapy	no grade ≥4 toxicity; median OS: 17.9 months (includes patients not treated with valproic acid)	Masoudi
valproic acid	retrospective cohort	high grade glioma	RT +/- various chemotherapy	no grade ≥3 toxicity; median OS: 16.5 months	Barker
valproic acid	retrospective cohort	high grade glioma	RT +/- various chemotherapy	toxicity not reported; median OS: 14.7 months	Sulman