nature portfolio

https://doi.org/10.1038/s41571-021-00579-w

Supplementary information

Radiotherapy as a tool to elicit clinically actionable signalling pathways in cancer

In the format provided by the authors and unedited

Supplementary Table 1. Current status of DDR inhibitors.

Target	Agent	Status	Indications*	Notes	Ref.
ATM	KU60019	Preclinical testing	N/A	Cooperates with RT to enhance type I IFN signaling in models of pancreatic cancer	1
ATR	Berzosertib	Clinical testing	Brain metastases Breast cancer HNSCC	Well tolerated as monotherapy and in combination with carboplatin or topotecan	2, 3 NCT02567422 NCT02589522 NCT04052555
	Ceralasertib	Clinical testing	Various solid tumors	Safely combined with weekly paclitaxel in melanoma patients, currently being tested in combination with palliative RT	4, 5 NCT02223923
CDK1 CDK2 CDK9	AZD5438	Discontinued	N/A	Discontinued due to tolerability issues	6
CDK4 CDK6	Abemaciclib	FDA approved for ER^+HER2^- advanced/metastatic breast cancer	Breast cancer Prostate cancer	Well tolerated in combination in with RT, with sporadic episodes of high-grade but reversible intestinal toxicity	7-9 NCT04298983 NCT04923542
	Palbociclib	FDA approved for ER^+HER2^- advanced/metastatic breast cancer	Breast cancer HNSCC Nasopharyngeal carcinoma	Well tolerated in combination in with RT, with sporadic episodes of high-grade but reversible intestinal toxicity	7-11 NCT03024489 NCT03691493 NCT04334330 NCT04563507 NCT04605562
	Ribociclib	FDA approved for ER^+HER2^- advanced/metastatic breast cancer	Breast cancer Glioma	Well tolerated in combination in with RT and associated to increased necrotic volume in 4 out of 10 patients with DIPG	7-9, 12, 13 NCT03355794
CHEK1	Prexasertib	Clinical testing	N/A	Well tolerated in combination with RT and cetuximab (but not cisplatin)	14
CHEK1 CHEK2	AZD7762	Discontinued	N/A	Discontinued due to unpredictable cardiac toxicity	15
DNA-PK	Peposertib	Clinical testing	Various solid tumors	Well tolerated as monotherapy, currently being investigated in combination with palliative RT and SOC chemotherapy	16 NCT02516813 NCT03724890 NCT03770689 NCT04068194 NCT04071236 NCT04172532

					NCT04533750 NCT04555577 NCT04750954
PARP1 PARP2	Fluzoparib	Clinical testing	NSCLC	Well tolerated in germline *BRCA1/2*-mutated ovarian cancer patients, currently being investigated in combination with camrelizumab after concurrent RT and chemotherapy	17 NCT04828395
	Niraparib	FDA approved for advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	Various solid tumors (>10 clinical trials)	Currently being investigated in combination RT and chemotherapy or immunotherapy, improved RT-induced $CD8^+$ T cell activation in a murine model of EGFR-mutated NSCLC	18 www.clinicaltrials.gov
	Olaparib	FDA approved for ovarian cancer and mCRPC exhibiting *BRCA1*, *BRCA2* or *ATM* mutations	Various solid tumors (>20 clinical trials)	Well tolerated in combination with RT in patients with locally advanced HNSCC and TNBC	19-22 www.clinicaltrials.gov
	Rucaparib	FDA approved for mCRPC exhibiting *BRCA1* or *BRCA2* mutations	TNBC	Currently being tested in combination with post-operative RT in patients with an incomplete response to neoadjuvant chemotherapy	NCT03542175
	Talazoparib	FDA approved for $HER2^-$ breast cancer exhibiting *BRCA1* or *BRCA2* mutations	Glioma Gynecological tumors SCLC TNBC	Currently being tested in combination with RT ± carboplatin or atezolimumab	NCT03968406 NCT04170946 NCT04690855 NCT04740190
WEE1	Adavosertib	Clinical testing	GBM GE carcinoma Glioma Gynecological tumors	Well tolerated in combination with RT and gemcitabine in patients with locally advanced pancreatic cancer	23 NCT01849146 NCT01922076 NCT03345784 NCT04460937

Abbreviations: DDR, DNA damage response; DIPG, diffuse intrinsic pontine glioma; ER, estrogen receptor; FDA, food and drug administration; GBM, glioblastoma; GE, gastroesophageal; HNSCC, head and neck squamous cell carcinoma; IFN, interferon; mCRPC, metastatic castration-resistant prostate cancer; N/A, not applicable; OS, overall survival; RT, radiation therapy; SCLC; small cell lung cancer; SOC, standard-of-care; TNBC, triple negative breast cancer. *in the context of RT.

Supplementary Table 2. Current status of RTK and PI3K signaling inhibitors.

Target	Agent	Status	Indications*	Notes	Ref.
AKT1	MK-2206	Clinical testing	N/A	Fails to improve the therapeutic activity of RT in GBM cells owing to aberrant MTOR activation	24
EGFR	AG1478	Preclinical testing	GBM	Increased the radiosensitivity of human GBM cells	25
	Cetuximab	FDA approved for $EGFR^+$ mCRC and HNSCC	Various solid tumors (>40 clinical rials)	Associated with improved locoregional control and OS (but also severe dermatitis) in patients with HNSCC receiving definitive RT	26-28 www.clinicaltrials.gov
	Erlotinib	FDA approved for EGFR-mutated metastatic NSCLC	NSCLC Pancreatic cancer	Associated with increased response rates to whole-brain RT in NSCLC patients with brain metastases	29 NCT00708448 NCT01013649 NCT02045446 NCT02714010 NCT02788058 NCT03119519 NCT03137771 NCT04193007
	Gefitinib	FDA approved for EGFR-mutated metastatic NSCLC	NSCLC	Associated with increased response rates to whole-brain RT in NSCLC patients with brain metastases	29 NCT02714010 NCT02788058 NCT03119519 NCT03381430 NCT04193007
	Nimotuzumab	Clinical testing	Various solid tumors (>10 clinical trials)	Well tolerated in combination with RT and chemotherapy in different settings, and linked to increased survival in patients with $EGFR^+$ GBM	30-32 www.clinicaltrials.gov
EGFR HER2	Lapatinib	FDA approved for advanced/metastatic $HER2^+$ breast cancer	Breast cancer GBM HNSCC	Well tolerated in combination with RT and associated to improved local control and OS in breast cancer (but not HNSCC) patients with brain metastases	33-35 NCT01591577 NCT01711658 NCT01622868 NCT01612351
FGFR1 FGFR2 FGFR3 FGFR4 IGF1R MARK VEGFR2	AZD4547	Clinical testing	N/A	Sensitizes NSCLC and glioma cell lines to RT, *in vitro* and *in vivo*	36, 37

FGFR1 FGFR2 FGFR3 FGFR4 VEGFR2	LY2874455	Clinical testing	N/A	Sensitizes multiple cancer cell lines to carbon ion RT	38
HER2	Trastuzumab	FDA approved for $HER2^+$ breast cancer, metastatic GE or gastric adenocarcinoma	Various solid tumors (>20 clinical trials)	Sporadically associated with cardiotoxicity when combined with RT, but also linked to improved locoregional control, PFS and OS in patients with $HER2^+$ breast cancer	39-45 www.clinicaltrials.gov
MET ALK ROS1	Crizotinib	FDA approved for ALK^+ systemic ALCL	Ganglioneuroblastoma GBM NSCLC	Sensitizes HNSCC cell lines to RT, *in vitro* and *in vivo*	46 NCT02270034 NCT03126916 NCT04193007
MET	JNJ38877605	Discontinued	N/A	Discontinued to excessive renal toxicity	47
	Tepotinib	Clinical testing	N/A	Sensitizes NSCLC cell lines to RT, *in vitro* and *in vivo*	48
MTOR	Everolimus	FDA approved for NETs of lung or GI origin	Bronchial NETs Glioma	Well tolerated in combination with RT and with chemoradiation in patients with prostate and locally advanced rectal cancer, but associated with treatment-related toxicities when combined with RT and temozolomide in GBM patients	49-51 NCT03352427 NCT03355794 NCT04665739
	Vistusertib	Clinical testing	Meningioma	Currently being investigated in recurrent meningioma patients after surgery and RT	NCT03071874
MTOR PI3Kα PI3Kβ PI3Kδ PI3Kγ	Apitolisib	Preclinical testing	N/A	Sensitizes HNSCC cell lines to RT	52
MTOR PI3Kα PI3Kβ PI3Kδ PI3Kγ	Dactolisib	Discontinued	N/A	Discontinued owing to excessive gastrointestinal toxicity and limited activity	53-55
PI3Kα	Alpelisib	FDA approved for advanced or metastatic ER^+HER2^- breast cancer bearing *PIK3CA* mutations	HNSCC	Well tolerated in combination with RT and cetuximab or cisplatin in patients with advanced HNSCC	56, 57 NCT02282371
	HS-173	Preclinical testing	N/A	Sensitizes pancreatic cancer cell lines to RT, *in vitro* and *in vivo*	58

	LY294002	Preclinical testing	N/A	Sensitizes multiple cancer cell lines to RT	25, 59, 60
	Taselisib	Clinical testing	N/A	Sensitizes HNSCC cell lines to RT, *in vitro* and *in vivo*	61
PI3Kα PI3Kδ	Pictilisib	Discontinued	N/A	Discontinued owing to excessive toxicity and poor clinical activity	
PI3Kα PI3Kβ PI3Kδ PI3Kγ	Buparlisib	Clinical testing	HNSCC	Well tolerated in combination with palliative RT in patients with NSCLC, but not when combined with RT and temozolomide in GBM patients	62-64 NCT02113878
VEGFA	Bevacizumab	FDA approved for various solid tumors	Various solid tumors (>40 clinical trials)	Associated with improved response rates to RT in patients with recurrent high-grade glioma	65 www.clinicaltrials.gov
VEGFR2	Apatinib	Clinical testing	Various solid tumors (>20 clinical trials)	Well tolerated when combined with RT in metastatic prostate cancer patients	66 www.clinicaltrials.gov
VEGFR1 VEGFR2 VEGFR3 c-Kit	Cediranib	Clinical testing	GBM	Associated with improved OS when combined with chemoradiation in GBM patients	67, 68 NCT01062425

Abbreviations: ALCL, anaplastic large cell lymphoma; FDA, food and drug administration; GBM, glioblastoma; GE, gastroesophageal; GI, gastrointestinal; HNSCC, head and neck squamous cell carcinoma; mCRC, metastatic colorectal cancer; N/A, not applicable; NET, neuroendocrine tumor; NSCLC; non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RT, radiation therapy; RTK, receptor tyrosine kinase; TNBC, triple negative breast cancer. *in the context of RT.

Supplementary Table 3. Current status of TGF-β and autophagy inhibitors.

Target	Agent	Status	Indications*	Notes	Ref.
TGFB1 TGFB2 TGFB3	Fresolimumab	Clinical testing	Breast cancer NSCLC	Well tolerated in combination with RT, linked to increased OS in patients with metastatic breast cancer	69 NCT02581787
TGFBR1	Galunisertib	Clinical testing	Breast cancer Glioma HCC Nasopharyngeal carcinoma	Well tolerated in combination with chemoradiation and temozolomide in glioma patients, the absence of OS benefits	70 NCT04605562
	LY364947	Preclinical testing	Breast cancer GBM NSCLC	Inhibited DDR coupled to increased radiosensitivity in vitro and potentiated RT-induced tumor control in vivo	71, 72
TGFBR1 TGFBR2	LY2109761	Preclinical testing	GBM	Inhibited DDR coupled to increased radiosensitivity in vitro and potentiated RT-induced tumor control in vivo	73
TGFBR2 PD-L1	Bintrafusp alfa	Clinical testing	Breast cancer ESCC Genitourinary cancer HNSCC ICC	Manageable tolerability as monotherapy	NCT03524170 NCT04220775 NCT04481256 NCT04708067 NCT04756505
Lysosomal degradation	CQ	Clinical testing	Brain metastases GBM	Linked to severe toxicities when combined at 200 mg/day with RT and temozolomide in GBM patients	74-76 NCT02432417 NCT04397679
	HCQ	Clinical testing	GBM	Not linked to OS benefit in GBM patients with combined at 600 mg/day with RT and temozolomide	77 NCT01494155

Abbreviations: CQ, chloroquine; ESCC, esophageal squamous cell carcinoma; GBM, glioblastoma; HCC, hepatocellular carcinoma; HCQ, hydroxychloroquine; HNSCC, head and neck squamous cell carcinoma; ICC, intrahepatic cholangiocarcinoma; N/A, not applicable; NSCLC, non-small cell lung cancer; MTD, maximum tolerated dose; OS, overall survival; RT, radiation therapy. *in the context of RT.

References

1. Zhang, Q., *et al.* Inhibition of ATM Increases Interferon Signaling and Sensitizes Pancreatic Cancer to Immune Checkpoint Blockade Therapy. *Cancer Res* **79**, 3940-3951 (2019).

2. Yap, T.A., *et al.* Phase I Trial of First-in-Class ATR Inhibitor M6620 (VX-970) as Monotherapy or in Combination With Carboplatin in Patients With Advanced Solid Tumors. *J Clin Oncol* **38**, 3195-3204 (2020).

3. Thomas, A., *et al.* Phase I Study of ATR Inhibitor M6620 in Combination With Topotecan in Patients With Advanced Solid Tumors. *J Clin Oncol* **36**, 1594-1602 (2018).

4. Dillon, M.T., *et al.* PATRIOT: A phase I study to assess the tolerability, safety and biological effects of a specific ataxia telangiectasia and Rad3-related (ATR) inhibitor (AZD6738) as a single agent and in combination with palliative radiation therapy in patients with solid tumours. *Clin Transl Radiat Oncol* **12**, 16-20 (2018).

5. Kim, S.T., *et al.* Phase I Study of Ceralasertib (AZD6738), a Novel DNA Damage Repair Agent, in Combination with Weekly Paclitaxel in Refractory Cancer. *Clin Cancer Res* **27**, 4700-4709 (2021).

6. Boss, D.S., *et al.* Safety, tolerability, pharmacokinetics and pharmacodynamics of the oral cyclin-dependent kinase inhibitor AZD5438 when administered at intermittent and continuous dosing schedules in patients with advanced solid tumours. *Ann Oncol* **21**, 884-894 (2010).

7. Ratosa, I., *et al.* Cyclin-Dependent Kinase 4/6 Inhibitors Combined With Radiotherapy for Patients With Metastatic Breast Cancer. *Clin Breast Cancer* **20**, 495-502 (2020).

8. Ippolito, E., *et al.* Concurrent radiotherapy with palbociclib or ribociclib for metastatic breast cancer patients: Preliminary assessment of toxicity. *Breast* **46**, 70-74 (2019).

9. Guerini, A.E., *et al.* A single-center retrospective safety analysis of cyclin-dependent kinase 4/6 inhibitors concurrent with radiation therapy in metastatic breast cancer patients. *Sci Rep* **10**, 13589 (2020).

10. Beddok, A., *et al.* Concurrent use of palbociclib and radiation therapy: single-centre experience and review of the literature. *Br J Cancer* **123**, 905-908 (2020).

11. Chowdhary, M., *et al.* Safety and Efficacy of Palbociclib and Radiation Therapy in Patients With Metastatic Breast Cancer: Initial Results of a Novel Combination. *Adv Radiat Oncol* **4**, 453-457 (2019).

12. Meattini, I., Desideri, I., Scotti, V., Simontacchi, G. & Livi, L. Ribociclib plus letrozole and concomitant palliative radiotherapy for metastatic breast cancer. *Breast* **42**, 1-2 (2018).

13. DeWire, M., *et al.* A phase I/II study of ribociclib following radiation therapy in children with newly diagnosed diffuse intrinsic pontine glioma (DIPG). *J Neurooncol* **149**, 511-522 (2020).

14. Yang, E.S., *et al.* A Phase 1b trial of prexasertib in combination with chemoradiation in patients with locally advanced head and neck squamous cell carcinoma. *Radiother Oncol* **157**, 203-209 (2021).

15. Sausville, E., *et al.* Phase I dose-escalation study of AZD7762, a checkpoint kinase inhibitor, in combination with gemcitabine in US patients with advanced solid tumors. *Cancer Chemother Pharmacol* **73**, 539-549 (2014).

16. van Bussel, M.T.J., *et al.* A first-in-man phase 1 study of the DNA-dependent protein kinase inhibitor peposertib (formerly M3814) in patients with advanced solid tumours. *Br J Cancer* **124**, 728-735 (2021).

17. Li, N., *et al.* An Open-label, Multicenter, Single-arm, Phase II Study of Fluzoparib in Patients with Germline BRCA1/2 Mutation and Platinum-sensitive Recurrent Ovarian Cancer. *Clin Cancer Res* **27**, 2452-2458 (2021).

18. Zhang, N., *et al.* PARP inhibitor niraparib as a radiosensitizer promotes antitumor immunity of radiotherapy in EGFR-mutated non-small cell lung cancer. *Clin Transl Oncol* **23**, 1827-1837 (2021).

19. Sonnenblick, A., de Azambuja, E., Azim, H.A., Jr. & Piccart, M. An update on PARP inhibitors--moving to the adjuvant setting. *Nat Rev Clin Oncol* **12**, 27-41 (2015).

20. Karam, S.D., *et al.* Final Report of a Phase I Trial of Olaparib with Cetuximab and Radiation for Heavy Smoker Patients with Locally Advanced Head and Neck Cancer. *Clin Cancer Res* **24**, 4949-4959 (2018).

21. Loap, P., *et al.* Combination of Olaparib and Radiation Therapy for Triple Negative Breast Cancer: Preliminary Results of the RADIOPARP Phase 1 Trial. *Int J Radiat Oncol Biol Phys* **109**, 436-440 (2021).

22. de Haan, R., *et al.* Phase I and Pharmacologic Study of Olaparib in Combination with High-dose Radiotherapy with and without Concurrent Cisplatin for Non-Small Cell Lung Cancer. *Clin Cancer Res* **27**, 1256-1266 (2021).

23. Cuneo, K.C., *et al.* Dose Escalation Trial of the Wee1 Inhibitor Adavosertib (AZD1775) in Combination With Gemcitabine and Radiation for Patients With Locally Advanced Pancreatic Cancer. *J Clin Oncol* **37**, 2643-2650 (2019).

24. Djuzenova, C.S., *et al.* Differential effects of the Akt inhibitor MK-2206 on migration and radiation sensitivity of glioblastoma cells. *BMC Cancer* **19**, 299 (2019).

25. Li, H.F., Kim, J.S. & Waldman, T. Radiation-induced Akt activation modulates radioresistance in human glioblastoma cells. *Radiat Oncol* **4**, 43 (2009).

26. Bonner, J.A., *et al.* Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* **354**, 567-578 (2006).

27. Bonner, J.A., *et al.* Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* **11**, 21-28 (2010).

28. Bonomo, P., *et al.* Incidence of skin toxicity in squamous cell carcinoma of the head and neck treated with radiotherapy and cetuximab: A systematic review. *Crit Rev Oncol Hematol* **120**, 98-110 (2017).

29. Zheng, M.H., *et al.* Combining Whole-Brain Radiotherapy with Gefitinib/Erlotinib for Brain Metastases from Non-Small-Cell Lung Cancer: A Meta-Analysis. *Biomed Res Int* **2016**, 5807346 (2016).

30. Du, X.J., *et al.* Efficacy and safety of nimotuzumab in addition to radiotherapy and temozolomide for cerebral glioblastoma: a phase II multicenter clinical trial. *J Cancer* **10**, 3214-3223 (2019).

31. Fleischhack, G., *et al.* Nimotuzumab and radiotherapy for treatment of newly diagnosed diffuse intrinsic pontine glioma (DIPG): a phase III clinical study. *J Neurooncol* **143**, 107-113 (2019).

32. Yamamoto, N., *et al.* Phase 2 Study of Nimotuzumab in Combination With Concurrent Chemoradiotherapy in Patients With Locally Advanced Non-Small-Cell Lung Cancer. *Clin Lung Cancer* **22**, 134-141 (2021).

33. Khan, M., Zhao, Z., Arooj, S., Zheng, T. & Liao, G. Lapatinib Plus Local Radiation Therapy for Brain Metastases From HER-2 Positive Breast Cancer Patients and Role of Trastuzumab: A Systematic Review and Meta-Analysis. *Front Oncol* **10**, 576926 (2020).

34. Harrington, K., *et al.* Randomised Phase II study of oral lapatinib combined with chemoradiotherapy in patients with advanced squamous cell carcinoma of the head and neck: rationale for future randomised trials in human papilloma virus-negative disease. *Eur J Cancer* **49**, 1609-1618 (2013).

35. Harrington, K., *et al.* Postoperative Adjuvant Lapatinib and Concurrent Chemoradiotherapy Followed by Maintenance Lapatinib Monotherapy in High-Risk Patients With Resected Squamous Cell Carcinoma of the Head and Neck: A Phase III, Randomized, Double-Blind, Placebo-Controlled Study. *J Clin Oncol* **33**, 4202-4209 (2015).

36. SenthilKumar, G., *et al.* FGFR Inhibition Enhances Sensitivity to Radiation in Non-Small Cell Lung Cancer. *Mol Cancer Ther* **19**, 1255-1265 (2020).

37. Ma, J., *et al.* Inhibition of Nuclear PTEN Tyrosine Phosphorylation Enhances Glioma Radiation Sensitivity through Attenuated DNA Repair. *Cancer Cell* **35**, 504-518.e507 (2019).

38. Darwis, N.D.M., *et al.* FGFR Signaling as a Candidate Therapeutic Target for Cancers Resistant to Carbon Ion Radiotherapy. *Int J Mol Sci* **20**, 4563 (2019).

39. Cao, L., *et al.* Trastuzumab improves locoregional control in HER2-positive breast cancer patients following adjuvant radiotherapy. *Medicine (Baltimore)* **95**, e4230 (2016).

40. Jeon, S.H., *et al.* Effects of trastuzumab on locoregional recurrence in human epidermal growth factor receptor 2-overexpressing breast cancer patients treated with chemotherapy and radiotherapy. *Breast Cancer Res Treat* **172**, 619-626 (2018).

41. Sun, G.Y., *et al.* Trastuzumab Provides a Comparable Prognosis in Patients With HER2-Positive Breast Cancer to Those With HER2-Negative Breast Cancer: Post Hoc Analyses of a Randomized Controlled Trial of Post-Mastectomy Hypofractionated Radiotherapy. *Front Oncol* **10**, 605750 (2020).

42. Abi Jaoude, J., *et al.* De-intensifying Radiation Therapy in HER-2 Positive Breast Cancer: To Boost or Not to Boost? *Int J Radiat Oncol Biol Phys* **108**, 1040-1046 (2020).

43. Chumsri, S., *et al.* Incidence of Late Relapses in Patients With HER2-Positive Breast Cancer Receiving Adjuvant Trastuzumab: Combined Analysis of NCCTG N9831 (Alliance) and NRG Oncology/NSABP B-31. *J Clin Oncol* **37**, 3425-3435 (2019).

44. Bonzano, E., Guenzi, M. & Corvò, R. Cardiotoxicity Assessment After Different Adjuvant Hypofractionated Radiotherapy Concurrently Associated with Trastuzumab in Early Breast Cancer. *In Vivo* **32**, 879-882 (2018).

45. Sayan, M., *et al.* Acute Cardiotoxicity With Concurrent Trastuzumab and Hypofractionated Radiation Therapy in Breast Cancer Patients. *Front Oncol* **9**, 970 (2019).

46. Luttich, L., *et al.* Tyrosine Kinase c-MET as Therapeutic Target for Radiosensitization of Head and Neck Squamous Cell Carcinomas. *Cancers (Basel)* **13**, 1865 (2021).

47. Lolkema, M.P., *et al.* The c-Met Tyrosine Kinase Inhibitor JNJ-38877605 Causes Renal Toxicity through Species-Specific Insoluble Metabolite Formation. *Clin Cancer Res* **21**, 2297-2304 (2015).

48. Nisa, L., *et al.* Targeting the MET Receptor Tyrosine Kinase as a Strategy for Radiosensitization in Locoregionally Advanced Head and Neck Squamous Cell Carcinoma. *Mol Cancer Ther* **19**, 614-626 (2020).

49. Narayan, V., *et al.* Phase 1 Trial of Everolimus and Radiation Therapy for Salvage Treatment of Biochemical Recurrence in Prostate Cancer Patients Following Prostatectomy. *Int J Radiat Oncol Biol Phys* **97**, 355-361 (2017).

50. Gelsomino, F., *et al.* A Dose-finding and Biomarker Evaluation Phase Ib Study of Everolimus in Association With 5-Fluorouracil and Pelvic Radiotherapy as Neoadjuvant Treatment of Locally Advanced Rectal Cancer (E-LARC Study). *Clin Colorectal Cancer* **16**, 410-415.e411 (2017).

51. Chinnaiyan, P., *et al.* A randomized phase II study of everolimus in combination with chemoradiation in newly diagnosed glioblastoma: results of NRG Oncology RTOG 0913. *Neuro Oncol* **20**, 666-673 (2018).

52. Glorieux, M., Dok, R. & Nuyts, S. The influence of PI3K inhibition on the radiotherapy response of head and neck cancer cells. *Sci Rep* **10**, 16208 (2020).

53. Wise-Draper, T.M., *et al.* A Phase Ib Study of the Dual PI3K/mTOR Inhibitor Dactolisib (BEZ235) Combined with Everolimus in Patients with Advanced Solid Malignancies. *Target Oncol* **12**, 323-332 (2017).

54. Rodon, J., *et al.* Phase 1/1b dose escalation and expansion study of BEZ235, a dual PI3K/mTOR inhibitor, in patients with advanced solid tumors including patients with advanced breast cancer. *Cancer Chemother Pharmacol* **82**, 285-298 (2018).

55. Salazar, R., *et al.* Phase II Study of BEZ235 versus Everolimus in Patients with Mammalian Target of Rapamycin Inhibitor-Naive Advanced Pancreatic Neuroendocrine Tumors. *Oncologist* **23**, 766-e790 (2018).

56. Dunn, L.A., *et al.* A Phase 1b Study of Cetuximab and BYL719 (Alpelisib) Concurrent with Intensity Modulated Radiation Therapy in Stage III-IVB Head and Neck Squamous Cell Carcinoma. *Int J Radiat Oncol Biol Phys* **106**, 564-570 (2020).

57. Day, D., *et al.* Phase I trial of alpelisib in combination with concurrent cisplatin-based chemoradiotherapy in patients with locoregionally advanced squamous cell carcinoma of the head and neck. *Oral Oncol* **108**, 104753 (2020).

58. Park, J.H., *et al.* Radiosensitization of the PI3K inhibitor HS-173 through reduction of DNA damage repair in pancreatic cancer. *Oncotarget* **8**, 112893-112906 (2017).

59. Kim, I.A., *et al.* Selective inhibition of Ras, phosphoinositide 3 kinase, and Akt isoforms increases the radiosensitivity of human carcinoma cell lines. *Cancer Res* **65**, 7902-7910 (2005).

60. Brognard, J., Clark, A.S., Ni, Y. & Dennis, P.A. Akt/protein kinase B is constitutively active in non-small cell lung cancer cells and promotes cellular survival and resistance to chemotherapy and radiation. *Cancer Res* **61**, 3986-3997 (2001).

61. Zumsteg, Z.S., *et al.* Taselisib (GDC-0032), a Potent beta-Sparing Small Molecule Inhibitor of PI3K, Radiosensitizes Head and Neck Squamous Carcinomas Containing Activating PIK3CA Alterations. *Clin Cancer Res* **22**, 2009-2019 (2016).

62. McGowan, D.R., *et al.* Buparlisib with thoracic radiotherapy and its effect on tumour hypoxia: A phase I study in patients with advanced non-small cell lung carcinoma. *Eur J Cancer* **113**, 87-95 (2019).

63. Wen, P.Y., *et al.* Phase I, open-label, multicentre study of buparlisib in combination with temozolomide or with concomitant radiation therapy and temozolomide in patients with newly diagnosed glioblastoma. *ESMO Open* **5**, e000673 (2020).

64. Matulonis, U.A., *et al.* Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. *Ann Oncol* **28**, 512-518 (2017).

65. Kulinich, D.P., *et al.* Radiotherapy versus combination radiotherapy-bevacizumab for the treatment of recurrent high-grade glioma: a systematic review. *Acta Neurochir (Wien)* **163**, 1921-1934 (2021).

66. Zhao, F., *et al.* Apatinib alone or combined with radiotherapy in metastatic prostate cancer: Results from a pilot, multicenter study. *Oncotarget* **8**, 110774-110784 (2017).

67. Andronesi, O.C., *et al.* Early changes in glioblastoma metabolism measured by MR spectroscopic imaging during combination of anti-angiogenic cediranib and chemoradiation therapy are associated with survival. *NPJ Precis Oncol* **1**, 20 (2017).

68. Batchelor, T.T., *et al.* Improved tumor oxygenation and survival in glioblastoma patients who show increased blood perfusion after cediranib and chemoradiation. *Proc Natl Acad Sci U S A* **110**, 19059-19064 (2013).

69. Formenti, S.C., *et al.* Focal Irradiation and Systemic TGFbeta Blockade in Metastatic Breast Cancer. *Clin Cancer Res* **24**, 2493-2504 (2018).

70. Wick, A., *et al.* Phase 1b/2a study of galunisertib, a small molecule inhibitor of transforming growth factor-beta receptor I, in combination with standard temozolomide-based radiochemotherapy in patients with newly diagnosed malignant glioma. *Invest New Drugs* **38**, 1570-1579 (2020).

71. Bouquet, F., *et al.* TGFbeta1 inhibition increases the radiosensitivity of breast cancer cells in vitro and promotes tumor control by radiation in vivo. *Clin Cancer Res* **17**, 6754-6765 (2011).

72. Hardee, M.E., *et al.* Resistance of glioblastoma-initiating cells to radiation mediated by the tumor microenvironment can be abolished by inhibiting transforming growth factor-β. *Cancer Res* **72**, 4119-4129 (2012).

73. Zhang, M., *et al.* Blockade of TGF-β signaling by the TGFβR-I kinase inhibitor LY2109761 enhances radiation response and prolongs survival in glioblastoma. *Cancer Res* **71**, 7155-7167 (2011).

74. Compter, I., *et al.* Chloroquine combined with concurrent radiotherapy and temozolomide for newly diagnosed glioblastoma: a phase IB trial. *Autophagy*, 1-9 (2020).

75. Rojas-Puentes, L.L., *et al.* Phase II randomized, double-blind, placebo-controlled study of whole-brain irradiation with concomitant chloroquine for brain metastases. *Radiat Oncol* **8**, 209 (2013).

76. Eldredge, H.B., *et al.* Concurrent Whole Brain Radiotherapy and Short-Course Chloroquine in Patients with Brain Metastases: A Pilot Trial. *J Radiat Oncol* **2**, 10.1007/s13566-13013-10111-x (2013).

77. Rosenfeld, M.R., *et al.* A phase I/II trial of hydroxychloroquine in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme. *Autophagy* **10**, 1359-1368 (2014).