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Supplemental Appendices for:
Use of Targeted Agents and Chemotherapy Concurrent with Stereotactic or Whole Brain Radiotherapy for Cerebral Metastases of Solid Tumors
Ann Hoeben

Supplemental Appendix A – Search Strategy

PubMed + Medline
((*name systemic therapy*) AND ((((brain metastasis) OR brain metastases) OR cerebral metastases) OR cerebral metastasis)) AND (((((((("Radiotherapy"[Mesh]) OR radiotherapy OR gamma knife surgery)) OR whole brain radiotherapy) OR WBRT) OR stereotactic radiotherapy) OR SRT) OR stereotactic radiosurgery) OR SRS)

Cochrane
((*name systemic therapy*) and ((((brain metastasis) or brain metastases) or cerebral metastases) or cerebral metastasis)) and ((((((((Radiotherapy or gamma knife surgery)) or whole brain radiotherapy) or WBRT) or stereotactic radiotherapy) or SRT) or stereotactic radiosurgery) or SRS)

Web Of Science
(((*name systemic therapy*) and ((((brain metastasis) or brain metastases) or cerebral metastases) or cerebral metastasis)) and ((((((((Radiotherapy) or gamma knife surgery) or whole brain radiotherapy) or WBRT) or stereotactic radiotherapy) or SRT) or stereotactic radiosurgery) or SRS))

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Supplemental Appendix B – Overview of trial characteristics[1]

	Trial type	N	Primary tumor	Radiotherapy treatment	Systemic therapy dosage	Primary study objective	Secondary study objectives
Capecitabine							
Chargari et al 2009	Retrospective Single-arm	5	Breast	WBRT (30 Gy in 10 fractions)	1000mg/m^2, BID,14 days	Radiographic response, toxicity, survival and local control.	-
Niravath et al 2014	Phase II Single-arm	12	Breast	WBRT (dose not reported)	1000mg/m^2, BID,14 days	PFS	-
Gemcitabine							
Maraveyas et al 2005	Phase I	25	NSCLC, Colorectal, Breast, Renal, Oesophageal	WBRT (30 Gy in 10 fractions)	25mg/m^2 weekly, 25-37.5-50.0, 62.5, 75mg/m^2 twice weekly	MTD	-
Huang et al 2007	Phase I	16	NSCLC	WBRT (37,5 Gy in 15 fractions)	400mg/m^2; 500mg/m^2; 600mg/m^2 700mg/m^2 day 1/8/15	MTD	-
Cisplatin							
Stewart et al 1982		14	Melanoma, lung, oropharyngeal, thyroid, testicular	WBRT (60 Gy in 7 weeks or 50 Gy followed by 15 Gy covering initial tumor site)	40mg/m^2 weekly	Researching radiosensitizing effect.	-
Carboplatin							
Guerrieri et al 2004	Phase III Dual-arm	42	NSCLC	WBRT (20 Gy in 4 fractions)	70mg/m^2/day	Survival	Objective response rate, symptom control, time to neurological progression,

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	Trial type	N	Primary tumor	Radiotherapy treatment	Systemic therapy dosage	Primary study objective	Secondary study objectives
							toxicity
Cisplatin, Vinorelbine, Ifosfamide							
Quantin et al 1999	Phase II	23	NSCLC	WBRT (3 cycles 18 Gy in 10 fractions)	Vinorelbine 30mg/m^2 day 1 and 8, Ifosfamide 1.5g/m^2 day 1-3, Cisplatin 100mg/m^2 day 2 (3 cycles).	Response rate and survival	Toxicity and compliance
Quantin et al 2010	Phase II	A:37 B:33	NSCLC	A+B: WBRT 3 cycles 18 Gy in 10 fractions	A: Vinorelbine 30mg/m^2 day 1 and 8, Ifosfamide 1.5g/m^2 day 1-3, Cisplatin 100mg/m^2 day 2 (3 cycles). B: Ifosfamide 3g/m^2 day 1-4 (3 cycles).	Response rate and safety profile	-
Cisplatin, Vindisine, Mitomycine							
Furuse et al 1997	Phase II	33	NSCLC	WBRT (40 Gy in 20 fractions)	Cisplatin 100mg/m^2 day 1 and 29. Vindisine 3mg/m^2 day 1, 8, 29, 39. Mitomycine 8mg/m^2 day 1 and 29.	Technical feasibility toxicity and tumor response	-
Pemetrexed, Cisplatin or carboplatin							
Chargari et al 2013	Retrospective	43	NSCLC	WBRT (30 Gy in 10 fractions or 20 Gy in 5 fractions)	Pemetrexed 500mg/m^2 as monotherapy or combined with cisplatin 75mg/m^2 or carboplatin 75mg/m^2 (median 4 cycles).	Radiographic response, survival and toxicity	-
Dinglin et al 2013	Phase II	42	NSCLC	WBRT (30 Gy in 10 fractions)	Pemetrexed 500mg/m^2, cisplatin 75mg/m^2 (maximum 6 cycles).	Efficacy and tolerability	-
Cisplatin, Vinorelbine							
Robinet et al 2001	Phase III	A: 86	NSCLC	A: no RT.	Cisplatin 100mg/m^2 day 1	OS and PFS	Toxicity

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		B: 35		B: WBRT (30 Gy in 10 fractions)	(median 2 cycles), Vinorelbine 30mg/m^2 day 1, 8, 15, 22 (median 3 cycles).		
Cisplatin, Etoposide							
Chen et al 2012	Phase II	36	SCLC	WBRT (30 Gy in 10 fractions)	Cisplatin 80mg/m^2 day 1, Etoposide 100mg/m^2 day 1-3 (3 cycles).	Response, survival and toxicity	-
Cisplatin, Paclitaxel + Vinorelbine or Gemcitabine							
Cortes et al 2003	Phase II	26	NSCLC	WBRT (30 Gy in 10 fractions)	Cisplatin 120mg/m^2 day 1, Paclitaxel 135mg/m^2 day 1, Vinorelbin 30mg/m^2 day 1 and 15 or gemcitabine 800mg/m^2 day 1 and 8 (median 3 cycles).	Feasibility, activity and toxicity	-
Sunitinib							
Chung et al 2012	Phase I	7	Renal, lung, breast, cervix and tongue.	SRS (15, 18 or 21 Gy)	25mg/day or 37.5 mg/day	Toxicity and tumor response	-
Wuthrick et al 2011	Phase Ib	12	Melanoma, NSCLC, HNSCC, adenoid cystic and chordoma.	Both (median dose 37.5 Gy)	37.5mg/day	Toxicity and safety profile	Radiographic tumor response at 1 month and urine biomarker changes
Sunitinib and/or Sorafenib							
Arneson et al 2014	Phase I	11	Not specified.	SRS (dose not reported)	Sorafenib 400mg OD or BID.	Safety, tolerability, maximum tolerated dose	
Staehler et al 2010	Case-series	106	Renal cell	SRS (median dose 20 Gy per lesion)	Sunitinib: 50mg OD, 4weeks on, 2 weeks off.	Local control	Toxicity and OS

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					Sorafenib: 400mg, BID		
Erlotinib							
Lind et al 2008	Phase I	11	NSCLC	WBRT (30 Gy in 10 fractions)	100mg/d & 150mg/d	Toxicity	OS, interval to progression, intracranial and extracranial tumor response
Zhuang et. al. 2013	Prospective Dual-arm	54	Lung adenocarcinoma	WBRT (30 Gy in 10 fractions)	150mg OD	Intracranial objective response rate and local progression-free survival	Toxicity, progression-free survival and OS
Welsh et al 2013	Phase II Single-arm	40	NSCLC	WBRT (2.5 Gy per day 5 days per week to 35 Gy)	150mg OD	OS	Radiologic response and safety
Olmez et al 2010	Retrospective Single-arm	8	NSCLC	WBRT (range 35-40 Gy)	150mg OD	Clinical response of BM, of extracranial disease and toxicity	
Cai et al. 2013	Retrospective Dual-arm	157	NSCLC	WBRT (range 29.73-41.42 Gy)	150mg OD erlotinib (n=43) OR 250mg OD gefitinib (n=22)	Adverse reactions and clinical effect	
Lee et. al. 2014	Phase II Dual-arm	80	NSCLC	WBRT (20 Gy in 5 fractions)	150mg OD	Neurological progression-free survival	QoL, adverse events
Lee et. al. 2012	Retrospective Dual-arm	43	NSCLC	WBRT (30-40 Gy) some local boosts to tumor sites to 50-60 Gy	Unknown	Radiological progression-free survival; overall survival	
Sperduto et al 2012	Phase III Dual-arm	41	NSCLC	Both 37.5 Gy WBRT, afterwards SRS in 24, 18 or 15 Gy)	150mg/day	OS	Time to CNS progression, performance status at 6 months, steroid dependence and cause of death
Gefitinib							
Wang et. al. 2014	Phase II Single-arm	37	NSCLC	WBRT 50 Gy	250mg OD	Efficacy and safety	

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	Trial type	N	Primary tumor	Radiotherapy treatment	Systemic therapy dosage	Primary study objective	Secondary study objectives
Zeng et al 2012	Retrospective Single-arm	90	NSCLC	WBRT (40 Gy in 20 fractions)	250mg OD	Efficacy	
Ma et al 2008	Phase II Single-arm	21	NSCLC	WBRT (40 Gy in 20 fractions)	250mg OD	Tumor response and QoL	Toxicity and survival
Cai et al. 2013	Retrospective Dual-arm	157	NSCLC	WBRT (range 29.73-41.42 Gy)	150mg OD erlotinib (n=43) OR 250mg OD gefitinib (n=22)	Adverse reactions and clinical effect	
Pesce et. al. 2012	Phase II Single-arm	16	NSCLC	WBRT (30 Gy in 10 fractions)	250 mg OD	OS	QoL and cognitive function
Lapatinib							
Lin et al. 2013	Phase I Single-arm	35	Breast (HER2+)	WBRT (37.5 Gy in 15 fractions)	Maximum 1500mg OD	MTD of concurrent lapatinib with WBRT	Volumetric CNS objective response (ORR), non-CNS ORR, progression-free survival, OS, site of first progression, proportion of patients progression free at 6 months and cause of death.
Vemurafenib							
Schulze et al 2014	Case-reports	2	Melanoma	WBRT (30 Gy in 10 fractions)	960mg BID	-	-
Liebner et al 2014	Case-reports	2	Melanoma	Variable	960mg BID	-	-
Narayana et al 2013	Retrospective Single-arm	12	Melanoma	Both (median dose SRS 20 Gy, WBRT 30 Gy)	960mg BID	Safety and efficacy	
Ahmed et. al. 2015	Retrospective Single-arm	24	Melanoma	SRS (median 24 Gy)	960mgBID	Local failure	Distant brain failure, OS, toxicity
Gaudy-Marqueste et. al. 2014	Retrospective Single-arm	24	Melanoma	Gamma-knife radiosurgery (40-56 Gy)	Not defined.	Safety	-
Rompoti et. al. 2013	Case-reports	4	Melanoma	WBRT or SRS (24-35 Gy)	960 mg BID	-	-

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Ipilimumab							
Silk et. al. 2013	Retrospective Dual-arm	70	Melanoma	WBRT (30-37.5 Gy) or SRS (14-24 Gy)	3mg/kg every 3 weeks	OS, time to progression in the brain, proportion of patients with a response to RT	-
Mathew et al 2013	Retrospective Duel-arm	58	Melanoma	SRS (median dose 20 Gy)	3 or 10mg/kg every 3 weeks	Local control, OS, freedom from new brain metastasis	-
Gerber et. al 2014	Retrospective Single-arm	13	Melanoma	WBRT (median dose 3000 cGy)	3mg/kg, 10mg/kg	Safety and efficacy	-
Tazi et. al. 2014	Retrospective Single-arm	10	Melanoma	SRS (doses not reported)	Not reported	OS time, time from first ipilimumab to death from any cause	-
Kiess et. al. 2015	Retrospective Single-arm	46	Melanoma	SRS (median dose 29 Gy, range 15-24 Gy)	3mg/kg (54%) or 10 mg/kg (46%) every 3 weeks.	OS, local control and regional control. Safety.	-
Trastuzumab							
Chargari et al 2010	Retrospective Single-arm	31	Breast (HER2+)	WBRT (30 Gy in 10 daily fractions)	2mg/kg weekly or 6mg/kg every 3 weeks	Efficacy and acute toxicity	-
Carlson et. al. 2014	Case-reports	4	Breast (HER2+)	SRS (16-24 Gy)	Not reported	-	-
Bevacizumab							
Lèvy et. al. 2014	Phase I	19	Breast, lung, ovary	WBRT (30 Gy in 10 fractions) from day 15.	15 mg/kg on day 1, 15 and 29.	Identify the recommended phase II dose.	Assess treatment-related parameters of BM regression.

[1] *NSCLC: non-small cell lung carcincoma, SCLC: small-cell lung carcinoma, HNSCC: head-neck squamous cell carcinoma, HER2: human endothelial growth factor receptor 2, WBRT: whole-brain radiotherapy, SRS: stereotactic radiosurgery, OD: once daily, BID: twice daily, PFS: progression-free survival, MTD: maximum tolerated dose, OS: overall survival, BM: brain metastases, QoL: quality of life, RT: radiotherapy, CNS: central nervous system.*

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Supplemental Appendix C – Working mechanisms and targeted receptors of reviewed systemic therapies

Systemic Therapy	Working mechanism[1]
Platinum analogs (carboplatin; cisplatin)	Covalent binding to DNA with preferential binding to specific subsite of guanine and adenosine. After binding to DNA it produces cross-links which results in inhibition of DNA synthesis and functions as well as inhibitors of transcription.
Taxanes (docetaxel; paclitaxel)	Bind to microtubules, enhancing tubuline polymerization and in this way inhibiting microtubule depolymerization, resulting in G2/M arrest, leading to inhibition of mitosis and cell division.
Gemcitabine	Replaces a nucleic acid (cytidine) during DNA replication which arrests tumor growth and results in apoptosis. Also inhibits RNR due to which DNA replication and repair arrests and apoptosis is induced.
Sunitinib	Inhibitor of: PDGFR-alpha, PDGFR-beta, VEGFR1, VEGFR2, VEGFR3, and other tyrosine kinases receptors (KIT, FLT-3, CSF-1R and RET)
Sorafenib	Inhibitor of: intracellular kinases located in both the tumour cell (c-Raf, V600E b-Raf, KIT and Fit3) and in the tumour vasculature (c-Raf, VEGFR2, VEGFR3 and PDGFR-beta)
Erlotinib	Inhibitor of EGFR which results in the inhibition of growth pathways induced by EGFR stimulation.
Gefitinib	Inhibitor of EGFR which results in the inhibition of growth pathways induced by EGFR stimulation.
Lapatinib	Inhibitor of HER1 and HER2 which results in the inhibition of the cell proliferation stimulated by these receptors.
Vemurafenib	Inhibitor of BRAF V600e which results in cell death by interrupting intercellular pathways.
Ipilimumab	Inhibitor of CTLA-4 which results in the activation of the cytotoxic T-cell response to tumor cells.
Trastuzumab	Antibody of the HER2/neu receptor which results in the inhibition of the cell proliferation stimulated by HER2.
Bevacizumab	Antibody of the VEGF-A receptor which slows the growth of angiogenesis.

[1] DNA: deoxyribonucleic acid, RNR: ribonucleotide reductase; PDGFR: platelet-derived growth factor receptors; VEGFR vascular endothelial growth factor receptor; KIT: KIT proto-oncogene receptor tyrosine kinase; FLT-3: fms-related tyrosine kinase 3; CSF1R: colony stimulating factor 1 receptor; RET: rearranged during transfection; c-RAF: c-rapidly accelerated fibrosarcoma; b-RAF: b-rapidly accelerated fibrosarcoma.'; Fit3: facilitator of iron transport 3; EGFR: endothelial growth factor receptor; HER: human epidermal growth factor receptor; CTLA-4: cytotoxic T-lymphocyte associated protein 4; VEGF: vascular endothelial growth factor