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Supplementary information

Management of brain metastases according to molecular subtypes

In the format provided by the authors and unedited

Supplementary Table 1. Selected studies of EGFR and ALK-targeted therapy for the treatment of patients with NSCLC brain metastases.

Author	Treatment	N. pts	Patient Population	Prior CNS radiotherapy	Response Data	Survival Data
Iuchi et al, 2013	Gefitinib	41	EGFR mutant NSCLC	No	87.8% response rate.	Median PFS 14.5 months and median OS 21.9 month. Exon 19 deletions compared to L858R mutation was associated with better outcomes (OS p=.025)
Soria et al, 2018 Ramalingam et al 2020	Osimertinib vs first-generation EGFR-TKI.	556	EGFR mutant NSCLC	Untreated and pretreated patients	6% of patients had CNS progression in the osimertinib group compared to 15% in the standard EGFR-TKI group.	osimertinib significantly increased PFS compared to first-generation TKIs (HR 0.46; 95% CI 0.37-0.57) Osimertinib significantly increased OS (38.6 months) compared to first generation EGFR-TKIs (31.8 months, P=0.046)
Solomon et al, 2016	Crizotinib vs pemetrexed plus cisplatin or carboplatin	79	ALK-positive NSCLC	Yes	Intracranial disease control rate was significantly higher with crizotinib at 12 weeks (85% vs 45% p <.001) and 24 weeks (56% vs 25%, p = .006)	PFS was longer in crizotinib group (HR .40, p<.001)
Peters et al, 2017	Alectinib vs crizotinib	303	ALK-positive NSCLC	Untreated and pretreated patients	12% of patients in alectinib group had CNS progression vs 45% in crizotinib group (HR .16, p<.001). CNS complete response was significantly more likely in the alectinib group compared to the crizotinib group (45% vs 9%, p<0.001).	PFS was longer in the Alectinib group (HR .47, p<.001)
Solomon et al, 2018	Lorlatinib	276	ALK-positive NSCLC	Untreated (the majority) and pretreated	In patients with at least one prior ALK inhibitor, 51 of 81 patients had an intracranial response (63%; 95% CI 51.5-73.4)	NA

Supplementary Table 2. Selected studies of HER2-targeted therapy for the treatment of patients with breast cancer and brain metastases.

Author	Treatment	N. pts	Patient Population	Prior CNS radiotherapy	CNS ORR	Median PFS**	Median OS
Lin et al, 2008	Lapatinib	39	HER2+ brain metastases	95%	2.6%	3.0 months	**Not reported**
Lin et al, 2009	Lapatinib	242	HER2+ brain metastases	100%	6%	2.4 months	**6.4 months**
Lin et al, 2009	Lapatinib + capecitabine (after progression on lapatinib monotherapy)	50	HER2+ brain metastases	100%	20%	3.6 months	**Not reported after crossover to combination**
Sutherland et al, 2010	Lapatinib + capecitabine	34	HER2+ brain metastases	94%	21%	5.1 months	**Not reported**
Metro et al, 2011	Lapatinib + capecitabine	22	HER2+ brain metastases	86%	32%	5.1 months	**27.9 months**
Bachelot et al, 2013	Lapatinib + capecitabine	45	HER2+ brain metastases	0%	66%	5.5 months	**17 months**
Freedman et al, 2016	Neratinib	40	HER2+ brain metastases	100%	8%	1.9 months	**8.7 months**
Freedman et al, 2019*	Neratinib + capecitabine	49	HER2+ brain metastases	92%	49% (lapatinib-naïve patients) 33% (lapatinib pre-treated patients)	5.5 months (lapatinib-naïve patients) 3.1 months (lapatinib pre-treated patients)	**13.3 months in lapatinib-naïve cohort; 15.1 months in the lapatinib pre-treated cohort**
Metzger et al, 2014*	Tucatinib + trastuzumab	41	HER2+ brain metastases	83%	2/17 patients treated at MTD in once-daily cohort; 1/17 patients treated at MTD in twice-daily cohort	3.4 months (once-daily cohort treated at MTD); 4.1 months (twice-daily cohort treated at MTD)	**9.1 months (twice-daily cohort); 17.9 months (once-daily cohort)**
Murthy et al, 2018 *	Tucatinib + trastuzumab + capecitabine	60	HER2+ metastatic breast cancer	92% (of the 12 patients with active brain metastases)	5/12 patients with active brain metastases	6.7 months in subset of patients with active brain metastases	**Not reported in brain metastasis subset**
Bartsch et al, 2015	Ado-trastuzumab emtansine	10	HER2+ brain metastases	80%	30%	5 months (intracranial PFS)	**Median OS not reached at time of reporting**
Jacot et al, 2016	Ado-trastuzumab emtansine	39	HER2+ brain metastases	92%	44%	6.1 months	**OS data not mature at time of reporting**
Murthy et al, 2019	**Tucatinib + trastuzumab + capecitabine**	**612**	**HER2_ metastatic breast cancer, with or without brain metastases**	**Not reported. Overall 291 patients with brain metastases enrolled.**	**Not reported**	**Medians 5.6 months vs 7.8 months (HR 0.54; p<0.0001) in primary endpoint population*** **	**Medians 17.4 months vs 21.9 months (HR 0.66, p=0.0048) in the overall population**

CNS ORR, central nervous system objective response rate; PFS, progression-free survival;

*denotes prospective clinical trial

****PFS includes both intracranial and extracranial events, unless otherwise noted**

*****In the forest plots for PFS, HR 0.46 (0.31 to 0.67) in the brain metastasis population, favoring the tucatinib combination arm**

Supplementary Table 3. Selected studies of chemotherapy and targeted therapies for the treatment of patients with breast cancer and brain metastases.

Author	Treatment	N. pts	Patient Population	Prior CNS radiotherapy	CNS ORR	Median PFS**	Median OS
Rivera et al, 2006	Capecitabine + temozolomide	24	Breast cancer brain metastases, any subtype	33% prior WBRT, prior SRS not reported	18%	12 weeks, reported as median time to progression in the brain	**Not reported**
Rosner et al, 1986	Doxorubicin + cyclophosphamide	6	Breast cancer brain metastases, any subtype	Not specified for patients receiving the AC regimen	17%	Not specified for patients receiving the AC regimen	**Not specified for patients receiving the AC regimen**
Linot et al, 2014	Doxorubicin + cyclophosphamide	29	Breast cancer brain metastases, any subtype	72%	41%	3.6 months	**Reported as 23 months from brain metastasis dx (rather than from treatment initiation)**
Franciosi et al, 1999	Cisplatin + etoposide	116 (56 with breast cancer)	Breast cancer brain metastases, any subtype, or NSCLC or melanoma	0%	38% (in breast cancer subset)	17 weeks (in breast cancer subset; reported as time to progression)	**7.1 months**
Christodoulou et al, 2005	Cisplatin + temozolomide	32 (15 with breast cancer)	Solid tumor brain metastases, any subtype	53% across all patients included	28% (40% in breast cancer subset)	2.9 months across all patients included	**5.5 months across all patients included**
Anders et al, 2014	Irinotecan + iniparib	37	Triple negative breast cancer brain metastases	84%	12%	2.1 months	**7.8 months**
Melisko et al, 2019	Irinotecan + temozolomide	30	Breast cancer brain metastases or LMD, any subtype	97%	7%	2.3 months overall (3.1 months excluding patients with LMD)	**4.9 months**
Anders et al, 2019	Nal-IRI	10	Breast cancer brain metastases, any subtype	100%	30%	Not reported. 2/10 patients on treatment $\geq$ 40 weeks.	**Not reported**
Kumthekar et al, 2016	ANG1005	72	Breast cancer brain metastases or LMD	94%	14% in evaluable patients with brain metastases; 22% in evaluable patients with LMD	2.8 months (all comers)	**7.8 months in patients with brain metastases; 8.0 months in patients with LMD**
Lu et al, 2015	Bevacizumab + cisplatin + etoposide	35	Breast cancer brain metastases, any subtype	100%	77%	6.1 months	**10.5 months**
Lin et al, 2013	Bevacizumab + carboplatin (+trastuzumab if HER2+)	38	Breast cancer brain metastases, any subtype	87%	63%	5.6 months	**14.1 months**

Anders et al,2019	Abemaciclib	58	ER+/HER2-negative breast cancer brain metastases	59%	5.6%	4.4 months	**13.4 months**

CNS ORR, central nervous system objective response rate; LMD, leptomeningeal disease; OS, overall survival; NSCLC, nonsmall cell lung carcinoma; AC, doxorubicin and cyclophosphamide

*denotes prospective clinical trial

****PFS includes both intracranial and extracranial events, unless otherwise noted**

Supplementary Table 4. Selected studies of BRAF inhibitors for patients with BRAF mutant melanoma and brain metastases

Author	**Treatment**	**N. pts**	**Patient population**	**Prior CNS radiotherapy**	**CNS ORR**	**Median PFS**
Long et al, 2012	Dabrafenib	172	V600E or V600K BRAF mutant	Cohort A: No Cohort B: WBRT or SRS	V600E: Cohort A: 39.2% Cohort B: 30.8% V600K: Cohort A: 6.7% Cohort B: 22.2%	V600E: Cohort A: 16.1 wks Cohort B: 16.6 wks V600K: Cohort A: 8.1 wks Cohort B: 15.9 wks
Dummer et al, 2014	Vemurafenib	24	BRAF mutant	WBRT or SRS	53% (16% PR)	3.9 months
McArthur et al, 2017	Vemurafenib	146	BRAF mutant	Cohort A : No Cohort B: WBRT or SRS	18% 20%	3.7 months 4.1 months
Davies et al, 2017	Dabrafenib + trametinib	92	V600E BRAF mutant	Cohort A : No Cohort B: SRS, WBRT or S	58% 56%	5.6 mos 7.2 mos

Supplementary Table 5. Selected studies of immunotherapy for patients with melanoma and brain metastases

Author	**Treatment**	**N. pts**	**Patient population**	**Prior CNS radiotherapy**	**CNS ORR**	**Median PFS**
Margolin et al, 2012	Ipilimumab	72	Melanoma	Cohort A : No* Cohort B: Yes	18% 5%	1.9 months 1.2 months
Tawbi et al, 2018-**2019**	Nivolumab + Ipilimumab	**119**	Melanoma	No*	**55%**	**IC° PFS at 9 months 59.5%**
Long et al, 2018-**2019**	Nivolumab + Ipilimumab vs Nivolumab	**76**	Melanoma	Cohort A : No* Cohort B: No* Cohort C: Yes	**57%** **20%** **6%**	**IC° PFS at 24 months** **49%** **15%** **6%**
Kluger et al, 2019	Pembrolizumab	23	Melanoma	No*	26%	2 months**

*asymptomatic patients not requiring steroids
**OS 17 months
*** NR: not reached
°IC: intracranial