Supplementary Online Content

Borges VF, Ferrario C, Aucoin N, et al. Tucatinib combined with ado-trastuzumab emtansine in advanced *ERBB2/HER2*-positive breast cancer: a phase 1b clinical trial. *JAMA Oncology*. Published online June 28, 2018. doi:10.1001/jamaoncol.2018.1812

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Incidence of treatment-emergent and tucatinib-related adverse events

Adverse Event	Regardless of Causality		Tucatinib-Related	
	300 mg BID Dose (N = 50)	350 mg BID Dose (N = 7)	300 mg BID Dose (N = 50)	350 mg BID Dose (N = 7)
All Grades in ≥ 20% of Patients				
Total Patient with Any AE	50 (100%)	7 (100%)	46 (92%)	7 (100%)
Nausea	36 (72%)	7 (100%)	27 (54%)	7 (100%)
Diarrhea	30 (60%)	4 (57%)	26 (52%)	4 (57%)
Fatigue	28 (56%)	5 (71%)	20 (40%)	5 (71%)
Epistaxis	22 (44%)	4 (57%)	-	-
Headache	22 (44%)	4 (57%)	-	-
Thrombocytopenia	21 (42%)	5 (71%)	-	-
Vomiting	21 (42%)	5 (71%)	16 (32%)	5 (71%)
Constipation	21 (42%)	2 (29%)	-	-
Decreased appetite	20 (40%)	3 (43%)	13 (26%)	3 (43%)
Hypokalemia	19 (38%)	3 (43%)	11 (22%)	2 (29%)
Aspartate aminotransferase increased	19 (38%)	4 (57%)	16 (32%)	2 (29%)
Cough	14 (28%)	2 (29%)	-	-
Dyspepsia	13 (26%)	0	-	-
Dry mouth	12 (24%)	3 (43%)	-	-
Alanine aminotransferase increased	13 (26%)	4 (57%)	11 (22%)	2 (29%)
Urinary tract infection	12 (24%)	1 (14%)	-	-
Dizziness	10 (20%)	3 (43%)	-	-
Anemia	10 (20%)	3 (43%)	-	-
Vision blurred	10 (20%)	2 (29%)	-	-
Hyperbilirubinemia	10 (20%)	1 (14%)	-	-
Blood alkaline phosphatase increased	10 (20%)	0	-	-
Grade 3 or Higher in ≥ 10% of Patients				
Total Patient with Any AE	37(74%)	6 (86%)	26 (52%)	5 (71%)
Thrombocytopenia	14 (28%)	3 (43%)	7 (14%)	1 (14%)
Hypokalemia	8 (16%)	1 (14%)	-	-
Alanine aminotransferase increased	7 (14%)	1 (14%)	6 (12%)	1 (14%)
Aspartate aminotransferase increased	7 (14%)	0	6 (12%)	0
Fatigue	6 (12%)	2 (29%)	-	-
Hypophosphataemia	6 (12%)	1 (14%)	-	-

eTable 2: Steady-state pharmacokinetic parameters of tucatinib

Cycle and Dose	Statistic	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-6}[a] (h*ng/mL)	AUC_{tau}[b] (h*ng/mL)	Cmax/Dose (ng/mL/mg)	AUC_{0-6}/Dose[a] (h*ng/mL/mg)	AUC_{tau}/Dose[b] (h*ng/mL/mg)
Cycle 2, 300 mg	**N**	27	27	27	12	27	27	12
	Mean	790	NC	3000	4430	2.63	9.99	14.8
	SD	329	NC	1030	1300	1.1	3.42	4.32
	CV%	41.6	NC	34.3	29.3	41.6	34.3	29.3
	Min	311	0	1140	2600	1.04	3.81	8.67
	Median	734	2	2920	4540	2.45	9.74	15.1
	Max	1590	6	5620	7270	5.3	18.7	24.2
Cycle 2, 350 mg	**N**	5	5	5	2	5	5	2
	Mean	1120	NC	4080	7120	3.21	11.7	20.3
	SD	525	NC	1870	NC	1.5	5.34	NC
	CV%	46.8	NC	45.8	NC	46.8	45.8	NC
	Min	541	1	1710	NC	1.55	4.88	NC
	Median	1250	1	5240	7120	3.57	15	20.3
	Max	1700	3	5680	NC	4.86	16.2	NC

a: last time point is 6 h

b: AUC_{tau} is extrapolated and denotes inclusion of >20% & <40% AUC