Ph Ib/II study of BKM120 plus trastuzumab in patients with trastuzumab-resistant HER2+ advanced breast cancer

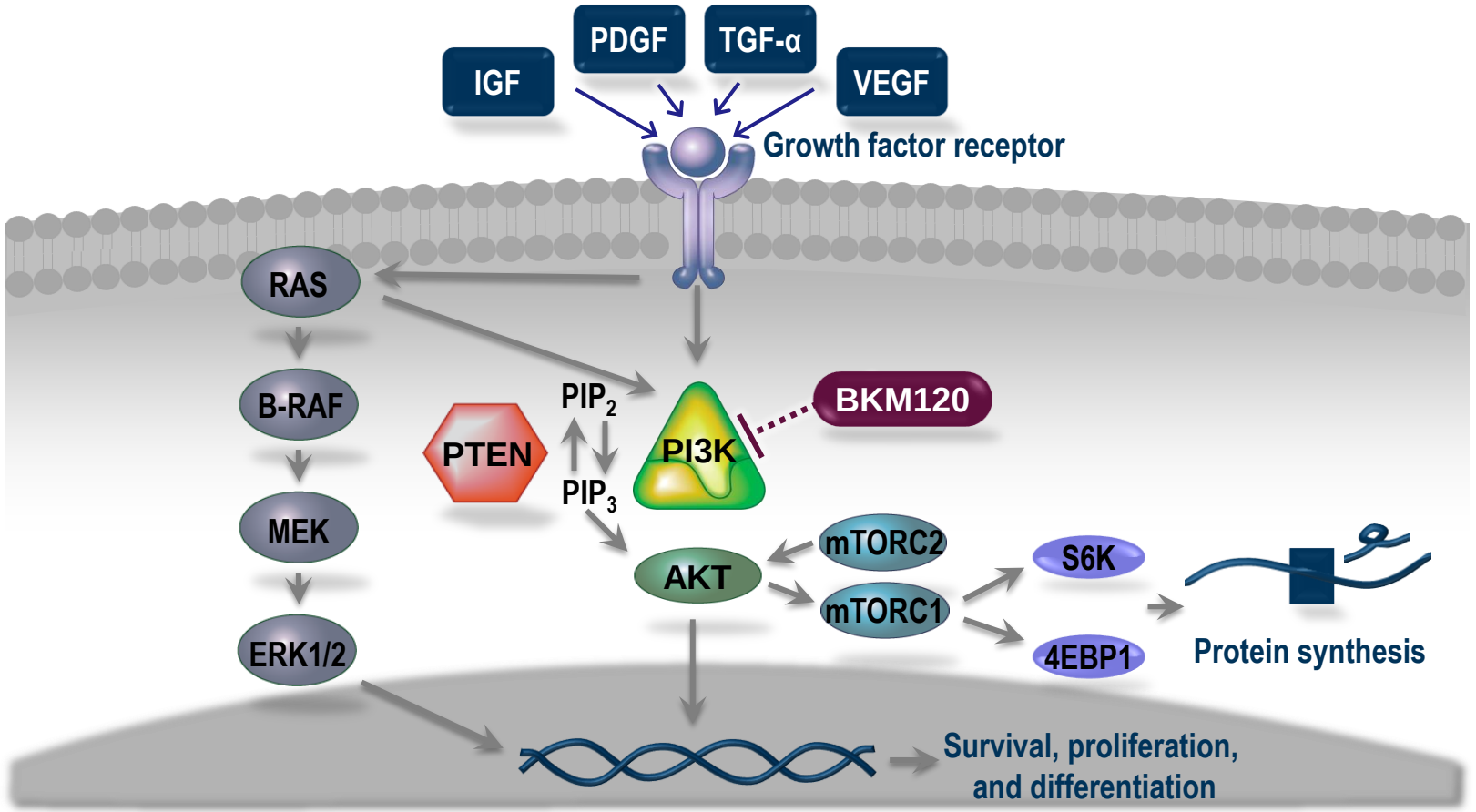
Barbara Pistilli[1], Ander Urruticoechea[2], Stephen Chan[3], Hyo Sook Han[4], Guy Jerusalem[5], Anthony Kong[6], Qinhua Ru[7], Sophie Ruquet[8], David Sternberg[7], Cristina Saura[9]

[1]Macerata Hospital, Macerata, Italy; [2]Catalan Institute of Oncology, Barcelona, Spain; [3]Nottingham University Hospital, Nottingham, UK; [4]Moffitt Cancer Center, Tampa, FL; [5]C.H.U. Sart-Tilman, Liege, Belgium; [6]Oxford University Hospitals NHS Trust, Oxford, UK; [7]Novartis Oncology, Florham Park, NJ; [8]Novartis Oncology, Paris, France; [9]Vall d'Hebron Hospital, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain

Disclosures

- This study is sponsored by Novartis Pharmaceuticals Corporation

Introduction



4EBP1, eukaryotic initiation factor 4E-binding protein 1; ERK, extracellular signal-related kinase; IGF, insulin-like growth factor; MEK, mitogen-activated protein/ERK kinase; mTORC, mammalian target of rapamycin complex; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol 4,5-bisphosphate; PIP_3, phosphatidylinositol 3,4,5-trisphosphate; PDGF, platelet-derived growth factor; PTEN, phosphatase and tensin homologue; TGF-α, transforming growth factor-alpha; VEGF, vascular epithelial growth factor.

BKM120 + trastuzumab: rationale in HER2+ breast cancer

- HER2 is overexpressed in 15–20% of all invasive breast cancers, and is associated with aggressive disease and poor prognosis[1]
- PI3K/AKT/mTOR pathway signalling is important for the oncogenic function of HER2[2]
- Activating alterations of the PI3K/AKT/mTOR pathway are frequently observed in HER2+ breast cancer, and include:[3]
  - Loss of PTEN in 22% of tumours
  - *PIK3CA* mutations in 23–33% of tumours
- PI3K/AKT/mTOR pathway activation has been linked to poor response and resistance to trastuzumab[4,5]

1. Shah S, *et al. Patholog Res Int* 2011;903202; 2. Yakes FM, *et al. Cancer Res* 2002;62:4132–4141;
3. Miller TW, *et al. Breast Cancer Res* 2011;13:224; 4. Berns K, *et al. Cancer Cell* 2007;12:395–402;
5. Esteva FJ, *et al. Am J Pathol* 2010;177:1647–1656.

BKM120 + trastuzumab: preclinical and clinical experience

- Single-agent anti-tumour activity in various cell lines and xenograft models[1]
- Significant tumour reduction observed in HER2-amplified BT474 tumour-bearing mice treated with BKM120 plus trastuzumab[1]
- BKM120 crosses the blood–brain barrier and inhibits PI3K signalling in the brain, as well as reducing the incidence of brain metastases *in vivo*[2,3]
- BKM120 demonstrated encouraging single-agent activity and safety in patients with advanced solid tumours[4], including breast cancer[5]
  - Activity also observed in the brain of a patient with breast cancer brain metastases[2]
- In the Phase Ib portion of this study, BKM120 plus trastuzumab showed preliminary signs of activity and was well tolerated[6]

BKM120 RP2D in combination with trastuzumab (2 mg/kg/week) = 100 mg/day[6]

RP2D, recommended phase II dose.

1. Maira SM, *et al. Mol Cancer Ther* 2012;11:317–328; 2. Maira M, *et al. ESMO* 2012;1675P (abstract);
3. Nanni P, *et al. PloS One* 2012;7:e39626; 4. Graña-Suárez B, *et al. ASCO* 2011;3043 (abstract);
5. Rodon J, *et al. SABCS* 2011;P3–16–01b (abstract);
6. Saura C, *et al. SABCS* 2011;PD09–03 (abstract).

CBKM120X2107: study design

Patients with HER2+ locally advanced or metastatic BC resistant to trastuzumab-based therapy

Ph I (dose escalation)
Oral, once-daily BKM120
(explored doses:
50 mg/day or 100 mg/day)
+ 2 mg/kg/week IV trastuzumab
N=18

Primary endpoint:
RP2D

Ph II (dose expansion)
Oral, once-daily BKM120
at the RP2D
+ 2 mg/kg/week IV trastuzumab
N=53

Primary endpoint:
ORR

Secondary endpoints:
DCR
PFS
OS
Safety
Pharmacokinetics

Exploratory endpoints:
PI3K/AKT/mTOR pathway activation status and relationship with clinical response

BC, breast cancer; DCR, disease control rate; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RP2D, recommended phase II dose.

CBKM120X2107: Ph II eligibility criteria

Key inclusion criteria

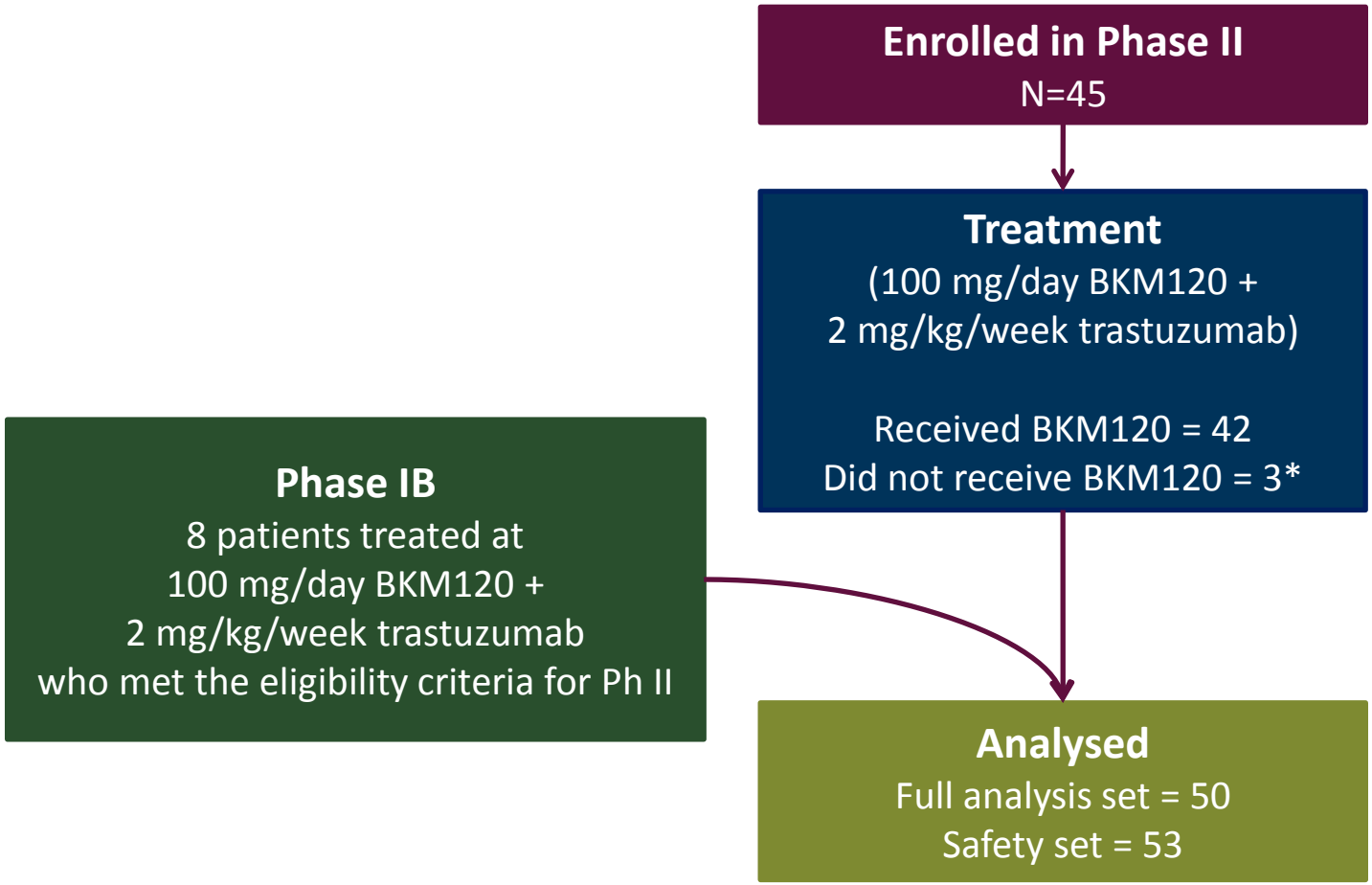
- Trastuzumab-resistant HER2+ locally advanced or metastatic breast cancer
- Disease progression as per RECIST v.1.0 on trastuzumab-based therapy within 16 weeks of first dosing
- ≥1 measurable lesion as per RECIST v.1.0
- ≤3 lines of cytotoxic chemotherapy
  - Trastuzumab, T-DM1 or lapatinib must be part of the most recent line of therapy
- ≥1 but ≤4 lines of HER2-directed therapy
- WHO performance status ≤2

Key exclusion criteria

- Previous treatment with a PI3K inhibitor
- Contraindication or intolerance to trastuzumab
- Untreated brain metastases
- Acute or chronic liver or renal disease or pancreatitis
- History of mood disorders or anxiety ≥CTCAE grade 3
- Poorly controlled diabetes mellitus (HbA_{1c} >8%)

CTCAE, Common Terminology Criteria for Adverse Events; HbA_{1c}; glycated haemoglobin; RECIST, Response Evaluation Criteria in Solid Tumors; T-DM1, trastuzumab emtansine; WHO, World Health Organization.

CBKM120X2107: Ph II analysis sets



*Three patients received loading dose (4 mg/kg) trastuzumab only.

Patient characteristics and tumour status

Patient characteristics	N=50*
Median age, years (range)	52 (28–75)
Aged <65 years, n (%)	42 (84)
Postmenopausal, n (%)	36 (72)
WHO PS 0/1, n (%)	21 (42)/29 (58)
Median no. prior antineoplastic regimens, n (range)†	3 (1–7)
Median no. prior cytotoxic chemotherapy regimens, n (range)†,‡	2 (0–4)
Median no. prior HER2-directed therapies, n (range)†,§	2.5 (1–5)

Tumour status	N=50*
Hormone receptor status, n (%)	
ER/PgR+	27 (54)
ER/PgR–	23 (46)
Median no. metastatic sites per patient, n (range)	3 (1–5)
Metastatic sites, n (%)	
Bone	31 (62)
Lung	28 (56)
Nodes	27 (54)
Liver	23 (46)
Brain	5 (10)
Skin	3 (6)
Others	24 (48)

*Full analysis set: 42 patients treated at the RP2D (100 mg/day BKM120) in Ph II, plus eight patients treated at the RP2D in Ph Ib who met the eligibility criteria for Ph II.

†Preliminary data.

‡Protocol deviation in three patients.

§Protocol deviation in one patient.

Data cut-off: 22 June 2012.

ER, estrogen receptor; PgR, progesterone receptor;

WHO PS, World Health Organization performance status.

Patient disposition and overall exposure to BKM120

Patient disposition	N=50*
Patients treated	
Treatment discontinued, n (%)	45 (90)
Treatment ongoing, n (%)	5 (10)
Primary reason for treatment discontinuation	
Adverse event(s), n (%)	11 (22)
Disease progression, n (%)	30 (60)
Death, n (%)	2 (4)
Consent withdrawn, n (%)	2 (4)
Exposure to BKM120 plus trastuzumab	**N=53†**
Median exposure, weeks (range)	9 (1–47)
Cumulative exposure, n (%)	
>12 weeks	19 (36)
>8 weeks	30 (57)
>4 weeks	41 (77)

*Full analysis set: 42 patients treated at the RP2D (100 mg/day BKM120) in Ph II, plus eight patients treated at the RP2D in Ph Ib who met the eligibility criteria for Ph II.

†Safety set: 45 patients treated in Ph II, plus eight patients treated at the RP2D (100 mg/day BKM120) in Ph Ib who met the eligibility criteria for Ph II.

Data cut-off: 22 June 2012.

Adverse events suspected to be related to study drug

Adverse events, n (%)	N=53*	
	All grades (≥15% patients)	Grade 3/4
Diarrhoea	19 (36)	–
Nausea	18 (34)	2 (4)
Rash	17 (32)	5 (9)
Asthenia	13 (25)	3 (6)
Alanine aminotransferase increased	12 (23)	6 (11)
Aspartate aminotransferase increased	12 (23)	4 (8)
Hyperglycaemia	12 (23)	2 (4)
Fatigue	11 (21)	1 (2)
Anxiety	9 (17)	2 (4)
Depression	9 (17)	2 (4)
Decreased appetite	8 (15)	–
Stomatitis	8 (15)	1 (2)

*Safety set: 45 patients treated in Ph II, plus eight patients treated at the RP2D (100 mg/day BKM120) in Ph Ib who met the eligibility criteria for Ph II.

Data cut-off: 22 June 2012.

Clinical efficacy of BKM120 plus trastuzumab

Best overall response (BOR)	N=50*
Complete response (CR), n (%)	1 (2)
Partial response (PR), n (%)	4 (8)
Stable disease (SD), n (%)	21 (42)
Progressive disease (PD), n (%)	20 (40)
Unknown, n (%)	4 (8)†
ORR (CR or PR), n (%; 90% CI)	**5 (10; 4.0–19.9)**
DCR (CR or PR or SD), n (%; 90% CI)	**26 (52; 39.5–64.3)**

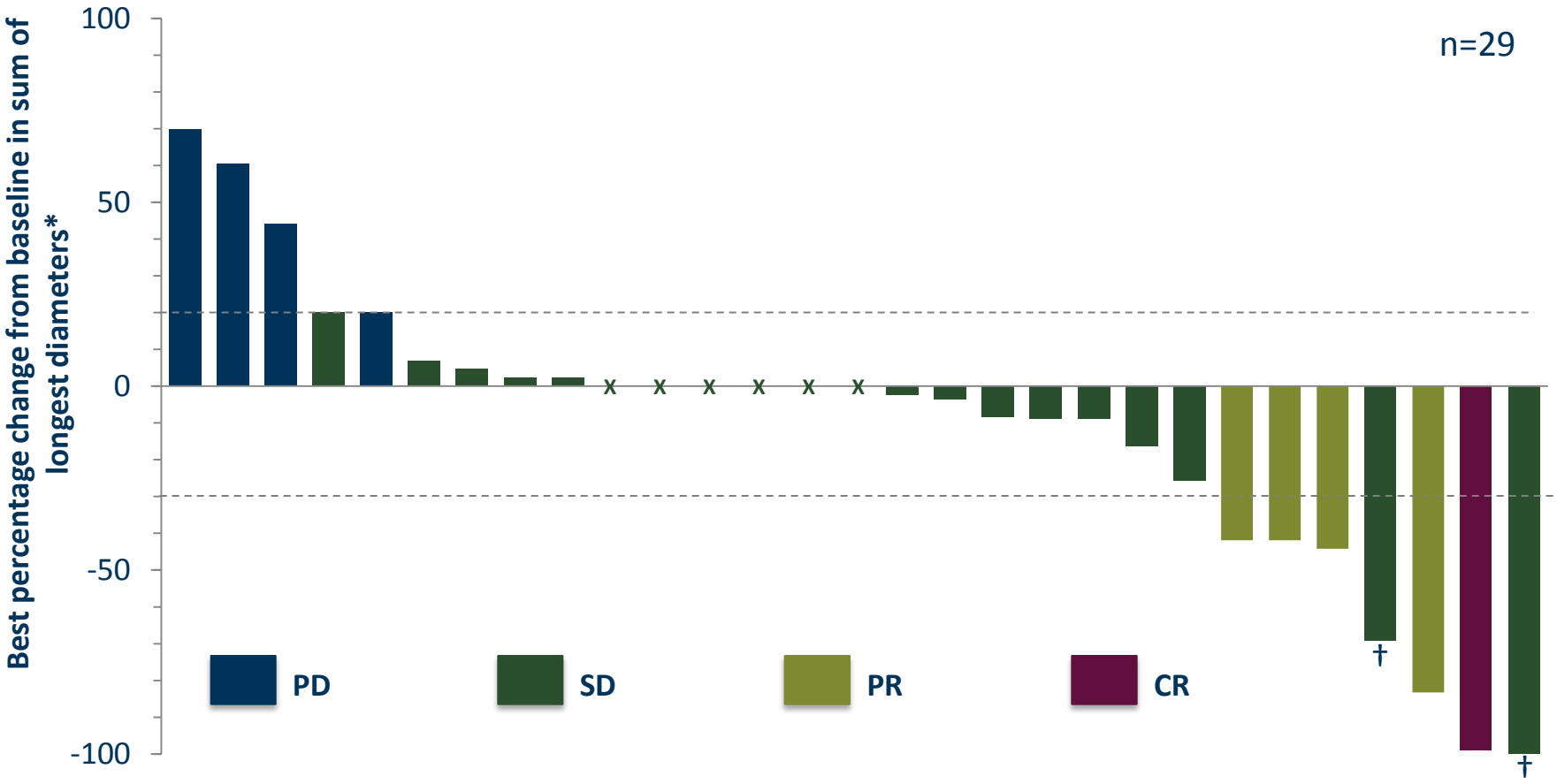
*In addition to the Ph II patients in the full analysis set (FAS), eight Ph Ib patients in the FAS met criteria for Ph II and received BKM120 at the RP2D (100 mg/day).

†Three patients did not have a post-baseline assessment. One patient received off-study therapy, and was therefore excluded.

CI, confidence interval.

Data cut-off: 22 June 2012.

Clinical efficacy of BKM120 plus trastuzumab



*Data shown comprise patients with known percentage change in target lesions (n=29).

†Unconfirmed partial responses.

Data cut-off: 22 June 2012.

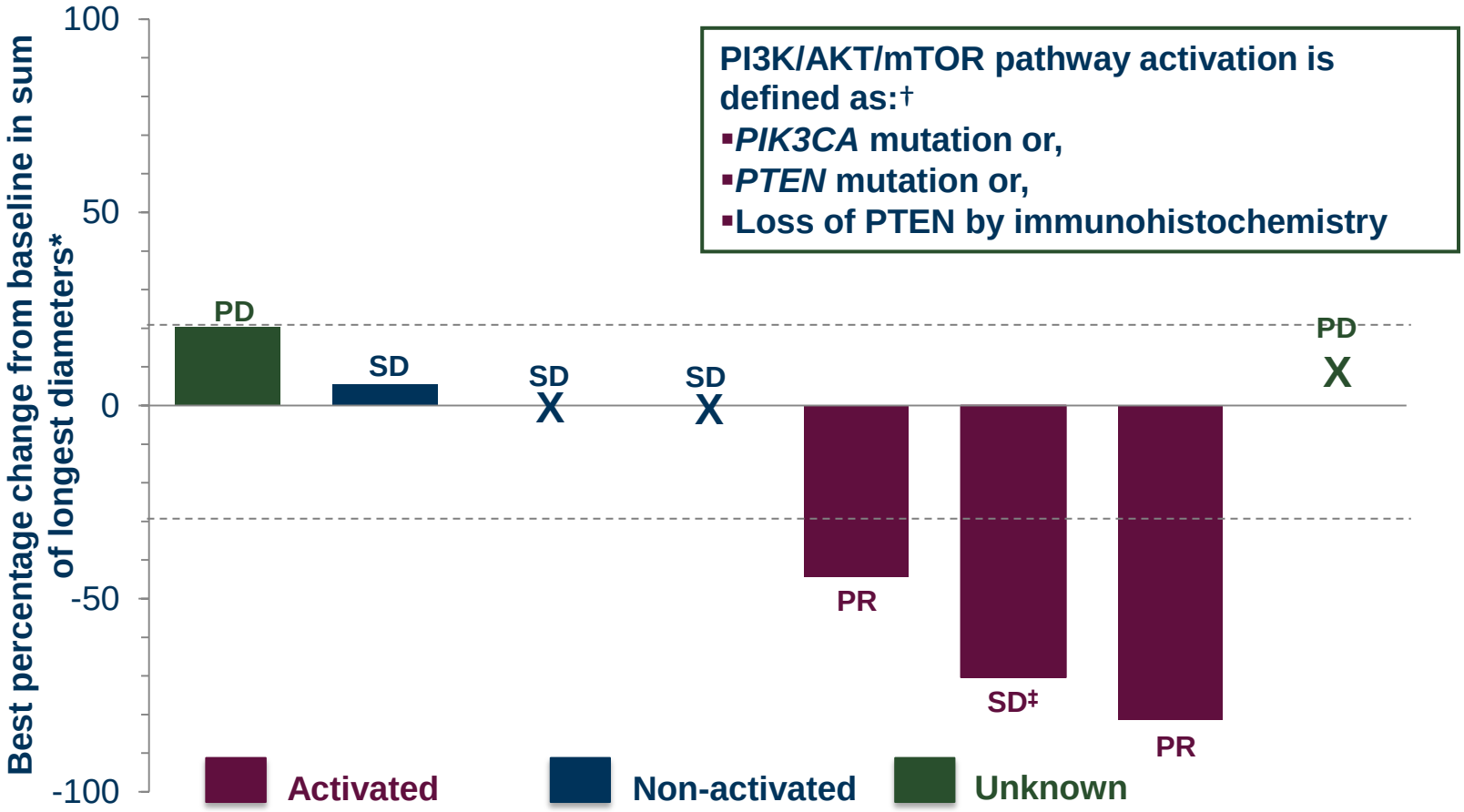
Outcome of patients with target brain lesions at baseline

Patient	Patient characteristics at baseline			BKM120 exposure (wks)	Response to BKM120 plus trastuzumab			
	Prior chemo	Prior HER2-directed therapy	BOR to last therapy		BOR	Best response in the brain	Best extracranial response	Reason for D/C
1	3 DTX, Cap, vinorelbine	3 trastuzumab/ pertuzumab or placebo, lapatinib, trastuzumab	PR	16	SD	SD	SD	**PD (brain)**
2	3 CP, Cap, GemCis	3 trastuzumab, lapatinib, trastuzumab	PD	22	SD	SD	SD	**PD (brain/ extracranial)**
3	2 FEC-T, vinorelbine	1 trastuzumab	SD	30+	SD	SD	SD	**Ongoing**

Cap, capecitabine; CP, carboplatin and paclitaxel; D/C, discontinuation; DTX, docetaxel; FEC-T, fluorouracil, epirubicin, cyclophosphamide, docetaxel; GemCis, gemcitabine and cisplatin.

Data cut-off: 22 June 2012.

Clinical efficacy by PI3K/AKT/mTOR pathway activation status*



*Population = Eight Ph Ib patients treated at the RP2D (100 mg/day BKM120) who met the eligibility criteria for Ph II.

†*PIK3CA* mutation in exons 9 or 20, as determined by SNaPshot genotyping assay; low or null PTEN expression, as defined by an immunohistochemistry H-Score <50.

Data cut-off: 22 June 2012.

‡Unconfirmed partial response·

Summary

- BKM120 (100 mg/day) plus trastuzumab was well tolerated, and adverse events were generally easily managed and reversible upon study-drug interruption/discontinuation
- Evidence of clinical efficacy was observed in patients with progressive disease resistant to trastuzumab
  - 1 patient had a complete response
  - 4 patients had partial responses
  - Objective response rate = 5/50 (10%)
  - Disease control rate = 26/50 (52%)
- Preliminary evidence of clinical activity in the brain was also observed
  - 3/3 patients with target brain lesions at baseline achieved stable disease
  - An expansion cohort in patients with brain metastases will open shortly
- The relationship between PI3K pathway activation status and clinical response is currently being explored

Acknowledgements

We would like to thank the patients and their families who participated in the CBKM120X2107 study