Methods

Study Design and Treatment

Additional secondary objectives were to further characterize antitumor activity, safety and tolerability, and pharmacokinetics in NSCLC expansion patients. The secondary efficacy endpoints for patients with *EGFR*wt MET IHC 3+ NSCLC were progression-free survival (PFS), duration of response (DOR), and disease control rate (DCR). The exploratory objective was to assess the correlation between the antitumor activity of capmatinib and *MET* GCN gain or amplification, as measured by FISH. Endpoints were ORR (by local investigator assessment and/or by blinded independent review committee [BIRC]), DOR, DCR, and PFS based on *MET* amplification defined in one of three groups: patients with *MET* GCN ≥6, GCN ≥4 and <6, or GCN <4. Patients were treated in 28-day cycles at the RP2D of capmatinib, 400 mg tablet or 600 mg capsule BID, as determined in the dose-escalation part (Bang Y-J, et al; manuscript submitted). Treatment was continued, provided there was no evidence of disease progression or excessive toxicity, and patients were continually reassessed for evidence of acute and cumulative toxicity.

Patients

Patients were excluded from the study if they had received previous or current treatment with a MET inhibitor or hepatocyte growth factor (HGF)–targeting therapy. Patients with symptomatic central nervous system (CNS) metastases that were neurologically unstable or required increasing doses of steroids to control and patients with any CNS deficits were excluded. Patients were ineligible if previous cytotoxic chemotherapy, radiotherapy, biologic therapy, or investigational agents were completed ≤ 4 weeks prior to dosing; non-cytotoxic small molecule therapy within ≤5 half-lives or ≤2 weeks prior to dosing; major surgery ≤2 weeks prior to dosing, or if they had experienced unresolved toxicity (grade >1) from previous anticancer therapy or radiotherapy (except alopecia).

Clinical Assessments

For patients with NSCLC from the original expansion group, assessments were performed locally using RECIST v1.0 and centrally (by BIRC) using both RECIST v1.0 and Novartis guidelines based on RECIST v1.1. For patients with NSCLC from the EGFRwt MET IHC 3+ group, assessments were performed locally and centrally based on RECIST v1.1. Assessments were carried out at screening, every 8 weeks beginning of cycle 3 and as required to confirm response, and at the end of treatment (if no scan within 30 days prior to end of treatment). Safety assessments were carried out based on all AEs, clinical laboratory data, and physical examinations.

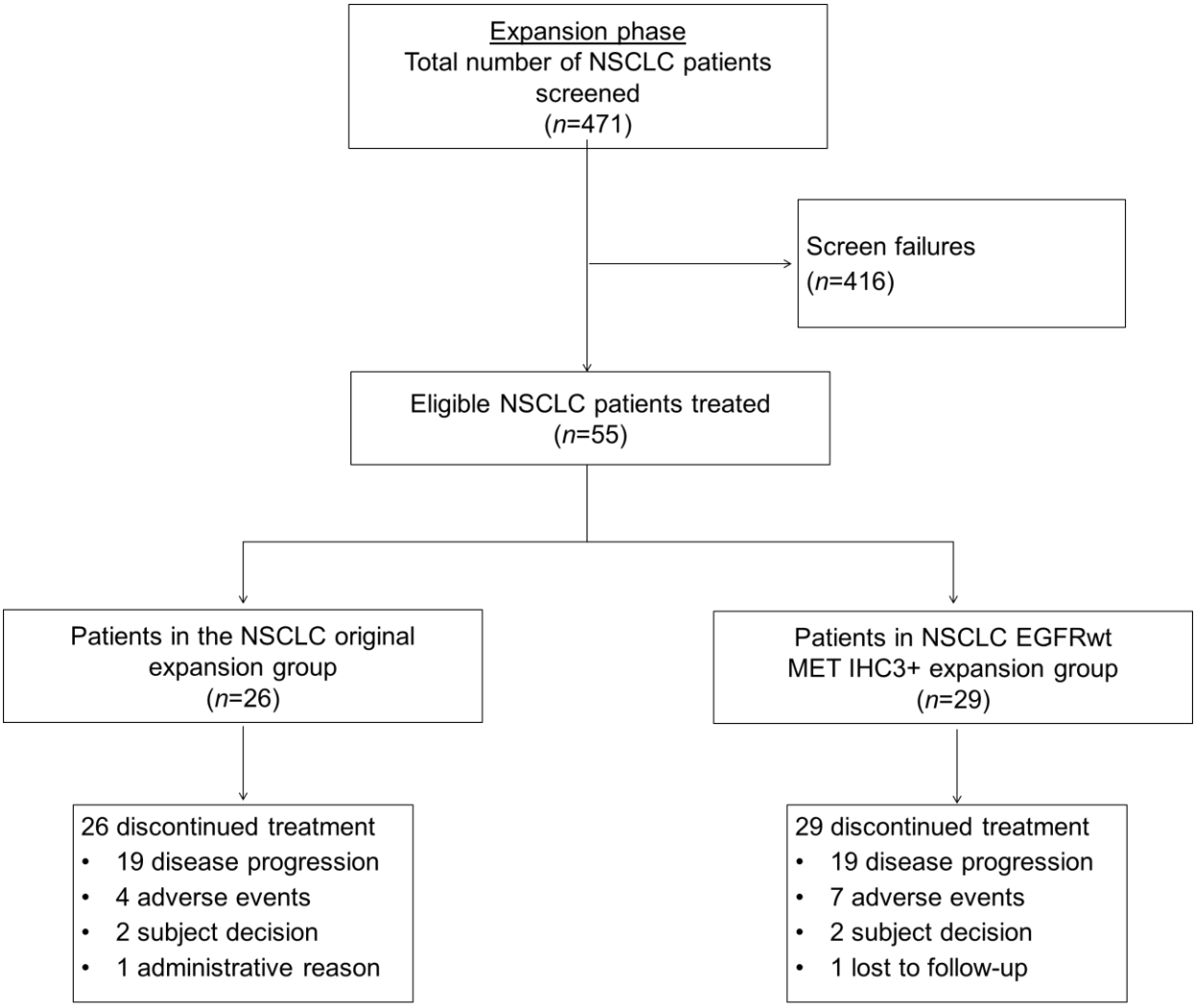
Statistical Analysis

During the expansion phase, initially 10 patients with NSCLC were expected to be enrolled. Enrollment was expanded by at least 15 additional patients, to have at least 25 patients per group if additional insight into the safety and/or efficacy was desired. The decision for such expansion of a group was to be made no later than 16 weeks from initial treatment of the last subject for that group and by the sponsor and study investigators after reviewing all available clinical data. ORR was the key secondary efficacy endpoint and was defined as the proportion of patients with measurable disease whose best overall response is either complete response (CR) or partial response (PR) according to RECIST v1.1. The ORR was presented by treatment group with an exact 95% confidence interval (CI), if response rate of 10% or higher was observed. Kaplan-Meier estimate of median PFS and rate at 3, 6, and 12 months, along with 95% CI, are summarized by treatment group per investigator and BIRC. A waterfall plot of best percentage change from baseline in sum of the longest diameters per investigator is presented for each treatment group. The incidence of treatment-emergent AEs (new or worsening from baseline) are summarized by primary system organ class, severity based on the Common Terminology Criteria for Adverse Events v4.0, type of AE, and relationship to the study drug by treatment group. The safety data are summarized by treatment group and disease subtypes.

Study oversight

This study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The protocol was approved by an institutional review board at each hospital and the responsible regulatory authorities whenever required. All patients provided written informed consent before any study procedures. The study was designed by the sponsor (Novartis Pharma AG) in consultation with investigators. The sponsor collected the data and analyzed them in conjunction with the authors.

Supplementary Figure S1. CONSORT diagram



At data cutoff: July 17, 2017

Supplementary Table S1. Best overall response based on BIRC assessment

	NSCLC Original Expansion Group *N*=26	**NSCLC EGFRwt MET IHC3+ Expansion Group *N*=29**
Complete response	0	1
Partial response	3	8
Stable disease	7	9
Progressive disease	9	6
Unknown	7	5
Overall response rate, n (%)	**3 (12)**	**9 (31)**
95% CI	[2.4-30.2]	15.3-50.8
Disease control rate, n (%)	**10 (39)**	**18 (62)**
95% CI	[20.2-59.4]	[42.3-79.3]

Abbreviations: BIRC, blinded independent review committee; CI, confidence interval; EGFRwt, epidermal growth factor receptor wild-type; IHC, immunohistochemistry; NSCLC, non–small-cell lung cancer

Supplementary Table S2. Biomarker profile by GCN and IHC status

Biomarker Status		GCN Status, n (%)									
		<4		≥4 and ≤6		≥6		Unknown		Total	
			ORR, n/N (%)		ORR, n/N (%)		ORR, n/N (%)		ORR, n/N (%)		ORR, n/N (%)
IHC status, n (%)	0	1 (2)	0/1 (0)	0		0	0	0	0	1 (2)	0/1 (0)
	1+	1 (2)	0/1 (0)	1 (2)	0/1 (0)	0	0	0	0	2 (4)	0/2 (0)
	2+	5 (9)	0/5 (0)	1 (2)	0/1 (0)	2 (4)	2/2 (100.0)	6 (11)	0/6 (0)	14 (25)	2/14 (14.3)
	3+	9 (16)	0/9 (0)	10 (18)	2/10 (20.0)	13 (24)	5/13 (38.5)	5 (9)	2/5 (40.0)	37 (67)	9/37 (24.3)
	Unknown	1 (2)	0/1 (0)	0	0	0	0	0	0	1 (2)	0/1 (0)
	Total	17 (31)		12 (22)		15 (27)		11 (20)		55 (100)	

Abbreviations: GCN, gene copy number; IHC, immunohistochemistry

Supplementary Table S3. Demographics and response in patients with *METΔex14* mutation-positive NSCLC

Gender	Age, Years	Race	Prior Therapies, n	Histology	MET IHC Status	MET GCN	Best % Change from Baseline in Target Lesions	Best Overall Response	PFS, Months
Female	81	Caucasian	0	Non-squamous	3+	NA	-47.62	Confirmed PR	6.9
Female	66	Caucasian	3	Squamous	3+	13.8	-13.95	SD	3.0*
Male	84	Caucasian	0	Non-squamous	3+	11.2	-30.07	Confirmed PR[¶]	5.1
Male	71	Caucasian	1	Other[†]	3+	13.6	-83.05[‡]	Confirmed CR	18.6

Abbreviations: CR, complete response; GCN, gene copy number; IHC, immunohistochemistry; NA, not available; NSCLC, non–small-cell lung cancer; PFS, progression-free survival; PR, partial response; SD, stable disease; RECIST, Response Evaluation Criteria in Solid Tumors

*Patient remained on therapy for an additional 6 months after progressive disease per RECIST v 1.1 due to prolonged clinical benefit

[†]Mixed histology (NSCLC with elements of adenocarcinoma, squamous and sarcomatoid carcinoma)

[‡]All target lesions selected for this patient were nodal lesions and were reported as 5 mm at this visit. As nodal lesions less than 10 mm are considered normal, CR was assigned per RECIST v1.1 guidelines

[¶]Patient had unconfirmed PR who discontinued before the confirmation of PR

Supplementary Table S4. Adverse events, suspected to be study drug–related (any grade occurring in ≥10% of patients and corresponding grades 3/4)

Preferred Term	**All Patients *N*=55**	
	All Grades n (%)	Grades 3/4 n (%)
Nausea	23 (42)	2 (4)
Peripheral edema	18 (33)	2 (4)
Vomiting	17 (31)	0
Fatigue	11 (20)	2 (4)
Diarrhea	10 (18)	1 (2)
Decreased appetite	9 (16)	1 (2)