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Head-to-head comparison of the dual-MEK inhibitor IMM-1-104 versus binimetinib in NRAS mutant melanoma models

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Session: **Poster Session A**
Session date and time: **Saturday, January 8, 4:45 pm-7:00 pm**

Disclosures

Peter J. King, Ph.D.

I have the following financial relationships to disclose:

Stockholder in Immuneering Corporation
Employee of Immuneering Corporation

I will not discuss off label use and/or investigational use in my presentation.

Human Melanoma Tumor Cell Line Profiles

Model	HRAS	NRAS	BRAF	PI3K	RTK/RAS	WNT	Hippo	HGF/cMET	FGFRs	MEK/ERK	MYC	IMM-1-104 EC_{50} [nM]
MM415		p.Q61L		var								20.5
MM127		p.G13R	p.G464E									140
SK-MEL-2		p.Q61R					var					144
MEL-JUSO	p.G13D	p.Q61L			var							435
A375			p.V600E				var	var	var			551
SK-MEL-28			p.V600E	var	var		var			var		702
SK-MEL-30		p.Q61K		var	var	var						1390
MeWo				var	var	var	var	var	var	var		2640
Hs852T		p.G12V			var		var		var		var	3660

* 3D-Tumor Growth Assay (3D-TGA)

IMM-1-104 is a dual-MEK inhibitor that is currently in IND-enabling studies

Molecular profile of 9 melanoma tumor cell lines based on WES (Immuneering Corp); *Humanized, ECM-based 3D tumor model (% EdU change)

Head-to-head comparison of Binimetinib, Selumetinib and IMM-1-104

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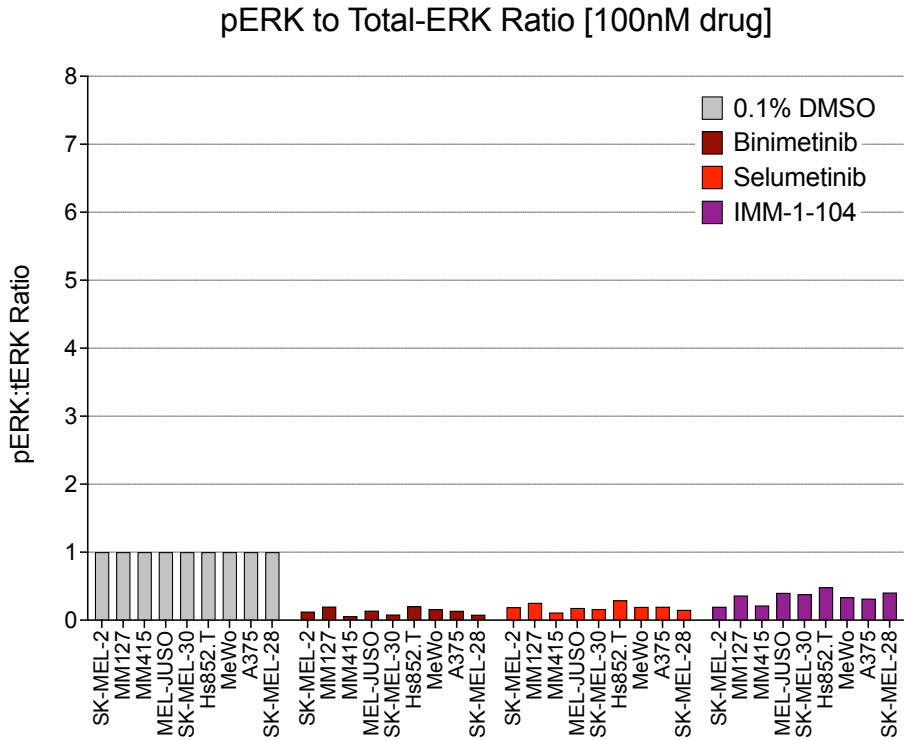

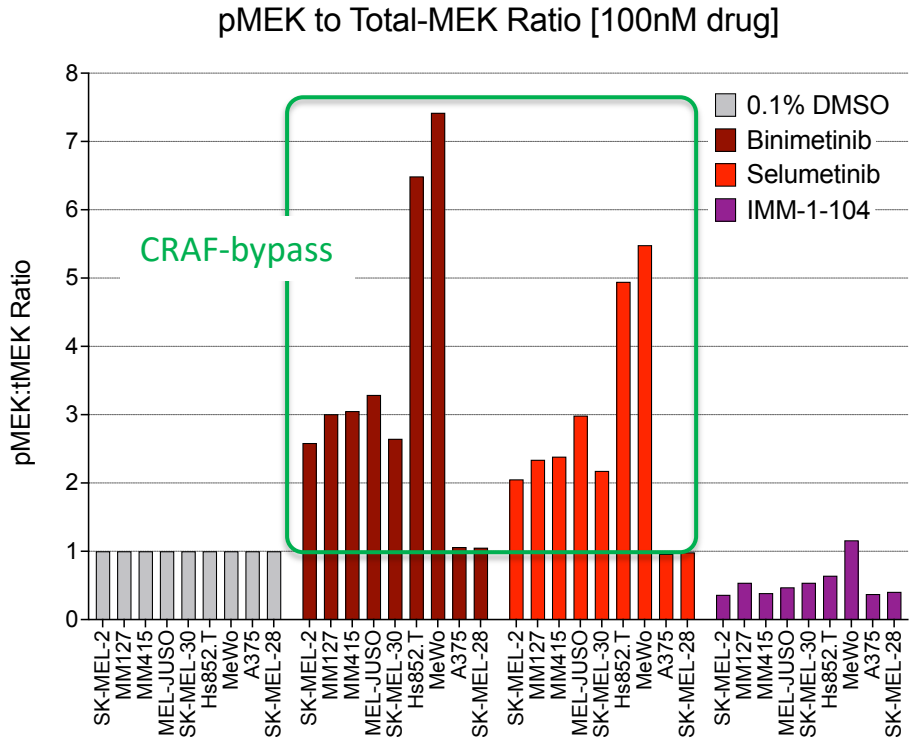

Cell-based 2D in vitro molecular assays were performed to assess cellular levels of phosphorylated and total ERK and MEK across 9 melanoma models

IMM-1-104 Reduced pERK and pMEK Across Multiple Molecular Profiles in Human Melanoma

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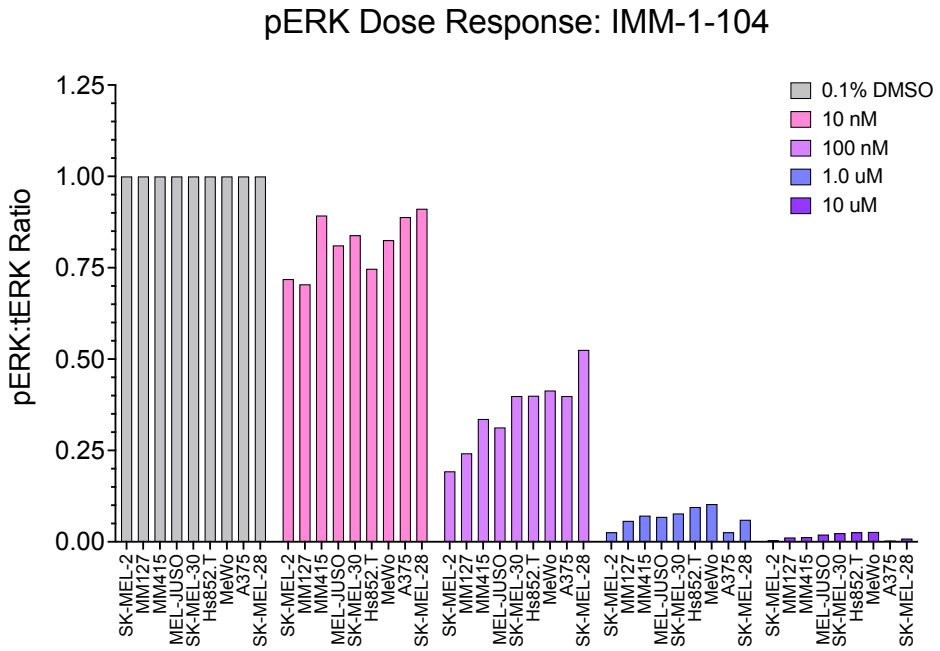

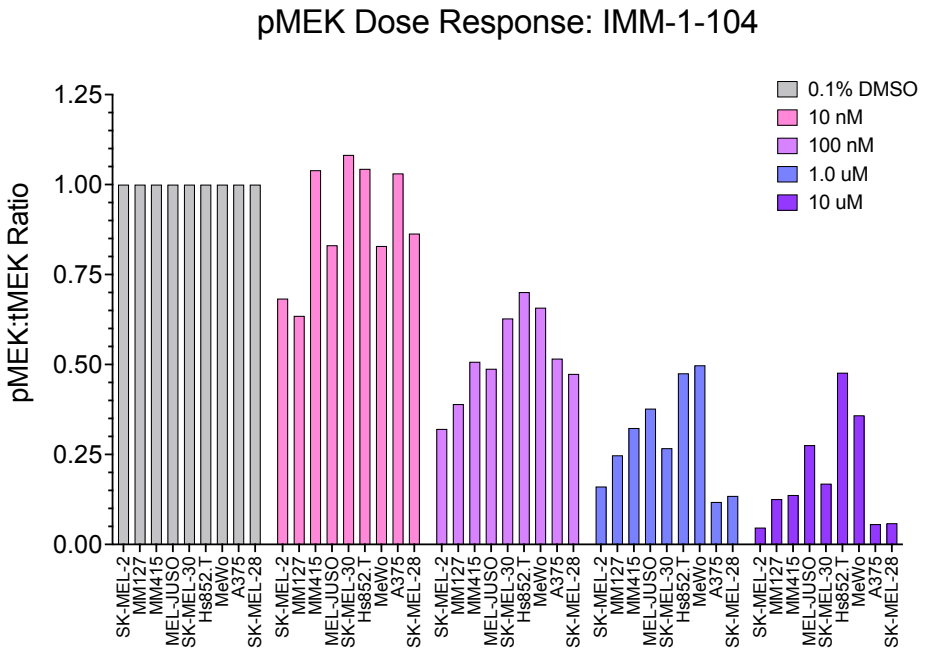

Cell-based 2D in vitro molecular assays were performed to assess cellular levels of phosphorylated and total ERK and MEK across 9 melanoma models

3D Tumor Pharmacology: IMM-1-104

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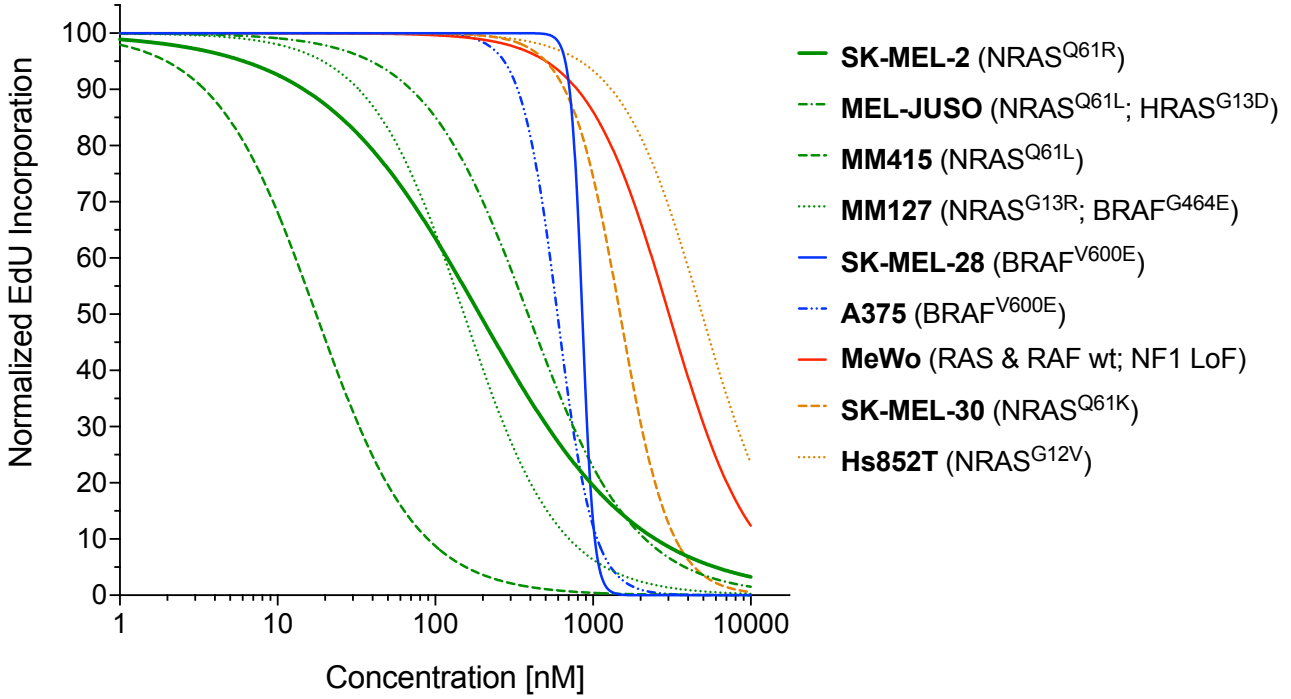
3D Tumor Growth Assay

Model	EC_{50} [nM]
SK-MEL-2	144
MEL-JUSO	435
MM415	20.5
MM127	140
SK-MEL-28	702
A375	551
MeWo	2,640
SK-MEL-30	1,390
Hs852T	3,660

% EdU 9 -point dose response: 1 nM to 10 uM



Cell-based 3D-TGA in vitro pharmacologic assays were performed across nine melanoma models; triplicate wells per each dose; EC_{50}'s cited

Phase 3 NEMO Study: Binimetinib

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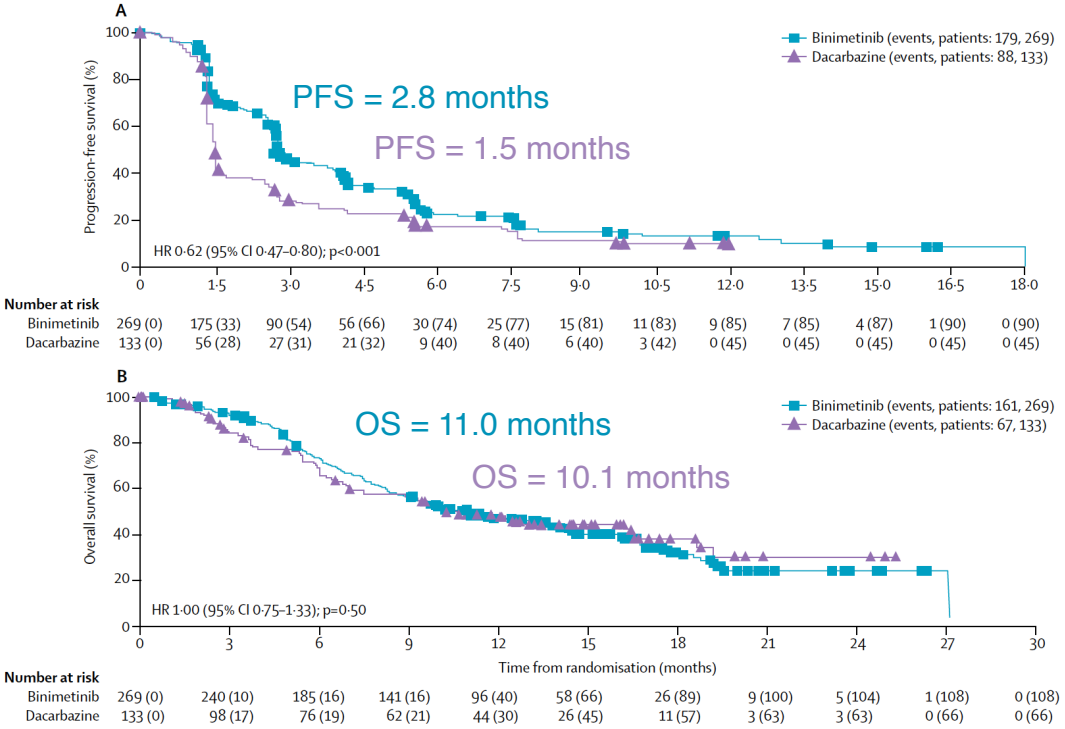

Dummer, et al 2017 Lancet S1470-2045(17)30180-8

Q61R
(~50%)

	Binimetinib (n=269)	Dacarbazine (n=133)
Age (years)	65 (18–90)	62 (27–89)
Sex		
Male	166 (62%)	85 (64%)
Female	103 (38%)	48 (36%)
NRAS mutation		
Gln61Lys	100 (37%)	51 (38%)
Gln61Leu	32 (12%)	17 (13%)
Gln61Arg	137 (51%)	64 (48%)
Wild-type	0	1 (1%)
ECOG performance status*		
0	193 (72%)	96 (72%)
1	76 (28%)	36 (27%)
Tumour stage at study entry†		
IIIC	10 (4%)	9 (7%)
IVM1a	27 (10%)	16 (12%)
IVM1b	45 (17%)	23 (17%)
IVM1c with normal LDH concentration	109 (41%)	50 (38%)
IVM1c with increased LDH concentration	78 (29%)	35 (26%)
LDH concentration‡		
Normal	184 (68%)	95 (71%)
High§	71 (26%)	32 (24%)
Missing	14 (5%)	6 (5%)
Previous immunotherapy	57 (21%)	28 (21%)
Previous ipilimumab¶	36 (13%)	17 (13%)
Previous anti-PD-1 or PD-L1¶	17 (6%)	7 (5%)
Patients who received previous lines of immunotherapy (used in therapeutic or metastatic setting)	49 (18%)	24 (18%)
1 line	43 (88%)	23 (96%)
≥2 lines	6 (12%)	1 (4%)

Data are median (range) or n (%). ECOG=Eastern Cooperative Oncology Group. LDH=lactate dehydrogenase. *One patient in the dacarbazine group had a performance status of 2. †Extent of melanoma according to American Joint Committee on Cancer stage. ‡Low and high categories of LDH defined by normal concentrations; no patients in either group were in the the low LDH category. §Discrepant LDH values due to missing or erroneously reported values at screening. ¶Metastatic setting.

Table 1: **Baseline characteristics**

Head-to-Head NRAS^{Q61R} Melanoma Pharmacology Study: Binimetinib vs. IMM-1-104

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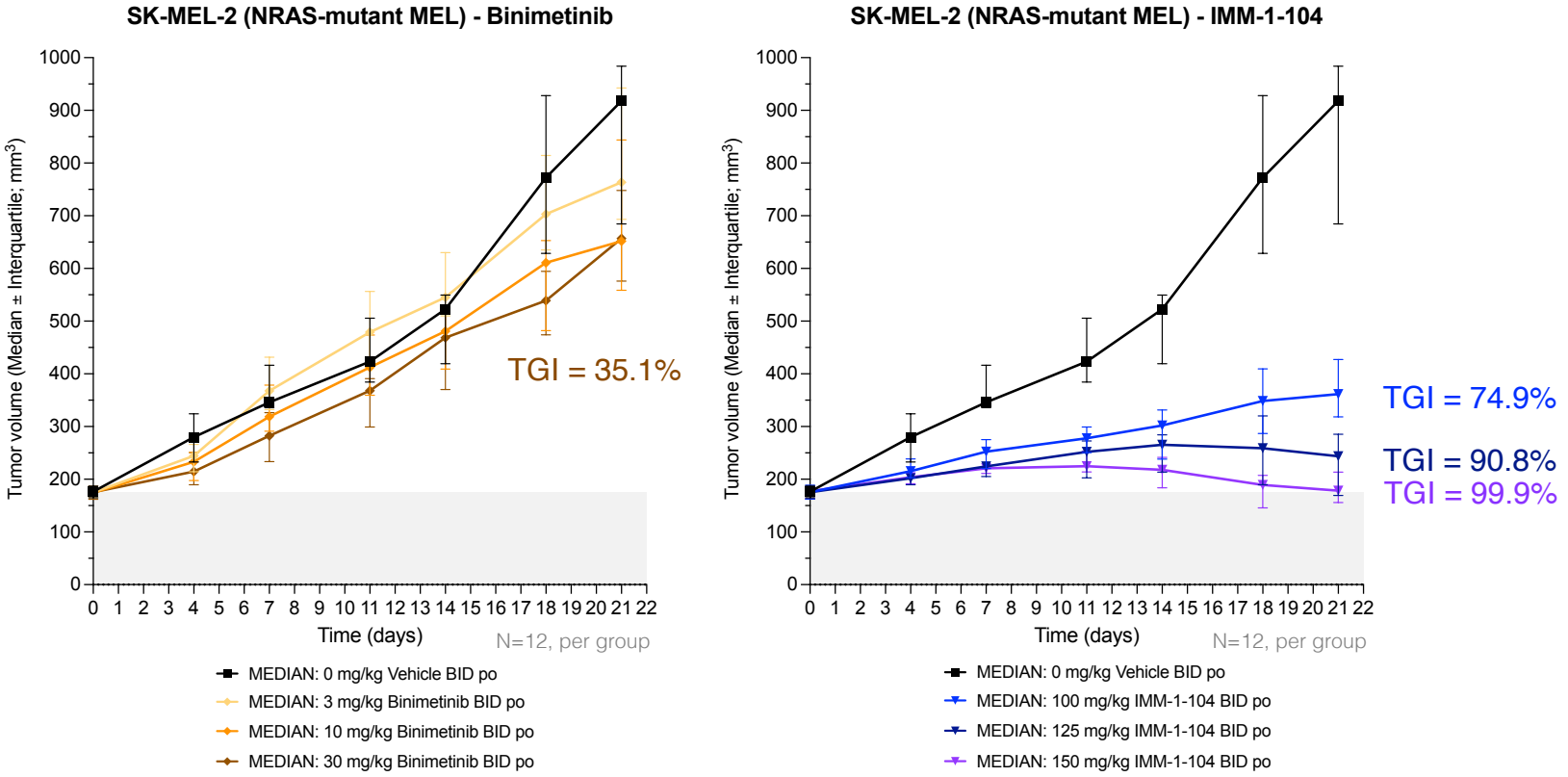

Conclusions

- In the phase 3 NEMO study published in Lancet (c. 2017), binimetinib failed to substantially improve overall survival vs. dacarbazine (11.0 vs. 10.1 months) in NRAS mutant melanoma patients and led to a ~50% increase in serious adverse events (34% vs. 22%).

- As the most common NRAS mutation in the NEMO study was Q61R, we chose to further model binimetinib vs. IMM-1-104 *in vivo* using SK-MEL-2, a tumor that displays a similar molecular profile to half of the patients in the phase 3 NEMO study.

- Collectively, our data suggest that binimetinib may not effectively control MAPK pathway reactivation in RAS mutant tumors. In contrast, the deep cyclic inhibition combined with a dual-MEK mechanism of action of IMM-1-104 may offer a unique therapeutic advantage over first generation MEK inhibitors in RAS mutant tumors.

Thank you for your attention

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Please visit our website for additional posters for IMM-1-104 presented at the EORTC-AACR earlier this year:

https://immuneering.com/publications/

Abstract

Introduction: Activating mutations in RAS or RAF are a common oncogenic event in patients with advanced solid tumors in skin, pancreas, lung and colon. Therapeutic options for these patients are limited. The median overall survival in NRAS mutant metastatic melanoma is less than one year in the salvage setting. MEK, which lies downstream of RAS and RAF, but upstream of ERK, is an attractive target to counter elevated MAPK signaling. While MEK inhibitors are selective, FDA registered MEK inhibitors are sensitive to pathway reactivation in RAS mutant tumors. This mechanistic limitation prompted chronic pathway inhibition strategies that contribute to on-target class-effect toxicities that limit clinical utility. Therefore, we developed a new approach for MEK inhibition. IMM-1-104 is a novel, allosteric dual-MEK inhibitor that disrupts phosphorylation of both MEK and its downstream target ERK and has a short plasma drug half-life, enabling deep cyclic inhibition with a near-zero drug trough.

Methods: IMM-1-104 was tested head-to-head vs. binimetinib across a series of preclinical experiments to better understand differential *in vivo* activity of each compound. Cell-based 2D and 3D *in vitro* biochemical and pharmacologic assays were performed across nine melanoma models. The SK-MEL-2 melanoma xenograft mouse model was used to evaluate single agent activity of IMM-1-104 (50, 100, 125, 150 mg/kg BID p.o.) vs. binimetinib (3, 10, 30 mg/kg BID p.o.) for 21 days treatment after tumors had reached 150 to 200 mm^3.

Results: Binimetinib treatment of RAS mutant tumors resulted in decreased pERK with a concomitant increase in pMEK. In contrast, IMM-1-104 led to reductions in both pERK and pMEK in SK-MEL-2 (NRAS-Q61R), MM127 (NRAS-G13R; BRAF-G464E), MM415 (NRAS-Q61L), MEL-JUSO (NRAS-Q61L; HRAS-G13D), A375 (BRAF-V600E), SK-MEL-28 (BRAF-V600E), SK-MEL-30 (NRAS-Q61K; BRAF-E275K), MeWo (RAS and RAF wildtype) and Hs852T (NRAS-G12V) cells. Head-to-head comparison *in vivo* showed binimetinib had little effect on curtailing growth of SK-MEL-2 melanoma tumors (Tumor Growth Inhibition (TGI) range = 20.6% to 35.6%), whereas IMM-1-104 resulted in 74.9% to 99.9% TGI, with the top two doses driving mid-cycle regressions.

Conclusions: In the phase 3 NEMO study published in Lancet (c.2017), binimetinib failed to improve overall survival vs. dacarbazine (11.0 vs. 10.1 months) in NRAS mutant melanoma patients and saw a 50% increase in serious adverse events (34% vs. 22%). As ~50% of these patients displayed the NRAS-Q61R mutation, we chose to model binimetinib vs. IMM-1-104 in SK-MEL-2 *in vivo*, a tumor that displays a similar molecular profile to half of the patients in the NEMO study. Collectively, our data suggest that binimetinib may not effectively control MAPK pathway reactivation in RAS mutant tumors whereas the deep, cyclic dual-MEK approach of IMM-1-104 may offer a unique therapeutic advantage over first generation MEK inhibitors in this indication.