Deep Cyclic Inhibition (DCI) of the MAPK pathway with IMM-6-415, alone and in combination with encorafenib, demonstrates anti-tumor activity and tolerability in RAF mutant tumors in vivo

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Introduction

A significant proportion of cancer patients have tumors addicted to uncontrolled MAPK signaling. Activating mutations in RAS or RAF are often directly responsible and have been observed in over 20% of human tumors[1]. Because MEK is downstream of RAS and RAF, it is an appealing drug target. However, MEK inhibitors have historically suffered from poor clinical durability, high toxicity and a susceptibility to pathway reactivation that has limited monotherapy activity in the RAS mutant setting. Unlike other MEK inhibitors, IMM-1-104 [NCT05585320] and IMM-6-415 are designed with distinctive features including both (1.) a unique target engagement mechanism that helps resist MAPK pathway reactivation and (2.) a pharmacokinetic (PK) profile that enables fast cadence deep cyclic inhibition (DCI). DCI drives pulsatile targeted inhibition that deprives tumor cells of sustained oncogenic pathway signaling. Additionally, the goal of DCI, by achieving an adequately low drug trough, is to improve drug tolerability by allowing normal healthy cells an opportunity to maintain homeostatic signaling between doses. To our knowledge, IMM-6-415's preclinical activity is driven by the shortest drug plasma half-life (0.3 hours in mice) of any MEK inhibitor developed to date.

Experimental Procedures

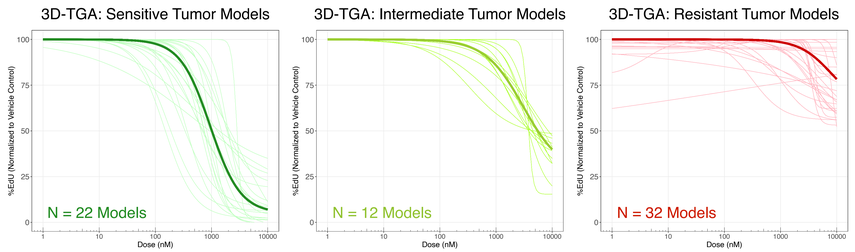
IMM-6-415 has demonstrated promising activity in RAS-mutant xenograft tumor models (SITC 2022)[2]. Here, the antitumor activity of IMM-6-415 was evaluated in over 60 humanized 3D tumor growth assays (3D-TGA), which included 30 BRAF class I-mutant tumor models. The humanized 3D-TGA better predicts *in vivo* tumor responses versus 2D culture and more accurately replicates human tumor biology[3,4] (Figure 1 and 6).

Additionally, multiple drug-drug combinations have been explored, including vertical drug combinations with BRAF inhibitors. IMM-6-415, binimetinib (MEK inhibitor) and encorafenib (BRAF inhibitor) were tested head-to-head as single agents and in combination with encorafenib in BRAF^{V600E} melanoma and colorectal subcutaneous tumor xenograft models in female BALB/c nude mice.

Benchmarking 3D-TGA Response to IMM-6-415

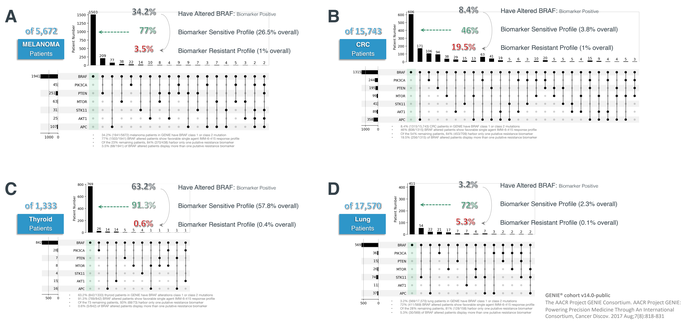
As monotherapy, IMM-6-415 demonstrated antitumor activity in over 50% (34 of 66) of the 3D-TGA models tested, including 30 BRAF-mutant preclinical models in which 19 (63%) showed activity. Similar to IMM-1-104, resistant models either lacked obvious MAPK pathway driver mutations or displayed parallel oncogenic pathway activation events. Likewise, sensitive and intermediate responses were strongly enriched for models harboring activation mutations in either RAS or RAF.

Figure 1: 3D-TGA IMM-6-415 Dose Responses (N = 66 Models; 11 Tumor Indications)



Cell lines were tested in the humanized 3D-TGA (N=66) and assigned response of sensitive (IC50 < 3uM), intermediate (IC50 ≥ 3uM and < 10uM), and resistant otherwise. The dark line on each plot represents the median of the individual curves.

Figure 2. Biomarker Profile of Patients Profiled in GENIE® v.14.0



Using the GENIE database, a targetable population was selected on the basis of BRAF class I/II mutations. This population was then assessed for co-occurrence of mutations in genes that may partially contribute to resistance mechanisms with intersecting sets indicating concurrent mutations in patients. The bar charts detail co-occurrence frequencies in OncoTree[5] cohorts: (A) SKCM, MEL; (B) COAD, READ, COADREAD; (C) THPA; and (D) LUAD.

Results

Both monotherapy and combination activity of IMM-6-415 were further explored in the A-375 (melanoma) and HT-29 (colorectal) BRAF^{V600E} tumor models. Monotherapy treatment with encorafenib or IMM-6-415 displayed superior tumor growth inhibition (TGI) when compared to binimetinib. The combination of IMM-6-415 plus encorafenib prompted greater TGI with superior durability of response when tested head-to-head against the combination of binimetinib plus encorafenib *in vivo* at reported human equivalent doses for registered drugs (Figures 3, 4, 5).

Figure 3. IMM-6-415 ± Encorafenib vs. Binimetinib ± Encorafenib in A-375

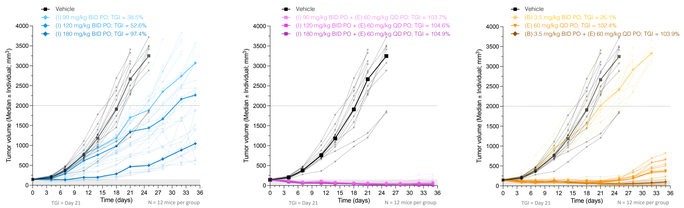
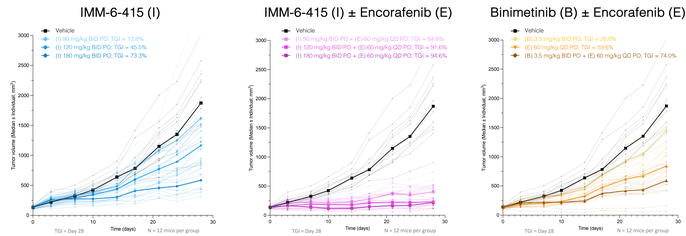


Figure 4. IMM-6-415 ± Encorafenib vs Binimetinib ± Encorafenib in HT-29



A-375 Melanoma & HT-29 Colorectal Cancer (CRC) BRAF^{V600E} xenograft tumor models in athymic nude mice. Binimetinib (MEK inhibitor) and encorafenib (BRAF inhibitor) were commercially purchased. Tumor Growth Inhibition (TGI) % = [1-(Ti-To)/(Ci-Co)]x100%. No median body weight loss was noted.

Deep Cyclic Inhibition (DCI) Promotes Deeper, More Durable Antitumor Responses

Figure 5. IMM-6-415 (I) ± Encorafenib (E) vs Binimetinib (B) ± Encorafenib in A-375

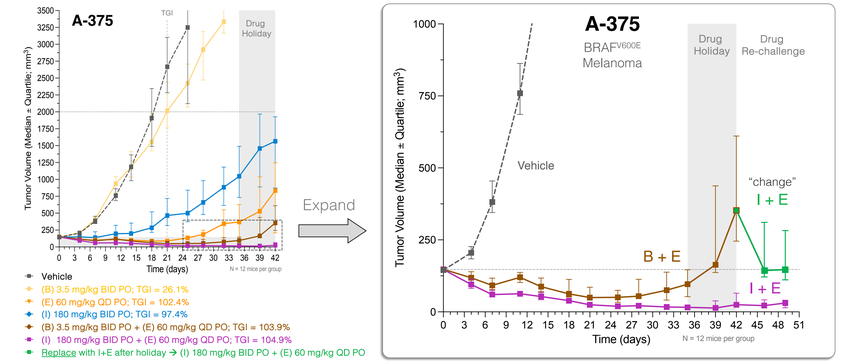
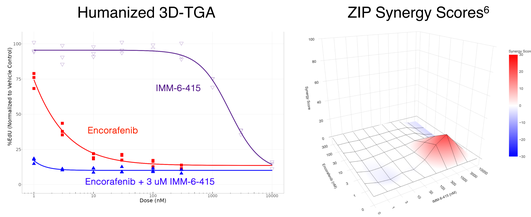


Figure 6. Synergy Evaluation of IMM-6-415 ± Encorafenib in A-375 Model in 3D-TGA



Thesis of Deep Cyclic Inhibition

- Pulsatile inhibition of MAPK at MEK
- Reduce loss of negative regulators
- Minimize adaptive resistance
- Delay onset of acquired resistance
- Improve tolerability and safety
- Expand combination opportunities
- Disrupt addiction to MAPK pathway

Conclusions

IMM-6-415 is a short-lived dual MEK inhibitor (MEKi) that works through Deep Cyclic Inhibition (DCI) and a fast pulsatile cadence (short half-life) that is distinctive from chronic MEKi. IMM-6-415 was optimized for twice daily oral dosing and has displayed promising antitumor activity and tolerability across a growing number of RAS and RAF mutant models (Universal MAPK activity). Building on earlier RAS mutant studies[2], we found that IMM-6-415 (pulsatile DCI MEKi) plus encorafenib achieved superior TGI and durability *in vivo* versus binimetinib (sustained MEKi) plus encorafenib in BRAF mutant colorectal cancer and melanoma models. These data are consistent with the thesis that MEK DCI can outperform chronic MEKi as monotherapy and in vertical drug combinations.

References

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