

Preclinical Evaluation of Potential Therapeutic Combinations with the Kirsten Rat Sarcoma (KRAS)^{G12D} Inhibitor INCB161734 with Chemotherapy, Growth Factor Disruption, or Immunotherapy in Pancreatic Cancer

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Abstract

Background: Kirsten Rat Sarcoma G12D (KRAS^{G12D}) mutation is found in ~40% of pancreatic ductal adenocarcinomas (PDACs); however, there are no approved agents targeting KRAS^{G12D}. INCB161734 is a potent, selective, and orally bioavailable KRAS^{G12D} inhibitor being assessed in a phase 1 study (NCT06179160). Early efficacy outcomes for KRAS^{G12D} inhibitors, including INCB161734, are encouraging, although fewer than half of patients with PDAC experience clinical response. We investigated whether INCB161734 combination therapies might improve therapeutic outcomes.

Methods: INCB161734-based combinations were tested in mice bearing subcutaneous PDAC tumours (xenograft and/or syngeneic). Combinations included INCB161734 with chemotherapy (gemcitabine + nab-paclitaxel [GEMNabP] or 5-fluorouracil + irinotecan + oxaliplatin + leucovorin [FOLFIRINOX]), the epidermal growth factor receptor (EGFR) antagonist cetuximab, or anti-programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) monoclonal antibodies. Animal studies were conducted under the supervision of the INCYTE Institutional Animal Care and Use Committee.

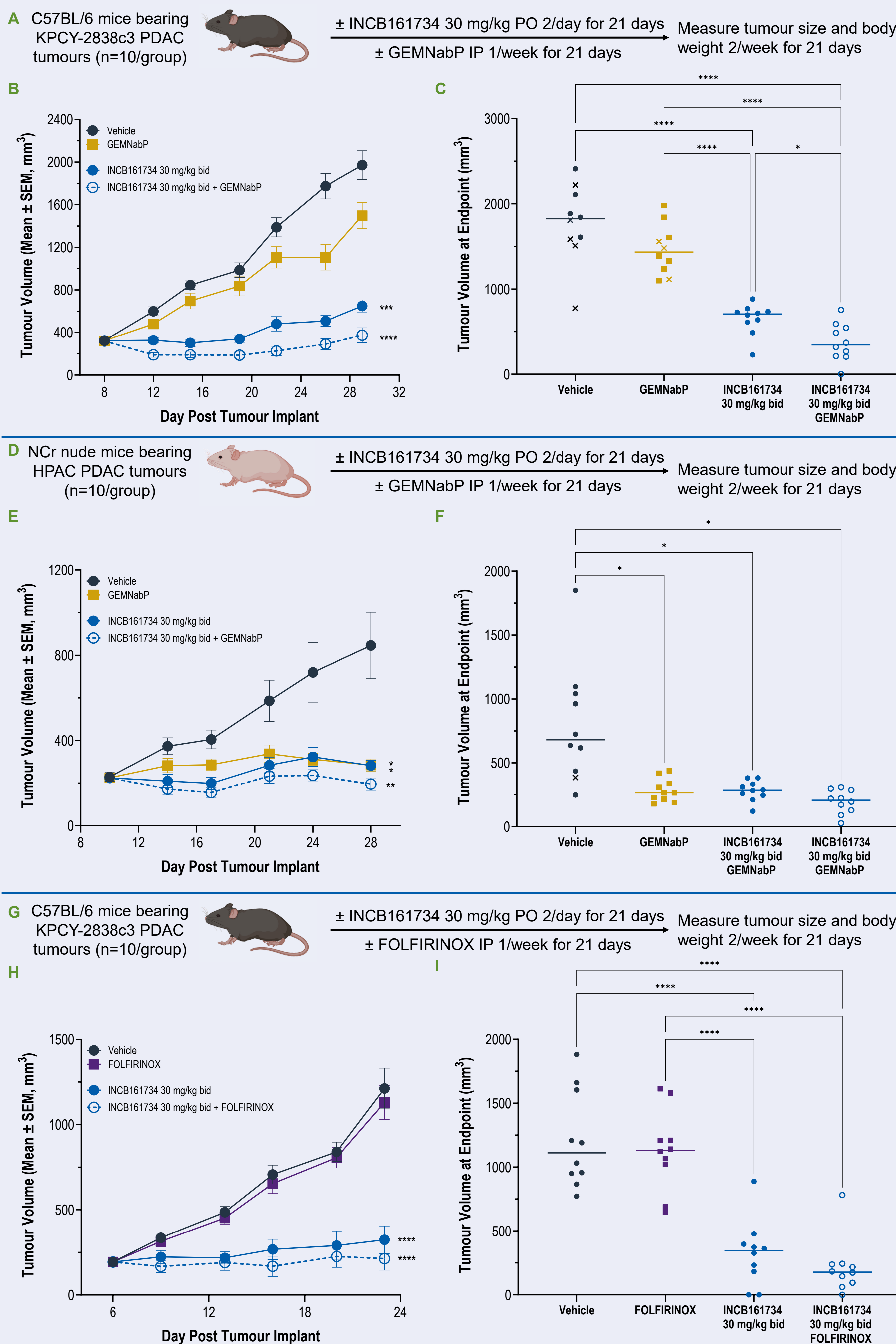
Results: INCB161734 with either chemotherapy regimen improved antitumour activity compared with monotherapy. Chemotherapy combinations were more effective in immune-competent than immune-deficient mouse models, suggesting an immunomodulatory aspect of KRAS^{G12D} inhibition. INCB161734 + cetuximab resulted in greater tumour growth inhibition than monotherapy, likely by preventing EGFR-induced (re)activation of wild-type RAS signalling. Finally, combining INCB161734 with anti-PD-(L)1 antibodies resulted in complete or near-complete tumour regressions in 90% of treated animals, with 80% of animals remaining tumour-free for ≥60 days after the end of treatment, further suggesting an immunomodulatory impact of KRAS^{G12D} inhibition. All combinations were well tolerated.

Conclusions: These results demonstrate that KRAS^{G12D} blockade via INCB161734 combined with chemotherapy, EGFR signalling disruption, or immune checkpoint blockade via PD-1/PD-L1 may have the potential to improve therapeutic efficacy in patients with PDAC.

Introduction

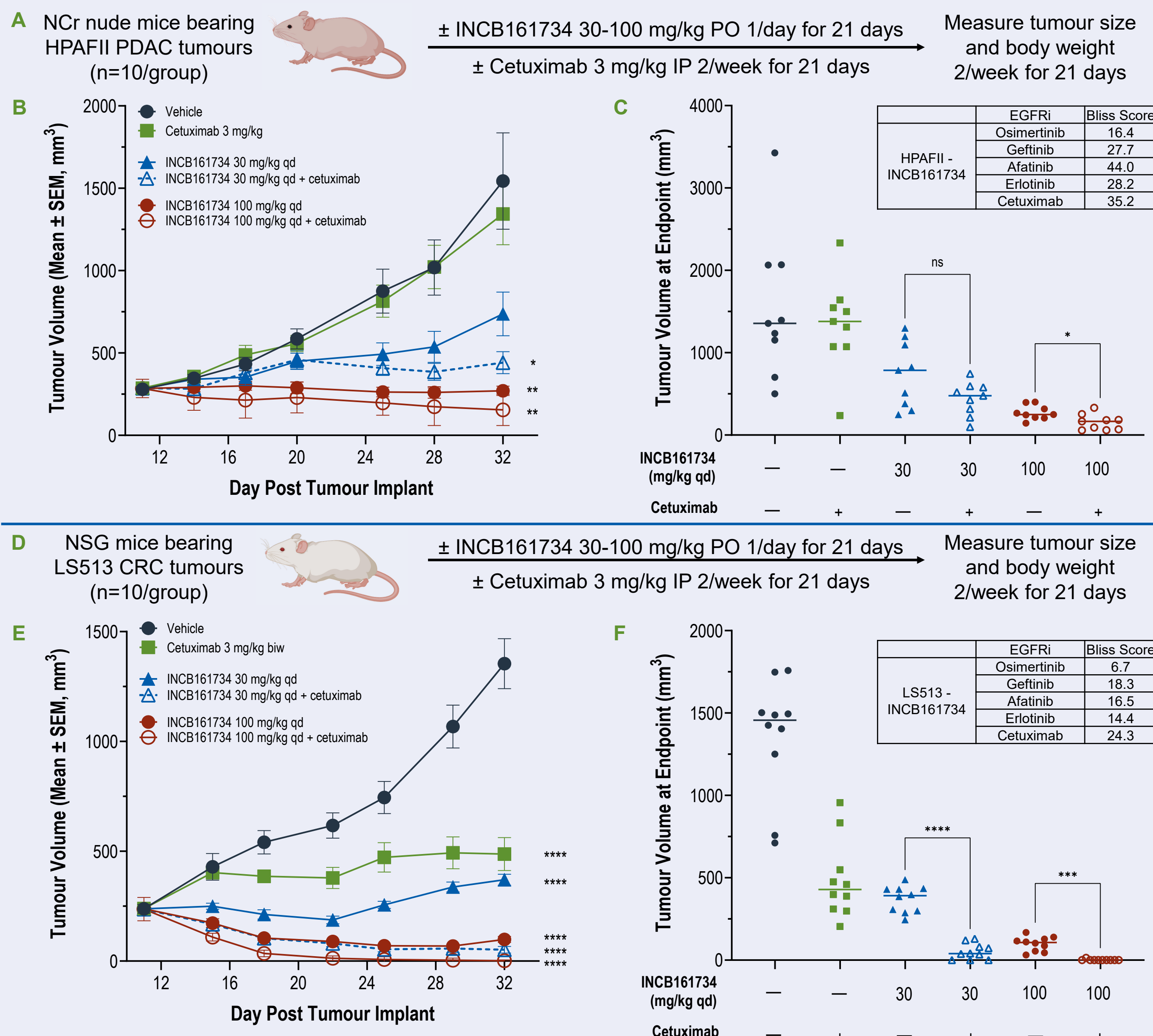
- KRAS mutations are found in ~23% of all solid tumours, and KRAS^{G12D} mutations are the most common, occurring in ~40% of patients with PDAC and ~30% of patients with colorectal cancer¹
- INCB161734 is a potent, selective, orally bioavailable KRAS^{G12D} inhibitor^{2,3}
 - Picomolar binding affinity to KRAS^{G12D}, ~80-fold selectivity over wild-type KRAS
 - Equal binding affinity to both GDP (RAS-OFF) and GTP (RAS-ON) forms of KRAS^{G12D}
 - Inhibits KRAS^{G12D} pathway and proliferation of KRAS^{G12D} mutant cells with nanomolar potency in *in vitro* cellular assays
 - Highly orally bioavailable in preclinical studies, supporting exposure >IC₉₀ at trough concentration (C_{trough})⁴
 - Well tolerated in preclinical studies
 - In clinical development (NCT06179160)

INCB161734 Antitumour Activity Is Enhanced When Combined with PDAC Chemotherapy



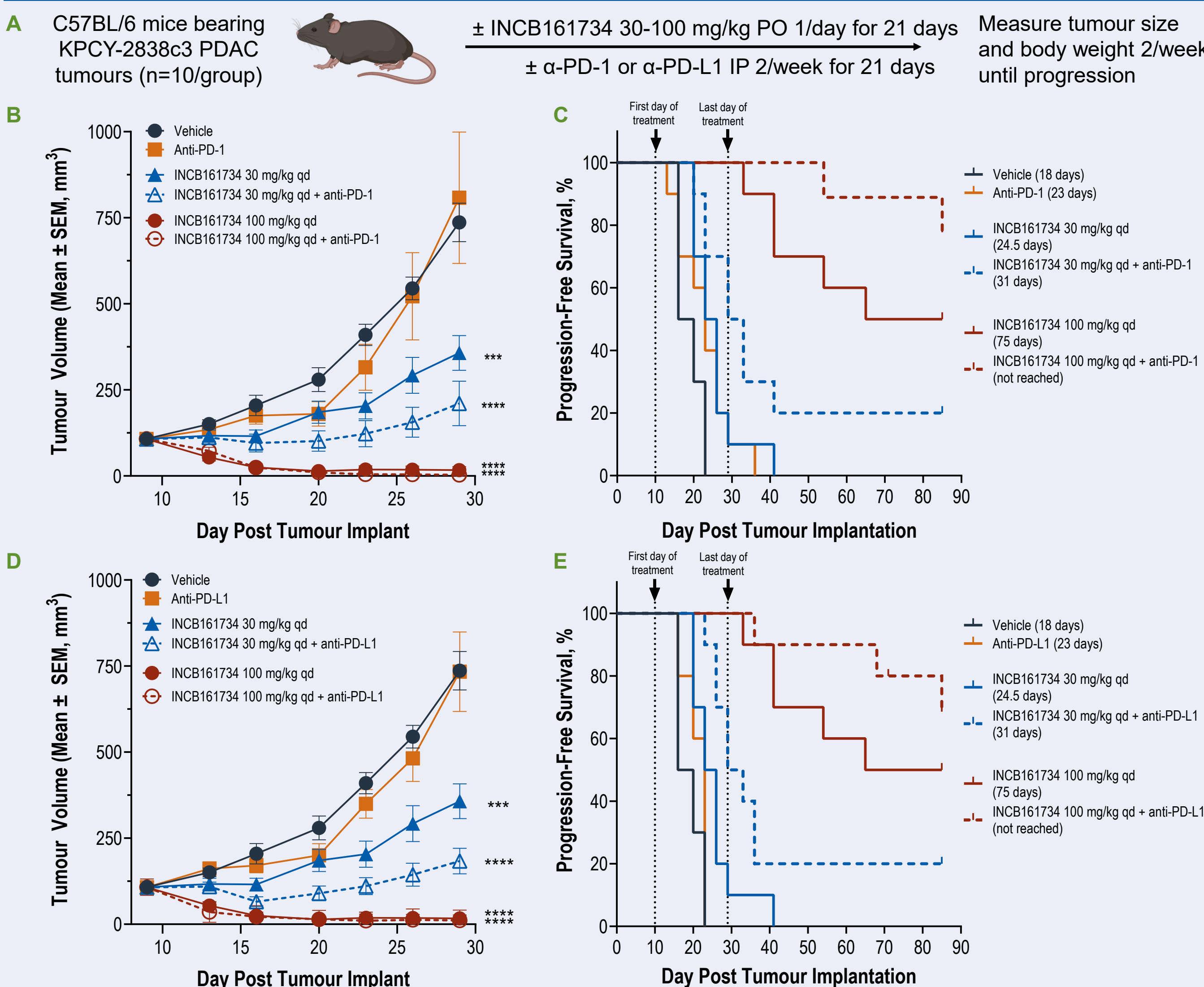
- The KRAS^{G12D} inhibitor INCB161734 exerted significant antitumour activity against KRAS^{G12D} mutant PDAC tumours as a monotherapy (A-I), and this was further enhanced when combined with PDAC standard-of-care chemotherapy regimens GEMNabP (A-F) or FOLFIRINOX (G-I)
 - (A-C) Syngeneic C57BL/6 mice bearing KPCy-2838c3 tumours were treated ± INCB161734 ± GEMNabP
 - (A) Study design, (B) tumour growth over time, and (C) tumour size at endpoint
 - Note that "X" symbols denote mice that were removed from study early due to tumour ulceration
 - (D-F) NCr nude mice bearing HPAC xenograft tumours were treated ± INCB161734 ± GEMNabP
 - (D) Study design, (E) tumour growth over time, and (F) tumour size at endpoint
 - Note that "X" symbols denote mice that were removed from study early due to tumour ulceration
 - (G-I) Syngeneic C57BL/6 mice bearing KPCy-2838c3 tumours were treated ± INCB161734 ± FOLFIRINOX
 - (G) Study design, (H) tumour growth over time, and (I) tumour size at endpoint
- Both combinations (INCB161734 + GEMNabP and INCB161734 + FOLFIRINOX) were well tolerated, without significant weight loss or other clinical tolerability signals

Combination INCB161734 + Cetuximab (EGFRi) Generates Superior Tumour Growth Inhibition



- The antitumour activity of INCB161734 in PDAC (A-C) and CRC (D-F) was significantly increased by combination with the EGFR inhibitor cetuximab
 - (A-C) NCr nude mice bearing HPACII xenograft tumours were treated ± INCB161734 ± cetuximab
 - (A) Study design, (B) tumour growth over time, and (C) tumour size at endpoint, including *in vitro* Synergy Score testing EGFR inhibitors in combination with INCB161734 in HPACII cells
 - (D-F) NSG mice bearing LS513 xenograft tumours were treated ± INCB161734 ± GEMNabP
 - (D) Study design, (E) tumour growth over time, and (F) tumour size at endpoint, including *in vitro* Synergy Score testing EGFR inhibitors in combination with INCB161734 in LS513 cells
- This combination was well tolerated, without significant weight loss or other clinical tolerability signals

INCB161734 Potentiates Immune Checkpoint Blockade, Generating Durable Antitumour Activity



- (A) Study design. C57BL/6 mice bearing syngeneic KPCy-2838c3 tumours were treated ± INCB161734 ± α-PD-1 (B-C) or α-PD-L1 (D-E)
- Combining INCB161734 and immune checkpoint blockade generates deeper and more durable immune responses, with more complete tumour regression or slowing during the dosing period and more animals remaining tumour-free for months after the end of treatment
- These combinations were well tolerated, without significant weight loss or other clinical tolerability signals

Conclusions

- INCB161734 is a novel, potent, selective, and orally bioavailable KRAS^{G12D} small molecule inhibitor that demonstrates considerable monotherapy activity in preclinical models
- This monotherapy activity can be further enhanced when INCB161734 is combined with other treatment modalities
 - Combinations with PDAC standard-of-care chemotherapy regimens generated significant additional efficacy over INCB161734 alone
 - Combinations with EGFR-blocking agents, such as cetuximab, drove significant antitumour activity, including partial or complete tumour regressions
 - KRAS^{G12D} blockade with INCB161734 in combination with immune checkpoint (anti-PD-1/PD-L1) blockade generated durable responses, with most animals (at the high dose) remaining tumour-free for more than 60 days after treatment ended
- INCB161734 was well tolerated as a monotherapy in preclinical models, and all the combinations described here were also well tolerated, with no evidence of meaningful weight loss or other tolerability signals
- These results demonstrate that combination therapies have the potential to improve therapeutic efficacy in PDAC
- INCB161734 is currently undergoing clinical evaluation as both monotherapy and in combination therapy settings (NCT06179160)

Disclosures

Farren, Roman, Wallower, Gallion, Smith, Wang, Kim: Employment and stock ownership – Incyte Corporation.

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