#LB174

DISCOVERY AND PRECLINICAL CHARACTERIZATION OF INCA00186, A HUMANIZED MONOCLONAL ANTIBODY ANTAGONIST OF CD73, AS A CANCER IMMUNOTHERAPY

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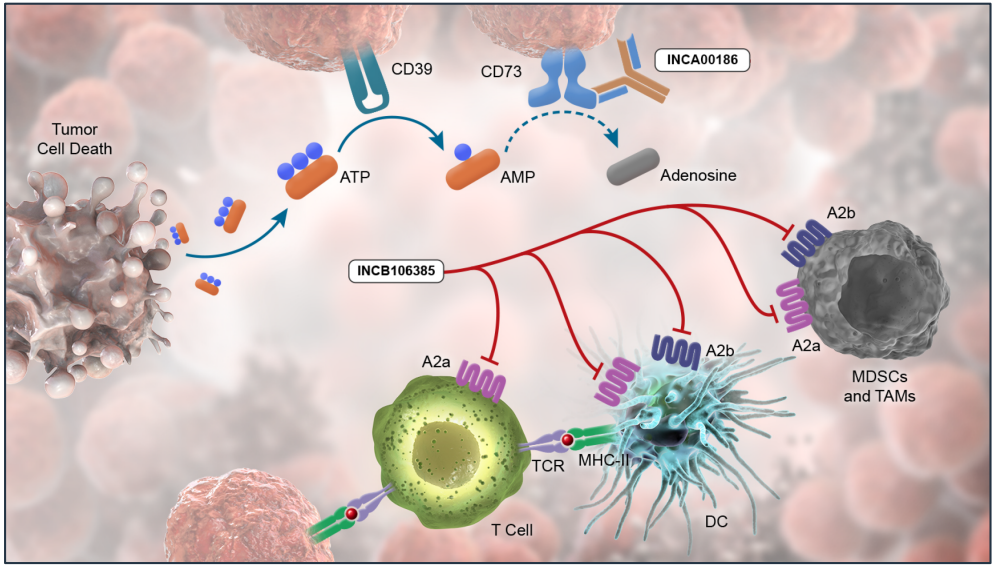
BACKGROUND



AMP, adenosine monophosphate; ATP, adenosine triphosphate; DC, dendritic cell; MDSC, myeloid-derived suppressor cells; MHC-II, major histocompatibility class 2; TAM, tumor-associated macrophage; TCR, T-cell receptor; TME, tumor microenvironment.

- Adenosine is a potent immunosuppressive metabolite present at high levels in the TME
- CD39 and CD73 are the major enzymes converting ATP to adenosine
- Increased flux through the adenosine pathway has been linked to resistance to clinically approved immune checkpoint therapies
- Pharmacologic inhibition of multiple nodes of the adenosine pathway is expected to be more effective in reversing the immunosuppressive activity of adenosine
  - INCB106385 to target A2a and A2b receptors
  - INCA00186 to target CD73 enzymatic function and adenosine production
- INCA00186 is a humanized, Fc-silenced IgG1 monoclonal antibody that potently antagonizes CD73 function by both decreasing cell surface expression and inhibiting enzymatic activity

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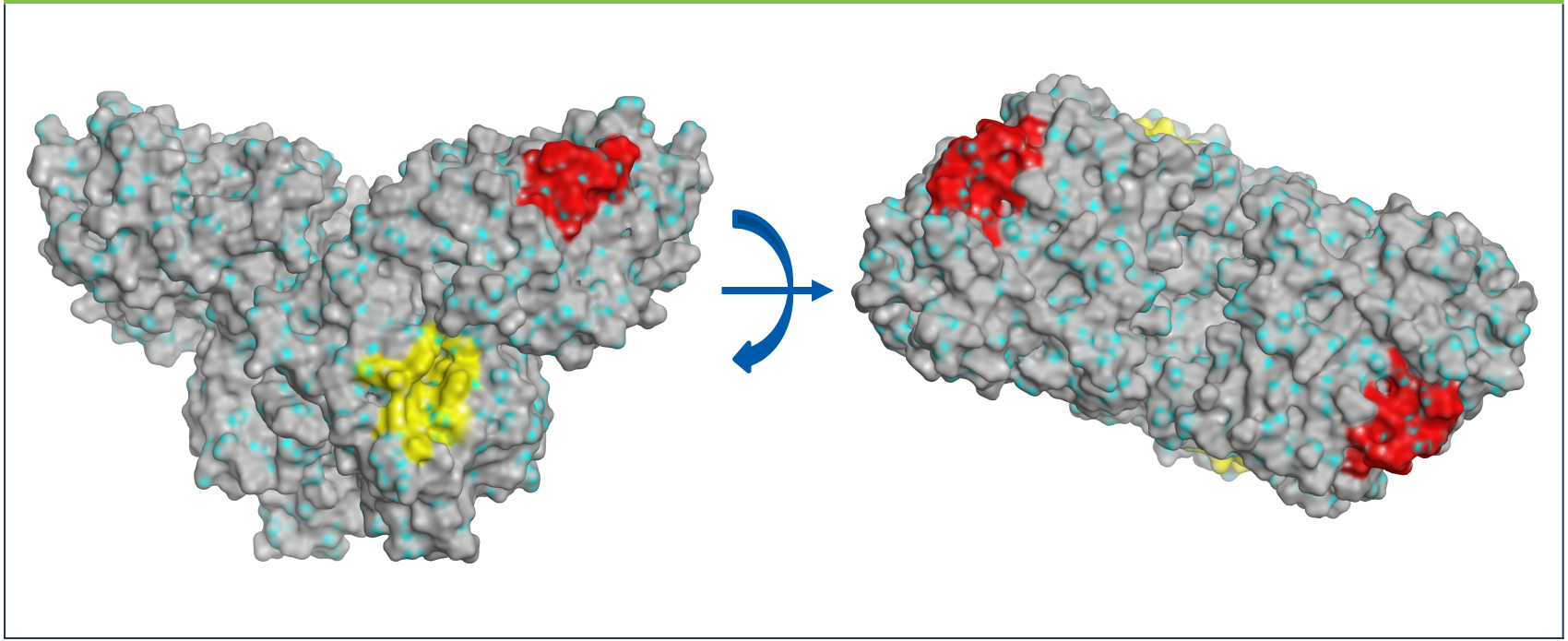
INCA00186 Does Not Bind to the Substrate Binding Site

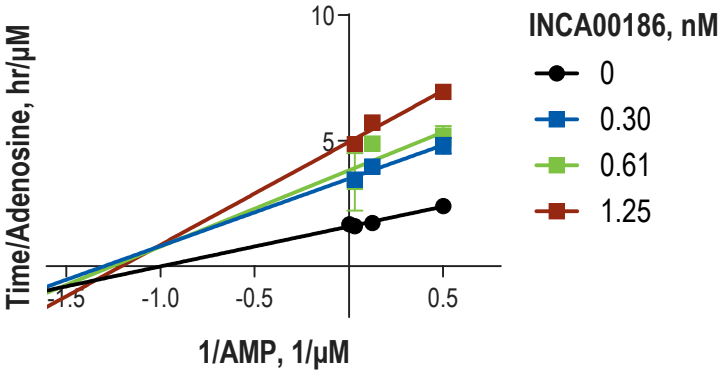


- INCA00186 binds distal (red) to the substrate binding site (yellow) as determined by HDX-MS

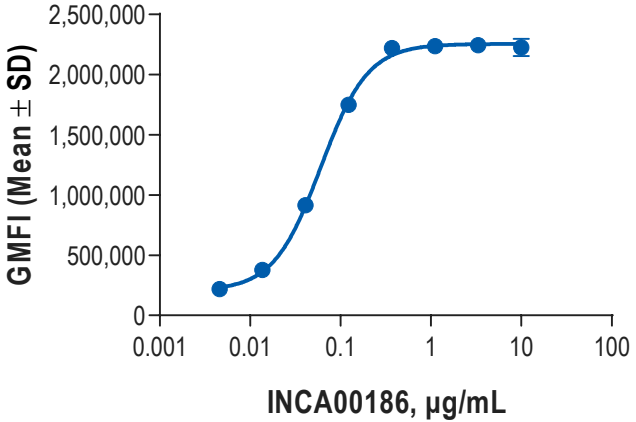
HDX-MS, hydrogen/deuterium exchange mass spectrometry. Data on file (Incyte Corporation).

INCA00186 Is a Potent Noncompetitive Inhibitor of CD73

Lineweaver-Burk Analyses of Mode of Inhibition



Binding on MDA-MB-231 Cells



INCA00186 Binding to Human CD73

Target	K_a, 1/Ms	K_d, 1/s	K_D, nM
Human CD73	1.50E+06	4.49E-04	0.30

- INCA00186 is a noncompetitive inhibitor and potently binds cell surface and soluble CD73

GMFI, geometric mean fluorescence intensity; K_a, association rate constant; K_d, dissociation rate constant; K_D, dissociation equilibrium constant; SD, standard deviation. Data on file (Incyte Corporation).

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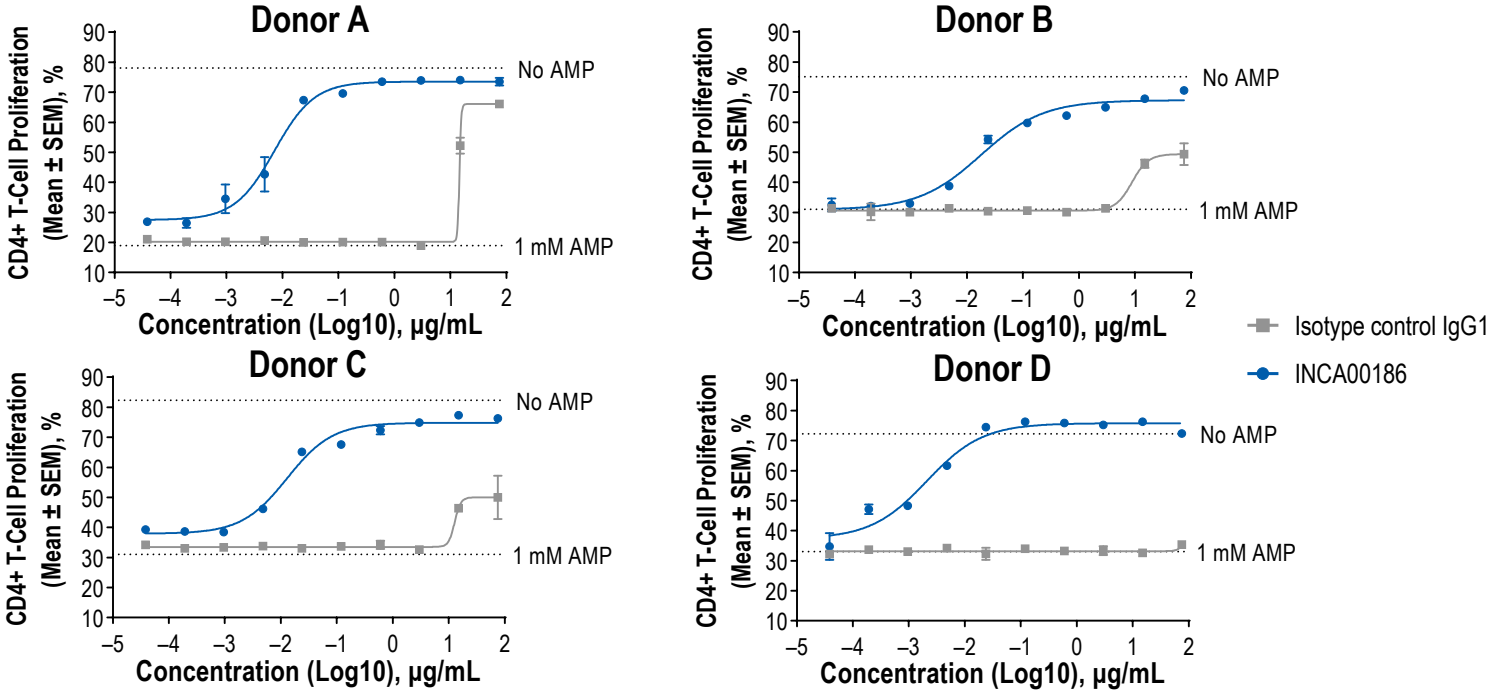
INCA00186 Restores Effector T-Cell Proliferation



- AMP-mediated immunosuppression is reversed by INCA00186 treatment with an EC_{50} of 0.009 ± 0.002 µg/mL (n = 9, mean ± SEM)

EC_{50}, half maximal effective concentration; SEM, standard error of the mean. Data on file (Incyte Corporation).

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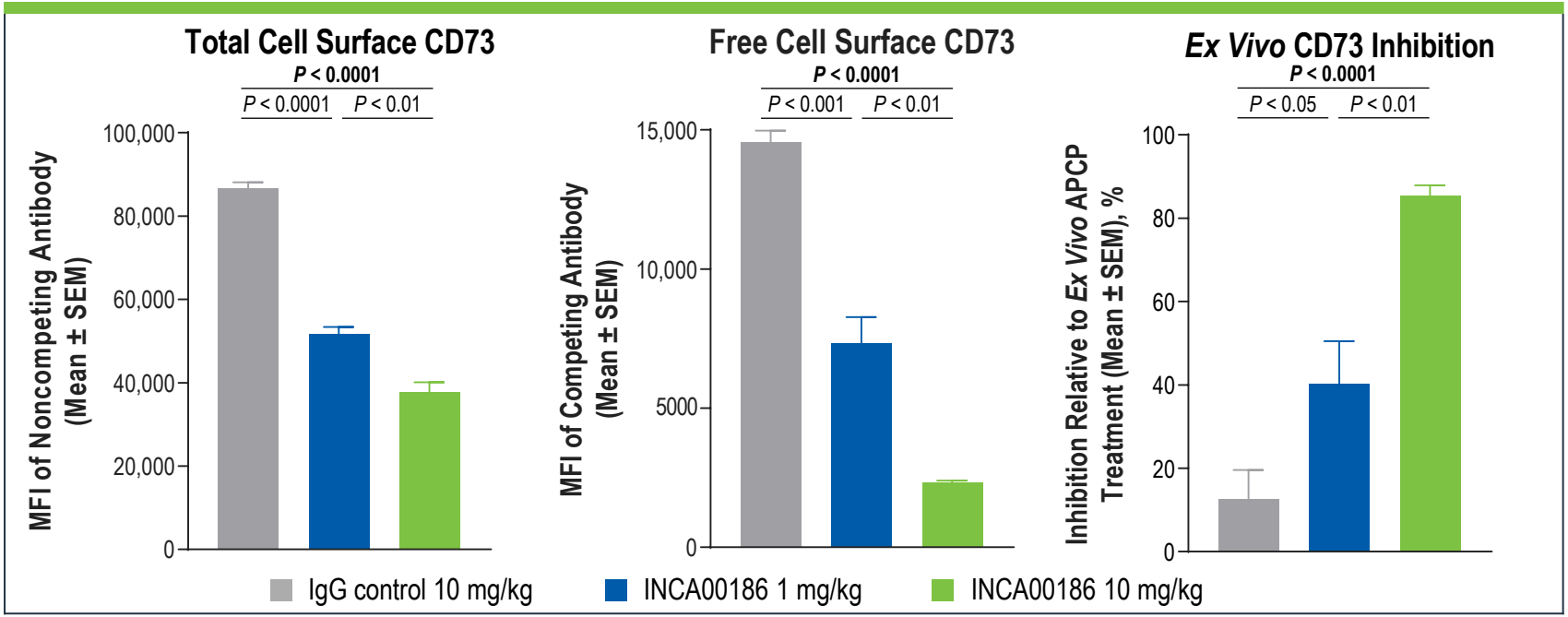
INCA00186 Binds to and Inhibits CD73 *In Vivo*



- In human A375 melanoma tumor model in CD34+ humanized NSG mice, INCA00186 treatment leads to a dose-dependent decrease in total and free cell surface CD73 and inhibits CD73 activity *ex vivo*

APCP, adenosine 5'-(α,β-methylene)diphosphate; MFI, mean fluorescence intensity. Data on file (Incyte Corporation).

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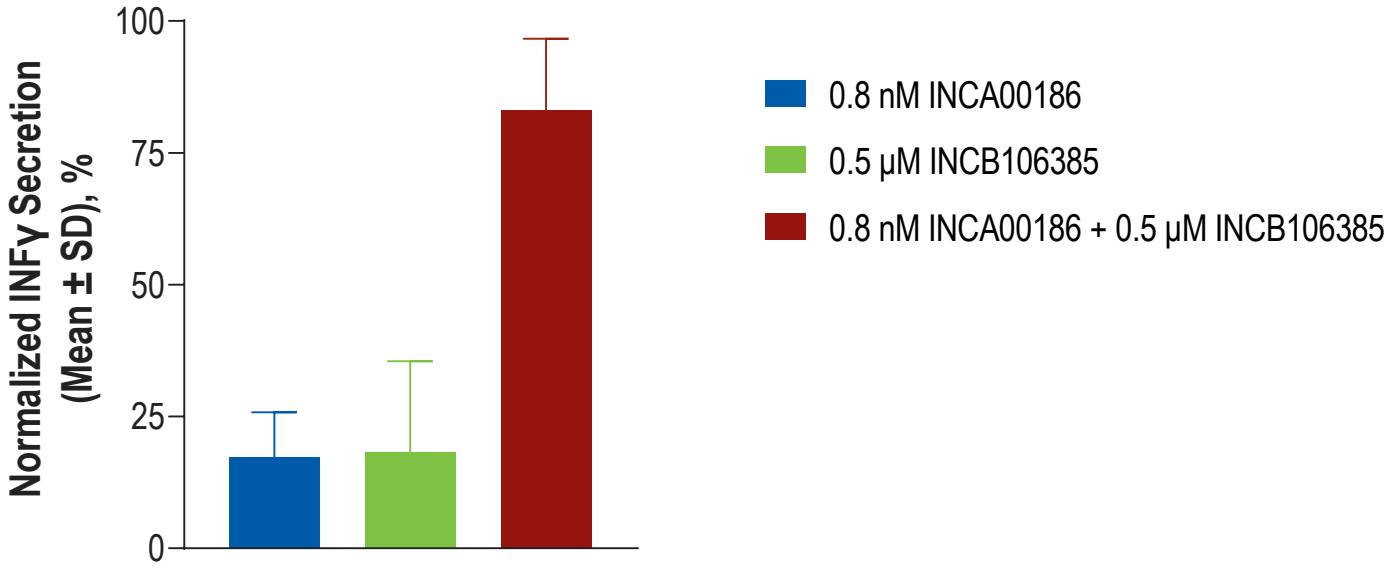
INCA00186 and INCB106385 Combination Restores Cytokine Secretion



- INCA00186 in combination with a potent and selective inhibitor of adenosine receptors A2a and A2b, INCB106385, increases IFNγ secretion by effector T cells in presence of high concentrations of immunosuppressive AMP

IFN, interferon. Data on file (Incyte Corporation).

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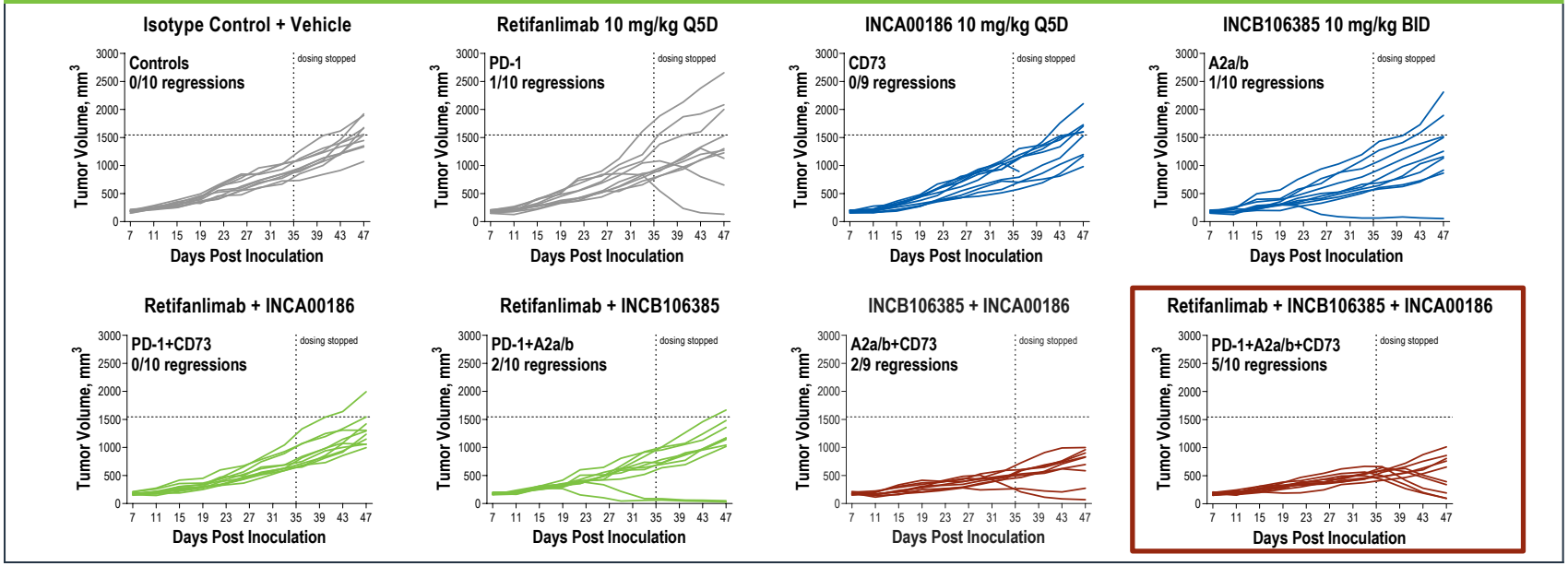
Combinations of INCA00186, INCB106385, and Retifanlimab Enhance Tumor Growth Control



- In human MDA-MB-231 breast tumor model in CD34+ humanized NSG mice, combinations including both INCA00186 and INCB106385 controlled tumor growth significantly better than monotherapies, and the addition of retifanlimab to combination increased the number of tumor regressions

Tumors were considered regressions if the tumor volume on day 47 was less than 500 mm^3 and there were at least 2 measurements with decreasing tumor volumes. BID, twice daily; PD-1, programmed cell death protein 1; Q5D, every 5 days. Data on file (Incyte Corporation).

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CONCLUSIONS

- INCA00186 is a humanized, Fc-silenced IgG1 monoclonal antibody that potently binds and antagonizes CD73 function
- INCA00186 is a noncompetitive CD73 inhibitor and highly active at high AMP concentrations
- INCA00186 reduces the total level of cell surface CD73 on tumor cells and decreases the overall activity
- In stimulated effector T cells cultured in the presence of high concentrations of immunosuppressive AMP, INCA00186 alone restores proliferation and the combination of INCA00186 and INCB106385 fully restores IFNγ secretion
- In a human A375 melanoma tumor model in CD34+ humanized NSG mice:
  - INCA00186 treatment decreases total cell surface CD73 and displays high receptor occupancy on tumor cells
  - INCA00186 treatment decreases CD73 activity in *ex vivo* assays of tumor homogenates
- In a human MDA-MB-231 breast tumor model in CD34+ humanized NSG mice:
  - Combination treatments including both INCA00186 and INCB106385 controlled tumor growth significantly better than monotherapies
  - Combination treatment with INCA00186, INCB106385, and retifanlimab resulted in the largest number of tumor regressions
- INCA00186 is being advanced to clinical development
- The combinatorial activity of INCA00186, INCB106385, and retifanlimab provide a compelling approach to adenosine pathway suppression as immunotherapies for patients with cancer

DISCLOSURES

- **Stewart, Buonpane, Zhou, Hansbury, Smith, Wang, Lu, Su, Awdew, Huang, Kulkarni, Harvey, Mondal, Wang, Stevens, Pratta, Behshad, Fanuka, Ren, Koblish, Nastri, Mayes:** Employment and stock ownership – *Incyte Corporation*

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