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Solid Tumor Spotlight: TGFβR2xPD-1 Bi-specific Antibody and KRAS G12D Inhibitor

ESMO 2025

October 19, 2025

Forward looking statements

Except for the historical information set forth herein, the matters set forth in this release contain predictions, estimates and other forward-looking statements, including any discussion of the potential and opportunities presented by INCA33890 and INCB161734 and plans for further development of the same.

These forward-looking statements are based on Incyte's current expectations and subject to risks and uncertainties that may cause actual results to differ materially, including unanticipated developments in and risks related to: further research and development and the results of clinical trials possibly being unsuccessful or insufficient to meet applicable regulatory standards or warrant continued development; the ability to enroll sufficient numbers of subjects in clinical trials and the ability to enroll subjects in accordance with planned schedules; determinations made by the FDA, EMA and other regulatory agencies; Incyte's dependence on its relationships with and changes in the plans of its collaboration partners; the efficacy or safety of Incyte's products and the products of Incyte's collaboration partners; the acceptance of Incyte's products and the products of Incyte's collaboration partners in the marketplace; market competition; unexpected variations in the demand for Incyte's products and the products of Incyte's collaboration partners; the effects of announced or unexpected price regulation or limitations on reimbursement or coverage for Incyte's products and the products of Incyte's collaboration partners; sales, marketing, manufacturing and distribution requirements, including Incyte's and its collaboration partners' ability to successfully commercialize and build commercial infrastructure for newly approved products and any additional products that become approved; greater than expected expenses, including expenses relating to litigation or strategic activities; variations in foreign currency exchange rates; and other risks detailed in Incyte's reports filed with the Securities and Exchange Commission, including its annual report on form 10-K and its quarterly report for form 10-Q for the quarter ended June 30, 2025. Incyte disclaims any intent or obligation to update these forward-looking statements.

Welcome & Opening Remarks

Pablo Cagnoni, MD

President and Head of Research & Development

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Agenda

Welcome & Opening Remarks	**Pablo Cagnoni, MD** Head of Research & Development
INCA33890: TGFβR2xPD-1 Bispecific Antibody	**Patrick Mayes, PhD** Executive Vice President, Chief Scientific Officer
INCB161734: Selective KRAS G12D Inhibitor	**Ekaterine Asatiani, MD** Group Vice President and Head of Early Development
Advancing Our Oncology Portfolio	**Steven Stein, MD** Chief Medical Officer
Q&A	**Incyte Team**

Microsatellite stable CRC

80-85% of all patients with colorectal cancer have MSS tumors[1]

More than 70% of CRC patients develop liver metastases[2,3]

MSS tumors are highly enriched for TGFb biology[4]

Treatment Challenges

1. MSS CRC is considered non-responsive to anti-PD-1 / PD-L1 therapy

2. More recent trials with novel immunotherapies ineffective in patients with liver metastases

1. Le DT et al. Science. 2017;357(6349):409-413. 2. Rothbarth J, van de Velde C. Treatment of liver metastases of colorectal cancer. Ann Oncol. 2005;16(Suppl 2):44–49. doi:10.1093/annonc/mdi702
3. FRESCO-2, LEAP-017, SUNLIGHT trials in MSS mCRC 4. Tauriello DVF et al. TGFβ drives immune evasion in genetically reconstituted colon cancer metastasis. Nature. 2018;554:538-543.

KRAS^{G12D} positive PDAC

KRAS^{G12D} is the most common mutation in PDAC (~40%)[1,2]

G12D-positive PDAC patients have a worse prognosis than those with wild-type[3-7]

Treatment Challenges

1. No KRAS G12D inhibitor approved or currently in pivotal trials
2. Clear need for a KRAS G12D inhibitor combinable with intensive chemotherapy

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1. Lee JK, et al. NPJ Precis Oncol. 2022;6:91. 2. Zehir A, et al. Nat Med. 2017;23:703-713. 3. Yousef A, et al. NPJ Precis Oncol. 2024;8:27. 4. Yousef A, et al. Mol Cancer Ther. 2023;22(12_Suppl):A111. 5. Hirose T, et al. J Clin Oncol. 2023;42(3_Suppl):105. 6. Yuan Y, et al. Int J Biol Markers. 2021;36(2):33-39. 7. Modest DP, et al. Ann Oncol. 2016;27(9):1746-1753

Rigorous decision making for continued development

- Establish single-agent activity and safety profile
- Demonstrate durability of response
- Validate profile when combined with standard of care
- Identify clear medical need in early lines of therapy in metastatic cancers

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INCA33890: TGFβR2×PD-1 bispecific antibody for the development of immune checkpoint inhibitor sensitive and insensitive cancers

Patrick Mayes, PhD Executive Vice President, Chief Scientific Officer

Ekaterine Asatiani, MD Group Vice President and Head of Early Development

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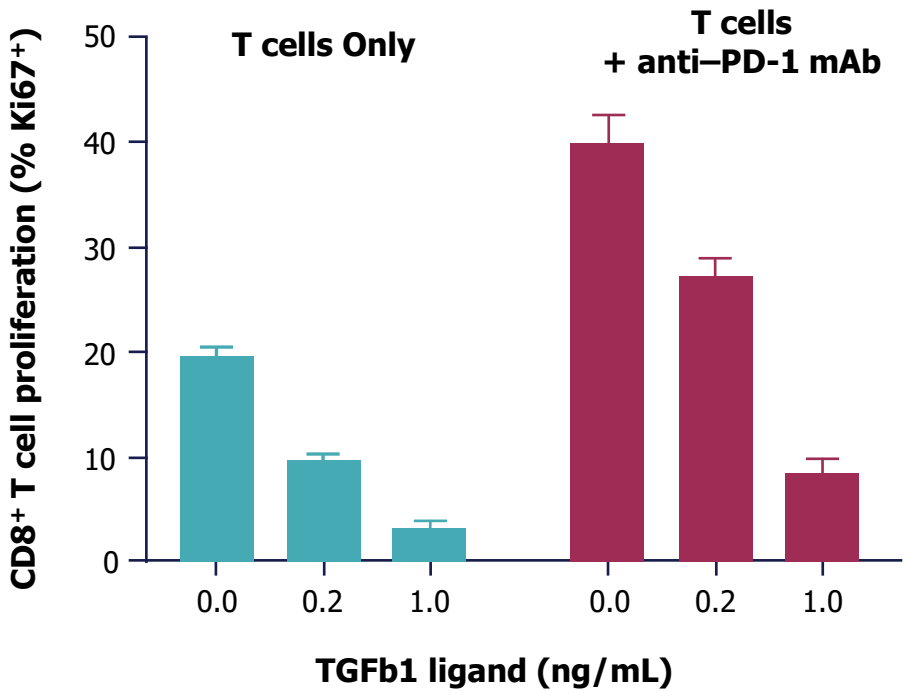
Key takeaways

- Solid tumors co-opt the TGFβ pathway, leading to immune evasion[1-4]
- INCA33890 **blocks the immunosuppressant effect of TGF-beta on T cells in the tumor microenvironment** and reactivates T-cells via PD-1 inhibition[5-8]
- INCA33890 has demonstrated promising **preclinical activity in colorectal cancer models**[8]
- Promising clinical efficacy seen in a multiple ICI sensitive and insensitive tumor types, including in patients with **MSS mCRC with and without active liver metastasis**

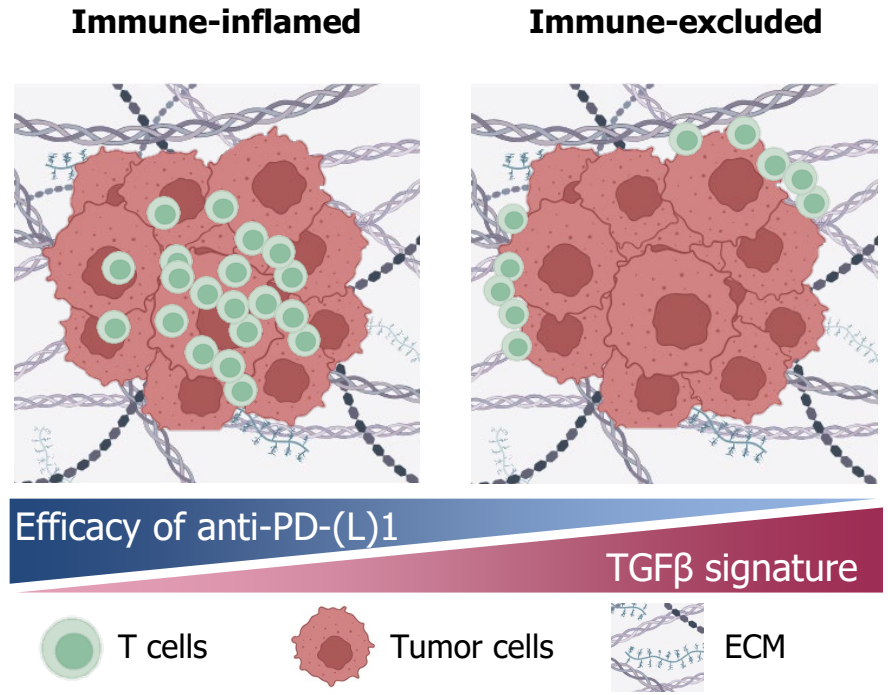
1. Deng Z, et al. Signal Transduct Target Ther. 2024;9:61. 2. Gulley JL, et al. Mol Oncol. 2022;16:2117-2134. 3. Massagué L. Cell. 2008;134:215-230. 4. Yi M, et al. Front Immunol. 2022;13:1061394. 5. Data on file, Incyte Corporation. 6. Yi M, et al. Front Immunol. 2022;13:1061394. 7. Bai X, et al. Onco Targets Ther. 2019;12:9527-9538. 8. Deng Z, et al. Signal Transduct Target Ther. 2024;9:61. 8 Wang LCS, et al. AACR 2023. Poster 2936.

TGFβ potently suppresses T cells and is associated with immune-excluded tumors that are resistant to anti-PD-(L)1 antibodies

TGFβ potently inhibits CD8+ T-cell proliferation ± PD-1 inhibition[1-3]



TGFβ is associated with an immune-excluded TME and PD-(L)1 nonresponse[2-4]



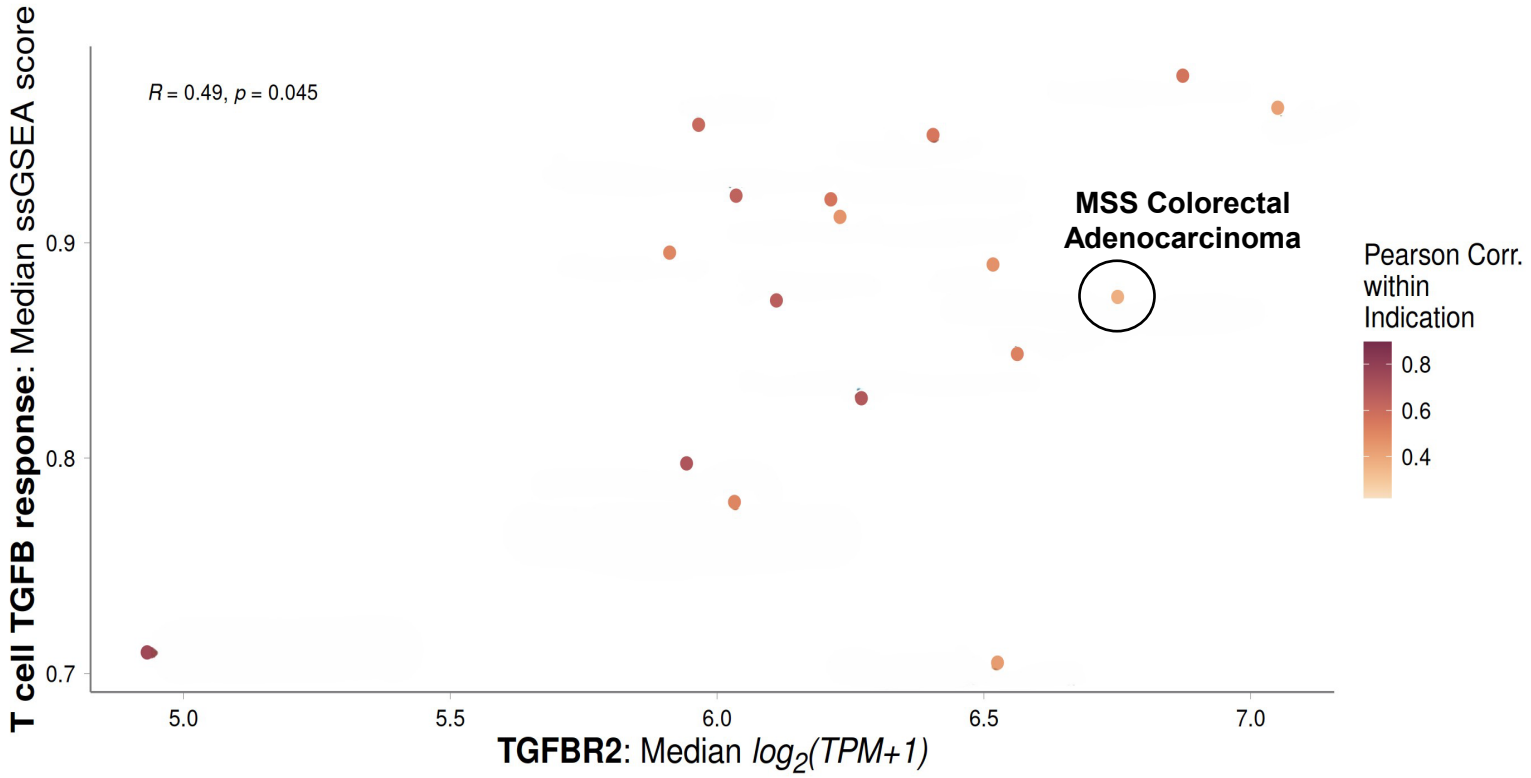
ECM= extracellular matrix; TME= tumor microenvironment

1. Data on file, Incyte Corporation. 2. Yi M, et al. *Front Immunol*. 2022;13:1061394. 3. Bai X, et al. *Onco Targets Ther.* 2019;12:9527-9538. 4. Deng Z, et al. *Signal Transduct Target Ther*. 2024;9:61.

Multiple solid tumor types are highly enriched for TGFβ biology in the tumor microenvironment including MSS-CRC

- Analysis measuring TGFBR2 expression level and T cell TGFβ gene signature response score across 16 common solid tumor indications using Tempus de-identified data[1]

- MSS CRC is one of the highest scoring solid tumor histologies for TGFβ biology



1. Tempus AI, Inc., 600 West Chicago Avenue, Suite 510, Chicago Illinois 60654

Dual targeting of TGFβR2 and PD-1 allows for potent inhibition of TGFβ signaling on T cells while avoiding systemic toxicity

OTHER APPROACHES[1-3]

Receptor-targeted approaches
TGFβR1 and 2

Approaches that inhibit **all TGFβ biology** systemically result in **toxicity**

Selective Ligand-targeted approaches
Latent and active forms of TGFβ1/2/3

Approaches that **partially inhibit TGFβ** result are **not efficacious**

OUR APPROACH

Cell-targeted approach

Cell-targeted approach allows for **maximal inhibition** while **avoiding systemic toxicity**[4]

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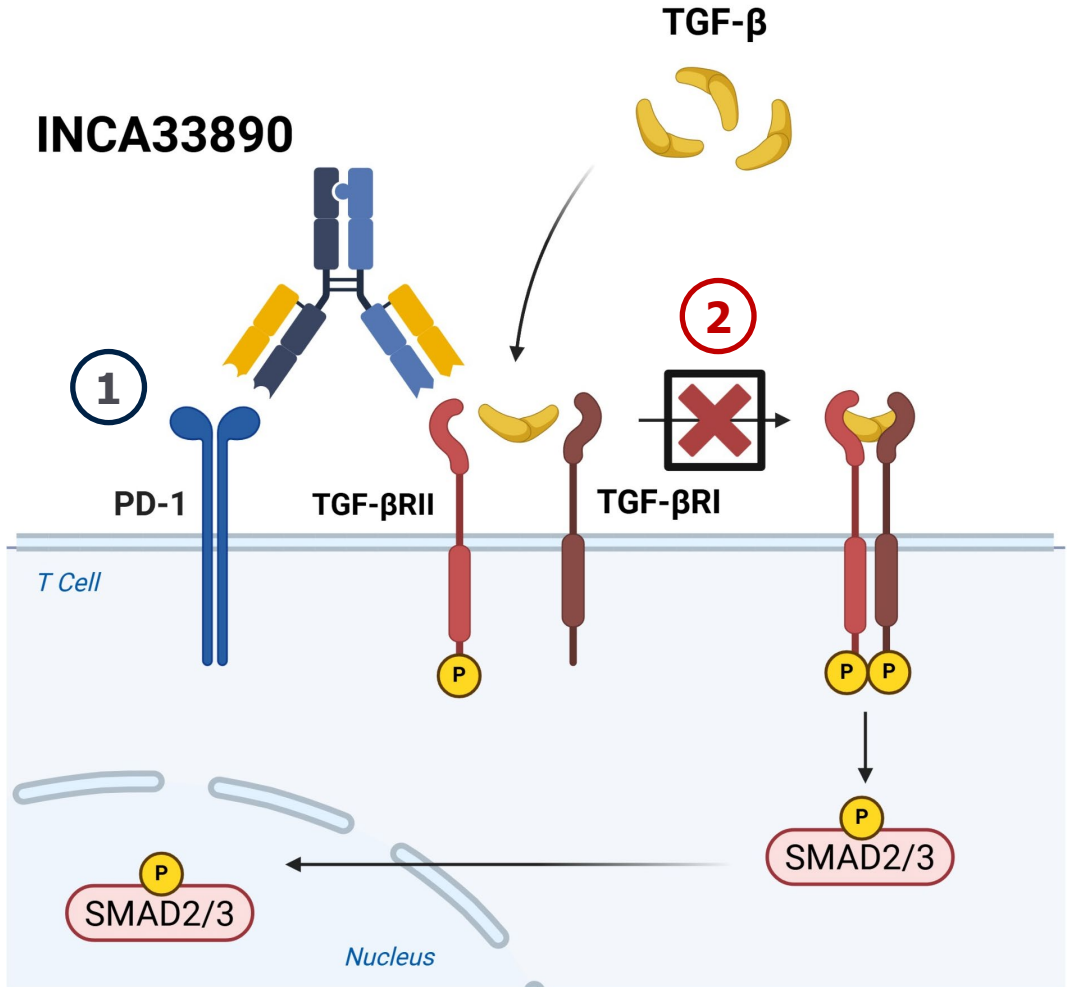
1. Deng Z, et al. Signal Transduct Target Ther. 2024;9:61. 2. Gulley JL, et al. Mol Oncol. 2022;16:2117-2134. 3. Massagué L. Cell. 2008;134:215-230. 4. Wang LCS, et al. AACR 2023. Poster 2936.

INCA33890 is a T cell-targeted inhibitor of TGFβ signaling

1. Uses "Dock and Block" approach through the generation of a **high-affinity PD-1 arm** to allow potent binding to PD-1-positive cells

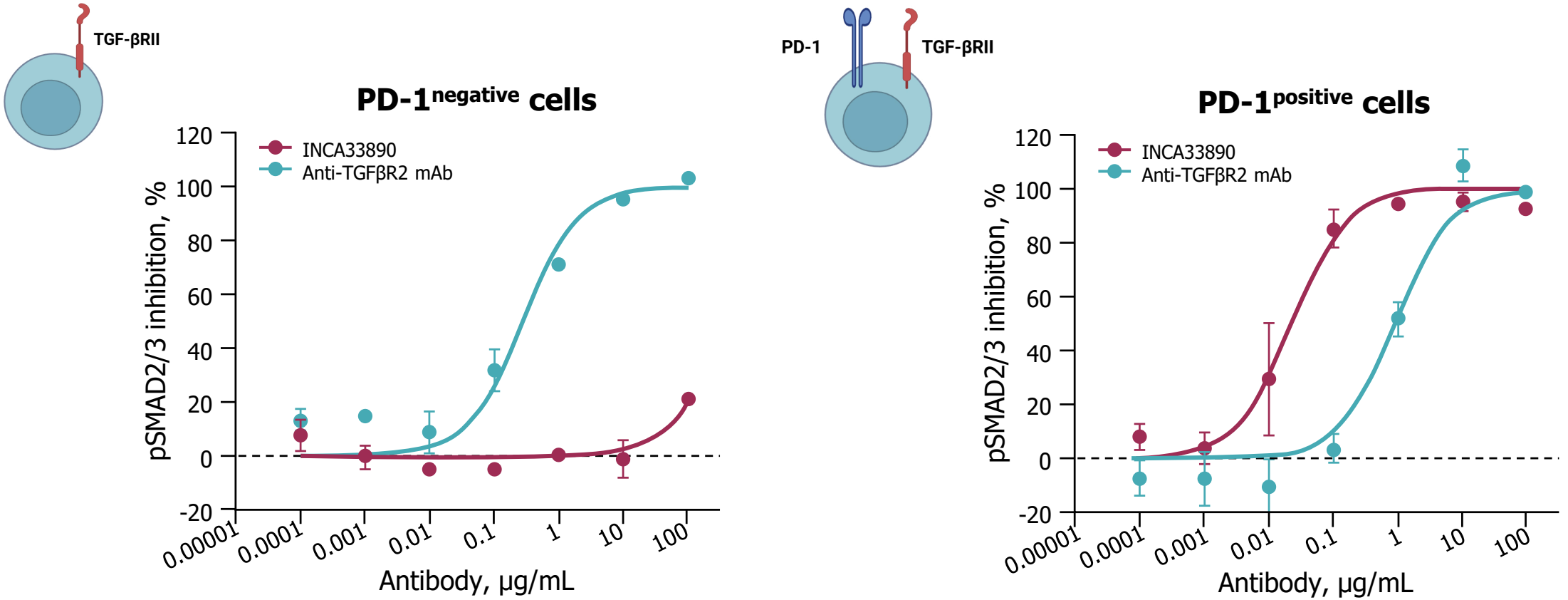
2. TGFβR2 arm was engineered to minimize binding to non-target cells but allows **potent binding and TGFβ signaling inhibition only when bound to PD-1**

Spare tissues where TGFβ signaling is important for normal function, and **avoid the known toxicity of broad TGFβ pathway blockade**



Wang LCS, et al. AACR 2023. Poster 2936.

INCA33890 conditionally inhibits TGFβ signaling in a PD-1 dependent manner



In isogenic Jurkat cells expressing TGFβR2 ± PD-1, INCA33890 potently inhibited TGFβ1/2-induced pSMAD activation in a PD-1–dependent manner

Wang LCS, et al. AACR 2023. Poster 2936.
pSMAD= phosphorylated SMAD

Potential first-in-class bispecific antibody for the treatment of checkpoint insensitive tumors

Strong scientific rationale

- Target tumor types with high TGFβ signaling in tumor microenvironment

Target tumor types with high unmet need

- Provide an Immunotherapy Option for Tumor Types with no approved ICI such as MSS-CRC

Enhance responsiveness of tumor types with approved PD-(L)1 therapies

- Improve response rates, extend DOR and survival in tumors that respond to ICIs

Preliminary Results from Phase 1 Study Evaluating INCA33890 in Advanced Solid Tumours

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Dose escalation and expansion trial evaluating INCA33890 in advanced solid tumors

Primary Objectives:
Safety and tolerability, DLTs, MTD and RDEs

Secondary Objectives:
PK, Efficacy (ORR, DCR, DOR)

Part 1a: Monotherapy Dose Escalation*

Patients with **select advanced/metastatic solid tumours** who **have progressed** or are **intolerant/ineligible** for SoC therapies (including ICIs)

Evaluated Doses (mg)
100, 300, 600, 900, 1200, 1500 (q2w IV)
900 (q4w IV)

Part 1b: Monotherapy Dose Expansion

MSS CRC, PDAC, Gastric/GEJ, OC, NSCLC, SCCHN

RDEs (mg)
300, 600, 900 (q2w IV)

Part 2a/b: Combination Dose Escalation & Expansion

INCA33890 (900 mg q2w) combination therapy in **MSS CRC** with:
FOLFOX + bev, FOLFIRI + bev, bev, cetuximab

*Hybrid statistical design for optimal definition of MTD/RDE(s); ≥3 patients/dose level. Part 1a (n=48), Part 1b (n=212)
bev, bevacizumab; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; GEJ, gastroesophageal junction cancer; ICI, immune checkpoint inhibitor; IV, intravenous; NSCLC, non-small cell lung cancer; OC, ovarian cancer; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic adenocarcinoma; PK, pharmacokinetics; q2w, every 2 weeks; q4w, every 4 weeks; RDE, recommended dose for expansion; SCCHN, squamous cell carcinoma of the head and neck; SoC, standard of care.

Baseline demographics and characteristics

	Total (N=260)
Age, median (range), years	60.5 (22-85)
Male sex, n (%)	133 (51.2)
ECOG PS, n (%)	
0	148 (56.9)
1	112 (43.1)
Cancer type, n (%)	
MSS CRC	114 (43.8)
PDAC	40 (15.4)
Gastric/GEJ	29 (11.2)
SCCHN	29 (11.2)
OC	29 (11.2)
NSCLC	12 (4.6)
Mesothelioma	3 (1.2)
Other*	4 (1.5)
Time since initial diagnosis, median (range), months	35.4 (7.3-195.5)
Time since advanced/metastatic diagnosis, median (range), months	25.9 (0.3-126.5)
Lines of prior therapy, median (range)	3 (1-9)

- As of July 25, 2025, 260 patients were enrolled and received INCA33890 as a monotherapy
- Treatment was ongoing in 52 patients (20.0%)
  - Primary reason for discontinuation was disease progression (68.8%)
  - 4.6% of patients discontinued due to AEs

*1 patient each with triple negative breast cancer, cervical cancer, melanoma, and renal cell carcinoma. Other reasons include death (2.7%), physician decision (1.5%), withdrawal by subject (1.5%), and other (2.0%).
CRC= colorectal cancer; ECOG PS= Eastern Cooperative Oncology Group performance status; GEJ= gastroesophageal junction cancer; MSS= microsatellite stable; NSCLC= non-small cell lung cancer; OC= ovarian cancer; PDAC= pancreatic adenocarcinoma; SCCHN= squamous cell carcinoma of the head and neck.

Safety summary

Safety profile similar across RDEs and comparable to approved ICIs

- 1500 mg q2w exceeded MTD [1 DLT (myocarditis) + additional irSAEs (DKA, encephalomyelitis, adrenal insufficiency)]
- RDEs of 300, 600, and 900 mg q2w were selected based on safety, PK, PD, and preliminary efficacy

TRAEs Across RDEs

TRAE, n (%)	300 mg q2w (n=99)	600 mg q2w (n=30)	900 mg q2w (n=110)	Total (n=239)
TRAE	58 (58.6)	23 (76.7)	58 (52.7)	139 (58.2)
Serious TRAE	10 (10.1)	4 (13.3)	6 (5.5)	20 (8.4)
Grade ≥3 TRAE	12 (12.1)	4 (13.3)	8 (7.3)	24 (10.0)
TRAE leading to dose delay	17 (17.2)	6 (20.0)	14 (12.7)	37 (15.5)
TRAE leading to treatment discontinuation*	8 (8.1)	3 (10.0)	2 (1.8)	13 (5.4)

irAE and IRR by Investigator, n (%)	300 mg q2w (n=99)		600 mg q2w (n=30)		900 mg q2w (n=110)		Total (n=239)
By Max Grade	G1-2	G3+	G1-2	G3+	G1-2	G3+	Any-grade
Immune-related AE	18 (18.2)	10 (10.1)	13 (43.3)	3 (10.0)	25 (22.7)	5 (4.5)	74 (31.0)
Infusion reaction AE	4 (4.0)	2 (2.0)	5 (16.7)	1 (3.3)	10 (9.1)	0 (0)	22 (9.2)

No significant events were revealed at the review of all treatment-emergent adverse events (TEAEs)
*TRAEs leading to discontinuation: 300 mg q2w (myocarditis, n=2; immune-mediated gastritis, anaphylactic reaction, IRR, ALT/AST increased, troponin increased, polyarthritis, n=1 each); 600 mg q2w (immune-mediated hepatitis, anaphylactic reaction, troponin T increased, n=1 each); 900 mg Q2W (encephalitis autoimmune, pneumonitis, n=1 each).
DKA, diabetes-related ketoacidosis; DLT, dose-limiting toxicity; irAE, immune-related adverse event; irSAE, immune-related serious adverse event; IRR, infusion-related reaction; PK, pharmacokinetics; PD, pharmacodynamics; q2w, every 2 weeks; RDE, recommended dose for expansion; TRAE, treatment-related adverse event.

Most common TRAEs across RDEs

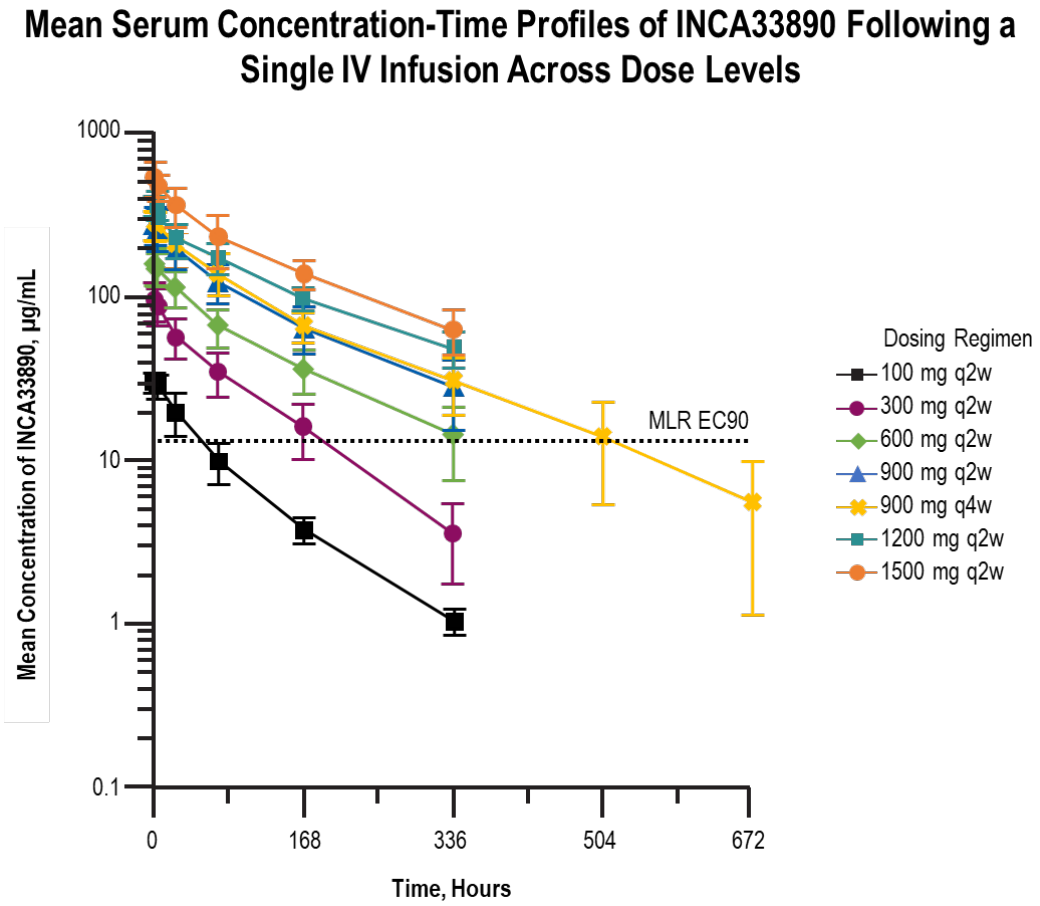
Most Common Any-Grade TRAEs (in ≥5% Across RDEs)

Preferred Term, n (%)	300 mg q2w (n=99)		600 mg q2w (n=30)		900 mg q2w (n=110)		Total (n=239)
By Maximum Grade	G1-2	G3+	G1-2	G3+	G1-2	G3+	Any-grade
Fatigue	14 (14.1)	0 (0)	5 (16.7)	0 (0)	14 (12.7)	0 (0)	33 (13.8)
Skin toxicity*	6 (6.1)	2 (2.0)	6 (20.0)	3 (10.0)	7 (6.4)	2 (1.8)	26 (10.9)
Pruritus	6 (6.1)	0 (0)	3 (10.0)	1 (3.3)	10 (9.1)	1 (0.9)	21 (8.8)
IRR	4 (4.0)	1 (1.0)	5 (16.7)	0 (0)	10 (9.1)	0 (0)	20 (8.4)
Nausea	5 (5.1)	0 (0)	5 (16.7)	0 (0)	7 (6.4)	0 (0)	17 (7.1)
Diarrhoea	5 (5.1)	0 (0)	1 (3.3)	0 (0)	9 (8.2)	0 (0)	15 (6.3)
Alanine aminotransferase increased	4 (4.0)	2 (2.0)	1 (3.3)	0 (0)	4 (3.6)	1 (0.9)	12 (5.0)

No significant events were revealed at the review of all TEAEs.
*Including: dermatitis, eczema, lichen planus, pustular psoriasis, rash, rash erythematous, rash maculo-papular, rash pustular
IRR, infusion-related reaction; q2w, every 2 weeks; RDE, recommended dose for expansion; TRAE, treatment-related adverse event.

PK, PD and immunogenicity

- Non-linear PK observed at doses of 100 - 1500 mg Q2W, likely due to target-mediated drug disposition at lower doses
  - Clearance rate: 0.022 - 0.044 L/h
  - Volume of distribution: 4.2 - 5.1 L
  - Half-life: 3.5 - 6.2 days
- 78% of patients developed INCA33890-specific treatment-emergent ADAs
  - Impact on PK was dose dependent, with no impact at doses ≥900 mg q2w
  - ADAs did not impact safety (including IRRs) or efficacy
- CD8 T cells increased in cycle 2 day 15 on treatment vs baseline biopsies (data not shown)
  - Extent of increase was greater in responders vs non-responders

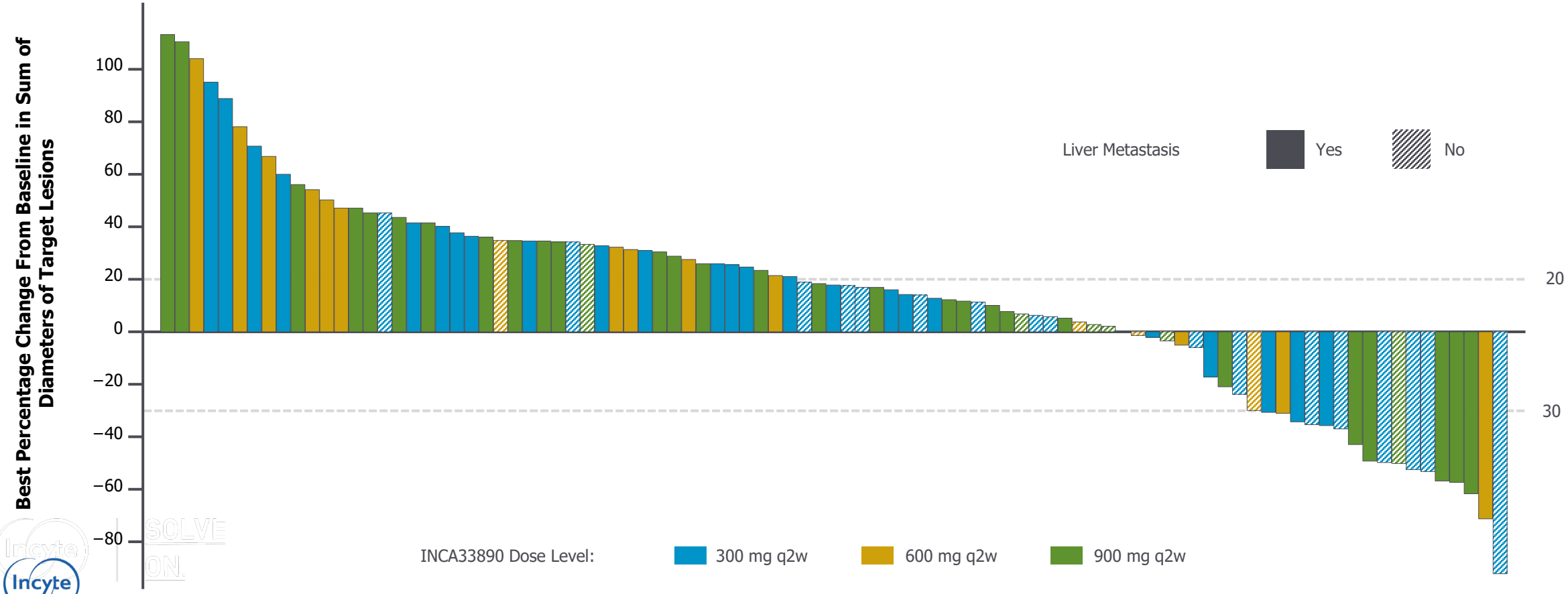


Data cutoff: July 25, 2025

ADA= anti-drug antibody; IRR= infusion-related reaction; IV= intravenous; PK= pharmacokinetics; PD= pharmacodynamics; q2w= every 2 weeks; q4w= every 4 weeks

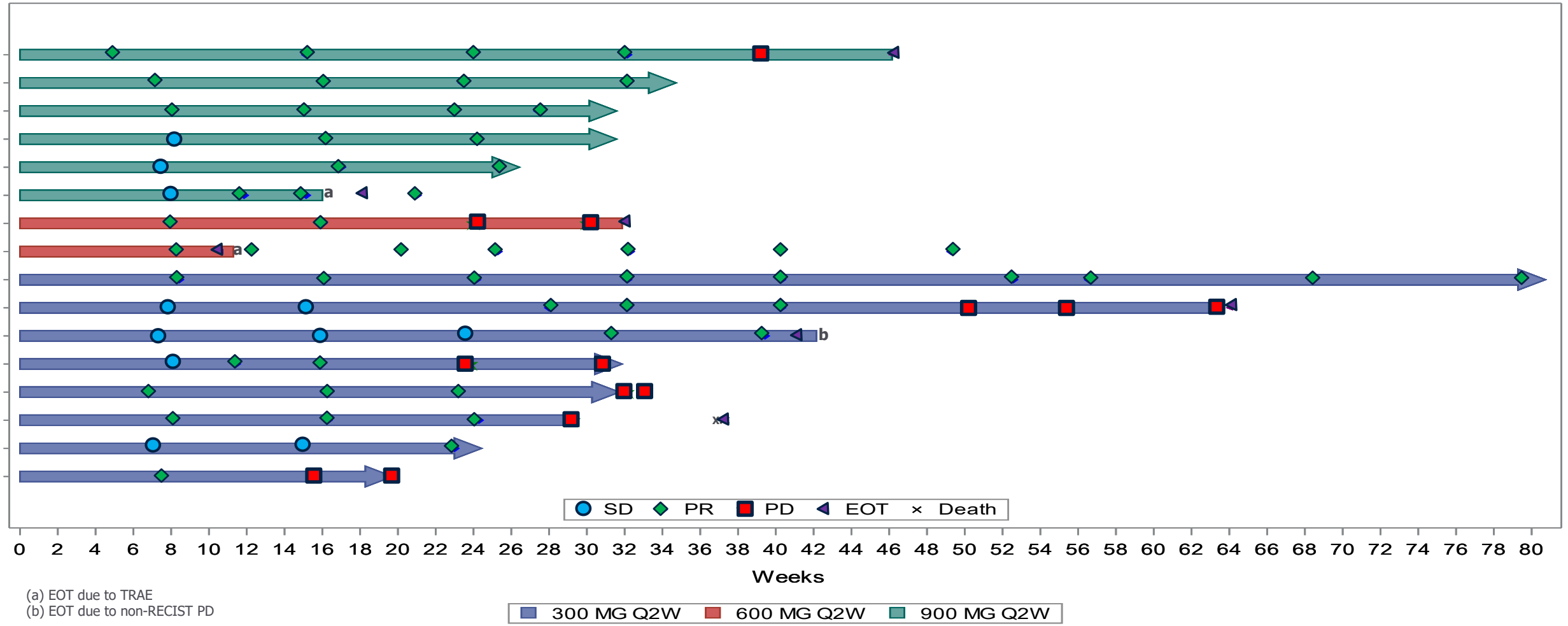
Efficacy in MSS CRC

- Among 105 patients treated at RDEs, 93.3% had ≥2 prior regimens and 71.4% had active liver metastases
- 16 patients responded (14 confirmed) (**ORR 15.2%**); median duration of therapy: 7.3 months
  - 9 had active liver metastases (**ORR 12.0%**, DCR 20.0%)
  - 7 had no liver metastases (**ORR 23.3%**, DCR 50.0%)
- ORR was similar across RDEs



CRC= colorectal cancer; DCR= disease control rate; MSS= microsatellite stable; ORR= overall response rate; q2w= every 2 weeks; RDE= recommended dose for expansion

Duration of treatment (MSS CRC responders)



(a) EOT due to TRAE
(b) EOT due to non-RECIST PD

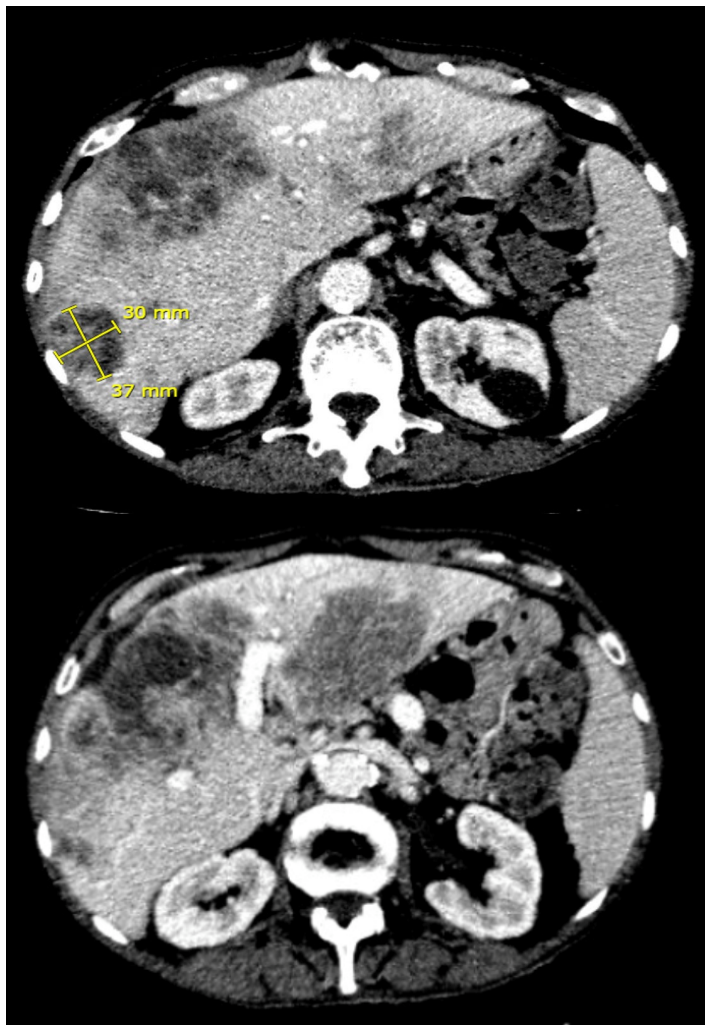
Efficacy in a case of MSS mCRC (300mg q2w)

Baseline characteristics

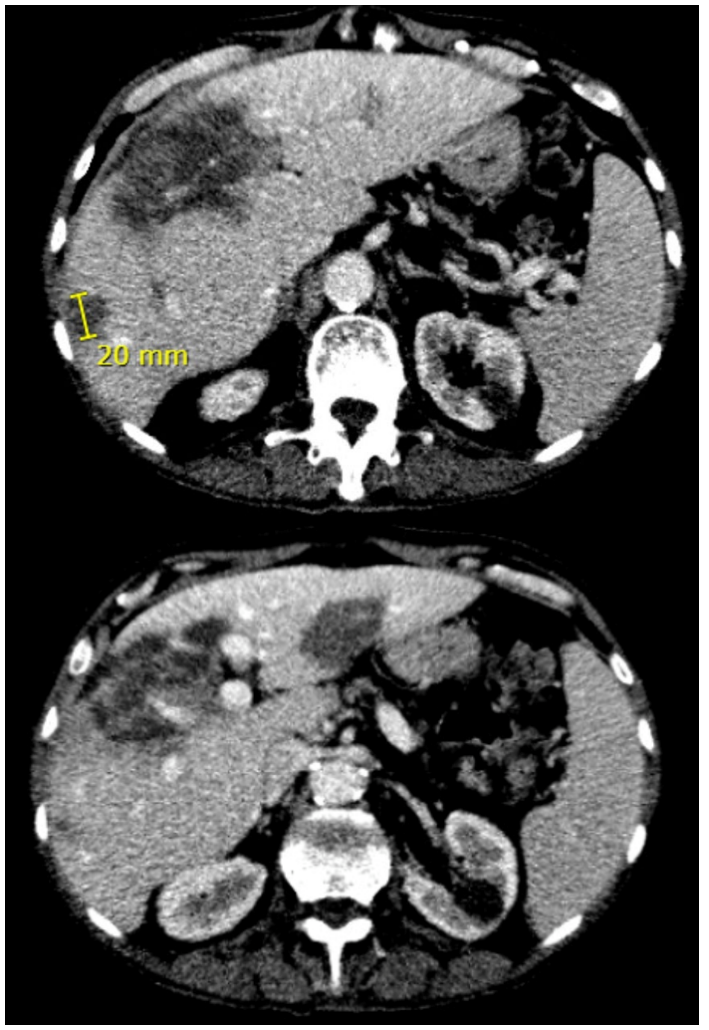
- 72-year-old man
- Stage IV MSS-mCRC with multiple liver, lung, and bone metastases
- Progressed on prior FOLFOX + bev and on FOLFIRI treatment

INCA33890 treatment course

- 300 mg q2w
- Achieved PR at 28wk, confirmed at 32wk
- Discontinued after 1 year of treatment because of PD (50 wk)



Baseline



16 weeks

Representative images of liver response; courtesy of Dr I Moreno.
bev, bevacizumab; CL, baseline; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; mCRC, metastatic colorectal cancer; mm, millimeter; MSS, microsatellite stable; PR, partial response; q2w, every 2 weeks.

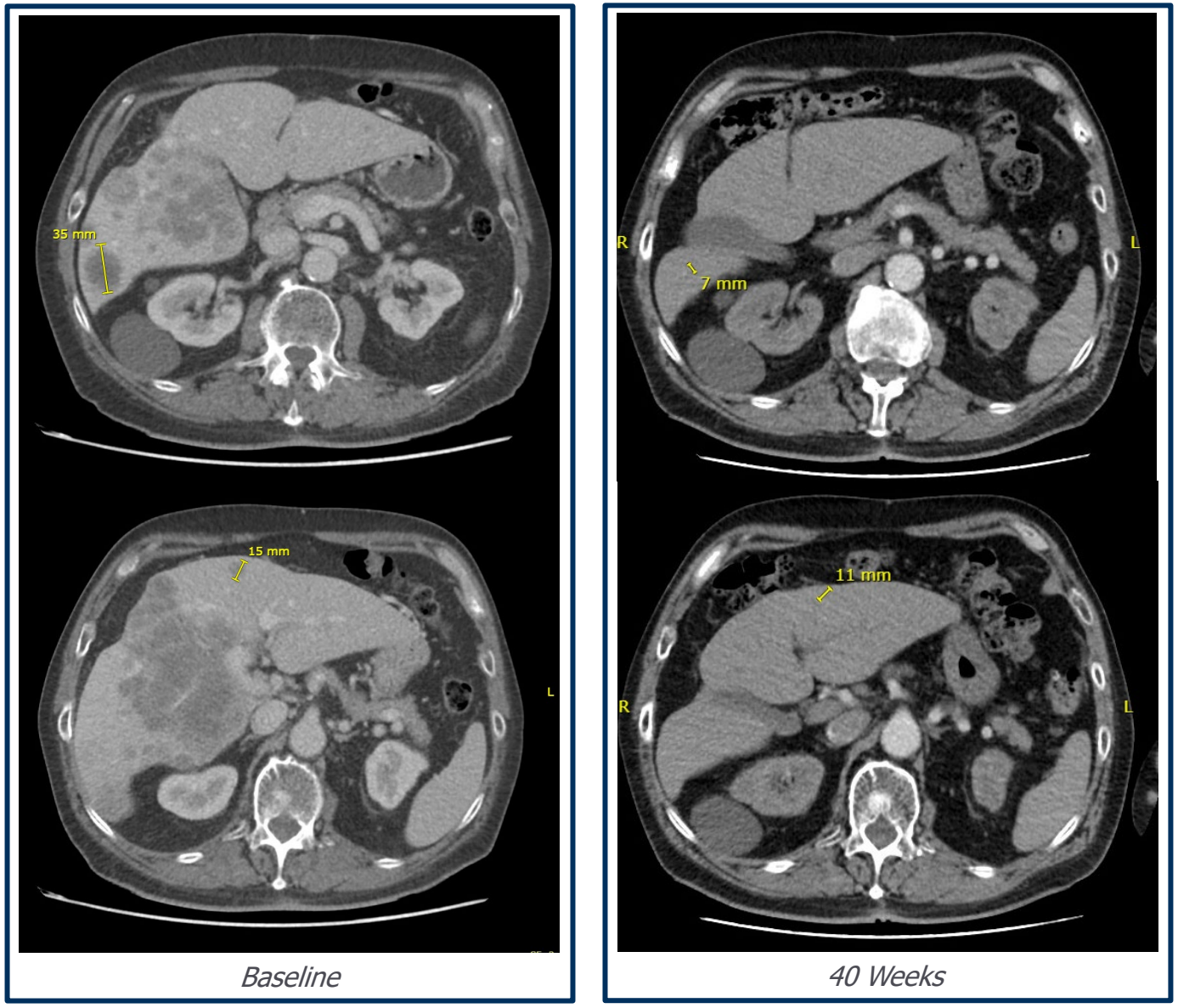
Efficacy in a case of MSS mCRC (900mg q2w)

Baseline characteristics

- 67-year-old man
- Stage IV MSS CRC with multiple liver metastases and nodal disease
- Progressed on prior FOLFOX + bev, FOLFIRI, trifluridine/tipiracil, STAT3 inhibitor (investigational)

INCA33890 treatment course

- 900mg q2w weeks
- Achieved PR at 8 wk, confirmed at 16 wk
- Currently on treatment (10+ months)



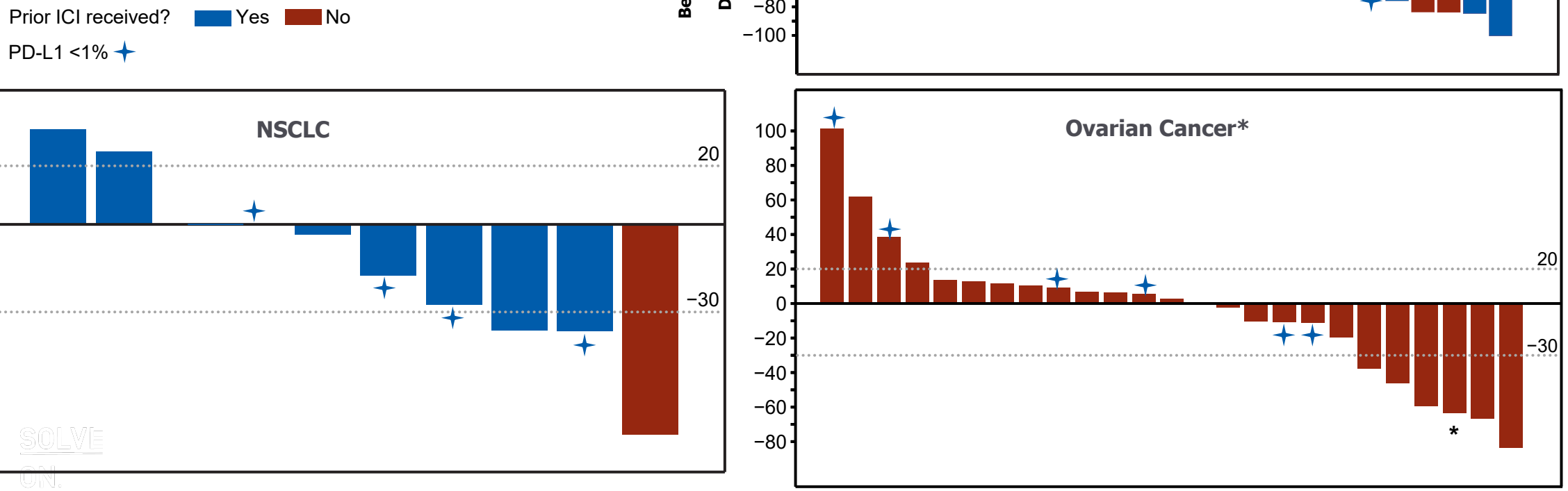
Baseline *40 Weeks*

Representative images of liver response; courtesy of Dr I Moreno.

BL, baseline; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; bev, bevacizumab; mCRC, metastatic colorectal cancer; mm, millimeter; MSS, microsatellite stable; PR, partial response; TL, target lesion; q2w, every 2 weeks.

Preliminary efficacy in other tumor types at RDEs

- **Responses** reported across **tumor types** and **PD-L1 expression levels**, including levels <1%
- **Responses** observed across tumor types in patients **previously refractory to ICIs**



*1 PR in patient originally treated at 1500 mg Q2W, de-escalated to 900 mg and responded. ICI, immune checkpoint inhibitor; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1; PR, partial response; SCCHN, squamous cell carcinoma of the head and neck

Combination with SOC well tolerated with expansion ongoing in 1L MSS CRC

Evaluation of INCA33890 in combination therapy in MSS CRC is underway

- Evaluating combinations with FOLFOX + bevacizumab, FOLFIRI + bevacizumab, bevacizumab, cetuximab

Cleared dose escalation across all combination groups with no DLT identified at RDE of 900mg q2w

- Combinations demonstrated good tolerability with no evidence of additive toxicity observed to date

Expansion is ongoing in combination with FOLFOX + bevacizumab to support Phase 3 initiation in 1L MSS CRC

Conclusions

- INCA33890 was generally well tolerated with **900 mg q2w** selected as **recommended dose based on PK, efficacy and safety profile**
- **Established single-agent activity** in checkpoint sensitive and insensitive tumor types, including MSS CRC
- Responses observed in **MSS CRC patients with and without active liver metastases**, an area not currently addressed with IO therapies
- **Combination with SOC** demonstrated good tolerability in dose escalation, with **no evidence of additive toxicity** observed to date; dose expansion is ongoing

Efficacy and safety data support advancing INCA33890 into 1L MSS CRC in combination with SOC

INCB161734: Selective KRASG12D inhibitor for the development of $KRAS^{G12D}$ mutated tumors

Ekaterine Asatiani, MD

Group Vice President and Head of Early Development

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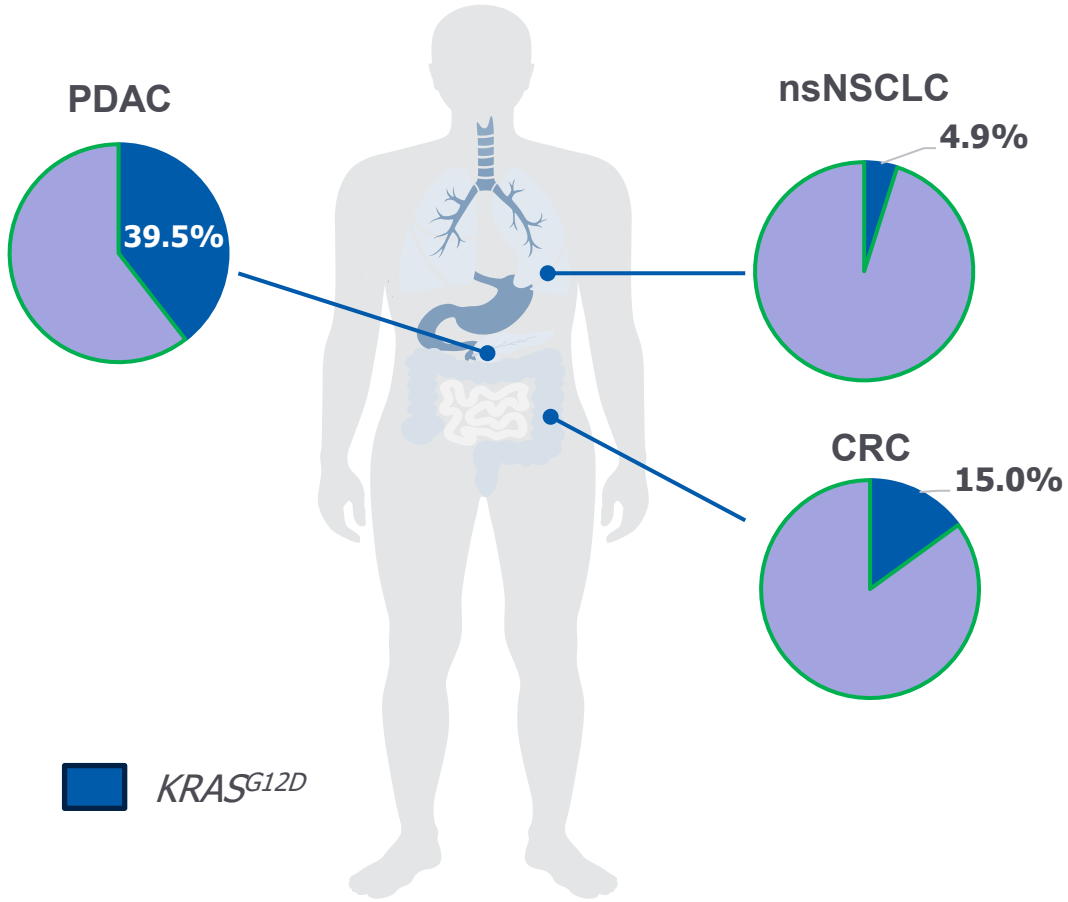
Key takeaways

- KRAS is one of the most frequently altered driver oncogenes in solid tumors, and **G12D** is the **most common KRAS mutant isoform** with a high incidence in PDAC[1,2]
- **INCB161734** is a **potent and selective on/off inhibitor** of G12D demonstrating robust antitumor activity in KRASG12D xenograft and syngeneic tumors[3]
- Early data suggest INCB161734 has the **potential to be the first G12D-targeted therapy in PDAC** patients with *KRAS*^{G12D} mutation

1. Lee JK, et al. NPJ Precis Oncol. 2022;6:91. 2. Zehir A, et al. Nat Med. 2017;23:703-713. 3. Farren MR, et al. Presented at: AACR; 2024; San Diego, CA. Poster 5900.

KRAS G12D in Cancer



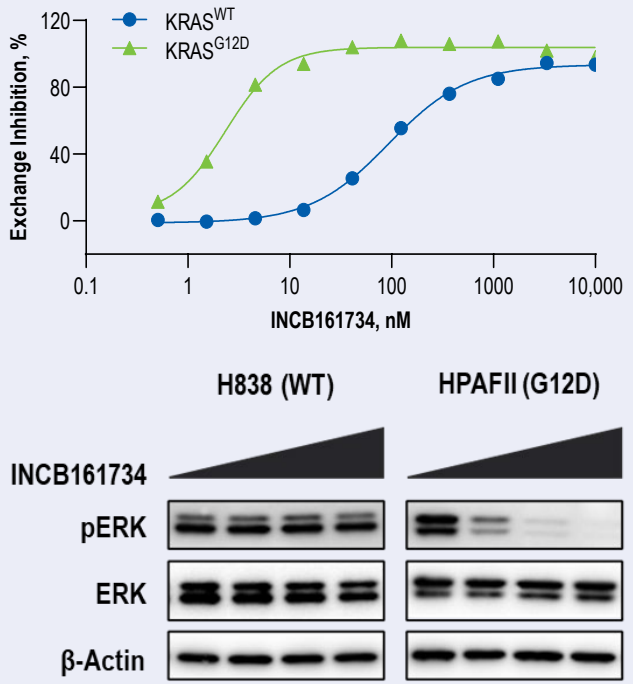
- KRAS proteins function as molecular switches, controlling multiple signaling cascades which promote cellular proliferation and survival[1,2]
- *KRAS*^{G12D} mutations are among the most common oncogenic drivers for PDAC, CRC, and nsNSCLC[3,4]
- KRAS^{G12D} is associated with poorer outcomes, including shorter OS, compared to KRAS WT and most other KRAS mutations[5-10]

1. Erlanson DA, Webster KR. Curr Opin Chem Biol. 2021;62:101-108. 2. Simanshu DK, et al. Cell. 2017;170:17-33. 3. Lee JK, et al. NPJ Precis Oncol. 2022;6:91. 4. Zehir A, et al. Nat Med. 2017;23:703-713. 5. Yousef A, et al. NPJ Precis Oncol. 2024;8:27. 6. Yousef A, et al. Mol Cancer Ther. 2023;22(12_Suppl):A111. 7. Hirose T, et al. J Clin Oncol. 2023;42(3_Suppl):105. 8. Yuan Y, et al. Int J Biol Markers. 2021;36(2):33-39. 9. Modest DP, et al. Ann Oncol. 2016;27(9):1746-1753. Carter Norton et al. KRAS Mutation Status and Treatment Outcomes in Patients With Metastatic Pancreatic Adenocarcinoma.JAMA Network Open. 2024;7(8):e2424737. doi:10.1001/jamanetworkopen.2024.24737
CRC, colorectal cancer; nsNSCLC, non-squamous non-small cell lung cancer; PDAC, pancreatic ductal adenocarcinoma.

INCB161734 is a potent and selective KRAS^{G12D} inhibitor

- Binds to both GDP (inactive) and GTP (active) forms of mutant KRAS G12D with picomolar affinity
  - At the switch II pocket
- Exhibits >80-fold selectivity for mutant KRAS^{G12D} over wild-type KRAS in biochemical and cellular assays
- Excellent oral bioavailability in higher preclinical species
- Demonstrates robust antitumor activity in *KRAS^{G12D}* xenograft and syngeneic tumors tumor models of PDAC

In Vitro Selectivity



Farren MR, et al. Presented at: AACR; 2024; San Diego, CA. Poster 5900.

Preliminary Phase 1 Results of INCB161734, A Novel Oral *KRAS*^{G12D} Inhibitor, In Patients With Advanced or Metastatic Solid Tumors

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Phase 1 trial evaluating INCB161734 in advanced or metastatic solid tumors

Primary Objectives:
Safety and tolerability, DLTs, MTD

Secondary Objectives:
PK, Efficacy (ORR, DCR, DOR)

Part 1a: Dose Escalation*

Patients with **locally advanced** or **metastatic** solid tumor with ***KRAS*^{G12D} mutation***

Evaluated Doses (mg)
200 qd, 400 qd, 600 qd, 1000 qd, 600 bid, 1600 qd

PD Cohort
- 600 mg qd, 1000 mg qd

Food Effect Cohort
- 1200 mg qd

Part 1b: Dose Expansion

PDAC, CRC, NSCLC, Other advanced solid tumors*

Randomized Optimization of RDEs (mg)
600 qd, 1200 qd

PDAC

RDE (mg)
1200 qd

Part 2a/b: Combination Dose Escalation & Expansion

INCB161734 combination therapy in **PDAC** with:
GEMNabP, mFOLFIRINOX, INCA33890

*Additional key inclusion criteria: Disease progression on prior standard therapy (monotherapy cohorts), ECOG PS 0-1, No prior treatment with a KRASG12D selective inhibitor
bid, twice daily; CRC, colorectal cancer; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEMNabP, nab-paclitaxel + gemcitabine; mFOLFIRINOX, modified leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, pharmacodynamic; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetics; qd, daily; RDE, recommended dose for expansion; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event

Patient disposition and baseline characteristics

- As of August 1, 2025, 138 patients were enrolled and received INCB161734 monotherapy
- Tumor types included:
  - PDAC (n=83, 60.1%)
  - CRC (n=46, 33.3%)
  - NSCLC (n=3, 2.2%)
  - OC (n=2, 1.4%)
  - AC, CCA, CUP, and GBC (all n=1, 0.7%)
- Treatment was ongoing in 75 patients (54.3%)
  - Primary reason for discontinuation was disease progression (n=52; 37.7%)*
  - No patients discontinued due to AEs

	All Patients (N=138)	PDAC (n=83)
Age, median (range), years ≥65 years, n (%)	61 (30, 85) 49 (35.5)	63 (38, 85) 37 (44.6)
Sex, female, n (%)	67 (48.6)	34 (41.0)
ECOG PS 0/1, n (%)	63 (45.7)/75 (54.3)	32 (38.6)/51 (61.4)
Liver metastases, n (%)	N/A	64 (77.1)
Total prior systemic therapies, median (range)	2.0 (1, 13)	2.0 (1, 6)
Prior systemic therapies in advanced/ metastatic setting,† n (%) 1 prior line, 2 prior lines ≥3 prior lines	 N/A N/A N/A	 13 (15.7) 43 (51.8) 27 (32.5)

*Other reasons: death (n=4; 2.9%), withdrawal (n=6; 4.3%), undefined (n=1, 0.7%). †Includes neoadjuvant or adjuvant therapy given within 6 months of advanced/metastatic disease development.
AC= appendiceal cancer; AE= adverse event; CCA= cholangiocarcinoma; CRC= colorectal cancer; CUP= cancer of unknown primary; ECOG PS= Eastern Cooperative Oncology Group performance status; GBC= gall bladder cancer; NA= not applicable; NSCLC= non-small cell lung cancer; OC= ovarian cancer; PDAC= pancreatic ductal adenocarcinoma

Safety in patients with KRAS^{G12D} positive advanced solid tumors

- No DLTs were reported in dose escalation; MTD was not reached
- No patients discontinued treatment due to TRAEs
- Most common TRAEs leading to dose reduction (n≥2) were nausea, decreased appetite, and fatigue

	TRAEs*					
	All Doses (n=136)		600 mg qd (n=43)		1200 mg qd (n=67)	
TRAE, n (%)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any TRAE	120 (88.2)	15 (11.0)	36 (83.7)	6 (14.0)	59 (88.1)	6 (9.0)
Serious TRAE	4 (2.9)	3 (2.2)	2 (4.7)	2 (4.7)	2 (3.0)	1 (1.5)
TRAEs leading to						
Interruption	21 (15.4)	8 (5.9)	5 (11.6)	3 (7.0)	9 (13.4)	3 (4.5)
Reduction	9 (6.6)	1 (0.7)	0	0	5 (7.5)	1 (1.5)
Discontinuation	0	0	0	0	0	0

No additional significant events were revealed at the review of all treatment-emergent adverse events (TEAEs).
*Assessed in patients who received ≥1 dose of study drug.
AE= adverse event; DLT= dose-limiting toxicity; MTD= maximum tolerated dose; qd= daily; TRAE= treatment-related adverse event

Most common TRAEs

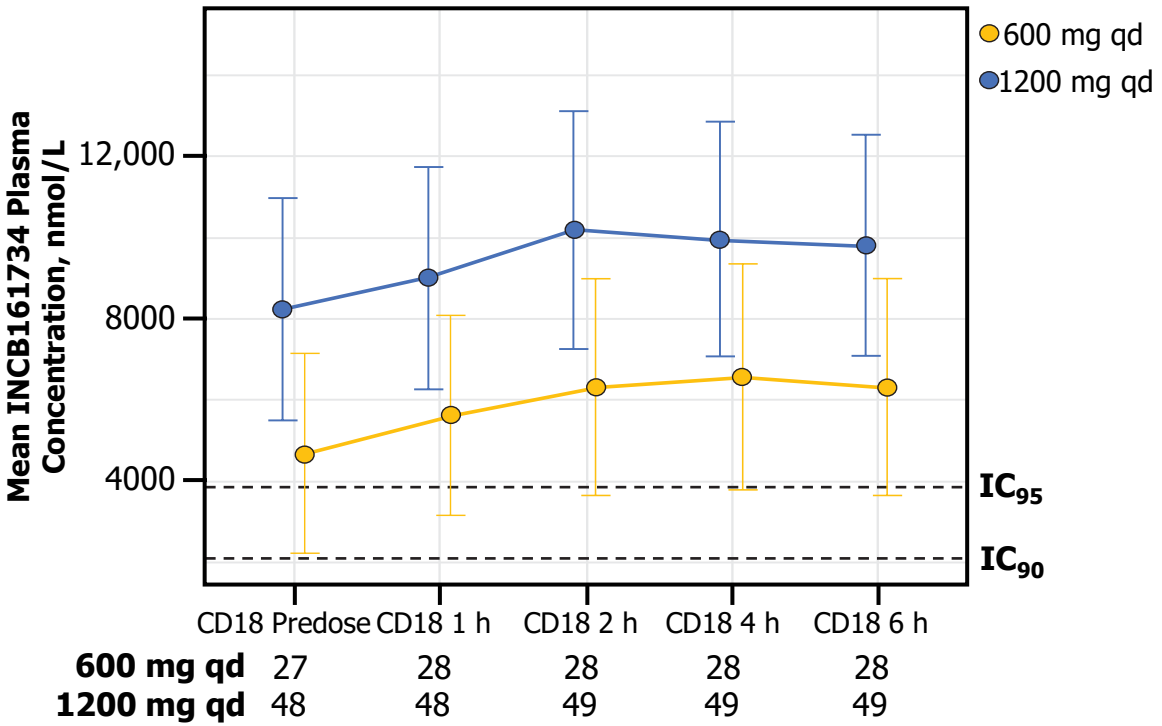
Most TRAEs were grade 1 and manageable

	Most Common TRAEs in Decreasing Order of Frequency (≥5%)*								
	All Doses (n=136)	600 mg qd (n=43)				1200 mg qd (n=67)			
Preferred term, n (%)	All Grades	All Grades	Grade 1	Grade 2	Grade ≥3	All Grades	Grade 1	Grade 2	Grade ≥3
Nausea	79 (58.1)	24 (55.8)	16 (37.2)	8 (18.6)	0	39 (58.2)	28 (41.8)	10 (14.9)	1 (1.5)
Diarrhea	69 (50.7)	19 (44.2)	14 (32.6)	4 (9.3)	1 (2.3)	36 (53.7)	29 (43.3)	6 (9.0)	1 (1.5)
Vomiting	62 (45.6)	15 (34.9)	12 (27.9)	3 (7.0)	0	35 (52.2)	26 (38.8)	9 (13.4)	0
Fatigue	24 (17.6)	6 (14.0)	4 (9.3)	2 (4.7)	0	12 (17.9)	10 (14.9)	2 (3.0)	0
Lipase increased	15 (11.0)	3 (7.0)	0	2 (4.7)	1 (2.3)	6 (9.0)	3 (4.5)	1 (1.5)	2 (3.0)
Decreased appetite	14 (10.3)	2 (4.7)	1 (2.3)	1 (2.3)	0	10 (14.9)	9 (13.4)	0 (0)	1 (1.5)
Amylase increased	10 (7.4)	1 (2.3)	0 (0)	1 (2.3)	0 (0)	4 (6.0)	1 (1.5)	3 (4.5)	0 (0)
Anemia	8 (5.9)	5 (11.6)	1 (2.3)	3 (7.0)	1 (2.3)	2 (3.0)	2 (3.0)	0 (0)	0 (0)
Dysgeusia	7 (5.1)	2 (4.7)	2 (4.7)	0 (0)	0 (0)	4 (6.0)	4 (6.0)	0 (0)	0 (0)

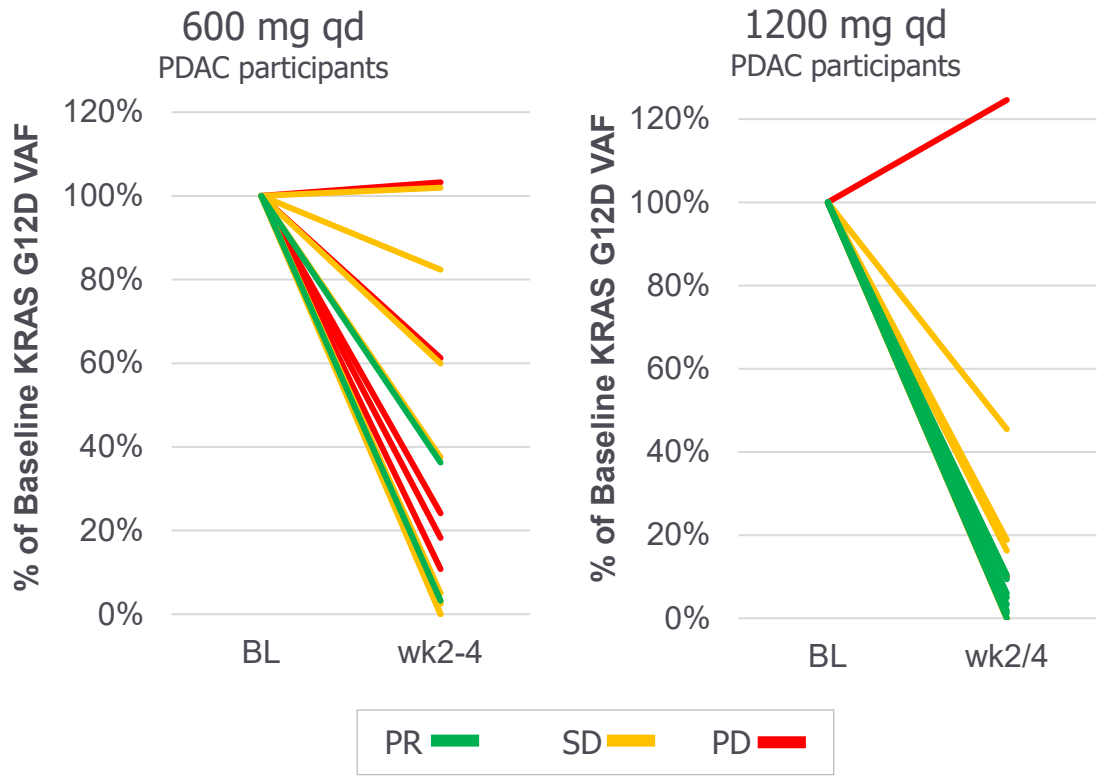
*Ordered by incidence of All Grade events for All Doses; events with ≥5% incidence are presented. Review of all TEAEs did not reveal any additional AEs of significance.
AE= adverse event; qd= daily; TEAE= treatment-emergent adverse event; TRAE= treatment-related adverse event

PK and PD analysis: achieved exposure provides high target engagement

At 1200 mg daily dose, INCB161734 levels exceeded IC95 concentration at steady state



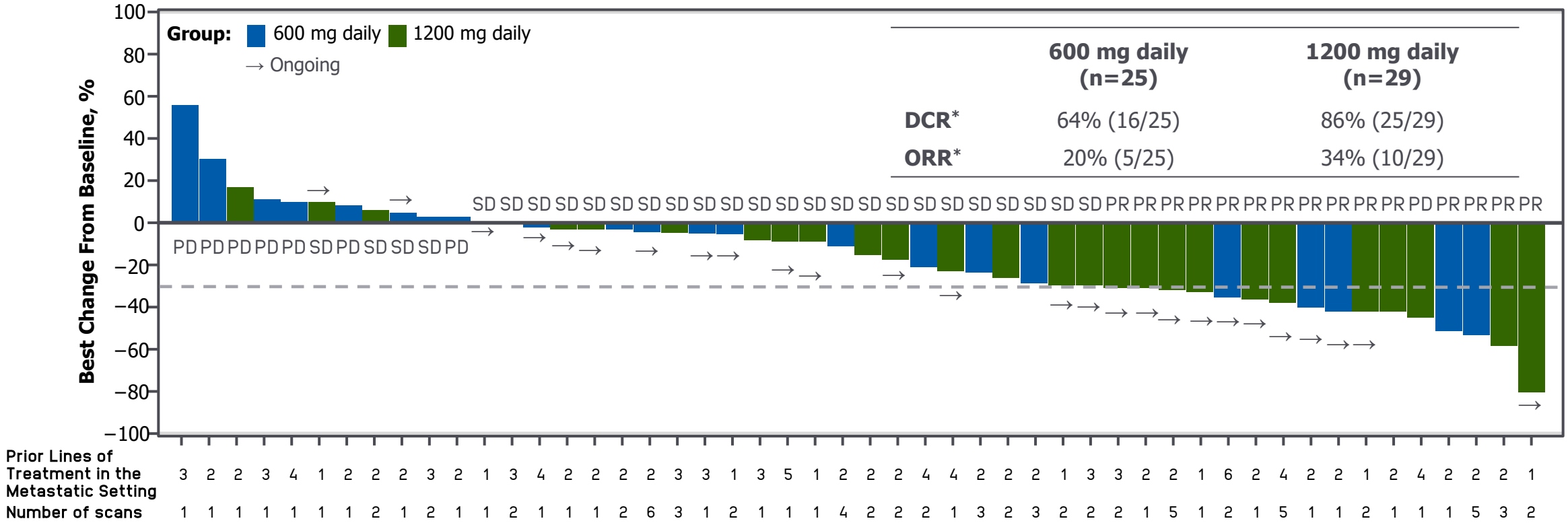
INCB161734 at ≥ 600 mg daily dose causes rapid molecular responses that correlate with objective response



All PK data were from Part 1b (monotherapy dose expansion). Error bars represent 1x standard deviation.
C= cycle; D= day; PK= pharmacokinetic; qd= daily

Antitumor activity in PDAC patients at selected RDEs

High ORR and DCR for patients with PDAC on both expansion doses



	600 mg daily (n=25)	1200 mg daily (n=29)
DCR*	64% (16/25)	86% (25/29)
ORR*	20% (5/25)	34% (10/29)

*Investigator-assessed in patients with ≥1 postbaseline scan (≥8 weeks of therapy) or clinical progression or death prior to the first RECIST assessment per investigator. DCR= disease control rate; ORR= objective response rate; PD= progressive disease; PDAC= pancreatic ductal adenocarcinoma; PR= partial response; qd= daily; RDE= recommended dose for expansion; RECIST= Response Evaluation Criteria in Solid Tumors; SD= stable disease

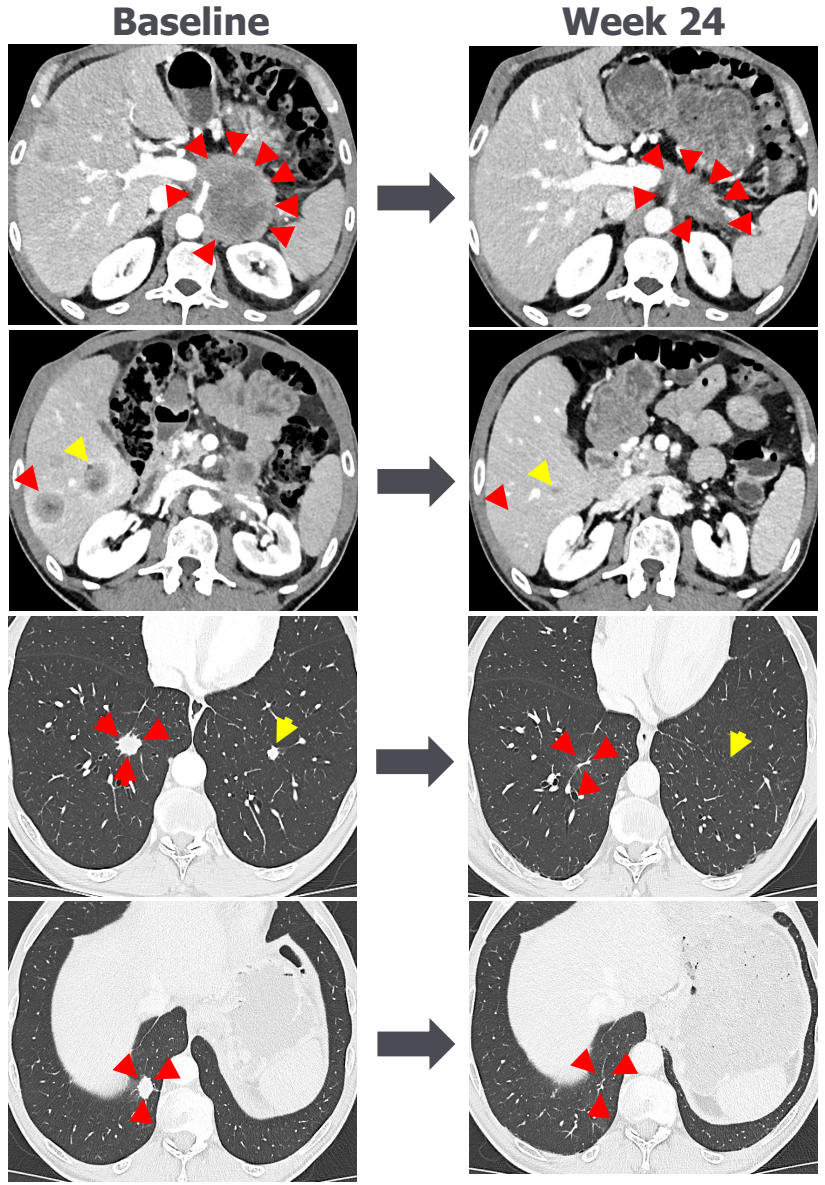
Efficacy in a case of metastatic PDAC

Patient baseline characteristics

- 69-year-old man with Stage IV PDAC
- Initial diagnosis in 2024
- Liver, lung and peritoneal metastases
- Previously progressed on FOLFIRINOX

INCB161734 treatment course

- 1200 mg qd without interruptions
- Confirmed deep PR of -80% in target lesion diameters at first scan and confirmed on 2 subsequent assessments
- Patient achieved molecular response by Week 4
- Patient completed 24 weeks of treatment and continues treatment (as of Sept. 2025)



Representative images of tumor response courtesy of Dr. Antoine Hollebecque.
BL= baseline; FOLFIRINOX= leucovorin calcium, fluorouracil, irinotecan hydrochloride, oxaliplatin; PDAC= pancreatic ductal adenocarcinoma; PR= partial response; qd= daily; VAF= variant allele frequency; Wk= week

Conclusions

- INCB161734 demonstrated a **manageable tolerability profile**, with mostly low-grade GI toxicity and low dose reduction and discontinuation rate
- **1200mg selected based on PK, safety and efficacy profile**
- Results show **promising early clinical efficacy** and a manageable safety profile in heavily pretreated patients with *KRAS*^{G12D} mutated advanced or metastatic solid tumors
- Monotherapy expansion in **PDAC at RDEs** ongoing to further assess durability of response
- Evaluation of INCB161734 at RDE of 1200 mg qd in **combination with SoC in PDAC** (GEMNabP, mFOLFIRINOX) is **ongoing**

PD= pharmacodynamics; PDAC= pancreatic ductal adenocarcinoma; PK= pharmacokinetics; QD= daily

Advancing towards the next phase of development

Steven Stein, MD

Chief Medical Officer

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Strong progress towards our advancement criteria

- Establish single-agent activity and safety profile
- Demonstrate durability of response
- Validate profile when combined with standard of care
- Identify clear medical need in early lines of therapy in metastatic cancers

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MSS CRC: Treatment pathway and opportunity for novel 1L treatment

One of the most common cancers and second leading cause of cancer-related deaths

- 1.9M people diagnosed with CRC; 22% (423k) are Stage IV CRC
- Low long-term survival for Stage IV (16% 5-year survival)

No IO therapies are approved for MSS CRC

- 95% of advanced CRC tumors are MSS and historically have been resistant to single agent immunotherapy
- Most IO therapies in development have demonstrated efficacy only in patients without active liver metastasis

Significant need for therapies with better outcomes

- SoC (1L): chemo + beva, chemo + EGFRi
- ORR: 50-60%, PFS: 8-11 months. OS: 30 months

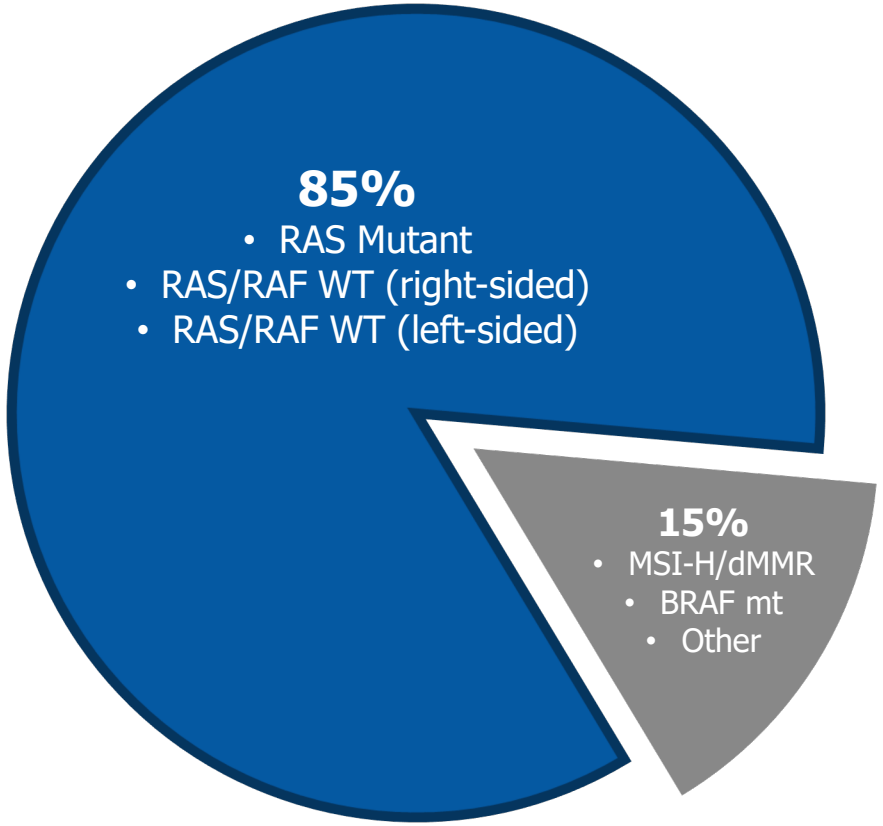
1. World Health Organization https://www.who.int/news-room/fact-sheets/detail/colorectal-cancer 2. SEER Cancer Facts CRC 3. Segal NH, et al. Clin Cancer Res. 2021;27(8):2200-2208

Clear opportunity for differentiation as 1L MSS CRC therapy

Opportunity to address majority of mCRC population with TGFβR2×PD-1 bispecific

- High TGF-β expression in tumor microenvironment
- Opportunity to establish a novel regimen in 1L MSS CRC that builds on current SoC (VEGF + chemo SOC)
- Addressing broadest population:
  - RAS Mut/WT, right and left-sided disease (85%)
  - Liver metastatic patients (~70%)

CRC Population by Diagnosis



Charting our path forward for TGFβR2×PD-1 bispecific

Proof of concept established in MSS CRC patients

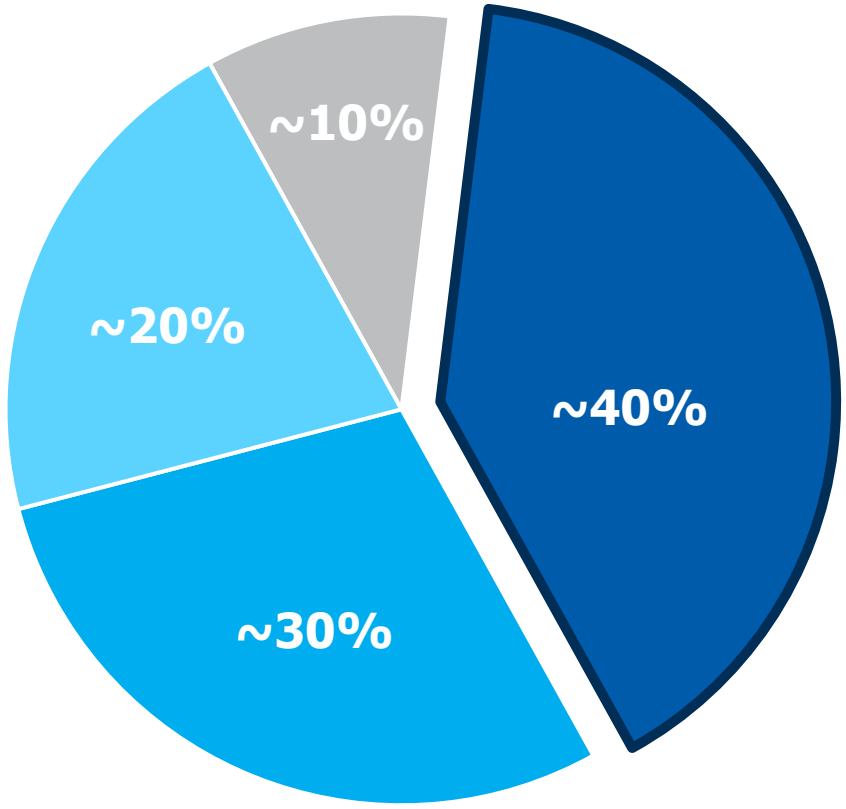
- ✓ Durable single-agent activity and manageable tolerability profile in late-line MSS CRC patients
- ✓ Responses observed in MSS CRC patients with and without active liver metastases
- ✓ Manageable profile provides opportunity for combinations and sustained therapy with current 1L SoC

Clear opportunity for differentiation for 1L MSS CRC

NEXT STEPS:

- **Planned initiation of Phase 3 registrational program in 2026**
  - Target Population: 1L mCRC patients in combination with SoC
  - Primary Endpoint: Progression Free Survival (PFS)

PDAC: Most RAS-addicted cancer with no targeted therapies for *KRAS*^{G12D} mutated patients



Metastatic PDAC is a rapidly progressive and high-mortality disease

- Low (~10%) 5-year survival rate[1,2]

~210,000 patients diagnosed with PDAC*

- >90% carry a KRAS mutation, of which ~40% having G12D variant[3]

1L and 2L metastatic treatment limited to combination or single agent chemotherapy

- Chemotherapy associated grade 3/4 toxicities (e.g., myelosuppression, neuropathies, other)
- SoC (1L): GEMNabP, mFOLFIRINOX
- ORR: 23-43%, mPFS: 5.5-8 months, mOS: ~8.5-11.7 months

* In the U.S, EU and JP

1. Siegel RL et al. CA Cancer J Clin. 2023;73(1):17-48. 2. SEER Cancer Stat Facts: Pancreatic Cancer. National Cancer Institute. 3. Lee JK, et al. *NPJ Precis Oncol*. 2022;6:91.

Opportunity for *KRAS*^{G12D} inhibitor in PDAC

Demonstrated single-agent activity data in PDAC patients and competitive safety profile

- ✓ Results show promising early clinical efficacy and a manageable safety profile in heavily pretreated (2L, 3L+) patients with *KRAS*^{G12D} mutated, advanced or metastatic solid tumors

First potential targeted therapy for *KRAS*^{G12D} mutated PDAC patients

NEXT STEPS:

- Ongoing work to enable early-line use in combination with SoC (GEMNabP, mFOLFIRINOX)
- Continue to evaluate patients to understand durability of response
- Align with regulators on next steps for registrational program, pending ongoing data collection

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Path forward in metastatic solid tumors

- ✓ **Addressing large patient populations with significant unmet need**
- ✓ **Evaluating in early line of therapy in patients with advanced/metastatic disease**

TGFβR2×PD-1 Bispecific Antibody (INCA33890)

- Efficacy and safety data support advancement into 1L MSS CRC in combination with SOC
- Opportunity to establish a novel regimen in broadest MSS CRC patient population
- **Initiating Phase 3 registrational program in early 2026**

$KRAS^{G12D}$ Inhibitor (INCB161734)

- Established single-agent activity and manageable safety profile in heavily pretreated patients with *$KRAS^{G12D}$* mutation
- Evaluation in combination with SoC in PDAC ongoing to inform use as 1L treatment
- **First potential targeted therapy for *$KRAS^{G12D}$* mutated PDAC patients**

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Q&A

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