

# A Phase 1 Study of INCA33890, a TGF $\beta$ R2 $\times$ PD-1 Bispecific Antibody, for Advanced Solid Tumours

Elena Garralda,<sup>1</sup> Markus Joerger,<sup>2</sup> Martin Gutierrez,<sup>3</sup> Victor Moreno,<sup>4</sup> Antonio Santoro,<sup>5</sup>  
Sreenivasa R. Chandana,<sup>6</sup> Irene Moreno,<sup>7</sup> Justin Moyers,<sup>8</sup> Yohann Loriot,<sup>9</sup> Philippe Cassier,<sup>10</sup>  
Petr Szturz,<sup>11</sup> Ruth Plummer,<sup>12</sup> Debra Josephs,<sup>13</sup> Jordi Rodon,<sup>14</sup> Benedito A. Carneiro,<sup>15</sup>  
Chiara Greggio,<sup>16</sup> Xiaohan Xu,<sup>17</sup> Yunlan Fang,<sup>17</sup> Thomas B. Karasic,<sup>17</sup> Filippo De Braud<sup>18</sup>

<sup>1</sup>Research Unit, Vall d'Hebron Institute of Oncology, Barcelona, Spain; <sup>2</sup>HOCH Health Ostschweiz, St Gallen, Switzerland; <sup>3</sup>John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; <sup>4</sup>START Madrid-FJD, University Hospital Fundación Jiménez Díaz, Madrid, Spain; <sup>5</sup>IRCCS Humanitas Research Hospital – Humanitas Cancer Center, Rozzano (Milan), Italy; <sup>6</sup>START Midwest, Grand Rapids, MI, USA; <sup>7</sup>START Madrid-CIOCC, Centro Integral Oncológico Clara Campal, Madrid, Spain; <sup>8</sup>The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA, USA; <sup>9</sup>Institut Gustave Roussy, University of Paris Sud, Villejuif, France; <sup>10</sup>Centre Léon Bérard, Lyon, France; <sup>11</sup>Lausanne University Hospital (CHUV), University of Lausanne (UNIL), Lausanne, Switzerland; <sup>12</sup>Northern Centre for Cancer Care, Freeman Hospital, and Newcastle University, Newcastle upon Tyne, UK; <sup>13</sup>Guy's and St Thomas' NHS Foundation Trust, London, UK; <sup>14</sup>The University of Texas MD Anderson Cancer Center, Houston, TX, USA; <sup>15</sup>The Legorreta Cancer Center at Brown University, Providence, RI, USA; <sup>16</sup>Incyte International Biosciences Sàrl, Morges, Switzerland; <sup>17</sup>Incyte Corporation, Wilmington, DE, USA; <sup>18</sup>Fondazione IRCCS 'Istituto Nazionale dei Tumori', Milan, Italy

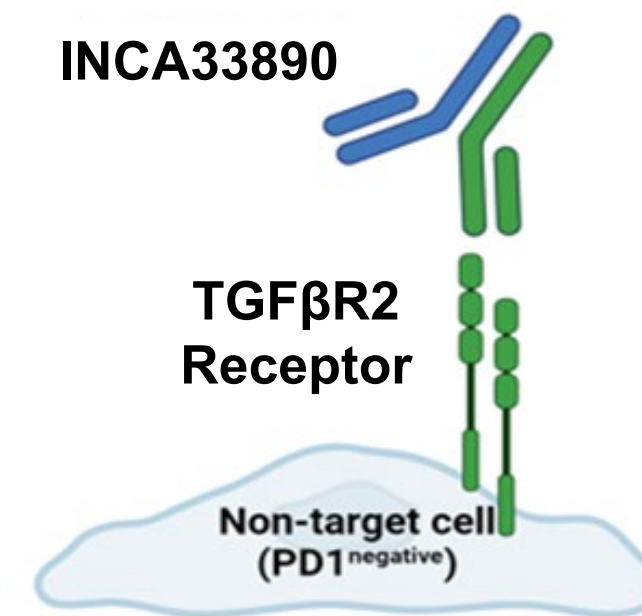
# Declaration of Interests

- **Research:** Novartis, Roche, ThermoFisher, AstraZeneca, Taiho, BeiGene, Janssen, Anaveon
- **Consultant/Advisor:** Roche, Ellipses Pharma, Boehringer Ingelheim, Janssen Global Services, Seattle Genetics, Skypta, Sotio, Sanofi, Anaveon, Abbvie, Astex Therapeutics, Alentis Therapeutics, Marengo Therapeutics, Hengrui, Incyte, Medpace, Medscape, Pfizer, Amgen, GenMab, GreyWolf, Gilead, Daiichi Sankyo
- **Speakers Bureau:** MSD, Roche, Novartis, SeaGen, PPD, Aran, TRRF, ESMO, Fundación SEOM, CDDF, Springer Nature, Karger, Doctaforum, Tactics, AEFI, Fundación ECO, MeetingPharma, AstraZeneca, Alcura, Horizon CME, ESO
- **Employment:** NEXT Oncology - IOB
- **Stocks:** 1TRIALSP

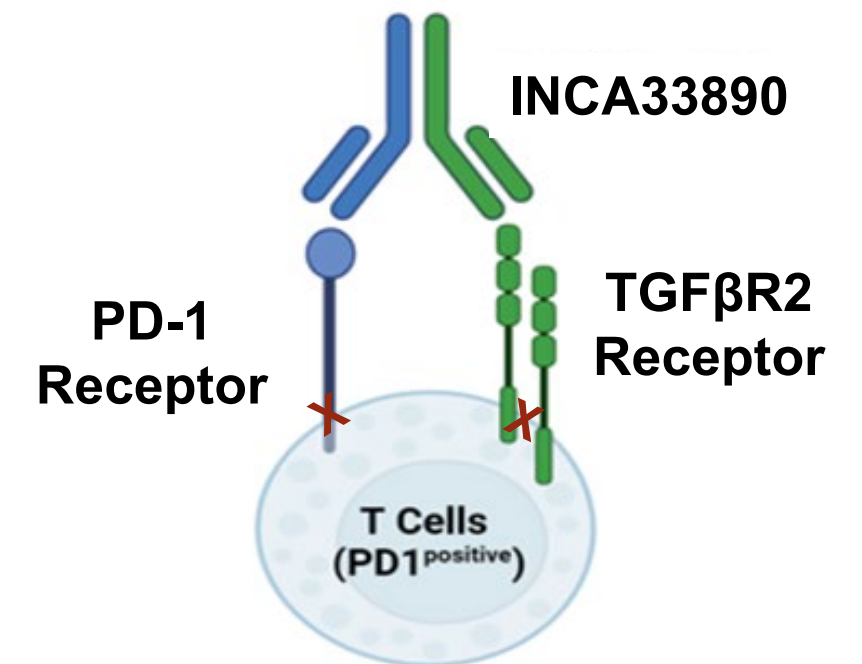
# Background

- TGF $\beta$  signalling in the TME diminishes ICI efficacy<sup>1-3</sup>
  - Inhibits T-cell proliferation and effector function
  - Promotes immune-excluded phenotype
- Broad TGF $\beta$  pathway inhibitors show limited efficacy and/or excess toxicity
  - eg, TGF $\beta$ /PD-1 trap molecules, and TGF $\beta$  small-molecule inhibitors
- INCA33890 is a first-in-class anti-TGF $\beta$ R2 $\times$ PD-1 bispecific common light-chain antibody<sup>4-6</sup>
  - Designed to target TME immune cells
  - Blocks both TGF $\beta$ R2 and PD-1 signalling pathways in PD-1<sup>+</sup> cells
  - No inhibition of TGF $\beta$  signalling in PD-1<sup>-</sup> cells
- INCA 33890-101 evaluated the safety and efficacy of INCA33890 in patients with advanced or metastatic solid tumours

**Weak Binding**  
No TGF $\beta$  Signalling Inhibition



**Strong Binding**  
Potent PD-1 and TGF $\beta$  Signalling Inhibition

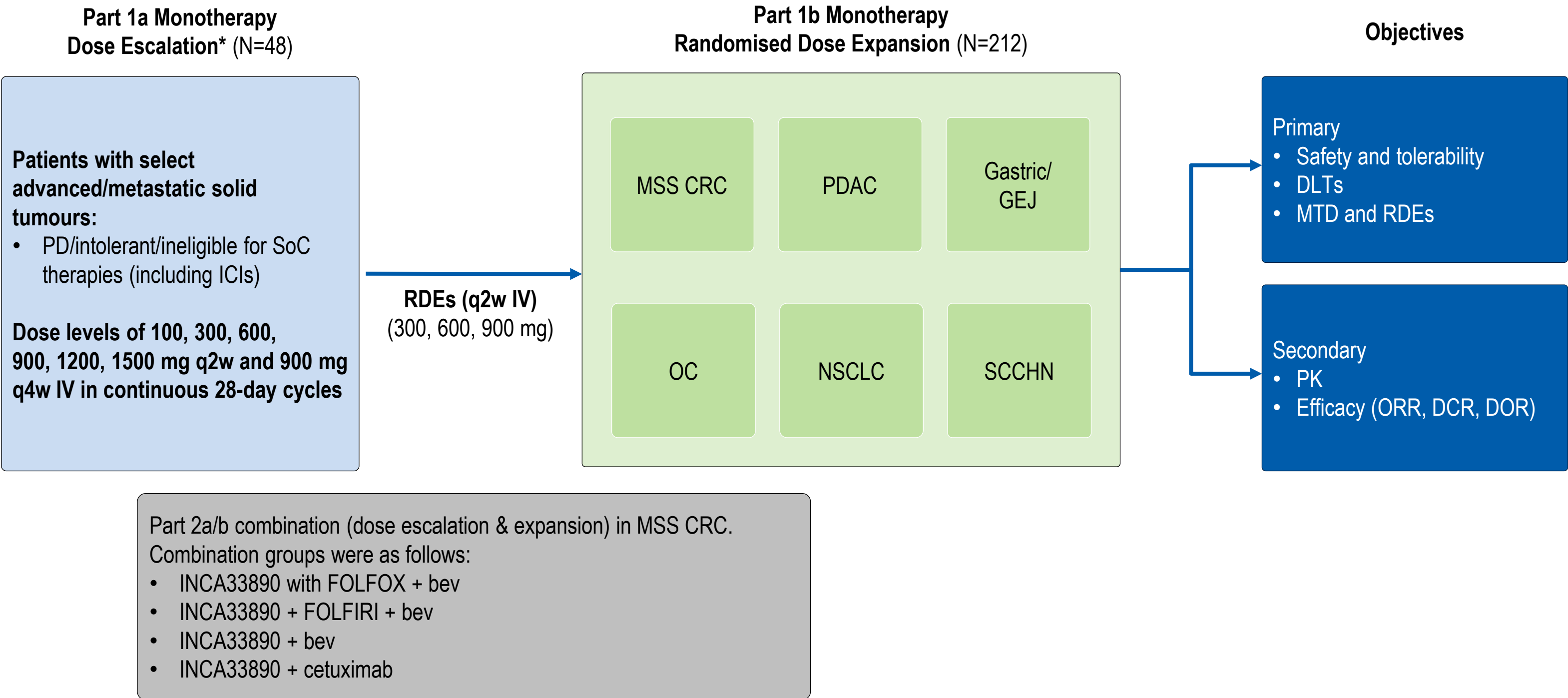


Elena Garralda

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

1. Mariathasan S, et al. *Nature*. 2018;554:544-548. 2. Sow HS, et al. *Cells*. 2019;8:320. 3. Li MO, et al. *Annu Rev Immunol*. 2006;24:99-146. 4. Wang LCS, et al. Presented at: AACR; 2023; Orlando, FL. Abstract 2936. 5. Guan J, et al. Presented at: AACR; 2025; Chicago, IL. Abstract 6071/12. 6. Kinder M, et al. Presented at: AACR; 2025; Chicago, IL. Abstract 4861/11. ICI, immune checkpoint inhibitor; PD-1, programmed death-1; TGF $\beta$ , transforming growth factor  $\beta$ ; TGF $\beta$ R2, transforming growth factor  $\beta$  type II receptor; TME, tumour microenvironment.

# Study Design



\*Hybrid statistical design for optimal definition of MTD/RDE(s); ≥3 dose levels, ≥3 patients/dose level.  
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; MSS, microsatellite stable; MTD, maximum tolerated dose;  
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.

Data cutoff: 25 July 2025

Elena Garralda

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.



# Baseline Demographics and Characteristics

Part 1a + 1b	Total (N=260)
Age, median (range), years	60.5 (22-85)
Male sex, n (%)	133 (51.2)
Race, n (%)	
White	195 (75.0)
Black or African American	5 (1.9)
Asian	8 (3.1)
Other, not reported, missing	52 (20.0)
Ethnicity	
Hispanic	14 (5.4)
Not Hispanic	202 (77.7)
Not reported, unknown, missing	44 (16.9)
ECOG PS, n (%)	
0	148 (56.9)
1	112 (43.1)

Part 1a + 1b	Total (N=260)
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)

Elena Garralda

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

\*Part 1a only. †1 patient each with triple-negative breast cancer, cervical cancer, melanoma, and renal cell carcinoma.  
 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

- INCA33890 doses up to 1200 mg q2w were well tolerated with no DLTs
- 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
- Safety profiles were similar across RDEs:
- Investigator-identified irAEs occurred in 31.0% of patients at RDEs
  - Grade 3 irAEs occurred in 7.5% of patients
  - 10 patients discontinued therapy due to irAEs
- Investigator-identified immune reactions occurred in 9.2% of patients
  - 2 patients had grade 4 anaphylaxis IRRs that led to discontinuation

TRAEs Across RDEs

	300 mg q2w (n=99)	600 mg q2w (n=30)	900 mg q2w (n=110)	Total (n=239)
TRAE, n (%)				
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)

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

	300 mg q2w (n=99)		600 mg q2w (n=30)		900 mg q2w (n=110)		Total (n=239)
Preferred term, n (%)							
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)
ALT increased	4 (4.0)	2 (2.0)	1 (3.3)	0 (0)	4 (3.6)	1 (0.9)	12 (5.0)

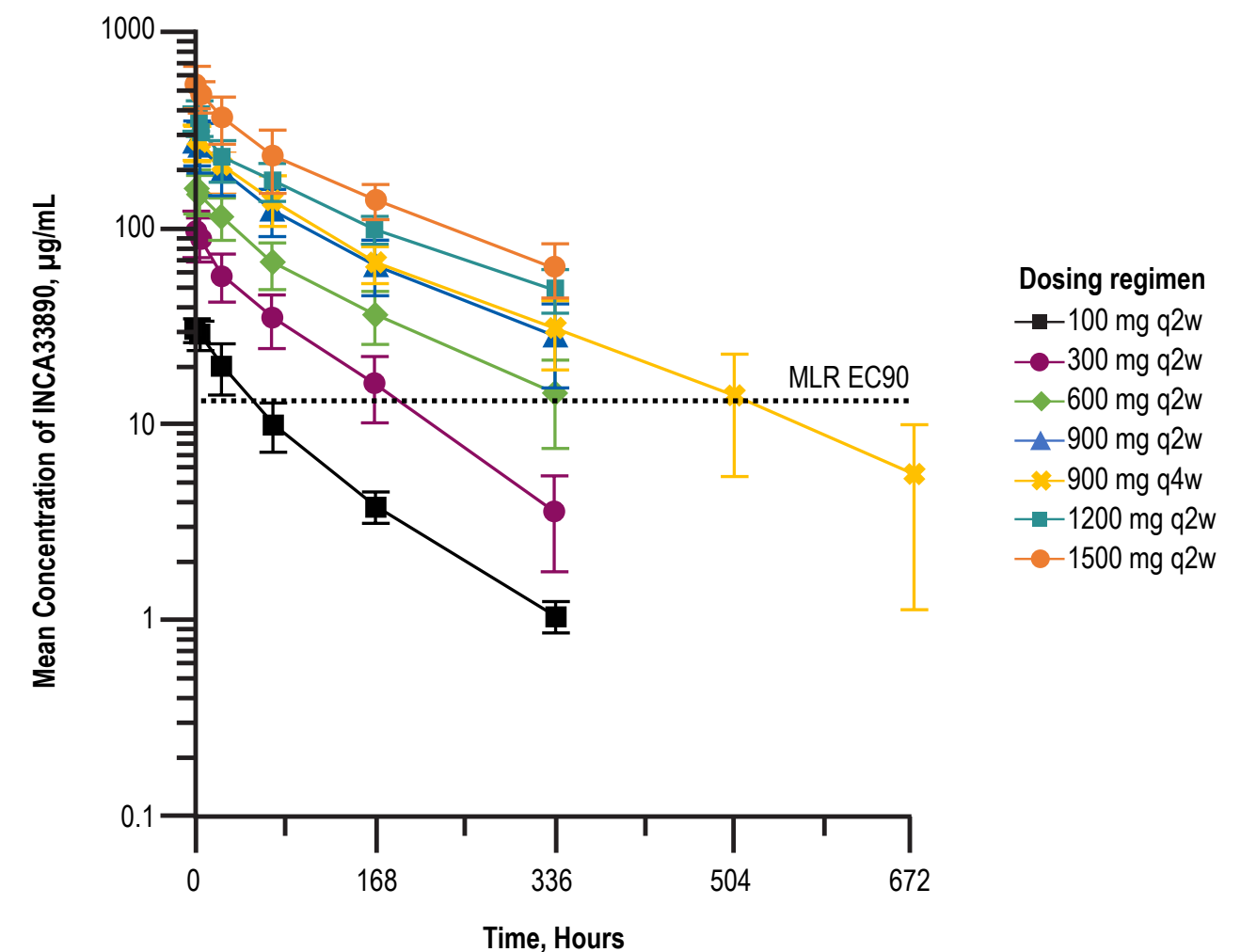
\*Grouped term including dermatitis, eczema, lichen planus, pustular psoriasis, rash, rash erythematous, rash maculo-papular, rash pustular.

ALT, alanine aminotransferase; DKA, diabetes-related ketoacidosis; DLT, dose-limiting toxicity; irAE, immune-related adverse event; IRR, infusion-related reaction; MTD, maximum tolerated dose; PD, pharmacodynamics; q2w, every 2 weeks; PK, pharmacokinetics; RDE, recommended dose for expansion; TRAE, treatment-related adverse event.

# INCA33890 PK, PD, and Immunogenicity

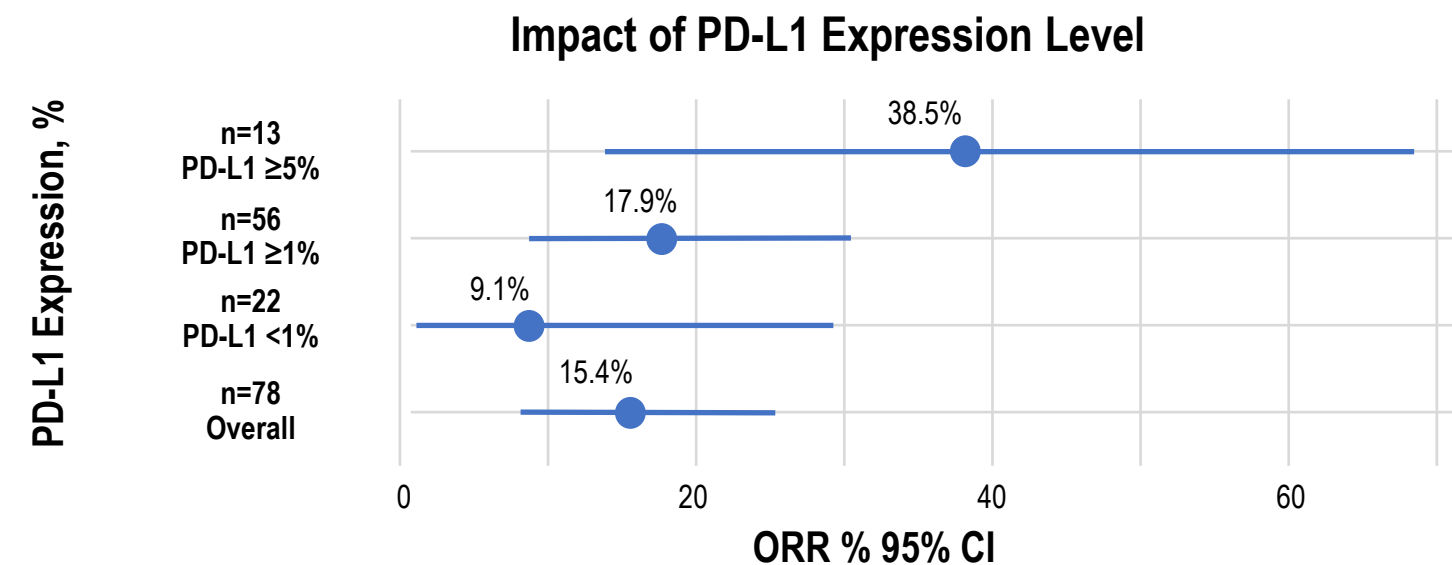
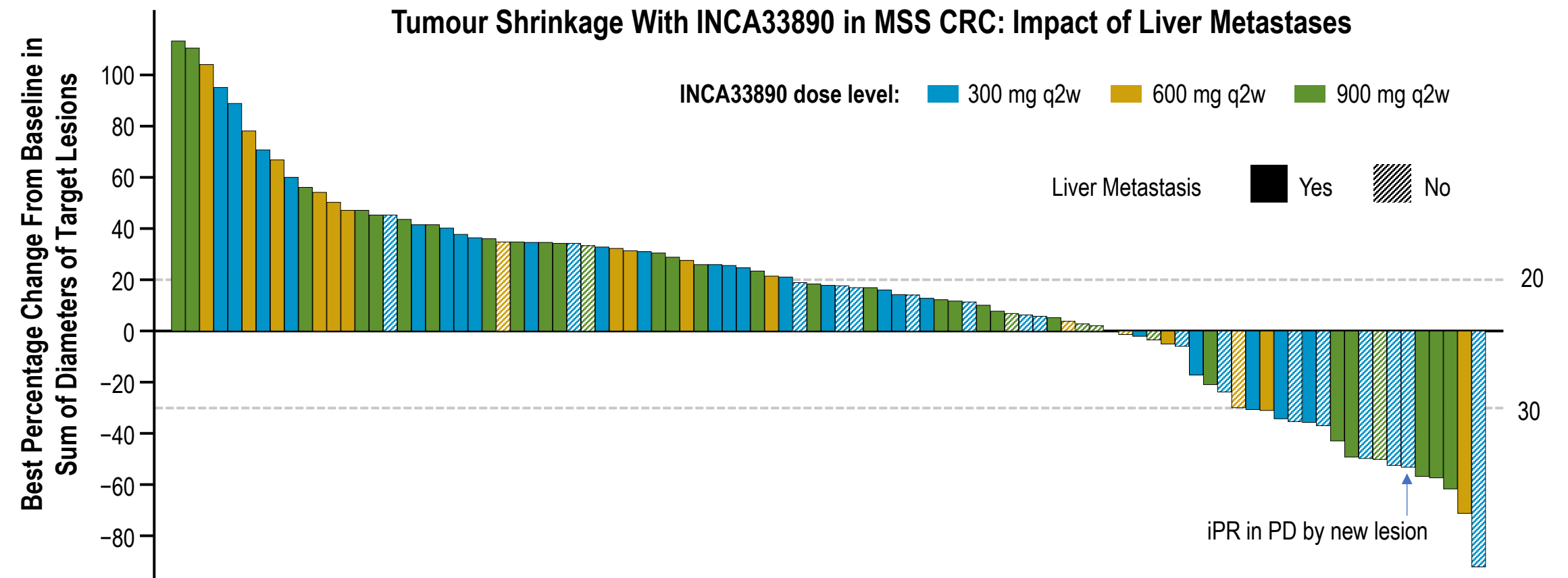
- Non-linear PK observed at doses of 100-1500 mg q2w, likely due to target-mediated drug disposition
  - Clearance rate: 0.022-0.044 L/h
  - Volume of distribution: 4.2-5.1 L
  - Half-life: 3.5-6.2 days
- 78% of patients developed INCA33890-specific treatment-emergent ADAs
  - Impact on PK appeared to be dose dependent, with no impact at doses  $\geq 900$  mg q2w
  - ADAs did not appear to 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

Mean Serum Concentration-Time Profiles of INCA33890 Following a Single IV Infusion Across Dose Levels



# 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%)
- INCA33890 ORR was similar across RDEs
- Higher PD-L1 expression may enhance INCA33890 efficacy



Elena Garralda

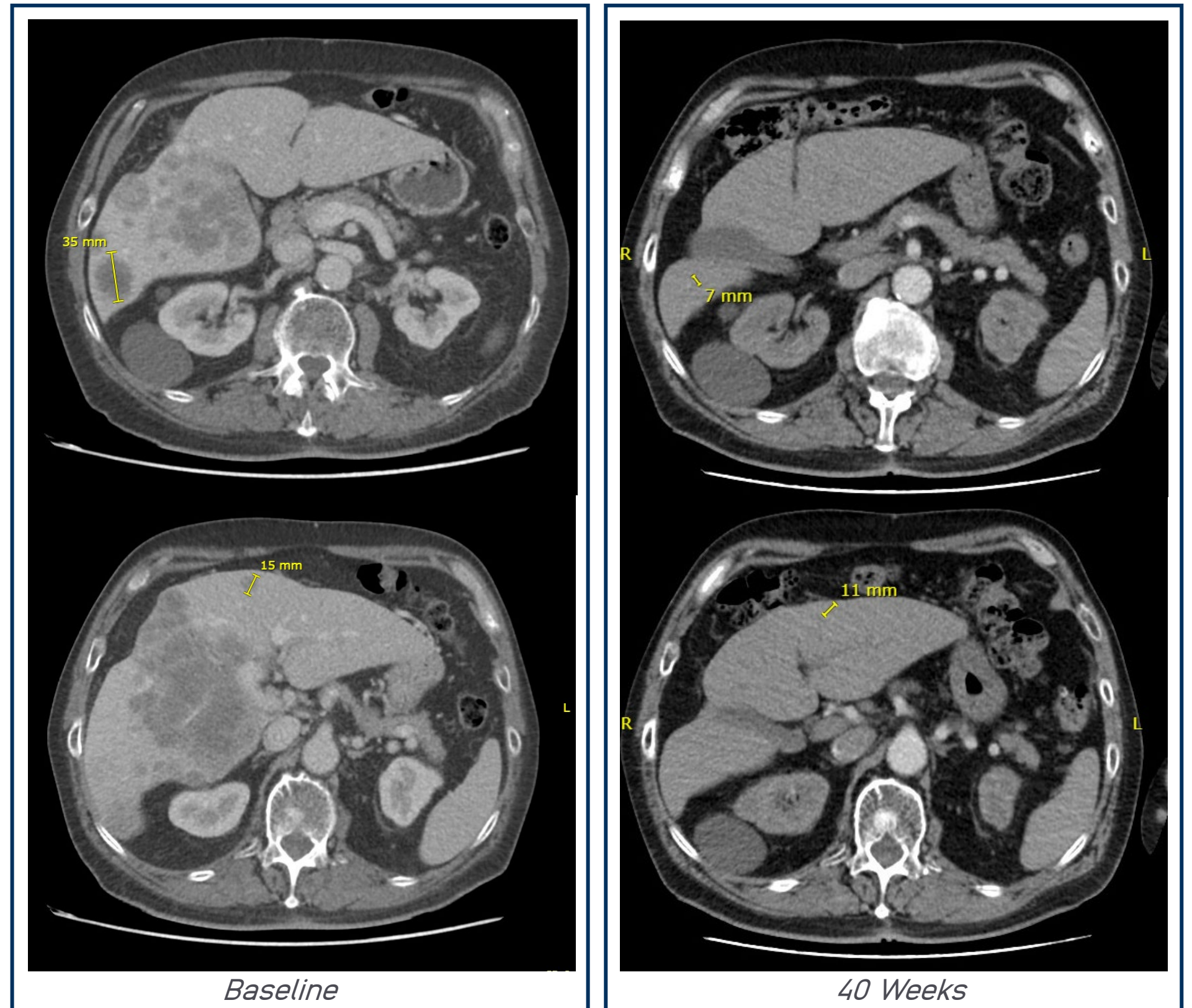
Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

CI, confidence interval; CRC, colorectal cancer; DCR, disease control rate; iPR, immune partial response; MSS, microsatellite stable; ORR, overall response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; q2w, every 2 weeks; RDE, recommended dose for expansion.



# Efficacy in a Case of MSS CRC

- A 67-year-old man with CRC who:
  - Had stage IV with multiple liver metastases and nodal disease
  - Progressed on prior FOLFOX + bev, FOLFIRI, trifluridine/tipiracil, STAT3 inhibitor (investigational)
  - Achieved ongoing PR with INCA33890 900 mg q2w, currently on treatment (10+ months)



Representative images of liver response; courtesy of Dr I Moreno.  
bev, bevacizumab; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; IV, intravenous;  
CRC, colorectal cancer; MSS, microsatellite stable; PR, partial response; q2w, every 2 weeks; STAT3, signal transducer and activator of  
transcription 3; q2w, every 2 weeks.

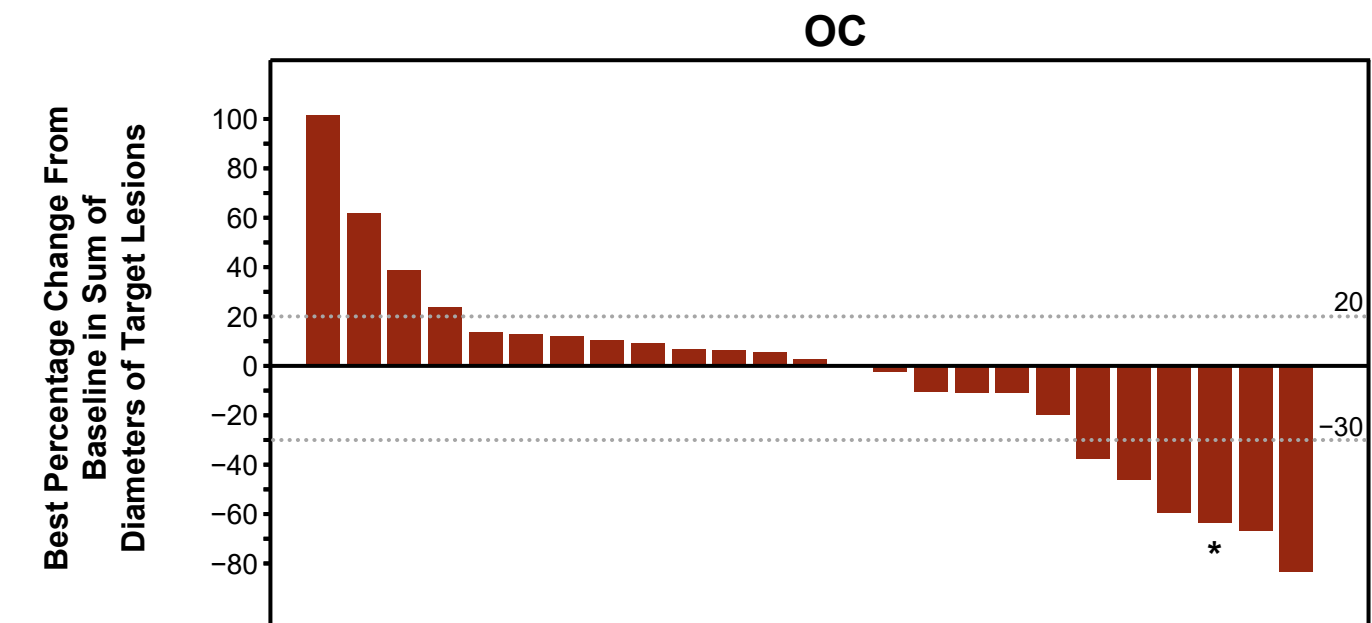
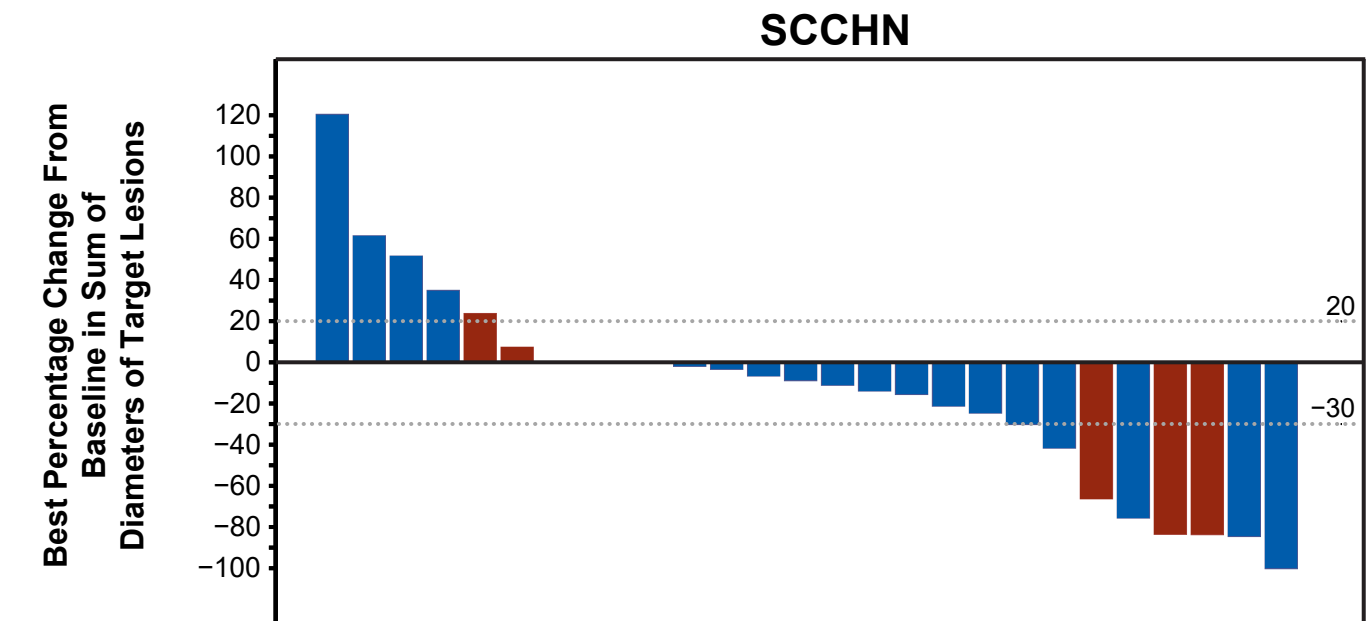
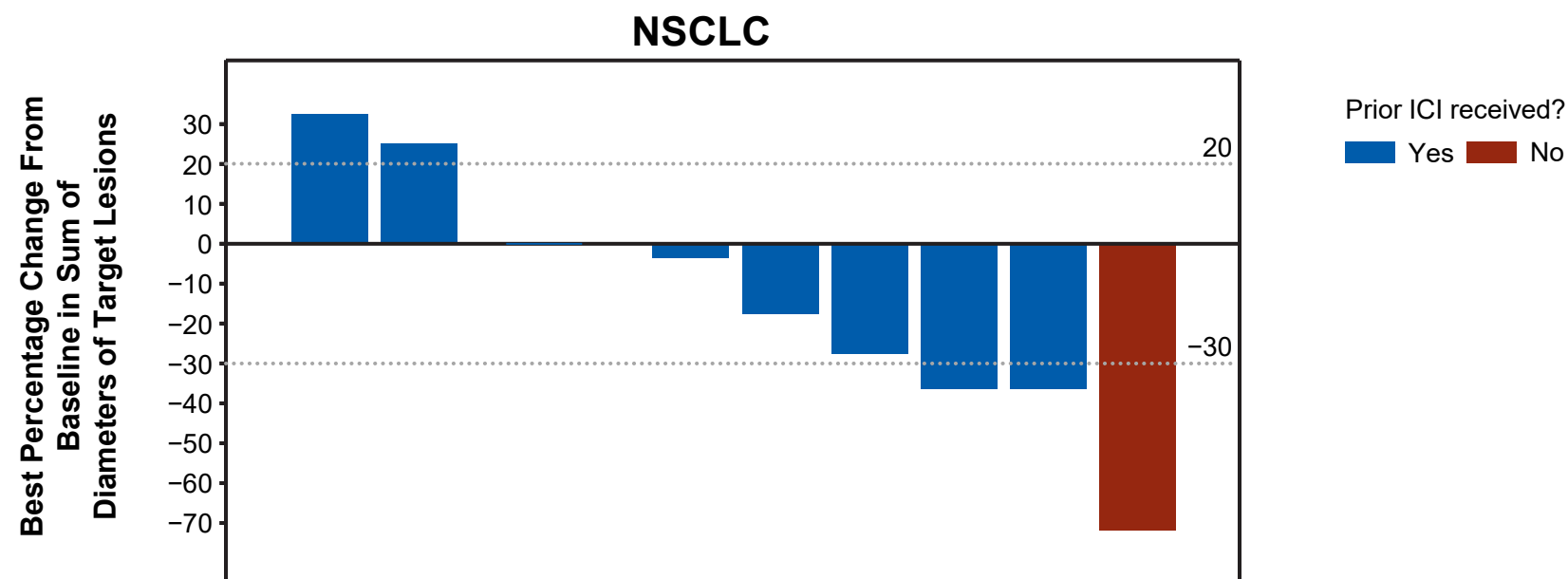
Elena Garralda

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

# Preliminary Efficacy in Other Tumour Types at RDEs

- Most patients had limited follow-up ( $\leq 16$  weeks)
- Responses were reported across tumour types and PD-L1 expression levels, including levels  $<1\%$

Tumour Type	n	CR	PR	SD	PD/NE
SCCHN	27	1	6	7	13
OC	28	2	3*	11	12
NSCLC	10	0	3	3	4
PDAC	36	0	2	6	28
Gastric/GEJ	29	0	1	7	21
Other†	5	0	1‡	1‡	3



Elena Garralda

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

\*1 PR in patient originally treated at 1500 mg q2w, de-escalated to 900 mg and responded. †MPM (n=2 each), TNBC, mel, CESC (n=1 each). ‡MPM.  
 CESC, cervical squamous cell carcinoma and endocervical adenocarcinoma; CR, complete response; GEJ, gastroesophageal junction cancer; ICI, immune checkpoint inhibitor; Mel, cutaneous malignant melanoma; MPM, malignant pleural mesothelioma; NE, not evaluable; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; PDAC, pancreatic adenocarcinoma; PR, partial response; q2w, every 2 weeks; RDE, recommended dose for expansion; SCCHN, squamous cell carcinoma of the head and neck; SD, stable disease; TNBC, triple-negative breast cancer.

# Conclusions

- The anti-TGFβR2×PD-1 bispecific antibody INCA33890 was generally well tolerated at doses up to 1200 mg q2w
- In 239 patients treated at RDEs:
  - irAEs occurred in 31.0% of patients
  - IRRs occurred in 9.2% of patients
- 900 mg q2w was selected as RP2D
  - Similar safety and efficacy were seen at 300, 600, and 900 mg q2w
  - ADAs impacted drug exposure for some patients at doses below 900 mg
- Responses were observed across multiple tumour types, including:
  - MSS CRC with active liver metastases
  - OC
  - ICI-refractory SCCHN and NSCLC
- Evaluation of INCA33890 in combination with SoC treatments in patients with CRC is ongoing

Elena Garraida

Content of this presentation is copyright and responsibility of the author. Permission is required for re-use.

ADA, anti-drug antibody; CRC, colorectal cancer; ICI, immune checkpoint inhibitor; irAE, immune-related adverse events; IRR, immune-related reaction; CRC, colorectal cancer; MSS, microsatellite stable; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PD-1, programmed death-1; q2w, every 2 weeks; RDE, recommended dose for expansion; RP2D, recommend phase 2 dose; SCCHN, squamous cell carcinoma of the head and neck; SoC, standard of care; TGFβR2, transforming growth factor β type II receptor.

- The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study
- This study was sponsored by Incyte Corporation (Wilmington, DE, USA)
- The authors gratefully acknowledge the collaboration with Merus N.V. for lead discovery and early-stage research activities
- Medical writing assistance was provided by Andrew Marson, PhD, of Envision Ignite, an Envision Medical Communications agency, a part of Envision Pharma Group, and funded by Incyte Corporation



To download Incyte  
presentations at this  
meeting, scan code

**European Society for Medical Oncology (ESMO)**

Via Ginevra 4, CH-6900 Lugano

T. +41 (0)91 973 19 00

[esmo@esmo.org](mailto:esmo@esmo.org)

[esmo.org](http://esmo.org)