9-ING-41, a small molecule selective Glycogen Synthase Kinase-3 Beta (GSK-3β) inhibitor -

Progress to date in adult patients with cancer

May 2020

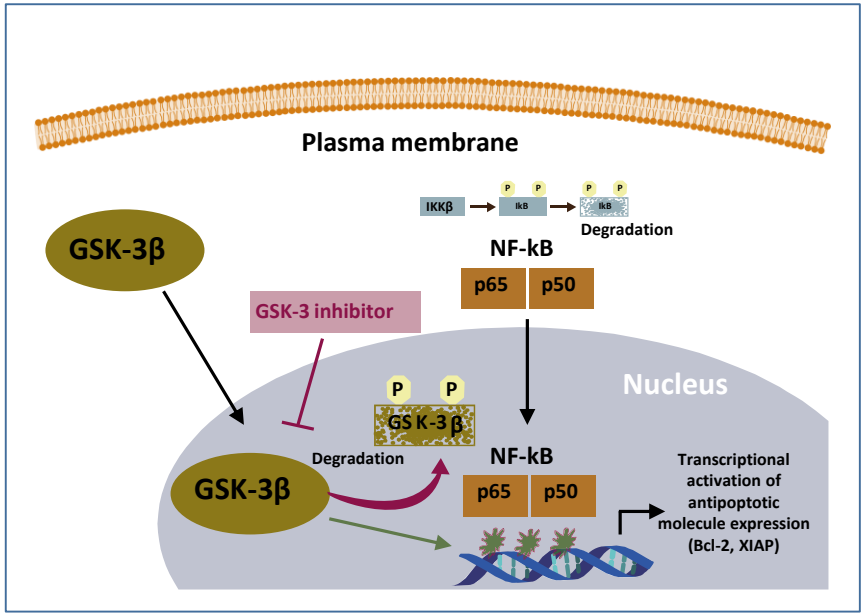
Reviewing data for 9-ING-41 presented by Dr Benedito A. Carneiro MD, MS[1] at ASCO 2020

- 9-ING-41 has dose-proportional pharmacokinetics
- It is well tolerated with no attributable SAEs
- Antitumor activity as monotherapy: ongoing CR in a patient with refractory BRAF-mutated melanoma
- Disease stability in combination with chemotherapy in patients previously exposed to the same chemotherapy agent(s)
- Phase 2 study of 9-ING-41 plus gemcitabine/nab-paclitaxel in previously untreated advanced pancreatic cancer patients underway
- Phase 2 study in patient with advanced myelofibrosis underway
- Phase 1 pediatric study underway
- Oral formulation in development

[1]Lifespan Cancer Institute, Brown University, Providence, RI

The relevance of Glycogen Synthase Kinase-3 Beta (GSK-3β) in cancer

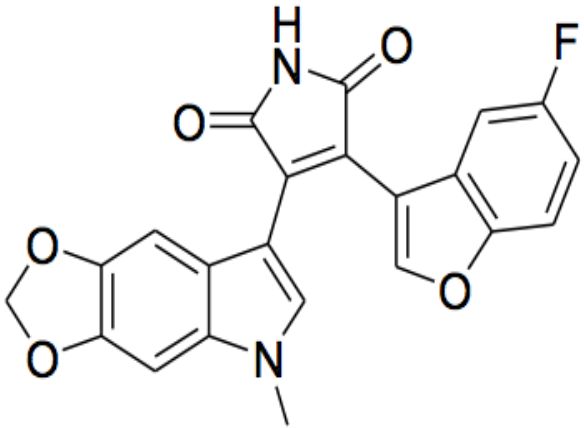
- Constitutively active serine-threonine kinase
- The increased expression and aberrant function has been implicated in the biology of numerous diseases, including cancer, inflammation, fibrosis, and neurodegeneration
- Positive regulator of NF-kB, promoting cancer cell survival and proliferation by facilitating chemoresistance
- In the nucleus, it regulates NF-kB binding to its target gene promoters and modulates oncogenes (e.g., b-catenin, cyclin D1, and c-Myc)
- ATR-mediated DNA damage response (DDR), cell cycle arrest, and tumor immune surveillance



Ding et al. Clin Cancer Res 2019. PMID: 31533931; Taylor et al. Immunity 2016. PMID: 26885856; Walz et al. Clin Cancer Res 2017. PMID:28053024; Ougolkov et al. Cancer Res 2005. PMID: 15781615

9-ING-41 - First clinically relevant small molecule potent selective GSK-3β inhibitor

- Reversible ATP-competitive inhibitor
- Inhibition of nuclear GSK-3β leads to its rapid degradation and is followed by downregulation of anti-apoptotic molecules (e.g., Bcl-2, XIAP, Bcl-XL)
- Significant pre-clinical antitumor activity in a broad spectrum of malignancies, including pancreatic cancer, GBM, lymphoma, neuroblastoma, breast cancer, ovarian cancer and bladder cancer models

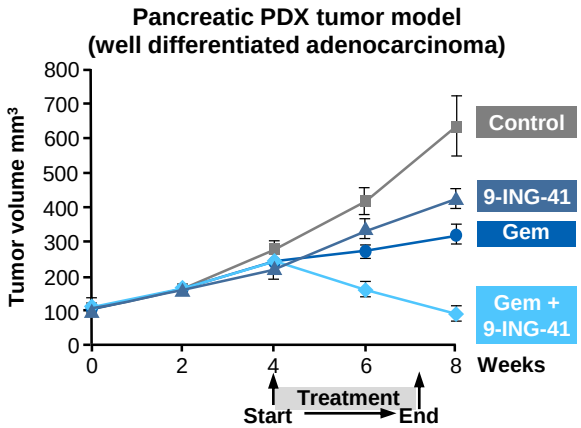


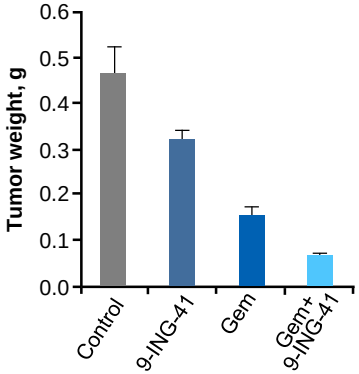
3-(5-Fluoro-benzofuran-3-yl)-4-(5-methyl-5H-[1,3]dioxolo[4,5-f]indol-7- yl)-pyrrole-2,5-dione

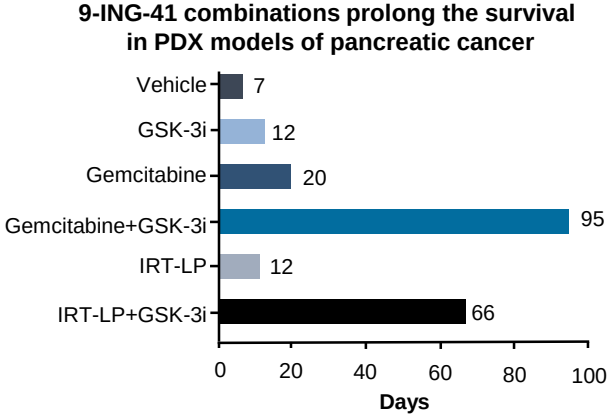
Ding et al. Clin Cancer Res 2019; Ugolkov et al. Transl Oncol 2017; Wu et al. Blood 2019; Ugolkov et al. Anticancer Drugs 2018; Pal et al. Mol Cancer Ther 2014; Ugolkov et al. Cancer Lett 2016; Kuroki et al. Sci Rep 2019; Hillard et al. Anticancer Drugs 2011
Benedito A. Carneiro, MD, MS

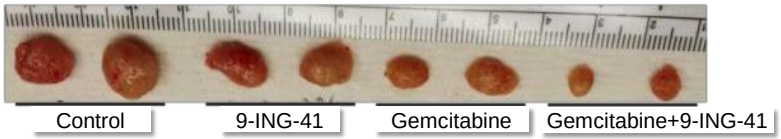
9-ING-41 shows pre-clinical activity in pancreatic cancer

- 9-ING-41 potentiates the antitumor effect of standard agents in pancreatic cancer cells
- 9-ING-41 enhances the antitumor effect of gemcitabine and liposomal irinotecan in pancreatic PDX Tumors In Vivo









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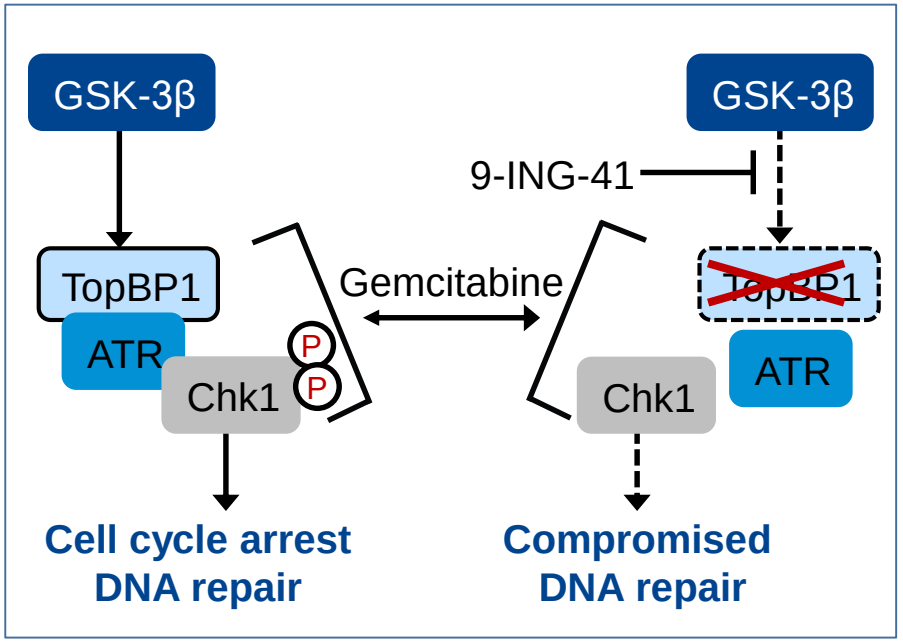
9-ING-41 sensitizes pancreatic cancer cells to chemotherapy

- Impairs TopBP1/ATR-mediated DNA damage response induced by gemcitabine



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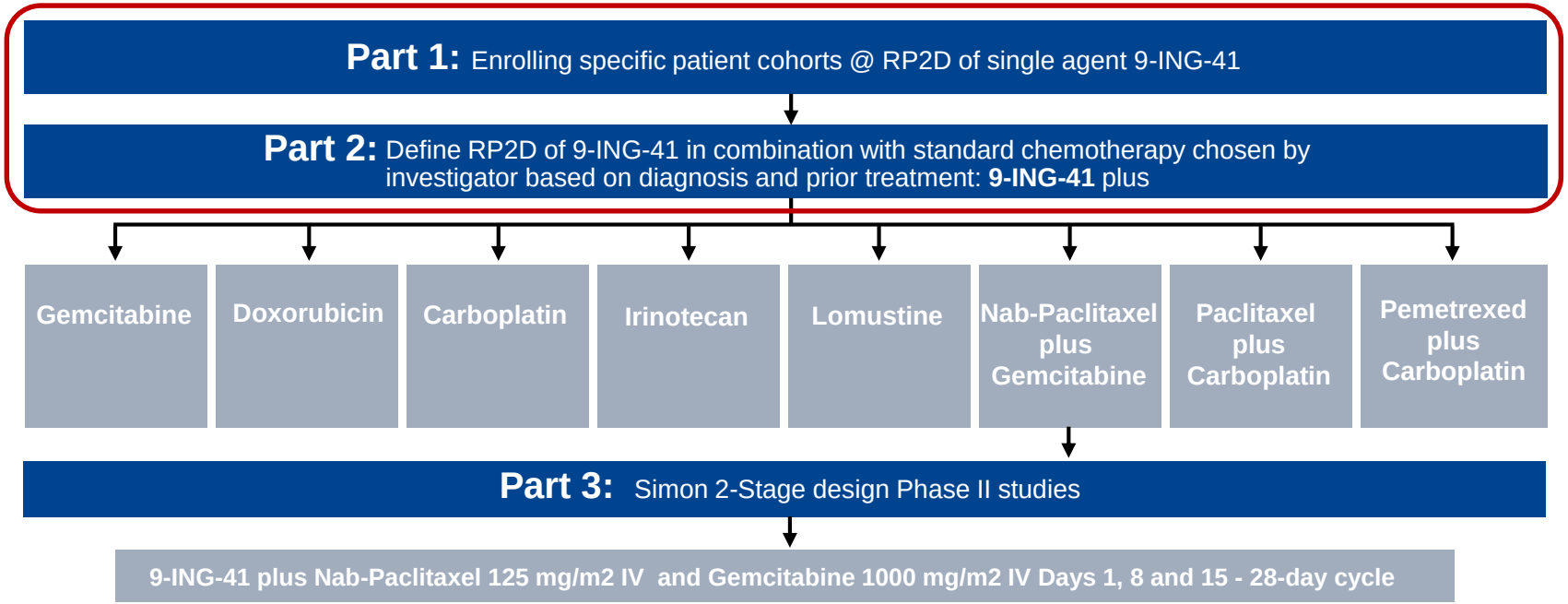
Actuate 1801: 9-ING-41 phase I/II study schema



- 9-ING-41 is given IV twice a week, on days 1 and 4

Study 1801 objectives

- **Phase 1 (parts 1 and 2):**
  - Evaluate the safety of 9-ING-41 as monotherapy (Part 1) and in combination with chemotherapies (Part 2) in patients with advanced malignancies using standard 3+3 dose escalation design
  - Determine the maximum tolerated dose (MTD) or the recommended Phase 2 study dose (RP2D)

- **Key eligibility:**
  - Relapsed or refractory malignancies
  - Adequate organ function
  - For part 2, patient must have received the chemotherapy for treatment of the same malignancy

Study 1801 part 1 and 2 results to date – data cutoff April 27th, 2020

- **Part 1: 9-ING-41 Single Agent Cohorts**
  - 1 – 1 mg/kg
  - 2 – 2 mg/kg
  - 3 – 3.3 mg/kg
  - 4 – 5 mg/kg
  - 5 – 7 mg/kg
  - 6 – 9.3 mg/kg
  - 7 – 12.4 mg/kg
  - 8 – 15 mg/kg

N = 57 pts enrolled

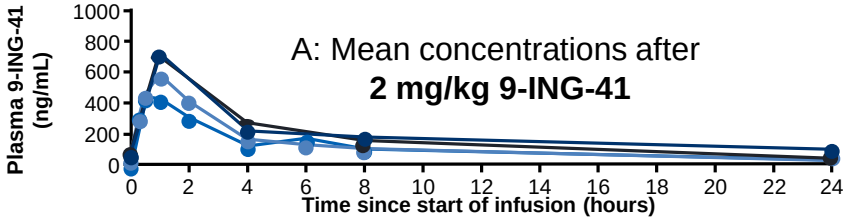
- **Part 2: Chemotherapy + 9-ING-41**
  - Carboplatin
  - Carboplatin/Paclitaxel
  - Doxorubicin
  - Gemcitabine
  - Gemcitabine/Nab-Paclitaxel
  - Irinotecan
  - Lomustine

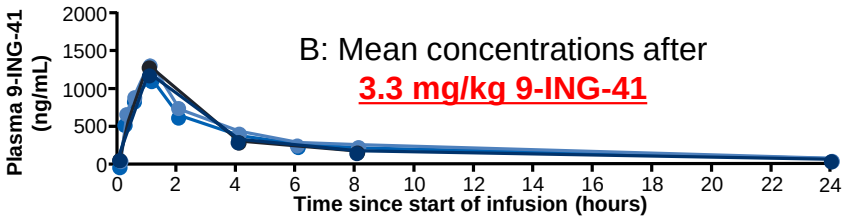
N = 116 pts enrolled

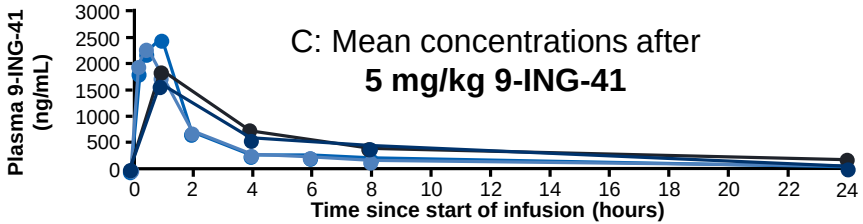
Patient demographics

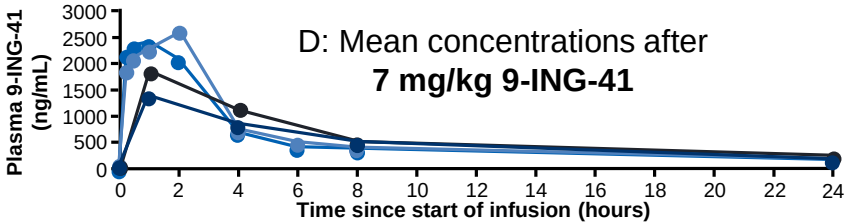
Baseline Characteristics		Part 1 (N = 56)	Part 2 (N = 99)
Median age, years (range)		61 (28–88)	61 (30-90)
Gender, n (%)	Male	30 (53.6%)	52 (52.5%)
	Female	26 (46.4%)	47 (47.5%)
Tumor Types, n	GI	26	58
	Thoracic	5	8
	GYN	2	8
	Breast	0	7
	GU	4	0
	Melanoma/Skin	8	2
	Sarcoma	2	1
	Lymphoma/Leukemia	3	0
	Head/Neck	1	5
	GBM/Gliomas	5	9
	Others	0	1
Prior systemic treatments, median (range)		2 (1–13)	3 (1–14)
ECOG Performance Status, n (%)	PS 0	19 (33.9%)	32 (32.3%)
	PS 1	36 (64.3%)	63 (63.6%)
	PS 2	1 (1.8%)	3 (3.0%)

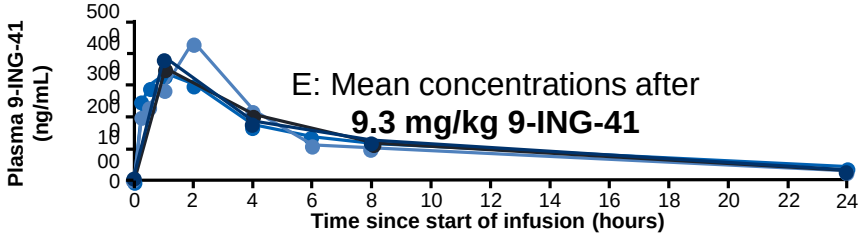
9-ING-41 pharmacokinetics: dose-proportional exposure

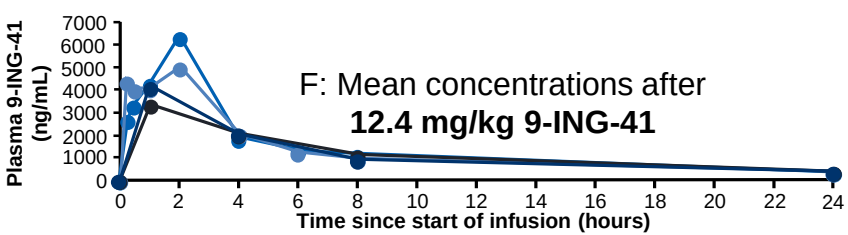






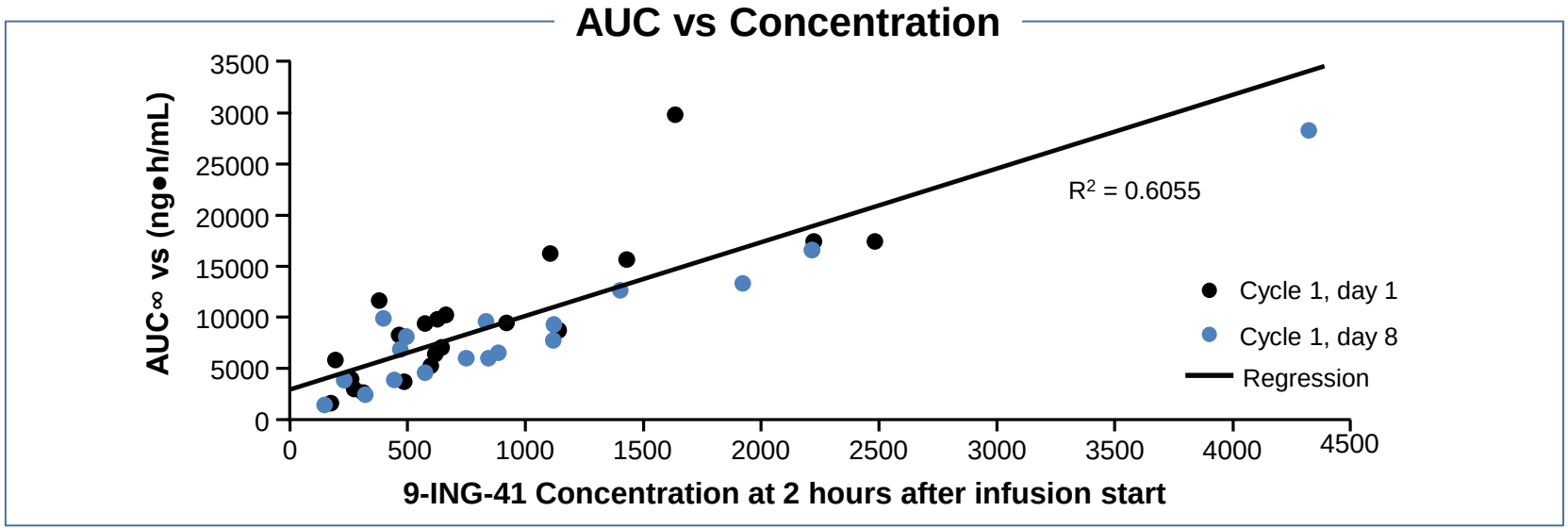






- The mean concentration-time profiles do not change with the repeated dosing at 3 and 4-day intervals.
- Most exposure occurs within 6 hours of start of infusion (SOI). Concentrations decline ~70-75% from peak by 6 hours after SOI, and by 80-90% from peak by 24 hours after SOI.

9-ING-41 single-agent pharmacokinetics



- 9-ING-41's mean terminal half-life is 12-20 hrs
- C_{max} and $AUC_{0\text{-}72}$ are dose proportional with no accumulation

9-ING-41 single-agent attributable adverse events (N= 56)

Adverse Event	Grade 1 N (%)	Grade 2 N (%)
Transient Vision Change	20 (35.7%)	2 (3.5%)
Infusion Reaction	2 (3.5%)	2 (3.5%)
Nausea	2 (3.5%)	1 (1.7%)
Vomiting	1 (1.7%)	0
Diarrhea	1 (1.7%)	0
Dyspepsia	0	1 (1.7%)

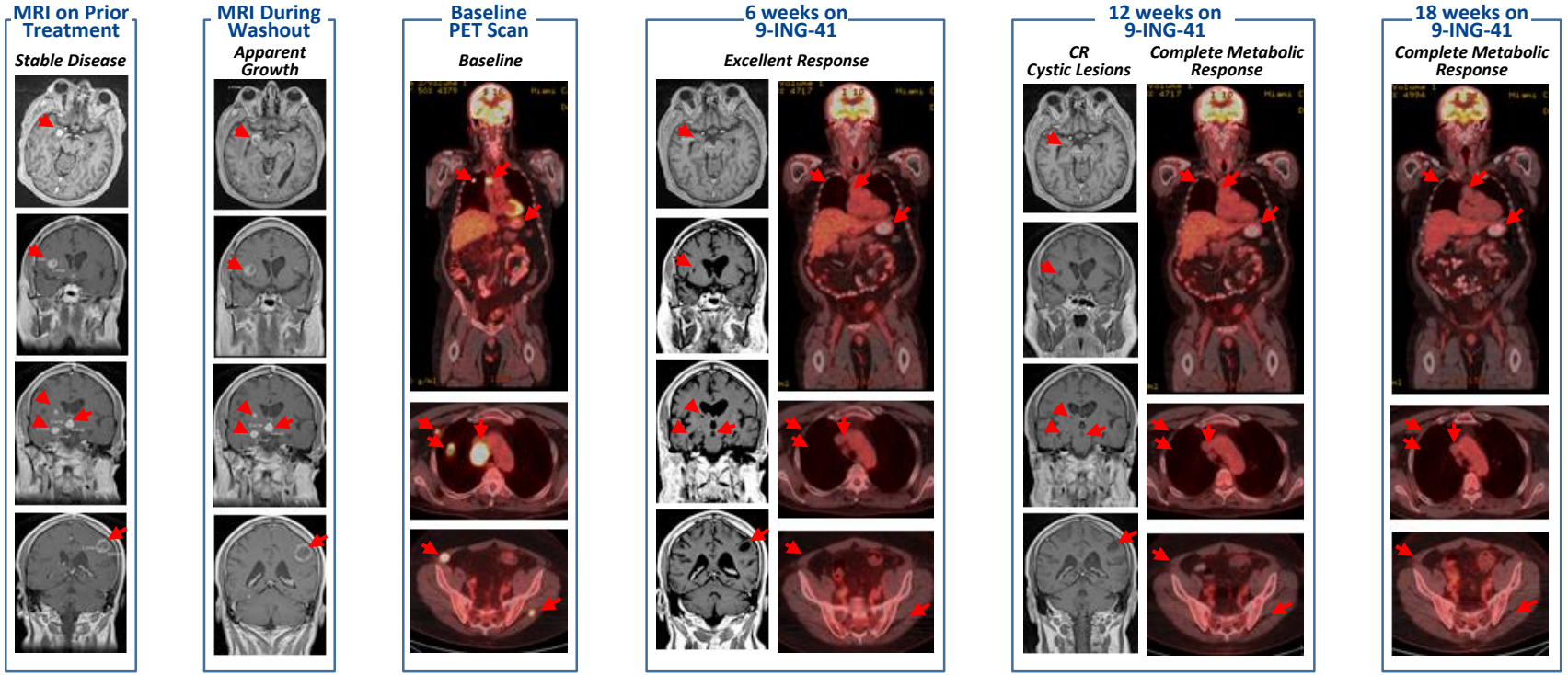
- No Grade 3 or Grade 4 attributable SAEs

9-ING-41 attributable adverse events combinations (interim)

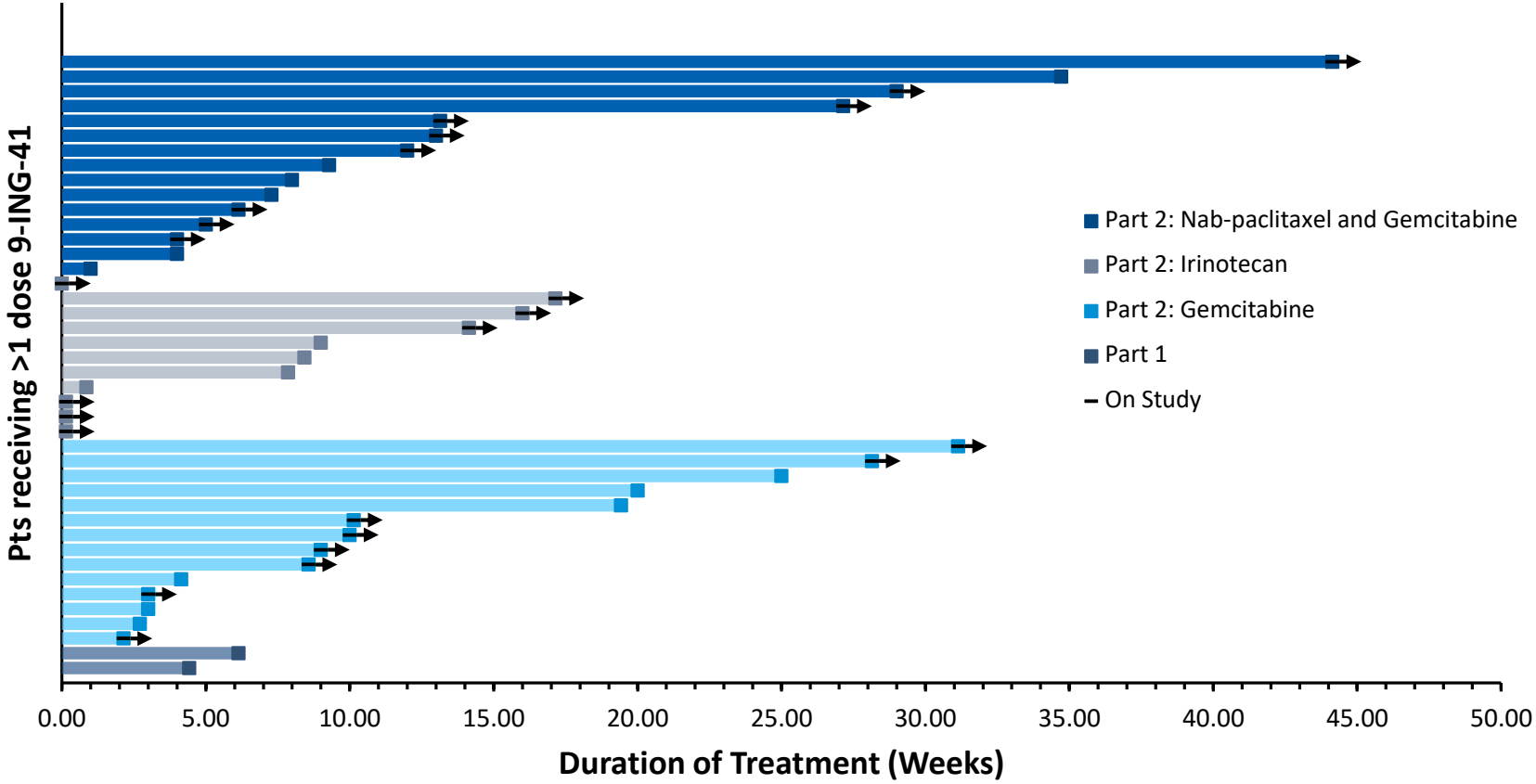
- **No Grade 3 or Grade 4 9-ING-41 attributable SAEs**
- No new or additional AEs
- No evidence of increased 9-ING-41 toxicity with chemotherapy
- **Potential RP2D 15 mg/kg**

9-ING-41 complete response in a patient with advanced melanoma

- 55 yo male with BRAF V600K mutated metastatic melanoma
- Refractory to immune checkpoint and BRAF/MEK inhibitors



Patients with pancreatic cancer in phase I (N=42)



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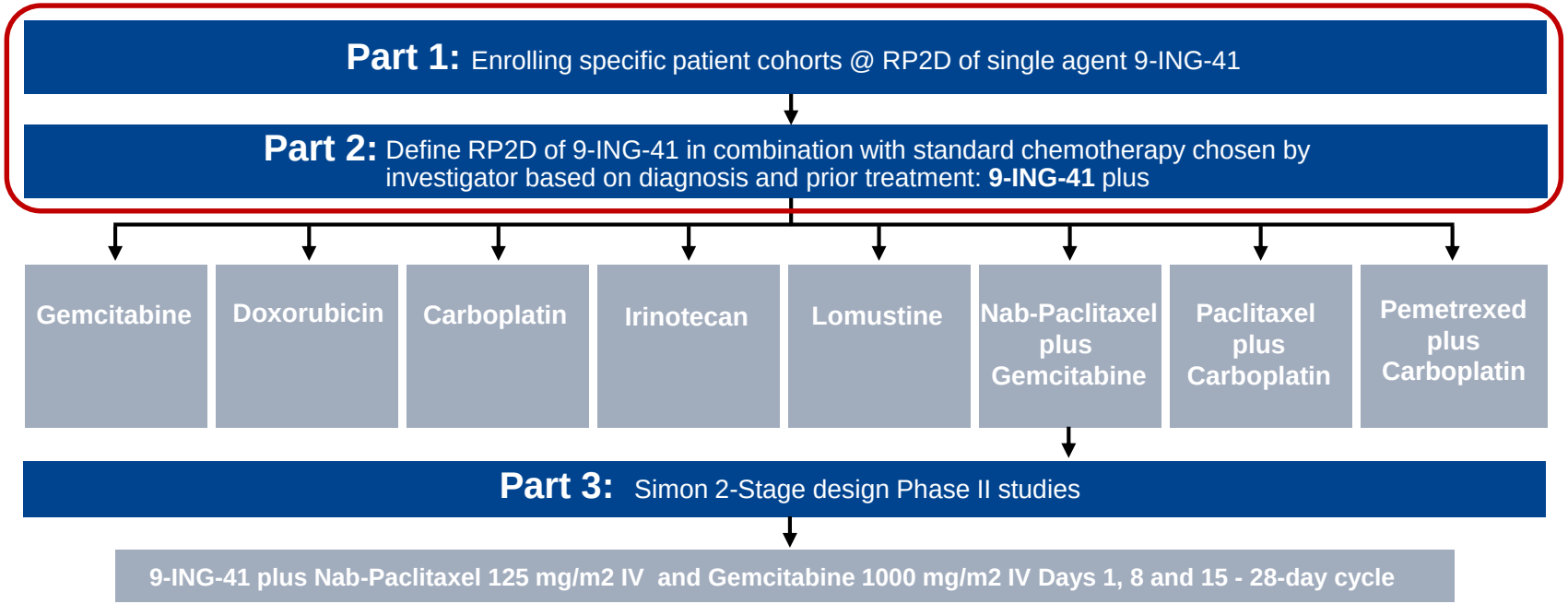

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Conclusions

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- Antitumor activity as monotherapy: ongoing CR in a patient with refractory BRAF-mutated melanoma
- Disease stability in combination with chemotherapy in patients previously exposed to the same chemotherapy agent(s)
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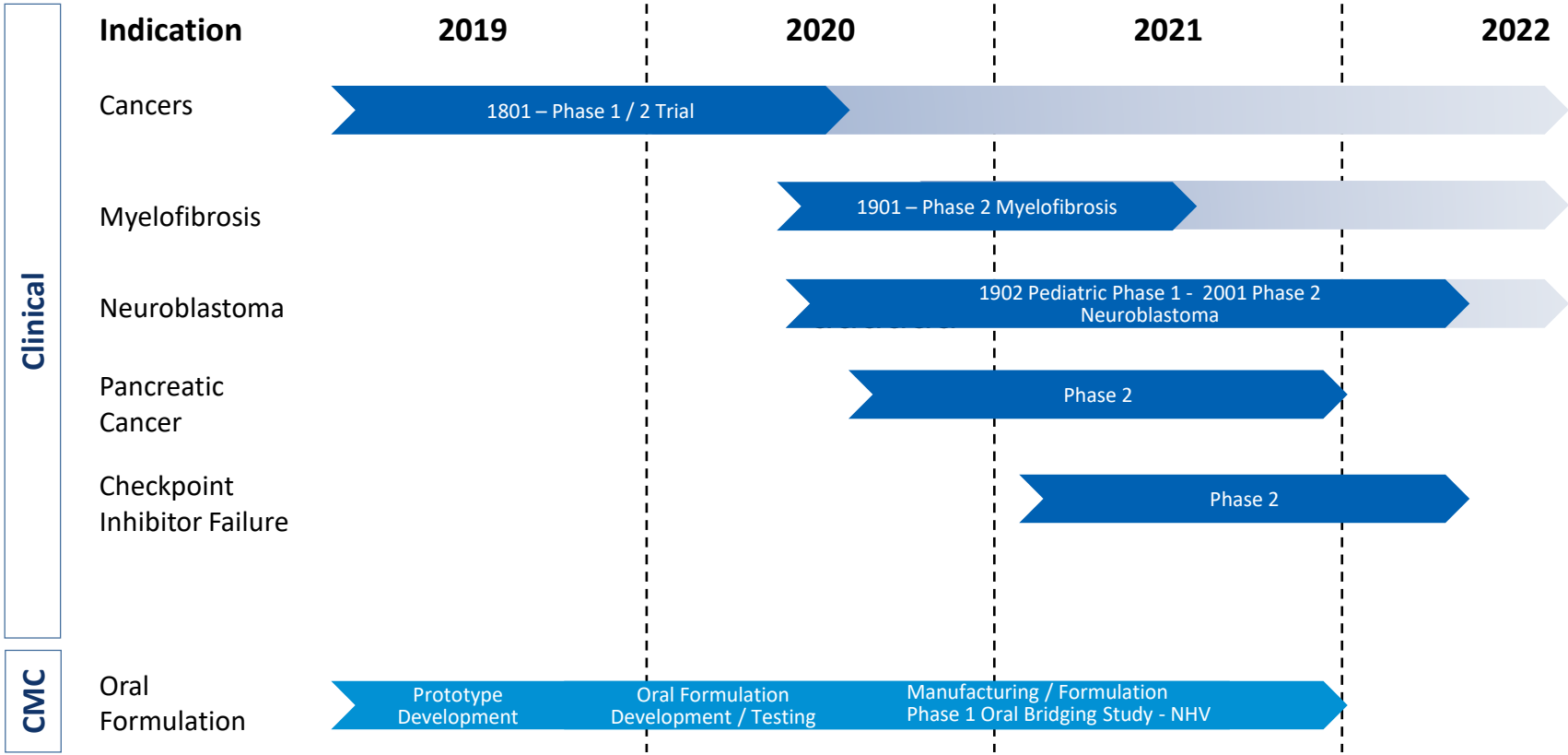
9-ING-41 development



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