Dazostinag (TAK-676) alone and in combination with pembrolizumab in patients with advanced/metastatic solid tumors: Data from phase 1 dose escalation

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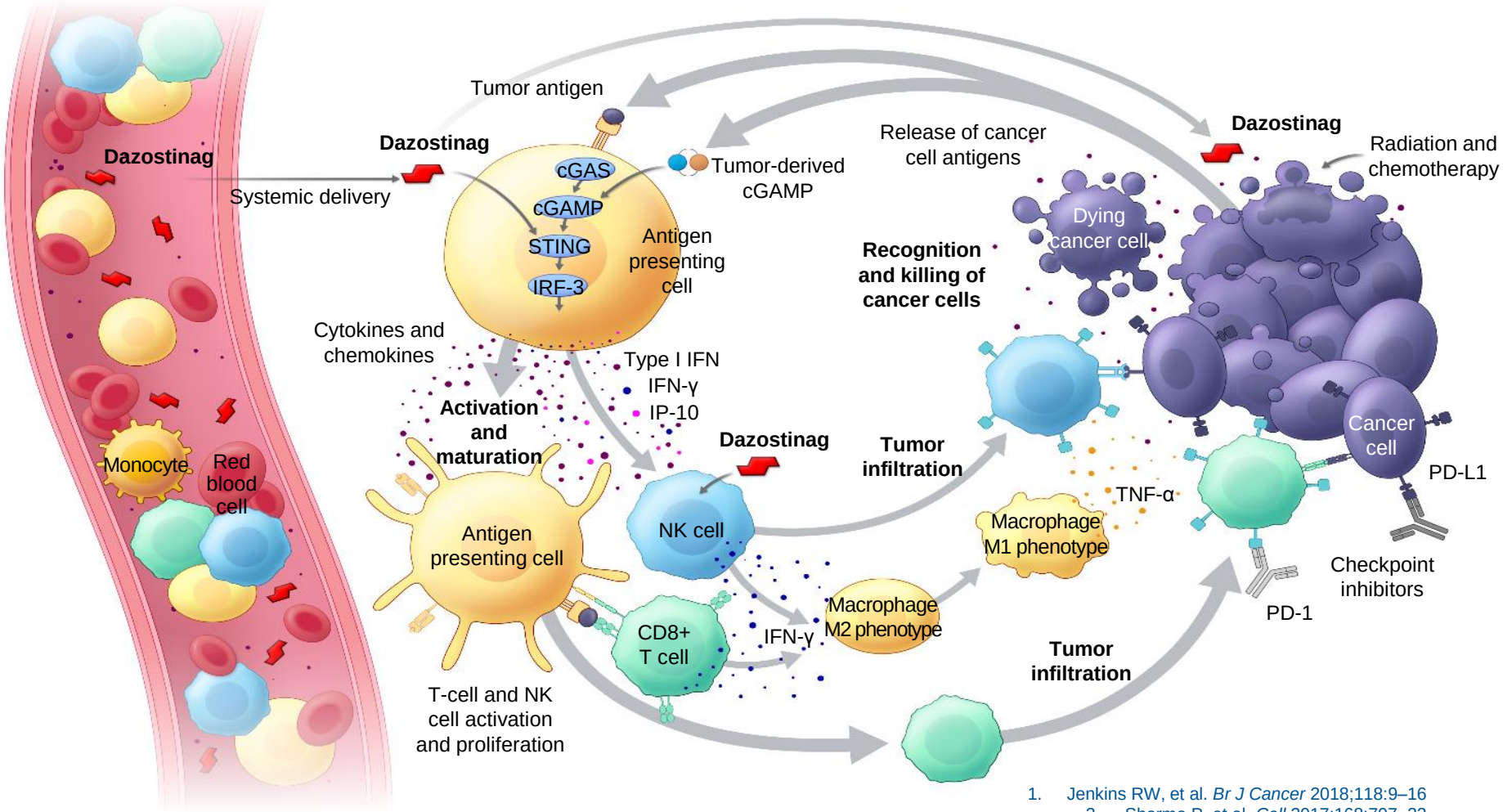
Dazostinag is a novel IV STING agonist that induces type I interferon and enhances anti-tumor immunity

- Immunotherapy resistance can in part be attributed to reduced interferon signaling[1–3]
- Dazostinag demonstrated anti-tumor activity as a single agent and in combination with CPIs in preclinical models[4,5]

Here we report dose escalation data from iintune-1, a phase 1/2 study of dazostinag alone and in combination with pembrolizumab in patients with advanced/metastatic solid tumors (NCT04420884)

Dazostinag mechanism of action

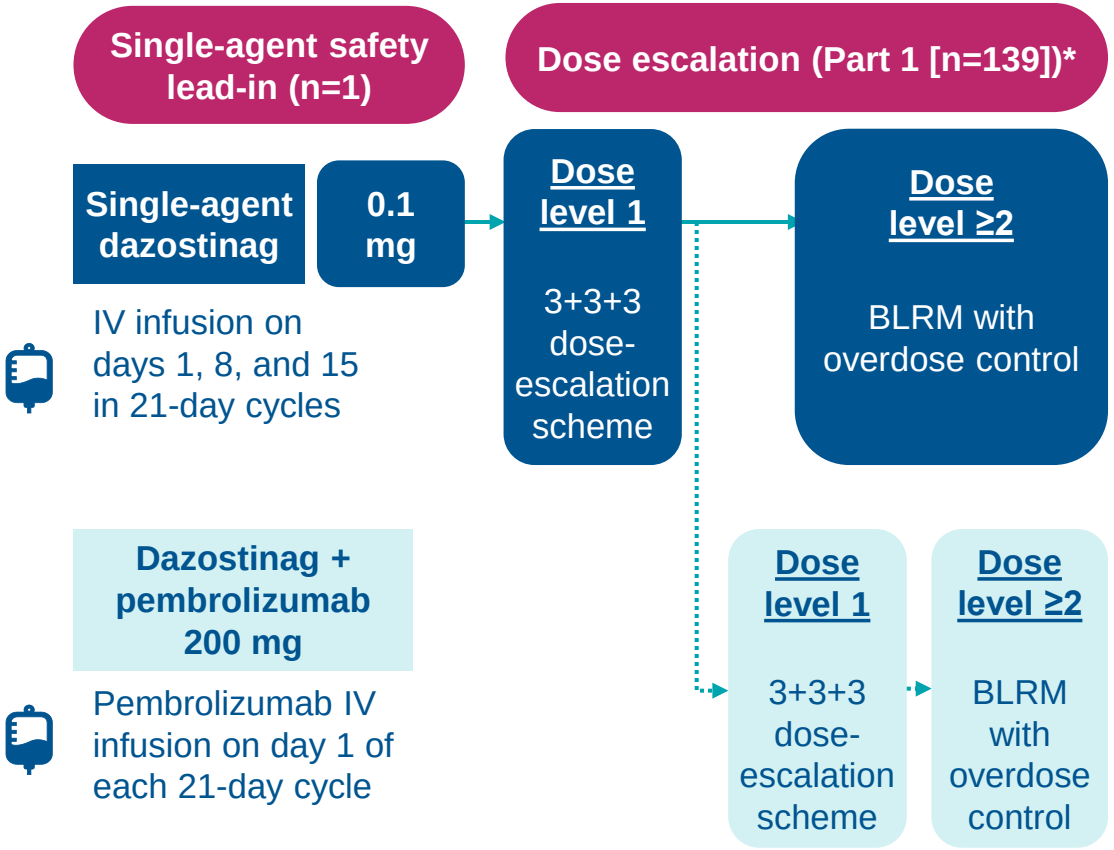


cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; cGAS, cyclic GMP-AMP synthase; CPI, checkpoint inhibitor; IFN, interferon; IP-10, interferon gamma-induced protein 10; IRF-3, interferon regulatory factor 3; IV, intravenous; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; STING, stimulator of interferon genes; TNF, tumor necrosis factor.

1. Jenkins RW, et al. *Br J Cancer* 2018;118:9–16
2. Sharma P, et al. *Cell* 2017;168:707–23
3. Liu D, et al. *Am J Clin Dermatol* 2019;20:41–54
4. Falchook GS, et al. *J Clin Oncol* 2021;39(15 suppl): Abstract#TPS2670
5. Appleman VA, et al. *Cancer Res* 2022; 82:3448

Dazostinag alone and in combination with pembrolizumab in patients with advanced/metastatic solid tumors – study schema and patient characteristics

Dose escalation schema (iintune-1)



Key patient demographics and disease characteristics

(data cutoff: 22 July 2024)

	Single-agent dazostinag 0.1–14 mg* n=50	Dazostinag with pembrolizumab 0.2–14 mg* n=90	Overall N=140
Median age, years (range)	60.5 (21–81)	62.0 (27–84)	61.5 (21–84)
Male, n (%)	21 (42.0)	53 (58.9)	74 (52.9)
ECOG PS, n (%)			
0	23 (46.0)	48 (53.3)	71 (50.7)
1	27 (54.0)	41 (45.6)	68 (48.6)
Missing	0	1 (1.1)	1 (0.7)
Median lines of prior therapy at study entry, n (range)	3.0 (0–10)	3.0 (0–10)	3.0 (0–10)
Prior checkpoint inhibitor, n (%)	23 (46.0)	35 (38.9)	58 (41.4)
Cancer type at initial diagnosis,† n (%)			
Colon/colorectal cancer	9 (18.0)	15 (16.7)	24 (17.1)
Pancreatic	4 (8.0)	7 (7.8)	11 (7.9)
Head & Neck	3 (6.0)	4 (4.4)	7 (5.0)
Other‡	13 (26.0)	22 (24.4)	35 (25.0)

*0.1 mg (single-agent only), 0.2 mg, 0.4 mg, 0.8 mg, 1.2 mg, 1.6 mg, 2.0 mg, 2.5 mg, 3.5 mg, 5.0 mg, 7.0 mg, 9.0 mg, 10.5 mg, and 14.0 mg; †>5 patients overall; ‡cholangiocarcinoma (n=3); basal cell carcinoma, squamous cell carcinoma of the parotid gland, parotid gland cancer with metastasis, bile duct carcinoma, alveolar saft part sarcoma, appendiceal mucinous adenocarcinoma, appendix carcinoma, salivary gland neoplasm, anal neuroendocrine carcinoma, malignant neoplasm of Ampulla de Vater, high-grade myxofibrosarcoma, sebaceous carcinoma, thymoma, intrahepatic cholangiocarcinoma, urachal adenocarcinoma, gastroesophageal junction cancer, leiomyosarcoma, left thigh undifferentiated pleomorphic sarcoma, low-grade mucinous carcinoma peritonei, neuroendocrine carcinoma of unknown primary, malignant neoplasm of renal pelvis, small-cell neuroendocrine carcinoma of the cervix, high-grade neuroendocrine carcinoma of the rectum, peritoneal mesothelioma, metastatic salivary gland carcinoma, squamous cell carcinoma of the penis, adenocarcinoma of the duodenum, metastatic neuroendocrine tumor of the sinus, undifferentiated sinonasal carcinoma, adenoid cystic carcinoma from salivary gland of head and neck, nasopharyngeal caner and duodenal cancer (n=1 each).

BLRM, Bayesian logistic regression model; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous.

Dazostinag demonstrated a manageable safety profile and linear PK across all dose levels, alone and with pembrolizumab

n (%), unless otherwise stated (data cut-off date: 22 July 2024)	Single-agent dazostinag 0.1–14 mg n=50	Dazostinag with pembrolizumab 0.1–14 mg n=90	Overall N=140
Number of treated cycles, median (range)	3.0 (1–23)	3.0 (1–42)	3.0 (1–42)
Number of doses, median (range)	8.0 (1–65)	8.5 (1–112)	8.0 (1–112)
$T_{½}$ (hour), mean (standard deviation)	1.4 (0.71)	1.5 (0.78)	1.4 (0.75)
TEAEs	50 (100)	90 (100)	140 (100)
Dazostinag-related TEAEs	37 (74.0)	75 (83.3)	112 (80.0)
Most common TEAEs, >25 patients overall			
Fatigue	16 (32.0)	33 (36.0)	49 (35.0)
Pyrexia	13 (26.0)	15 (16.7)	28 (20.0)
Chills	14 (28.0)	13 (14.4)	27 (19.3)
Nausea	19 (38.0)	31 (34.4)	50 (35.7)
Diarrhoea	11 (22.0)	19 (21.1)	30 (21.4)
Vomiting	10 (20.0)	19 (21.1)	29 (20.7)
Decreased appetite	14 (28.0)	20 (22.2)	34 (24.3)
Headache	13 (26.0)	21 (23.3)	34 (24.3)
Cytokine Release Syndrome (CRS)	12 (24.0)	27 (30.0)	39 (27.9)
Grade ≥3 TEAEs	20 (40.0)	44 (48.9)	64 (45.7)
Grade ≥3 dazostinag-related TEAEs	3 (6.0)	7 (7.8)	10 (7.1)
Serious TEAEs	18 (36.0)	41 (45.6)	59 (42.1)
Serious dazostinag-related TEAEs	3 (6.0)	10 (11.1)	13 (9.3)
On-study deaths (unrelated to dazostinag)	2 (4.0)	6 (6.7)	8 (5.7)
TEAEs leading to dazostinag dose discontinuation	5 (10.0)	5 (5.6)	10 (7.1)
TEAEs leading to dazostinag dose modification	20 (40.0)	39 (43.3)	59 (42.1)

- Dazostinag demonstrated dose-proportional PK from 0.1–14 mg in both single-agent and combination arms, with no accumulation between consecutive doses
- No MTD was observed up to 14 mg; no added toxicity was seen with the combination
- One DLT (GI bleeding) was reported in a patient who received dazostinag 9 mg with pembrolizumab
- CRS was reported in 28% of patients; all events were grade 1–2, manageable, and mostly resolved within 24 hours
- Discontinuations from study occurred mostly from disease progression (63%) and were due to TEAEs in 5.7% of patients, with no frequent cause

DLT, dose-limiting toxicity; GI, gastrointestinal; MTD, maximum tolerated dose; PK, pharmacokinetics; $T_{½}$, elimination half-life; TEAE, treatment emergent adverse event.

Clinical responses were observed with dazostinag in combination with pembrolizumab across multiple dose levels

Best overall response (response-evaluable population)
(data cutoff: 22 July 2024)

2 cPR

Patient with adenoid cystic carcinoma (ACC)

ACC of the breast and lung metastasis
(no prior anti-PD-L1)

Dazostinag 14 mg with pembrolizumab

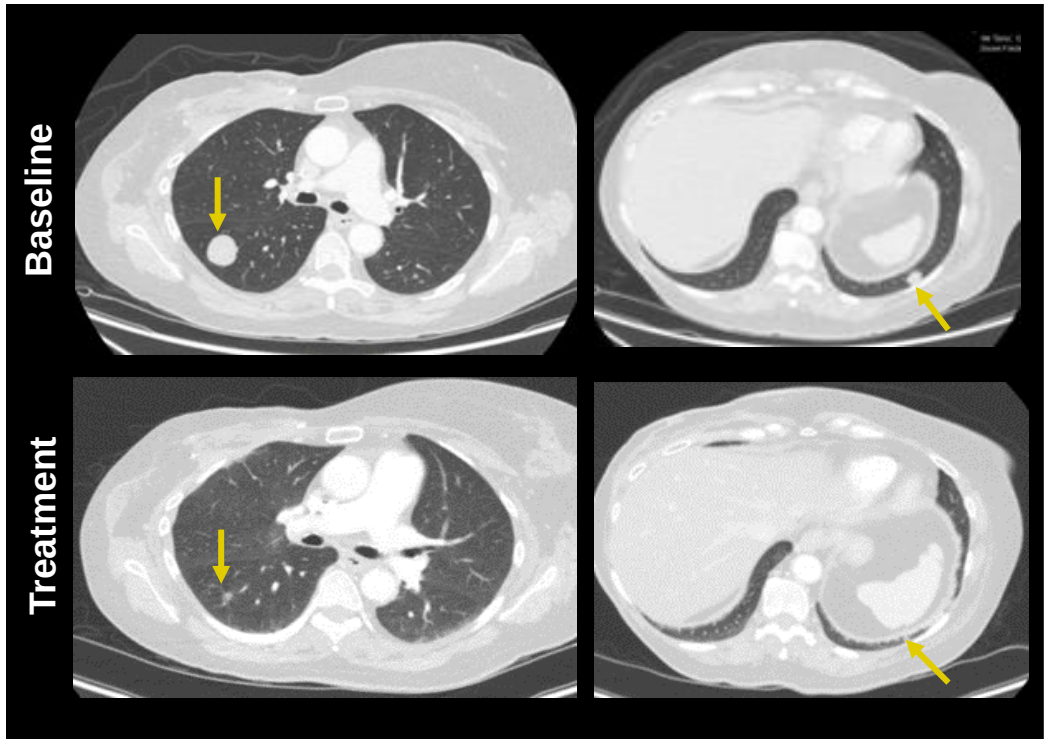
-60% (cPR at C9), remains on treatment

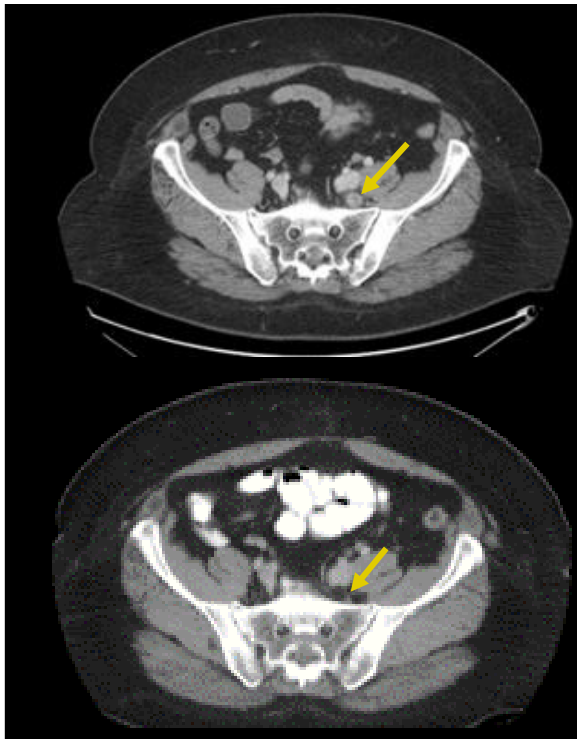
Patient with small-cell neuroendocrine (SCN) of the cervix

Cervical SCN, with left pelvic node
(prior atezolizumab)

Dazostinag 5 mg with pembrolizumab

-60% (cPR at C6), PD at C15

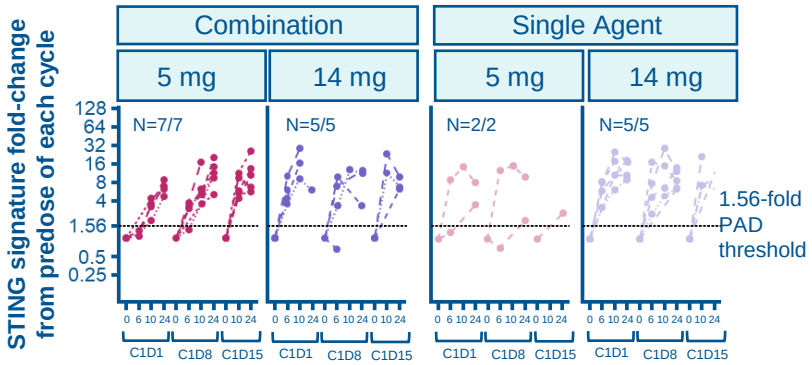


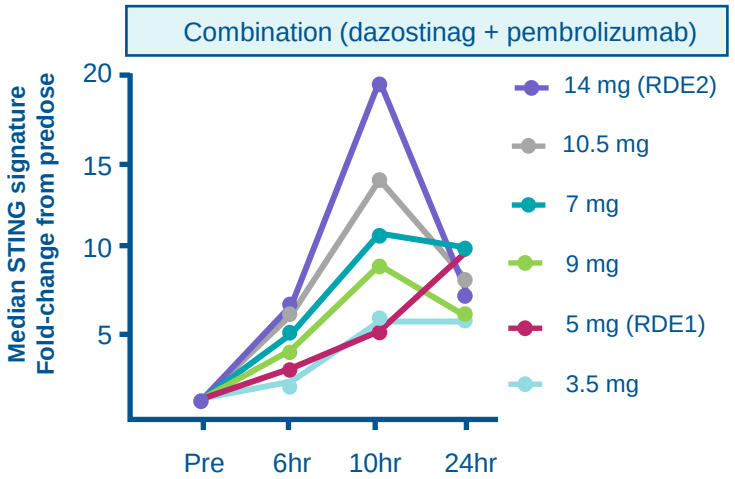


C, cycle; c, confirmed; CR, complete response; NA, not assessed; NE, not evaluated; PD, progressive disease; PR, partial response; SD, stable disease.

Dazostinag induces robust pharmacodynamic responses in the periphery and tumor microenvironment

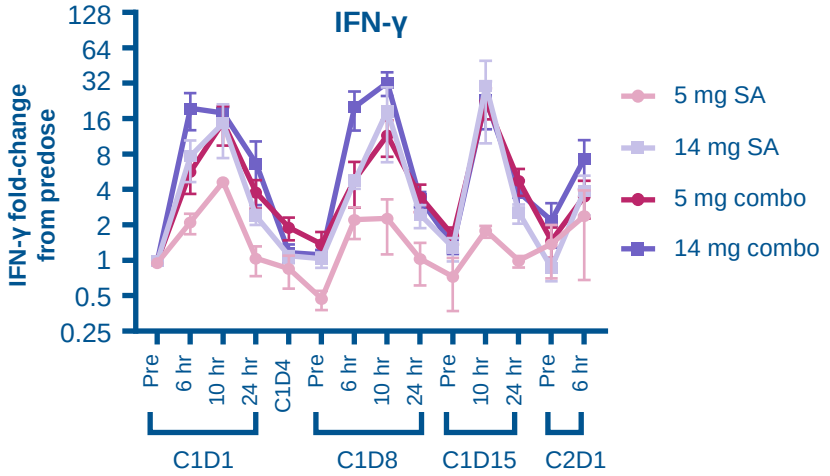
Increased fold induction of STING gene signature (peripheral blood cells)*

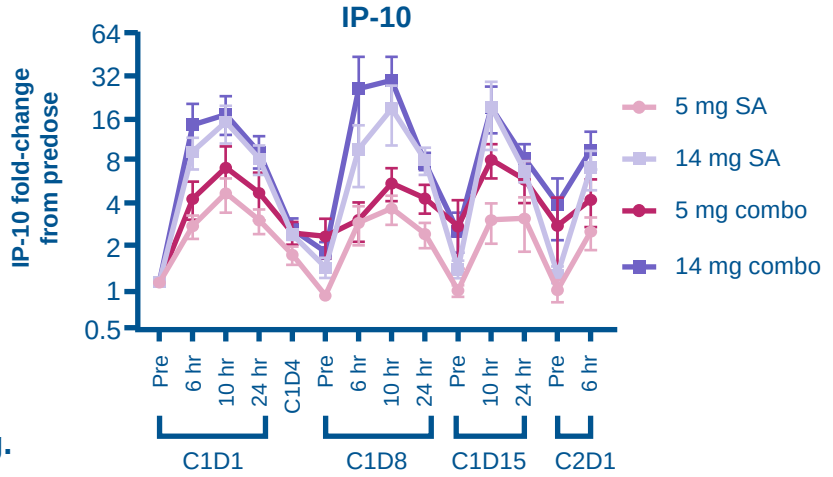




***RDE 1 = 5 mg dazostinag; RDE 2 = 14 mg dazostinag.**

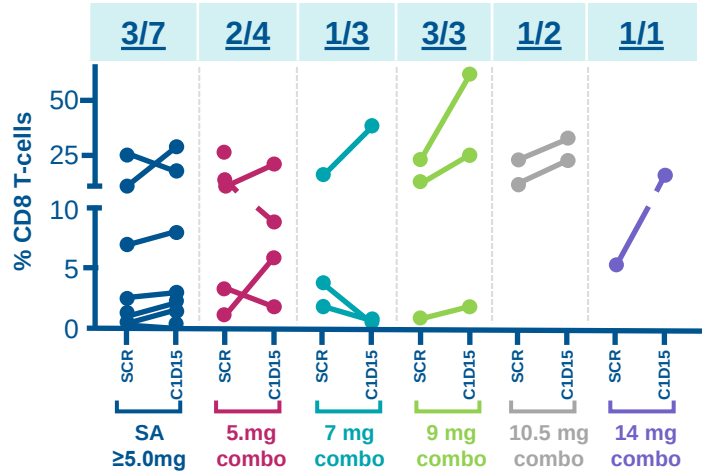
Dose-dependent increased production of IFN-γ and IP-10 cytokines (plasma)*



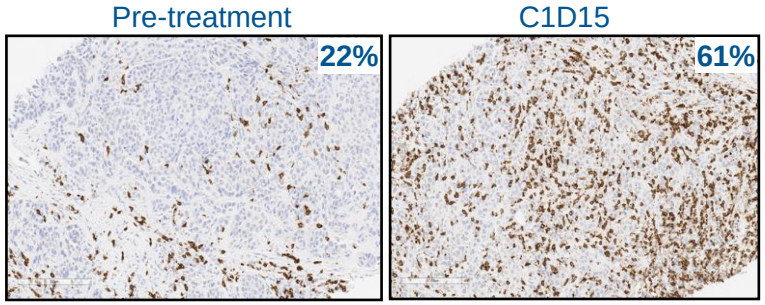


Increased levels of CD8⁺ T-cells in tumors (biopsies)

11 of 20 patients with ≥ 1.75-fold increase in CD8⁺ T-cells from baseline



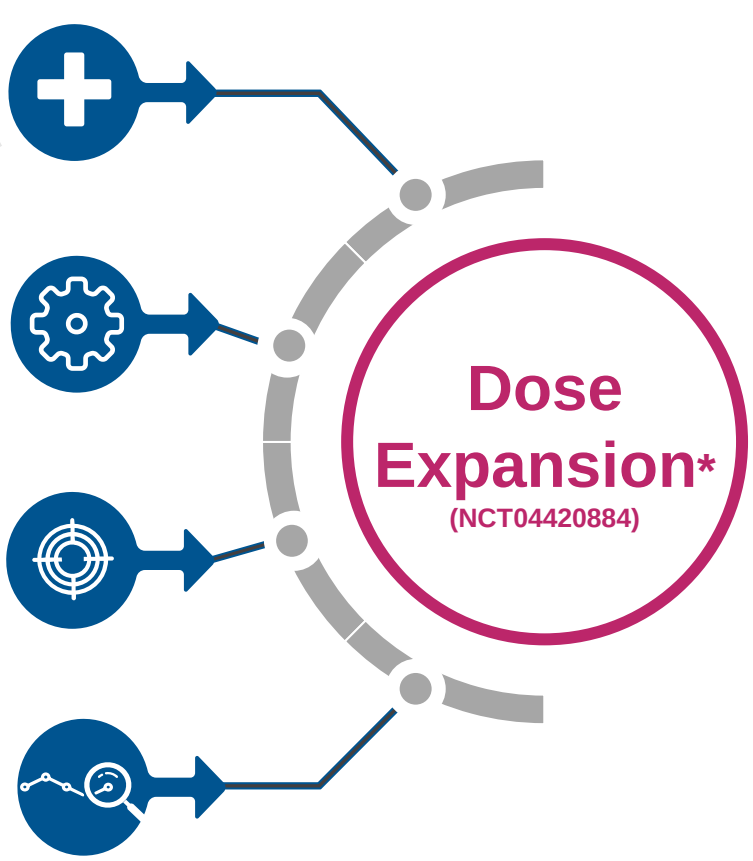
CD8⁺ T-cells in a patient with TNBC (dazostinag 9 mg + pembrolizumab)



hr, hour; PAD, pharmacologically active dose; RDE, recommended dose for expansion; SA, single agent; SCR, screening; TNBC, triple-negative breast cancer.

Conclusions

- Dazostinag IV (alone or with pembrolizumab) had a manageable safety profile across all dose levels
- Translational data demonstrates peripheral STING signature activation and cytokine induction, and CD8+ T-cell recruitment to the tumor microenvironment
- Encouraging clinical activity was seen in combination with pembrolizumab for multiple dose levels and tumor types
- The recommended dose for expansion was determined as 5 mg, with 14 mg identified as the second dose for dose optimization



- Patients with recurrent/metastatic **SCCHN** (1L) and a PD-L1 CPS ≥1 (Part 2A)
- Patients with recurrent/metastatic **SCCHN** (1L) and any CPS receiving dazostinag + pembrolizumab + chemotherapy† (Part 2B)
- Patients with previously treated MSI-H/dMMR metastatic **CRC** (≥3L) (Part 3A)
- Patients with MSS/pMMR **CRC** (3L) (Part 3B)

*Dose expansion phase is open and ongoing. Response-evaluable patients; all expansion cohorts will include an early futility analysis performed separately.
†Carboplatin (target area under the curve of 5 mg/mL/minute) or cisplatin (100 mg/m^2), and 5-fluorouracil (1000 mg/m^2/day for 4 days) every 3 weeks for a maximum of 6 cycles.
1L, first-line; 3L, third-line; CPS, combined positive score; CRC, colorectal cancer; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; MSS/pMMR, microsatellite stable/mismatch repair proficient; SCCHN, squamous cell carcinoma of the head and neck.