Phase 1b study of dazostinag plus pembrolizumab after hypofractionated radiotherapy in patients with non-small-cell lung cancer, triple-negative breast cancer, or head and neck squamous-cell carcinoma

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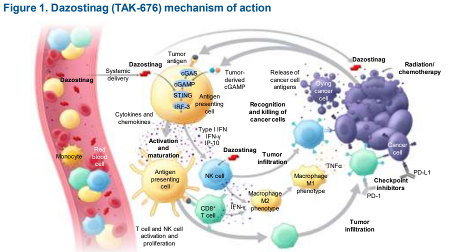
Benjamin T. Cooper,[1] Daniel Olson,[2] Wade T. Iams,[3] David B. Page,[4] Yuan Yuan,[5] Naamit K. Gerber,[1] Jason J. Luke,[6] John Gibbs,[7] Richard C. Gregory,[7] Kwok-Kin Wong,[8] Jiehui Deng,[8] Samanthi A. Perera,[7] Kai Ding,[7] Emily R. Roberts,[7] Allison Berger,[7] Camilla L. Christensen Ross,[7] Erica Xin Tong,[7] Angel E. Maldonado López,[7] Vicky A. Appleman,[7] E. Jane Leonard,[7] Alex Parent,[7] Yu-Chung Huang,[7] Camden Bay,[7] Cong Li,[7] Neil B. Lineberry,[7] Jeffrey Raizer,[7] Steven J. Chmura[2]

[1]NYU Langone School of Medicine, New York, NY, USA; [2]University of Chicago, Chicago, IL, USA; [3]Vanderbilt University, Nashville, TN, USA; [4]Robert W. Franz Cancer Center, Providence Cancer Institute, Portland, OR, USA; [5]Cedars Sinai Medical Center, Los Angeles, CA, USA; [6]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA, USA; [7]Takeda Development Center Americas, Inc. (TDCA), Lexington, MA, USA; [8]Laura & Issac Perlmutter Cancer Center, NYU Langone Health, New York, NY, USA

Background

- Despite checkpoint inhibitors (CPIs) having helped revolutionize cancer treatment, primary and secondary resistance remains a challenge[1,2]
- Stimulating innate immune cells to develop a proinflammatory tumor environment that activates Type I interferon (IFN-I) signaling may help overcome CPI resistance[2]
- The cyclic GMP-AMP Synthase (cGAS)–STimulator of INterferon Genes (STING) pathway is an important modulator of the innate immune system via induction of IFN-I and other inflammatory cytokines[3,4]
- Radiotherapy has immune-modulating effects resulting from the generation of cytosolic DNA and tumor antigens associated with radiation-induced cell death[5]
  - Combining fractionated radiation with immunotherapy has the potential to simultaneously kill cancer cells and stimulate anti-tumor immunogenicity; however clinical studies investigating the combined effect of radiotherapy and CPIs in solid tumors show varying degrees of anti-tumor activity (ORR ranging from 13.2–45.9%),[6–9] with optimal agents for combination, treatment sequence, drug and radiation doses still to be determined[10]
  - Cytosolic DNA produced following tumor cell death after radiation therapy activates the STING pathway resulting in antitumor immunogenicity[11, 12]
- Dazostinag (TAK-676) is a novel, small molecule, synthetic STING agonist, optimized for systemic delivery that activates the innate immune system and mobilizes adaptive immunity (**Figure 1**)[13]
- Preclinically, hypofractionated focal radiotherapy followed by dazostinag treatment resulted in local IFN-gamma (IFN-γ) production and improved tumor control versus either treatment alone in an EMT-6 tumor-bearing mouse model[14]
- In an ongoing, first-in-human, phase 1/2 study (NCT04420884, iintune-1), dazostinag with/without pembrolizumab, was well tolerated and demonstrated preliminary anti-tumor activity[15, 16]
- We present data from a phase 1b study investigating the safety and preliminary anti-tumor activity of dazostinag combined with pembrolizumab following radiotherapy in patients with solid tumors (NCT04879849)

Figure 1. Dazostinag (TAK-676) mechanism of action



cGAMP, cyclic guanosine monophosphate-adenosine monophosphate; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; IP-10, interferon gamma induced protein 10; IRF-3, interferon regulatory transcription factor 3; NK, natural killer; PD-L1, programmed cell death-ligand 1; TNF, tumor necrosis factor.

Methods

Study design and patients

- This was an open-label, phase 1, dose-escalation study of dazostinag plus pembrolizumab following radiotherapy
- Eligible patients were adults (≥18 years) with advanced/metastatic non-small-cell lung cancer (NSCLC), triple-negative breast cancer (TNBC), or squamous-cell carcinoma of the head and neck (SCCHN) who had progressed on CPI therapy

Study treatment

- Patients received 8 Gy x 3 fractions of image-guided radiotherapy (between Days -8 and -2) followed by intravenous (IV) pembrolizumab 200 mg on Day 1 plus escalating cohorts of dazostinag IV (explorable range: 0.2–5.0 mg) on Days 1, 8, and 15 of a 21-day cycle, with ≥40h between the last radiation fraction and administration of dazostinag plus pembrolizumab (**Summary Panel**)
  - Dazostinag dose levels were selected per safety findings from the iintune-1 phase 1 study (NCT04420884), with dose escalation guided by the Bayesian Optimal Interval design

Study objectives

- The primary objective was safety and tolerability of the dazostinag and pembrolizumab combination following radiotherapy
- A key secondary objective was preliminary anti-tumor activity of combination therapy following radiation, locally (in the radiation field) and systemically (non-irradiated lesions)
- Exploratory objectives included determining whether dazostinag plus pembrolizumab following radiotherapy resulted in changes in peripheral blood and in non-irradiated tumors, consistent with activation of innate and/or adaptive immune responses

Question

What is the safety and tolerability profile of dazostinag in combination with pembrolizumab following hypofractionated radiotherapy in patients with solid tumors?

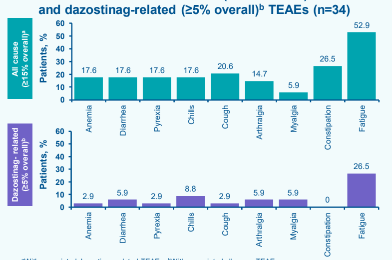
Methods

Patients with advanced/metastatic solid tumors (N=34) → **Radiation 8 Gy x3** → ≥40h[a] → **Pembrolizumab 200 mg IV (D1) + Dazostinag 0.2–5.0 mg IV (D1, 8, 15)** → Treated in 21-day cycles until disease progression, intolerance, or withdrawal of consent

[a]Radiation received between Days -8 and -2, with ≥40h between the last fraction and administration of dazostinag and pembrolizumab.

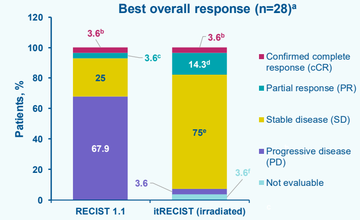
Results

Most common all cause (≥15% overall)[a] and dazostinag-related (≥5% overall)[b] TEAEs (n=34)



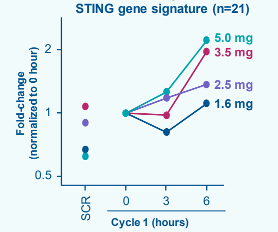
[a]With associated dazostinag-related TEAEs; [b]With associated all cause TEAEs

Best overall response (n=28)[a]



[a]Two patients did not receive dazostinag + pembrolizumab and 4 patients did not have post-treatment imaging evaluation; [b]Patient with cCR (NSCLC, 2.5 mg cohort); [c]Patient with cPR (SCCHN, 5.0 mg cohort); [d]Two patients with cPR (NSCLC, 0.2 and 3.5 mg dazostinag; respectively classified as SD and PD per RECIST), and two other patients with unconfirmed PR (TNBC, 1.6 mg cohort; SCCHN, 2.5 mg cohort; both classified as PD per RECIST) who did not have timely confirmation imaging; [e]Includes 11 patients with unconfirmed SD who did not have timely confirmation imaging; [f]Patient with TNBC (3.5 mg cohort).

Pharmacodynamics STING gene signature (n=21)



STING 19 signature score fold-change normalized to Cycle 1, 0 hour. Median fold-change across patients per dose per time point was plotted. SCR, screening.

Key take away

- **Dazostinag ≤5.0 mg combined with pembrolizumab after radiotherapy was well-tolerated across all tumor types, and showed signs of anti-tumor activity in patients with advanced/metastatic NSCLC or SCCHN who progressed on CPIs**
- **Pharmacodynamic analyses demonstrated consistent STING agonism across multiple dazostinag dose levels**

Results

Patient disposition, baseline characteristics and treatment exposures

- At data cut-off of July 3, 2024, 34 patients had been enrolled, two of whom did not receive dazostinag or pembrolizumab following radiotherapy due to adverse events (AEs)/symptomatic deterioration
- Among all 34 patients, median age was 61.0 years (range, 38–91) and 19 (55.9%) patients were male; 15 patients (44.1%) had NSCLC, 9 (26.5%) had TNBC, and 10 (29.4%) had SCCHN (**Table 1**)
- Patients had received a median of 6 prior lines of therapies (range, 3–13); prior therapies included anti-PD-(L)1 agents in 33 of 34 patients
- Overall, 32 patients received dazostinag in combination with pembrolizumab across 7 dosing cohorts (dazostinag 0.2 to 5.0 mg; **Table 1**)
  - All patients received radiotherapy; the median number of unique anatomic sites that may have been radiated was 3 (range, 3–9)
  - The locations for radiotherapy were: lung (n=14, 41.2%); lymph node (n=6, 17.6%); liver (n=5, 14.7%); chest wall and bone (n=4, 11.8% each); abdomen, adrenal gland, axilla, back, breast, kidney, right chest wall, scalp lesion, soft tissues (n=1 each), and target tumor (n=3); patients could have received treatment on multiple locations
  - Patients received a median of 6 (2–40) doses of dazostinag across a median of 2 (1–14) treatment cycles
- All patients have discontinued the study; reasons for discontinuation included progressive disease (n=24, 70.6%), AEs and symptomatic deterioration (n=4, 11.8% each), and withdrawal by patient (n=1, 2.9%)

Safety profile

- An overview of safety is provided in **Table 2**
- Overall, 33 (97.1%) patients reported treatment-emergent AEs (TEAEs, **Table 2**), none of which were considered dose-limiting toxicities; the most common TEAEs were fatigue, constipation and cough (**Summary Panel**)
- Radiation-related TEAEs were reported in 12 patients (35.3%), with fatigue being the most common (n=6, 17.6%); there were no radiation-related serious TEAEs
- Dazostinag-related TEAEs were reported in 17 (50%) patients; the most common were fatigue (n=9, 26.5%), chills (n=3, 8.8%), diarrhea, arthralgia, and myalgia (n=2, 5.9% each) (**Summary Panel**)
- Dazostinag-related grade ≥3 TEAEs were reported in 3 patients: grade 3 anemia (0.4 mg cohort), grade 3 lipase increased (0.8 mg cohort), and grade 4 thrombocytopenia (the 5.0 mg cohort)
- Three patients discontinued dazostinag due to the following TEAEs: blood bilirubin increased (0.8 mg cohort), liver function test increased (0.2 mg cohort), and muscular weakness (5.0 mg cohort); and one patient in the 0.8 mg cohort had an infusion-related reaction, which led to dazostinag infusion interruption
- Two patients (n=5.9%) reported immune-related AEs: optic nerve disorder (3.5 mg cohort) and lichenoid keratosis (2.5 mg cohort)

Table 1. Patient characteristics at baseline (safety analysis set)

n (%), unless otherwise stated	Radiation only[a] 8 Gy x3 (n=2)	Radiation + dazostinag + pembrolizumab: Dazostinag 0.2 mg (n=4)	Dazostinag 0.4 mg (n=2)	Dazostinag 0.8 mg (n=4)	Dazostinag 1.6 mg (n=3)	Dazostinag 2.5 mg (n=7)	Dazostinag 3.5 mg (n=6)	Dazostinag 5.0 mg (n=6)	Overall (N=34)
Median age, years (range)	73.0 (68–78)	49.0 (38–65)	65.5 (61–70)	56.0 (43–65)	61.0 (48–70)	67.0 (38–91)	64.0 (40–75)	54.5 (41–69)	61.0 (38–91)
Male	2 (100)	2 (50.0)	2 (100)	3 (75.0)	1 (33.3)	4 (57.1)	2 (33.3)	3 (50.0)	19 (55.9)
Race									
White	2 (100)	3 (75.0)	2 (100)	3 (75.0)	1 (33.3)	6 (85.7)	4 (66.7)	3 (50.0)	24 (70.6)
Black	0	0	0	1 (25.0)	2 (66.7)	0	1 (16.7)	1 (16.7)	5 (14.7)
Others[b]	0	1 (25.0)	0	0	0	1 (14.3)	1 (16.7)	2 (33.3)	5 (14.7)
Type of cancer									
NSCLC	1 (50.0)	2 (50.0)	1 (50.0)	1 (25.0)	2 (66.7)	3 (42.9)	3 (50.0)	2 (33.3)	15 (44.1)
TNBC	0	1 (25.0)	0	1 (25.0)	1 (33.3)	1 (14.3)	2 (33.3)	3 (50.0)	9 (26.5)
SCCHN	1 (50.0)	1 (25.0)	1 (50.0)	2 (50.0)	0	3 (42.9)	1 (16.7)	1 (16.7)	10 (29.4)
Positive mutation									
NSCLC	1 (50.0)[c, d]	2 (50.0)[d]	0	1 (25.0)[e]	2 (66.7)[d]	3 (42.9)[d, e]	3 (50.0)[d, e]	2 (33.3)[d]	14 (41.2)
TNBC[d]	0	0	0	1 (25.0)[d]	0	1 (14.3)[d]	2 (33.3)[d, f]	3 (50.0)[d]	7 (20.6)
SCCHN									
p16-positive	0	1 (25.0)	1 (50.0)	2 (50.0)	0	1 (14.3)	1 (16.7)	0	6 (17.6)
Median number of prior lines of therapy (range)	9.5 (8–11)	5.0 (3–11)	6.5 (3–10)	7.0 (4–11)	9.0 (3–10)	5.0 (3–10)	5.5 (3–10)	6.0 (3–13)	6.0 (3–13)
Prior radiotherapy	2 (100)	4 (100)	1 (50.0)	3 (75.0)	2 (66.7)	6 (85.7)	5 (83.3)	5 (83.3)	28 (82.4)

[a]Patients who received at least one dose of radiation and discontinued the study before treatment with dazostinag or pembrolizumab; [b]Includes Asian and not reported; [c]*BRAF*; [d]Other; [e]*KRAS*. [f]*BRCA2*.

Table 2. Safety summary (safety analysis set)

n (%)	Radiation only[a] 8 Gy x3 (n=2)	Radiation + dazostinag + pembrolizumab: Dazostinag 0.2 mg (n=4)	Dazostinag 0.4 mg (n=2)	Dazostinag 0.8 mg (n=4)	Dazostinag 1.6 mg (n=3)	Dazostinag 2.5 mg (n=7)	Dazostinag 3.5 mg (n=6)	Dazostinag 5.0 mg (n=6)	Overall (N=34)
Any TEAE	2 (100)	4 (100)	2 (100)	4 (100)	3 (100)	7 (100)	5 (83.3)	6 (100)	33 (97.1)
Grade ≥3 TEAEs	1 (50.0)	0	1 (50.0)	4 (100)	1 (33.3)	3 (42.9)	2 (33.3)	4 (66.7)	16 (47.1)
Serious TEAEs	1 (50.0)	0	1 (50.0)	3 (75.0)	1 (33.3)	3 (42.9)	0	3 (50.0)	12 (35.3)
TEAEs leading to dazostinag dose modification	1 (50.0)	2 (50.0)	1 (50.0)	3 (75.0)	0	4 (57.1)	3 (50.0)	4 (66.7)	18 (52.9)
TEAEs leading to dazostinag discontinuation	1 (50.0)	1 (25.0)	0	1 (25.0)	0	0	0	1 (16.7)	4 (11.8)
Deaths (on-study)	1 (50.0)	0	0	0	0	0	0	0	1 (2.9)[b]

[a]Patients who received at least one dose of radiation and discontinued the study before treatment with dazostinag or pembrolizumab.
[b]One death occurred in the 'radiation only' cohort. SAE, serious adverse event.

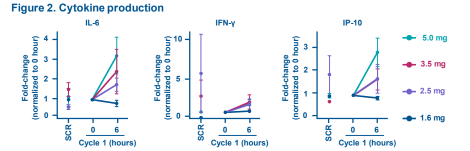
Clinical activity

- Antitumor activity, per Response Evaluation Criteria in Solid Tumors 1.1 (RECIST), was confirmed in two (7.1%) of 28 patients in the response-evaluable analysis set (**Summary Panel**):
  - One patient with grade 3 (poorly differentiated) NSCLC and who was *KRAS*-negative in the 2.5 mg cohort had a confirmed complete response
  - One patient with grade 3 (poorly differentiated) SCCHN (located in the nasopharynx) and p16-negative in the 5.0 mg cohort had a confirmed partial response (cPR)
- Using the modified intratumoral immunotherapy RECIST criteria (itRECIST) in irradiated lesions only, there were four (14.3%) patients with a PR (**Summary Panel**):
  - Two patients with NSCLC in the 0.2 and 3.5 mg cohorts who achieved cPRs
  - Two patients with unconfirmed PRs (uPR) and no timely confirmation imaging in the 1.6 mg (TNBC) and 2.5 mg (NSCLC) cohorts
- The median duration of response was 9.26 months overall (per RECIST), and not-estimable for irradiated and non-irradiated lesions (per itRECIST)

Pharmacokinetics and pharmacodynamics

- Dazostinag demonstrated dose-proportional pharmacokinetics, with maximal concentrations reached at the end of the infusion (**data not shown**)
  - PK profile was consistent with the iintune-1 study, which did not include radiotherapy[16]
- Preliminary pharmacodynamic analysis in peripheral blood showed induction of a STING gene signature (median 2.2-fold at 5 mg) (**Summary Panel**), and cytokines, including IFN-γ and IP-10 (2.3- and 2.7-fold at 5 mg, respectively) at 6 hours post-systemic treatment (**Figure 2**)
- Pre-treatment and on-treatment tumor biopsies evaluated by scRNA sequencing in one patient revealed enrichment of the IFN-γ gene set and a 2.4-fold increase in abundance of NK/NKT cells (**data not shown**)

Figure 2. Cytokine production



Cytokine expression fold-change normalized to Cycle 1, 0 hour.

Conclusions

- Overall, the combination of dazostinag with pembrolizumab following radiotherapy was well-tolerated in patients with advanced/metastatic NSCLC, TNBC, or SCCHN who had progressed on CPIs
- Flu-like symptoms, such as fatigue, chills and pyrexia, were among the most common TEAEs reported (all-cause and dazostinag-related) and are indicative of interferon pathway activation
- Despite having progressed on prior CPIs, this study reported signs of clinical activity with one patient having a complete response and one patient having a partial response per RECIST 1.1 criteria
- Pharmacodynamic biomarker induction was shown to be consistent with STING agonism across multiple dose levels
- These findings, along with those of the ongoing iintune-1 study suggest that dazostinag combined with CPIs[16] and/or with fractionated radiotherapy provided benefit for some patients with advanced/metastatic solid tumors who have progressed on CPIs. Further research is needed to understand which patients might benefit from this treatment option

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