Updated Phase 1 and preliminary Phase 2 results from a study of evalstotug (BA3071), an anti–CTLA-4 conditionally active biologic, with or without nivolumab, in advanced solid tumors

Abstract #497
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Background

- Evalstotug (BA3071) is a Conditionally Active Biologic (CAB) anti–CTLA-4 monoclonal antibody where the CDR of ipilimumab is modified to bind at tumor cell acidic pH but not at normal pH (**Figures 1, 2**). These modifications result in[1]
  - Preserved affinity and epitope with equivalent E_{max} (maximum drug effect) and EC_{50} in preclinical models.
  - Similar $T_{1/2}$ and exposure in primates and humans.
  - Reduced toxicity as monotherapy and in combination with anti–PD-(L)1 therapy, enabling higher dosing and increased antitumor activity (**Figure 3**).

Figure 1. Evalstotug is a next-generation adaptation of ipilimumab

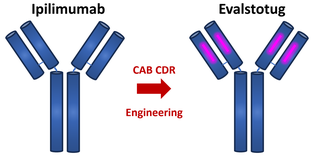
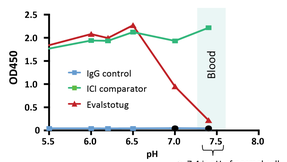


Figure 2. pH-dependent binding of CAB-anti–CTLA-4



Note: ICI comparator is an ipilimumab analog. Figure modified from Chang HW, et al. *Proc Natl Acad Sci USA*. 2021.

- CABs are not masked or caged and do not require enzymatic cleavage for activation.
- CABs reduce off-tumor immune-related adverse events, enhance host immunity, avoid tissue-mediated drug disposition, and improve PK.
- Population PK modeling suggests that a 700-mg flat dose will enable over 94% of pts to maintain C_{min} levels > EC_{50} throughout treatment, potentially driving clinical benefit (**Figure 4**).
- Phase 1 study evaluated the safety and antitumor activity of evalstotug ± anti–PD-1 therapy in pts with advanced solid tumors.
- Preliminary Phase 2 results in first-line metastatic and unresectable pts are also reported.

Figure 3. Evalstotug was associated with reduced GI toxicity in nonhuman primates and reduced proliferation of peripheral CD4+ T cells

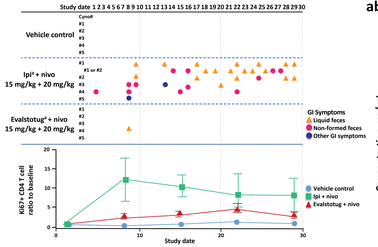
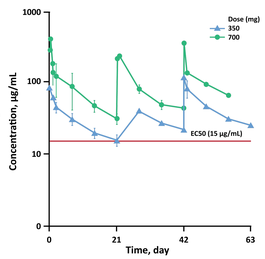


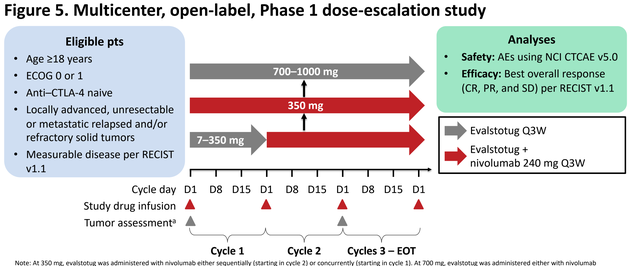
Figure 4. Mean (±SD) concentration vs time profiles in Phase 1 dose escalation cohorts: C_{min} of evalstotug ≥350 mg is above preclinically determined EC_{50}



Note: Figure modified from Chang HW, et al. *Proc Natl Acad Sci USA*, 2021.
[a]Ipilimumab analog or evalstotug 15 mg/kg (+11 mg/kg human dose) + nivolumab 20 mg/kg (≈14.6 mg/kg human dose) both administered QW for 4 weeks.

Methods

Figure 5. Multicenter, open-label, Phase 1 dose-escalation study



Note: At 350 mg, evalstotug was administered with nivolumab either sequentially (starting in cycle 2) or concurrently (starting in cycle 1). At 700 mg, evalstotug was administered either with nivolumab sequentially (starting in cycle 2) or as monotherapy. Treatment continued until confirmed disease progression per RECIST v1.1 or unacceptable toxicity.
[a]Response assessment was performed Q6W for 24 weeks, then Q12W until progression.

Results

All results are from a data cut of July 26, 2024, unless otherwise specified.

Phase 1 study population

- 23 pts were treated with evalstotug (7–1000 mg) ± nivolumab (**Table 1**).
- Mean pt age was 62 years. 15 (65%) pts were male, and 20 (87%) were Caucasian.
- 13 (57%) pts had ECOG 0; 10 (43%) had ECOG 1.
- Pts received a median of 3 prior lines of therapy; all pts had experienced failure of anti–PD-1 therapy.

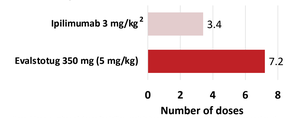
Table 1. Pt characteristics (N=23)

Tumor type, n (%)	
Melanoma	6 (26)
Gastric	5 (22)
Renal cell	4 (17)
Cervical	3 (13)
NSCLC	2 (9)
Urothelial	1 (4)
SCLC	1 (4)
Neuroendocrine parathyroid carcinoma	1 (4)

Phase 1 treatment duration

- Mean (median) duration of evalstotug 350 mg therapy in Phase 1 was 150 (127) days.
- Pts treated with evalstotug received more doses (overall mean, 7.0; 350 mg cohort mean, 7.2) compared with reported ipilimumab dosing (**Figure 6**),[2] with 3 pts still receiving treatment.

Figure 6. Mean number of evalstotug 350 mg doses vs ipilimumab



Note: Mean number of doses for ipilimumab is based on a retrospective observational study. Evalstotug 350 mg and 700 mg are dose-equivalent to ipilimumab 5 mg/kg and 10 mg/kg, respectively.

Phase 1 safety

- Most related AEs were low grade; no related grade 4 or 5 AEs (**Figure 7**).
- All grade 3 related TEAEs (n=5)

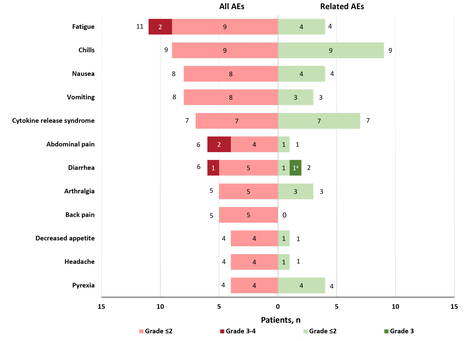
CRS-associated events (n=2; 9%)
1. New-onset atrial fibrillation (only AE to meet DLT criteria; 700 mg)[d,p]
2. Hypertension[p]

Immune-mediated (n=3; 13%)
1. Tubular interstitial nephritis (1000 mg)[d,t]
2. Endocrine (hyperglycemia/DKA; 700 mg)[p]
3. GI (lipase increase and gastritis/diarrhea)[d,p]

[d]Pt discontinued secondary to grade 3 related AEs; [t]treated in combination with anti–PD-1 therapy; [p]prophylactic tocilizumab.

- Grade 2 CRS was observed 4–6 hours post infusion in pts receiving 700 mg and 1000 mg, which was mitigated by prophylactic tocilizumab.
- No DLT were observed at 1000 mg of evalstotug monotherapy, and MTD was not reached; 1 pt receiving 1000 mg was dose reduced to 700 mg owing to grade 2 CRS.

Figure 7. Most frequent Phase 1 TEAEs of any grade (≥15% of pts)



[i]mAE that occurred with increased lipase and gastritis.

Phase 1 efficacy

- Phase 1 confirmed responses (3 of 8 pts on evalstotug 350 mg; **Figure 8**).
  - CR: Cervical carcinoma.
  - PRs: Cutaneous melanoma (with dose escalation) and gastroesophageal carcinoma.
- Phase 1 disease control rate, 52%, with 9 SD; 4 pts with prolonged responses.
  - 3 pts (2 with cutaneous melanoma, 1 with SCLC) without progression for >1 year.
  - 1 pt with uveal melanoma without progression for 9.8 months.
  - 3 pts remain on therapy (2 with cutaneous melanoma, 1 with neuroendocrine parathyroid carcinoma).

Figure 8. Phase 1 percentage change in target lesions from baseline (N=23)

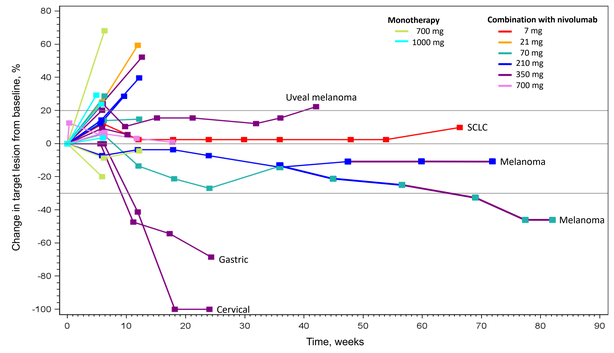
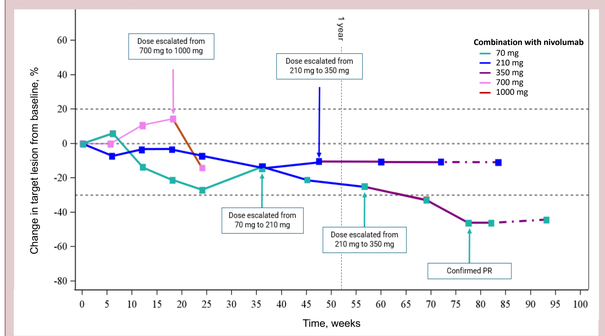
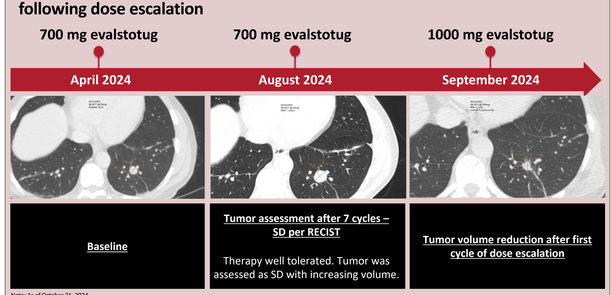


Figure 9a. Increased exposure to evalstotug regains tumor control, including 2 pts with subsequent tumor reduction to date



Note: Dashed lines indicate live data. Phase 2 data are from a live data cut as of October 31, 2024, and are subject to change.

Figure 9b. 57-year-old male with stage III cutaneous melanoma (BRAF-wt) who was enrolled after excision and adjuvant investigational anti–PD-1 and anti–LAG-3 combination therapy. Pt rapidly achieved tumor volume reduction following dose escalation



Note: As of October 31, 2024.

All first-line unresectable and/or metastatic melanoma pts show tumor reduction, and no pts have discontinued treatment due to progression to date

- N=8 (7 pts in Phase 2, 1 pt in Phase 1); all in combination with a PD-1 inhibitor (**Table 2**).
- To date, all 8 pts continue to experience tumor reduction and clinical benefit with continued follow-up.
- 2 pts treated with prior adjuvant IO experienced grade 3 imAEs that readily responded to standard treatments; pts continued to show tumor reduction without progression.
- Pts received a median of 9 doses of evalstotug + anti–PD-1 therapy.

Note: Phase 2 data are from a live data cut as of October 31, 2024, and are subject to change.

Table 2. Unresectable and/or metastatic melanoma pt characteristics and experience (N=8), with 4 out of 8 responses to date

Evalstotug dose (mg)	Age (y)	Sex	ECOG	Prior treatment	Best change in target lesion (%)	Response to evalstotug	Grade 3 imAE
350	34	M	0	None	–54%[a]	cPR	None
350	54	F	0	Adjuvant anti–PD-1 for 3 mo	–83%	cCR	None
350	63	M	0	Adjuvant anti–LAG-3/anti–PD-1 for 11 mo	–9%	SD	Colitis (resolved within 3 wks)
350	59	F	0	Adjuvant anti–PD-1 for 12 mo	–6%	SD	None
700	73	M	0	Adjuvant anti–PD-1 for 7 mo	–38%	PR (confirming)	None
700	57	F	1	Neoadjuvant anti–PD-1 for 12 mo	–8%	SD	Pneumonitis and pancreatitis (resolved within 1 mo)
70 ➢210 ➢350 (**Figure 9a**)	75	F	1	Adjuvant anti–PD-1 for 11 mo	–46%	cPR	None
700 ➢1000 (**Figures 9a, 9b**)	57	M	0	Adjuvant anti–LAG-3/anti–PD-1 for 3 mo	–14%	SD	None

Note: All pts were White.
[a]Pt with acral subungual melanoma (rare and difficult to treat) who initially experienced tumor growth with new lesions; investigator continued treatment per protocol resulting in cPR.

- Phase 2 is currently accruing for first-line melanoma (evalstotug 700 mg + pembro), first-line non-squamous NSCLC (evalstotug 350 mg + pembro ± chemotherapy), and treatment-naive stage IIB/IIIA or recurrent NSCLC (evalstotug 700 mg + pembro + chemotherapy).

Conclusions

- **All (8/8) metastatic and unresectable melanoma pts achieved tumor reduction with evalstotug + PD-1 antibody with acceptable tolerability; no discontinuations due to progression observed to date.**
- **Intrapatient evalstotug dose escalation regained tumor control with acceptable safety.**
- **Low incidence and severity of imAEs, consistent with evalstotug's tumor selectivity.**
- **Final dose optimization is underway; Phase 3 registrational melanoma trial planned for 2025.**

Disclosures

OH: Consulting and advisory boards for Alkermes, Amgen, Bactonix, BeiGene, BioAtla, Bristol Myers Squibb, Eisai, Georgiamune, GigaGen, Grit Bio, GSK, Idera, Immunocore, Incyte, Instil Bio, IO Biotech, Iovance, Janssen, KSQ, Merck, Moderna, Novartis, Obsidian, Pfizer, Regeneron, Roche Genentech, Sanofi, Seattle Genetics, Tempus, Vial, and Zelluna; speakers bureau for Bristol Myers Squibb, Immunocore, Novartis, Pfizer, and Regeneron; stock in Bactonix; contracted research (institution) from Aduro, Akeso, Amgen, Arcus, BioAtla, Bristol Myers Squibb, CytomX, Exelixis, GSK, Idera, Immunocore, Incyte, Iovance, Merck, Merck Serono, Moderna, NextCure, Novartis, Pfizer, Regeneron, Roche Genentech, Seattle Genetics, Torque, and Zelluna.

Abbreviations

AE, adverse event; C, cycle; CAB, conditionally active biologic; cCR, confirmed complete response; CD, cluster of differentiation; CDR, complementarity determining region; C_{min}, minimum concentration; cPR, confirmed partial response; CR, complete response; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte associated protein 4; Cyno, cynomolgus macaque; D, day; DKA, diabetic ketoacidosis; DLT, dose-limiting toxicity; EC_{50}, estimated concentration to achieve 50% maximum tumor growth inhibition; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; GI, gastrointestinal; ICI, immune checkpoint inhibitor; IgG, immunoglobulin G; imAE, immune-mediated adverse event; IO, immuno-oncology; ipi, ipilimumab; Ki67, antigen Kiel 67; LAG-3, lymphocyte-activation gene 3; MTD, maximum tolerated dose; NCI, National Cancer Institute; nivo, nivolumab; NSCLC, non–small cell lung cancer; OD, optical density; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; pembro, pembrolizumab; PK, pharmacokinetics; PR, partial response; pt, patient; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; QW, every week; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer; SD, stable disease; T1/2, half-life; TEAE, treatment-emergent adverse event; v, version; wt, wild-type.

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