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Updated Results from a Study of Evalstotug (BA3071), an Anti–CTLA-4 Conditionally Active Biologic

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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

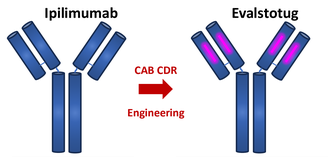
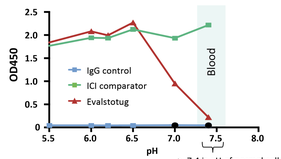


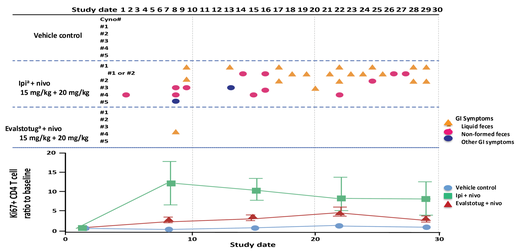
Figure 2. pH-dependent binding of CAB-anti–CTLA-4



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

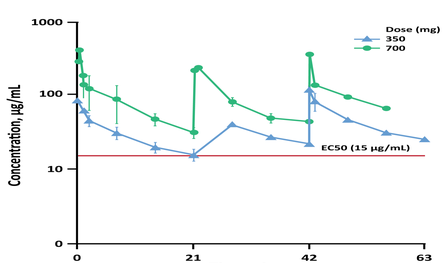
- CABs are not masked or caged and do not require enzymatic cleavage for activation.
- CABs reduce off-tumor immune-related adverse events, enhance host immunity, avoid tissue-mediated drug disposition, and improve PK.
- Population PK modeling suggests that a 700-mg flat dose will enable over 94% of 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



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.

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}



Phase 1 Experience

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.

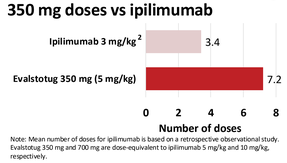
Table 1. Pt characteristics (N=23)

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 5**),[2] with 3 pts still receiving treatment.

Figure 5. 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 6**).
- 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]

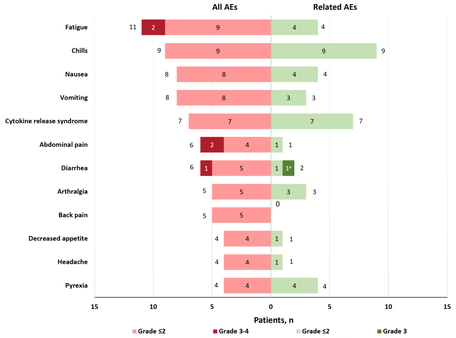
Immune-mediated (n=3; 13%)

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



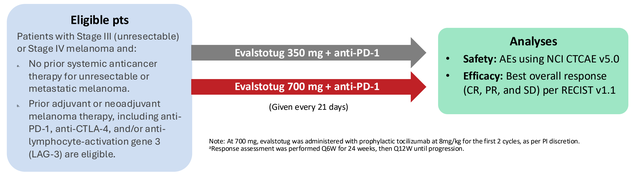
[i]mAE that occurred with increased lipase and gastritis.

Phase 1 Efficacy

- Phase 1 confirmed responses (3 of 8 pts on evalstotug 350 mg;).
  - 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).

Phase 2 – 1L Melanoma

Figure 7. Phase 2 – Cohort C1 – Melanoma study design



Note: At 700 mg, evalstotug was administered with prophylactic tocilizumab at 8mg/kg for the first 2 cycles, as per PI discretion.
[a]Response assessment was performed Q8W for 24 weeks, then Q12W until progression.

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**).
- 88% had previously received prior anti-PD1 adjuvant treatment.

Efficacy

- **Confirmed ORR of 50%** (4/8 patients)
- To date, all patients continue to experience tumor reduction and clinical benefit with continued follow-up.

Safety

- No >G1 CRS
- 2 pts with prior PD-1 adjuvant therapy experienced G3 imAEs (colitis, n=1; pneumonitis/pancreatitis, n=1) that readily responded to standard treatments; both pts continued to experience tumor reduction without progression.

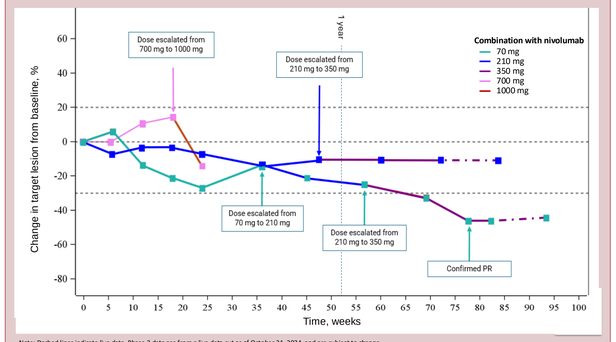
Note: Phase 2 data are from a live data cut as of October 31, 2024, and are subject to change.

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
350	34	M	0	None	–54%[a]	cPR
350	54	F	0	Adjuvant anti–PD-1 for 3 mo	–83%	cCR
350	63	M	0	Adjuvant anti–LAG-3/anti–PD-1 for 11 mo	–9%	SD
350	59	F	0	Adjuvant anti–PD-1 for 12 mo	–6%	SD
700	73	M	0	Adjuvant anti–PD-1 for 7 mo	–38%	cPR
700	57	F	1	Neoadjuvant anti–PD-1 for 12 mo	–8%	SD
70 ➢210 ➢350 (**Figure 8a**)	75	F	1	Adjuvant anti–PD-1 for 11 mo	–46%	cPR
700 ➢1000 (**Figures 8a, 8b**)	57	M	0	Adjuvant anti–LAG-3/anti–PD-1 for 3 mo	–14%	SD

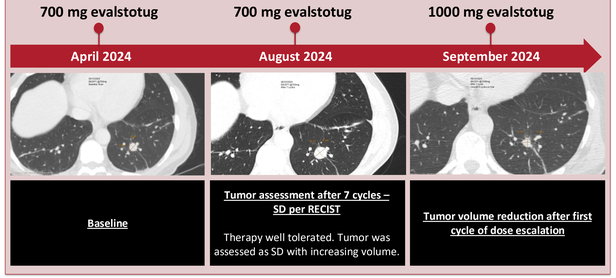
Note: All pts were White.
[a]Pt with acral subungual melanoma (rare and difficult to treat) who initially experienced tumor growth with new lesions; investigator continued treatment per protocol resulting in cPR.

Figure 8a. 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 8b. 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.

Conclusions

- **~ 5 or 10 mg/kg of evalstotug + PD-1 antibody reasonably well-tolerated for extended treatment intervals.**
- **No discontinuations due to progression observed to date.**
- **43% confirmed ORR (1 CR and 2PRs) achieved among 7 pts with unresectable/metastatic melanoma refractory to prior PD-1 adjuvant therapy.**
- **50% (4 of 8 pts) confirmed ORR.**

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; $T_{1/2}$, half-life; TEAE, treatment-emergent adverse event; v, version; wt, wild-type.

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Disclosures

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2. Mohr P, et al. *J Eur Acad Dermatol Venereol*. 2018;32(6):962-971.

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