# Phase 1 study of evalstotug (BA3071), an anti–CTLA-4 conditionally active biologic, in combination with nivolumab in advanced solid tumors

Abstract #2602

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## Background

- Evalstotug (BA3071) is a conditionally active biologic (CAB) anti–CTLA-4 monoclonal antibody designed to block the interaction of CTLA-4 with its ligands in the low pH conditions of the tumor microenvironment (TME), which leads to increases in cytotoxic T cells (CD8+) and depletion of regulatory T cells.[1]

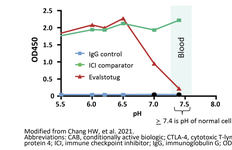
This study evaluated the safety and antitumor activity of evalstotug ± anti–PD-1 therapy in patients with advanced solid tumors.

CABs are –

- minimally altered in the complementarity determining region (CDR) to permit binding to exposed sites only within the acidic TME (**Figure 1**).
- reversibly bound in the acidic TME and are designed to reduce off-tumor immune-related adverse events and immunogenicity, avoid tissue-mediated drug disposition, and improve pharmacokinetics.
- not masked or caged and do not require enzymatic cleavage for activation.

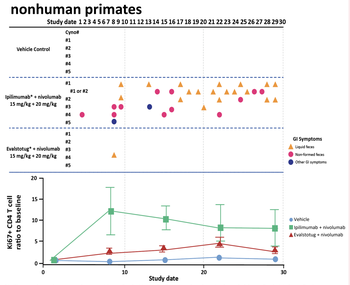
- In a nonhuman primate model of immune checkpoint inhibitor immunotoxicity, the combination of evalstotug + nivolumab was associated with **less GI toxicity and reduced activation of CD4+ T cells in peripheral blood** relative to ipilimumab + nivolumab (**Figure 2**).[1] These findings underpin the potential safety advantages of CAB technology.

**Figure 1. pH-dependent binding of CAB-anti-CTLA-4**




Modified from Chang HW, et al. 2021.
Abbreviations: CAB, conditionally active biologic; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ICI, immune checkpoint inhibitor; IgG, immunoglobulin G; OD, optical density.

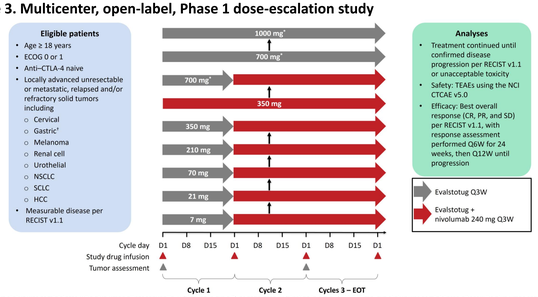
**Figure 2. Evalstotug reduced GI toxicity in nonhuman primates**




*Ipilimumab analog or evalstotug 15 mg/kg (=11 mg/kg human dose) + nivolumab 20 mg/kg (=14.6 mg/kg human dose) both administered Q3W for 4 weeks. Modified from Chang HW, et al. 2021.
Abbreviations: CD, cluster of differentiation; Cyno, cynomolgus macaque; GI, gastrointestinal; Q3W, once weekly.

## Methods

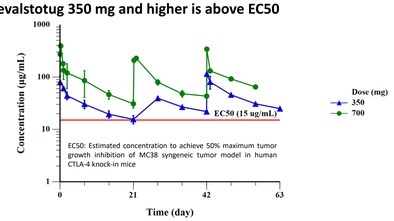
**Figure 3. Multicenter, open-label, Phase 1 dose-escalation study**




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. *Prophylactic tocilizumab was administered at doses of evalstotug 700 mg and above. †Includes gastric and gastroesophageal junction carcinoma, as well as adenocarcinoma arising from the lower esophagus.
Abbreviations: cyc, cycle; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; CTLA-4, cytotoxic T-lymphocyte associated protein 4; D, day; ECOG, Eastern Cooperative Oncology Group; EOT, end of treatment; HCC, hepatocellular carcinoma; NCI, National Cancer Institute; NSCLC, non–small cell lung cancer; PR, partial response; Q3W, every 3 weeks; Q6W, every 6 weeks; Q12W, every 12 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer; SD, stable disease; TEAE, treatment-emergent adverse event, v, version.

## Results

**Figure 4. Evalstotug mean (±SD) concentration vs time profiles in Phase 1 dose escalation cohorts: $C_{min}$ of evalstotug 350 mg and higher is above EC50**




EC50: Estimated concentration to achieve 50% maximum tumor growth inhibition of MC38 syngeneic tumor model in human CTLA-4 knock-in mice

**Accounting for PK variability, population PK modeling suggests that 1000 mg flat dose will enable over 98% of patients to maintain $C_{min}$ levels > EC50 throughout treatment, potentially driving clinical benefit**

## Results (continued)

All results are from a data cut of March 29, 2024, unless otherwise specified.

**Study population**

- Twenty-one patients were treated with evalstotug (7–1000 mg) ± nivolumab.
- Mean patient age was 62 years. Thirteen (62%) patients were male, and 19 (90%) patients were White.
- Thirteen (62%) patients had ECOG 0, and 8 (38%) patients had ECOG 1.
- Patients received a median of 3 prior lines of therapy; all patients had experienced failure of anti–PD-1 therapy (**Table 1**).

**Treatment duration**

- Mean (median) duration of evalstotug 350 mg therapy was 150.3 (126.5) days.
- Patients treated with 350 mg evalstotug received more doses (mean, 7.2) compared with reported ipilimumab or tremelimumab dosing[2-4] (**Figure 5**).

**Patient disposition (no dose reductions occurred)**

- Dose escalations in 2 patients with cutaneous melanoma were well-tolerated (**Figure 6**).
- Three patients have tolerated their first 1-gram evalstotug infusion, and clearance of this dose level is anticipated by early June.

**Safety**

- Most related AEs were low grade (fever, chills, vomiting, diarrhea, pyrexia, arthralgia, nausea); no related grade 4 or 5 events (**Table 2**).
- Signs and symptoms consistent with low grade cytokine release syndrome (CRS) 4 to 6 hours post infusion among 3 patients who received 700 mg; managed by employing prophylactic tocilizumab for evalstotug at doses ≥700 mg.
- All Grade 3 related events (TEAEs; N=4 pts; **Tables 2 and 3**):
  - CRS-like events: 1) New onset atrial fibrillation (only AE to meet DLT criteria) 2) Hypertension.
  - Immune mediated: 3) Endocrine: Hyperglycemia/DKA 4) GI: Lipase increase and gastritis/diarrhea.
- Only 2 treatment related discontinuations; no treatment related deaths.
  - Grade 3 related atrial fibrillation.
  - Grade 3 related gastritis; resolved with steroids.

**Efficacy (as of April 30, 2024)**

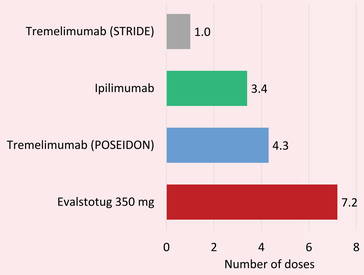
- Responses (3 of 8 patients who received evalstotug 350 mg).
  - CR: Cervical carcinoma (confirmed).
  - PR: Gastroesophageal carcinoma (confirmed) and cutaneous melanoma (unconfirmed – still on therapy; **Figure 7**).
- Disease control rate: 52%.
  - Three patients (2 with cutaneous melanoma, 1 with small cell lung cancer) without progression for >1 year.
  - One uveal melanoma patient without progression for 9.8 months.

**Table 1. Patient clinical characteristics**

| Total (N=21) | | Prior # of treatments |
|---|---|---|
| **Tumor type, n (%)** | | |
| Melanoma | 6 (29) | 1–4 |
| Gastric | 4 (19) | 2–6 |
| Renal cell | 4 (19) | 1–6 |
| Cervical | 3 (14) | 1–3 |
| NSCLC | 2 (10) | 3–7 |
| Urothelial | 1 (5) | 4 |
| SCLC | 1 (5) | 3 |

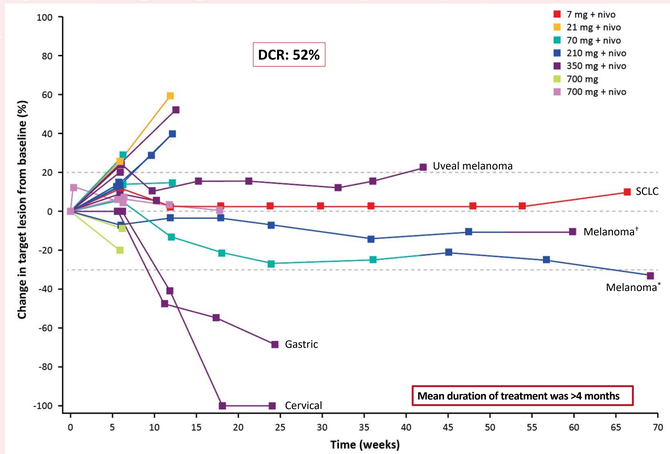
Abbreviations: NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.

**Figure 5. Doses of evalstotug (350 mg cohort) vs reported anti–CTLA-4 agents**




Mean number of doses is shown for the 350 mg cohort of evalstotug. Mean number of doses is shown for ipilimumab and is based on a retrospective observational study.[2] Tremelimumab dosing is based on the prescribed STRIDE[3] and POSEIDON regimens.[4]
Abbreviation: CTLA-4, cytotoxic T-lymphocyte associated protein 4.

**Figure 6. Percentage change from baseline in target lesions (N=20)**




*Patient with cutaneous melanoma enrolled at evalstotug 70 mg was dose escalated to 210 mg at 42 weeks and 350 mg at 69 weeks. Dose escalations were well-tolerated.
†Patient with cutaneous melanoma enrolled at evalstotug 210 mg was dose escalated to 350 mg at 52 weeks. Dose escalation was well-tolerated.
Abbreviations: nivo, nivolumab; SCLC, small cell lung cancer.

**Table 2. All TEAEs of any grade (≥15% of patients) regardless of causality**

| NUMBER OF PATIENTS WITH ANY, n (%) | All AE | | Related | |
|---|---|---|---|---|
| | All grades | Grade 3-4 | All grades | Grade 3-4 |
| **All (N=21)** | 20 (95) | 10 (48) | 17 (81) | 4 (19) |
| Fatigue | 9 (43) | 2 (10) | 3 (14) | 0 |
| Chills | 8 (38) | 0 | 8 (38) | 0 |
| Vomiting | 7 (33) | 0 | 3 (14) | 0 |
| Diarrhea | 5 (24) | 1 (5) | 2 (10) | 1 (5)* |
| Pyrexia | 5 (24) | 0 | 5 (24) | 0 |
| Arthralgia | 5 (24) | 0 | 3 (14) | 0 |
| Nausea | 5 (24) | 0 | 3 (14) | 0 |
| Abdominal pain | 4 (19) | 1 (5) | 1 (5) | 0 |
| Pruritus | 4 (19) | 0 | 4 (19) | 0 |
| Headache | 4 (19) | 0 | 1 (5) | 0 |
| Back pain | 4 (19) | 0 | 0 | 0 |

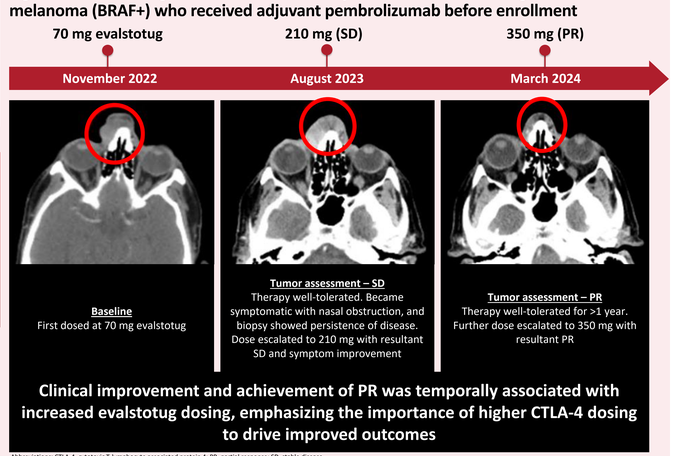
*Refer to results section.
Abbreviations: AE, adverse event; TEAE, treatment-emergent adverse event.

**Table 3. Summary of TEAEs (no grade 4/5 related TEAEs were observed)**

| NUMBER OF PATIENTS WITH ANY, n (%) | 7 mg + nivo (N=1) | 21 mg + nivo (N=1) | 70 mg + nivo (N=3) | 210 mg + nivo (N=3) | 350 mg + nivo (N=6) | 700 mg ± nivo (N=6) | 1000 mg mono (N=1) | Total (N=21) |
|---|---|---|---|---|---|---|---|---|
| **TEAE** | 1 (100) | 1 (100) | 3 (100) | 3 (100) | 6 (100) | 6 (100) | 0 | 20 (95) |
| Related | 1 (100) | 0 | 2 (67) | 2 (67) | 6 (100) | 6 (100) | 0 | 17 (81) |
| **≥Grade 3 TEAE** | 1 (100) | 0 | 2 (67) | 1 (33) | 3 (50) | 3 (50) | 0 | 10 (48) |
| Related | 0 | 0 | 0 | 0 | 2 (33) | 2 (33) | 0 | 4 (19) |
| **Serious TEAE** | 1 (100) | 0 | 1 (33) | 0 | 2 (33) | 3 (50) | 0 | 7 (33) |
| Related | 0 | 0 | 0 | 0 | 1 (17) | 3 (50) | 0 | 4 (19) |

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.
Abbreviations: mono, monotherapy; nivo, nivolumab; TEAE, treatment-emergent adverse event.

**Figure 7. PR following dose escalation in a 75-year-old female with stage IV cutaneous melanoma (BRAF+) who received adjuvant pembrolizumab before enrollment**




**Clinical improvement and achievement of PR was temporally associated with increased evalstotug dosing, emphasizing the importance of higher CTLA-4 dosing to drive improved outcomes**

Abbreviations: CTLA-4, cytotoxic T-lymphocyte associated protein 4; PR, partial response; SD, stable disease.

## Conclusions

- **High doses of evalstotug are associated with manageable safety that allows patients to continue treatment for extended intervals.**
- **Relatively low incidence and severity of immune-mediated AEs were observed.**
- **Multiple patients experienced prolonged progression-free survival (>39 weeks); confirmed responses were observed in patients receiving high doses of evalstotug.**
- **A Phase 3 trial of evalstotug in first-line metastatic/unresectable BRAF-mutated melanoma is anticipated to initiate by year's end.**

## References

1. Chang HW, et al. *Proc Natl Acad Sci USA*. 2021;118(9):e2020606118.
2. Mohr P, et al. *J Eur Acad Dermatol Venereol*. 2018;32(6):962-971.
3. Abou-Alfa GK, et al. *NEJM Evid*. 2022;1(8):EVIDoa2100070.
4. Tremelimumab AstraZeneca: EPAR. European Medicines Agency. April 4, 2023.

## Disclosures

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## Clinical Trial Identifier

A Phase 1/2 Study of BA3071 as Monotherapy and in Combination With a PD-1 Blocking Antibody in Patients With Advanced Solid Tumors. **Clinical trial registry number: NCT05180799.**

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