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Adverse event management during treatment with bintrafusp alfa, a bifunctional fusion protein targeting TGF-B and PD-L1: treatment guidance based on experience in clinical trials

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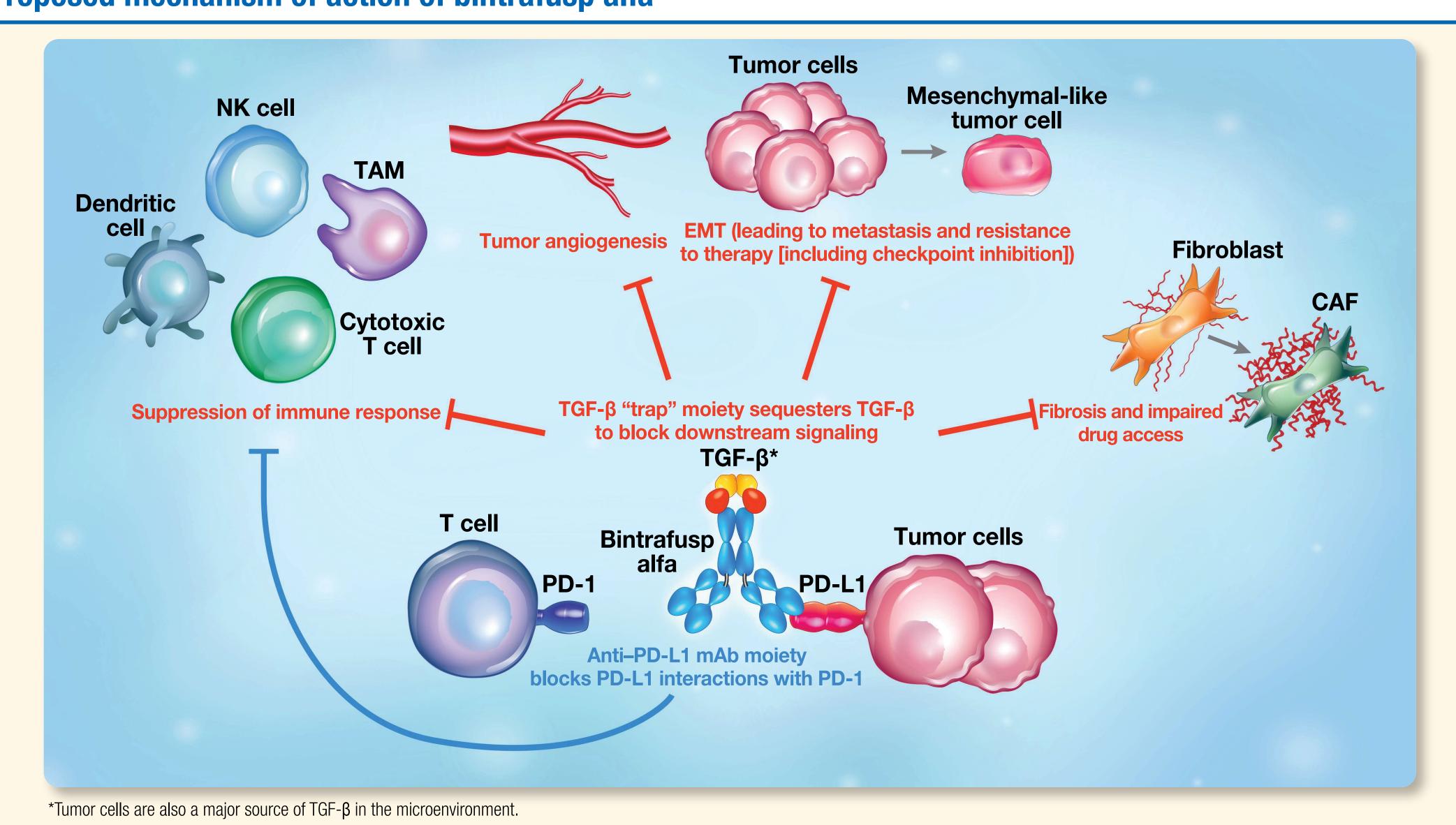
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INTROPID CLINICAL TRIALS

- Bintrafusp alfa demonstrated clinical activity and manageable safety in patients with heavily pretreated solid tumors from the two phase 1 studies, INTR@PID 001 (NCT02517398) and INTR@PID 008 (NCT02699515)
- Bintrafusp alfa AEs of special interest included TGF-β inhibition-mediated skin AEs, irAEs, anemia, bleeding events, and IRRs
- Bintrafusp alfa-associated AEs observed to date were mostly mild to moderate and effective management will be essential to minimize treatment interruptions and to maintain patients' QOL

Proposed mechanism of action of bintrafusp alfa



- Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor to function as a TGF-β "trap" fused to a human IgG1
- The bifunctional nature of bintrafusp alfa might allow for simultaneous, colocalized inhibition of two nonredundant immunosuppressive pathways, TGF-β and PD-L1, within the TME
- antibody blocking PD-L1^{1,2}

METHODS

- INTR@PID 001 and 008 studies
- the early identification and management of these AEs which may help to mitigate the impact of bintrafusp alfa-associated AEs on patients and potentially increase treatment duration

Most patients were male (67.3%), were aged <65 years (59.6%), and had received ≥2 prior anticancer regimens (58.3%)

Any grade: 4.0%

Grade ≥3

- The most common primary tumor type was NSCLC (27.1%); other primary tumor types included HCC (17.5%), BTC (5.0%), and cervical (2.5%)
- TRAEs of any grade occurred in 68.3% of patients (n=414), and TRAEs grade ≥3 occurred in 22.3% of patients (n=53) permanently discontinued treatment due to TRAEs

: KAs occur most commonly in older light-skinned patients with a

patients treated with ICIs. Treatment of KAs varies based on the number of

lesions and level of symptomatology. For sporadic KAs, surgical excision

chemotherapy, cryotherapy, ablative lasers, radiotherapy, or photodynamic

standard of care. Close follow-up is recommended for re-evaluation and for

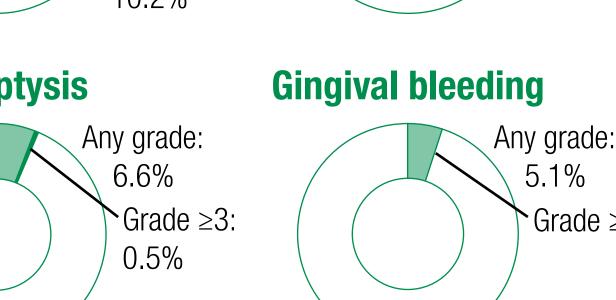
is the standard-of-care, with alternative options including intralesional

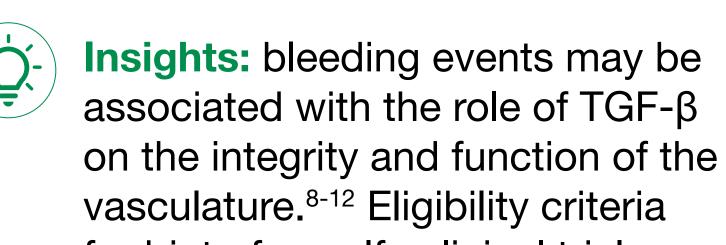
therapy. Observation may also be sufficient, as KAs can spontaneously

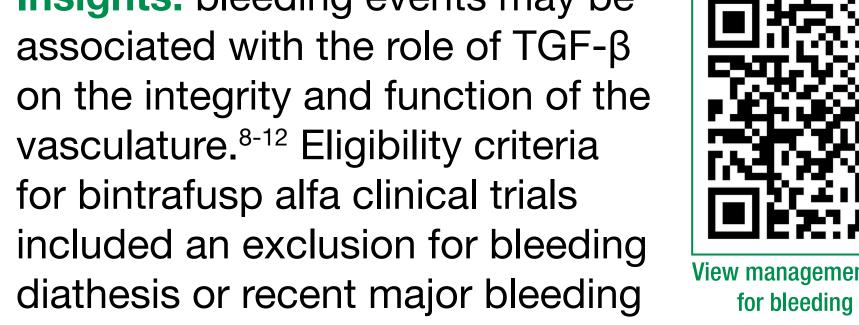
regress. Treatment approaches should be based on local guidelines and

refer to a dermatologist experienced with management of

Bleeding events Any bleeding events







Management: mild to moderate mucosal bleeding events (eg, epistaxis, gingival bleeding, hematuria,

hemoptysis) are clinically manageable and usually resolve without the need for bintrafusp alfa discontinuation

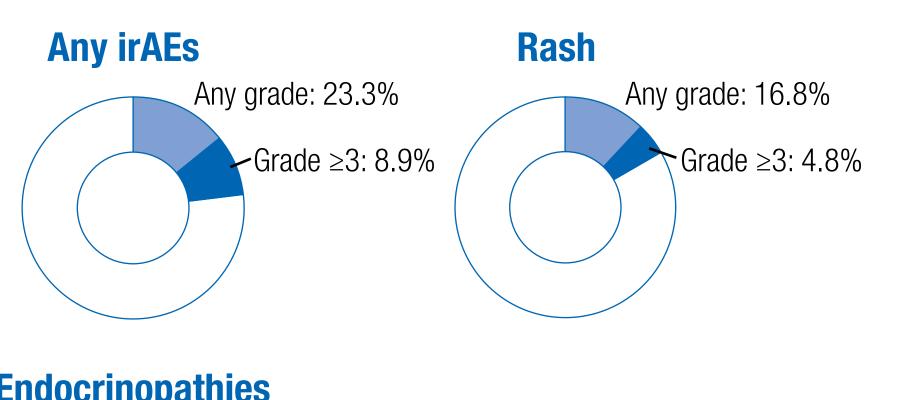
Bleeding events of any grade occurred in 39.3% of patients (n=238). The most common types of bleeding events (in ≥5% of patients) were epistaxis, hemoptysis,and gingival bleeding. Most bleeding events were mild or moderate in severity; the most common grade ≥3 bleeding events were GI hemorrhage (1.3%) and tumor hemorrhage (1.7%).

Immune-related adverse events

inhibition-mediated skin AEs were KAs and SCCs.

Any grade: 11.9%

Grade ≥3: 2.8%



TGF-β inhibition—mediated skin adverse events

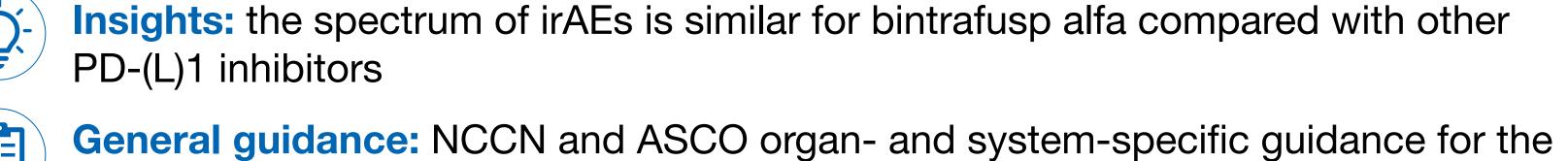
TGF-β inhibition—mediated skin AEs of any grade occurred in 11.9% of patients

(n=72) and were generally mild or moderate. The most common TGF-β

Any grade: 8.1%

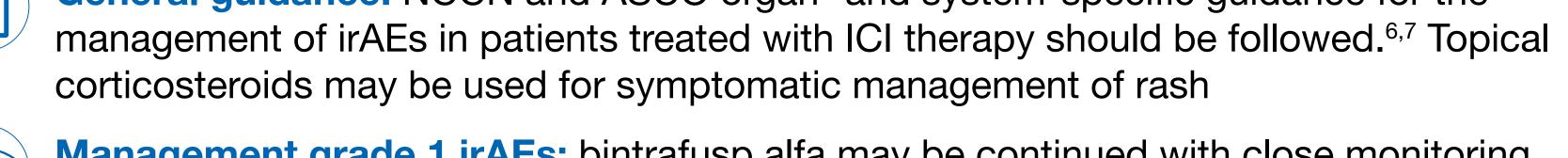
Grade ≥3: 0.8%

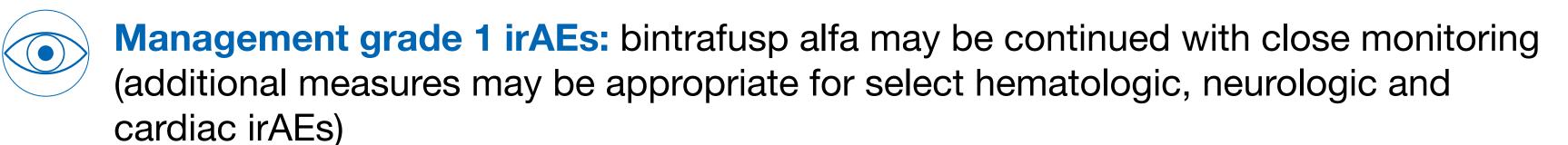
irAEs of any grade occurred in 23.3% of patients (n=141). The most common types of irAEs were rash and endocrinopathies. No other types of irAEs occurred in ≥5% of patients. Most irAEs were mild or moderate in severity.

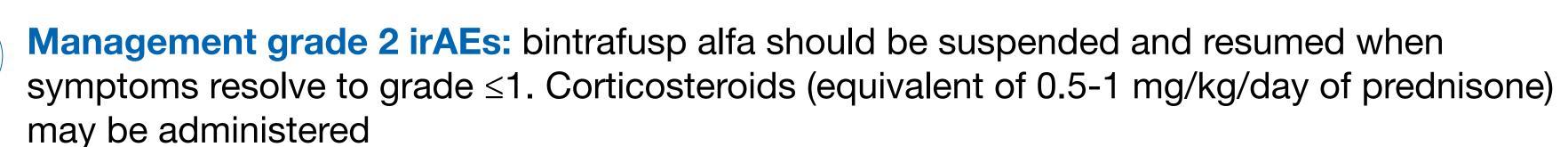


monitoring of resolution and recurrence

history of sun damage³⁻⁵







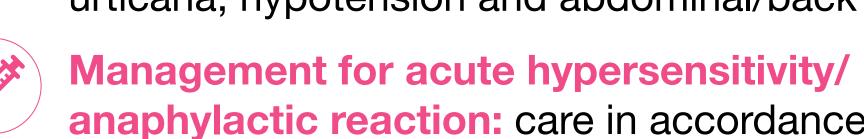
Management grade 3 and 4 irAEs: bintrafusp alfa should generally be suspended (grade 3) or permanently discontinued (grade 4), and high dose corticosteroids should be administered. Immunosuppressive therapy (eg, infliximab) may be required in refractory cases. For grade 4 endocrinopathies controlled with hormone replacement, treatment may continue

View detailed irAE management guidance

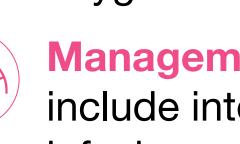
Any IRR Any grade: 6.3%

Infusion-related reactions

IRRs occurred in 6.3% of patients (n=38). Most IRRs were mild or moderate in severity. An IRR grade ≥3 occurred in 1 patient (0.2%). Monitoring: monitor patients on the day of and day after infusion for symptoms of hypersensitivity, including pyrexia, flushing, chills, wheezing, dyspnea, urticaria, hypotension and abdominal/back pain



anaphylactic reaction: care in accordance with best available medical practice should be provided, including (as applicable) epinephrine injection, intravenous dexamethasone, and cardiovascular and oxygen saturation monitoring¹³



Management for moderate IRRs: strategies may include interruption of the infusion, slowing the infusion rate, and providing symptomatic treatment



CONCLUSION

 Most bintrafusp-alfa associated AEs were mild to moderate in severity. Timely and effective management strategies to mitigate the impact of common AEs could improve patients' QOL, time on treatment and may ultimately lead to better treatment outcomes

- We analyzed AEs observed in 606 patients receiving a 1200 mg dose of bintrafusp alfa in the phase 1
- With the aim of optimizing patients' treatment experience and outcomes, we provide guidance for

Any anemia

8. Walshe TE, et al. PLoS One. 2009;4:e5149.

9. Cunha SI, et al. Circ Res. 2017;121:981-99.

10. Sounni NE, et al. Dis Model Mech. 2010;3:317-32.

Anemia

Anemia of any grade occurred in 30.5% of patients (n=185). Anemia grade ≥3 occurred in 18.0% of patients (n=109).



Monitoring: hematology assessment should be performed at baseline, prior to each dose, at the end-of-treatment and 28 (±5) days post treatment

Management: anemia may be managed with standard clinical approaches, including hematologic evaluation, interventional radiology or endoscopy as appropriate. All relevant hematologic testing should be done prior to blood transfusion, if clinically feasible



View anemia management

Abbreviations

AE, adverse event; **ASCO**, American Society of Clinical Oncology; **BTC**, biliary tract cancer; **CAF**, cancer-associated fibroblast; **EMT**, epithelial-mesenchymal transition; **GI**, gastrointestinal; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; IRR, infusion-related reaction; IV, intravenous; KA, keratoacanthoma; NCCN, National Comprehensive Cancer Network; NK, natural killer; NSAID, nonsteroidal anti-inflammatory drug; NSCLC, non-small cell lung cancer; QOL, quality of life; **SCC**, squamous cell carcinoma; **TAM**, tumor-associated macrophage; **TME**, tumor microenvironment; **TNBC**, triple-negative breast cancer; **TRAE**, treatment-related adverse event.

References

- 1. Strauss J, et al. Clin Cancer Res. 2018;24:1287-95.
- 2. Lan Y, et al. Sci Transl Med. 2018;10:eaan5488.
- 3. Schwartz RA, et al. J Am Acad Dermatol. 1994;30:1-19. 4. Kwiek B, Schwartz RA. J Am Acad Dermatol. 2016 Jun;74:1220-33. 11. Zonneville J, et al. BMC Cancer. 2018;18:670.
- 5. Claeson M, et al. JAMA Dermatol. 2020 Dec 1:156:1324-1332. 12. Mitra MS, et al. Toxicol Sci. 2020:175:24-34. 6. Brahmer JR, et al. J Clin Oncol. 2018;36:1714-68. 7. NCCN Clinical Practice Guidelines in Oncology for Management of
- 13. Resuscitation Council UK emergency treatment of anaphylactic reactions: guidelines for healthcare providers. Accessed July 27 Immunotherapy-Related Toxicities V.3.2021. Accessed July 8, 2021. 2021. https://www.resus.org.uk/pages/reaction.pdf

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Disclosures

B. C. Cho reports advisory roles for KANAPH Therapeutic Inc, Brigebio therapeutics, Cyrus therapeutics, Guardant Health; consulting (NIH) for dual PD-L1 and TGF-β inhibition in HPV-positive malignancies. All other authors have no relationships to disclose. roles for Novartis, AstraZeneca, Boehringer Ingelheim, Roche, Bristol Myers Squibb, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, Merck

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