SMAC mimetic and BET inhibitor – a promising combination for solid cancer treatment?

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Introduction

SMAC mimetics (SMACm), drugs that mimic natural antagonists of inhibition of Apoptosis (IAP) are in clinical trials for hematological malignancies and solid cancers. The clinical benefit for patients in monotherapy was not evident. Hence, current SMACm focus on combinations, in particular with checkpoint inhibitors and/or radiation therapy.

The BET family protein BRD4 is a "reader" of epigenetic information and binds to acetylated chromatin to act as a key regulator of transcription. BET inhibitors (BETi) were tested in numerous clinical trials as novel treatment option for hematological malignancies and solid cancers. Like SMACm, monotherapy with BETi showed only moderate clinical activity showing the importance of combination strategies.

BI 891065 is a monovalent, oral SMACm with a favorable safety profile allowing continuous dosing, and is in Clinical Phase I nations trials.

BETi are not just epigenetic regulators but also directly affect cell death suggesting potential for broader applicability. BETi are not tumor cell death pathways. Multiple points of interference can be steered by SMAC mimetics; hematological malignancies and solid cancers.

I. Rationale underlying the combination of SMACm and BETi

II. Selectivity and potency profiles of BI SMACm and BETi

III. Broad synergy of SMACm and BETi across cancer cell lines

IV. In vivo combination of SMACm and BETi in CDX models

V. Immune-modulatory effects of SMACm and BETi in syngeneic PDAC model

Conclusions

- These data demonstrate the potential of a SMACm/BETi combination for the treatment of solid cancer.
- Up to 30% of cancer cell lines of different tumor origin showed in vitro synergy.
- Mechanistically, the interaction of the BET inhibitor with the reduction of dUTP at the TRF2 and of KARP which sensitize cells to SMAC mimetic induced cell death.
- Data from syngeneic rodent models and PDAC xenografts indicate that BETi/SMACm combination has the potential to induce durable tumor control and might serve as future treatment approach in this tumor type.

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