Combination activity of the MEK inhibitor pimasertib and the hypoxia-activated prodrug TH-302 in pancreatic and biliary tract tumor xenograft models

Ma J, Syed S, Crowley L, Shaw J, Ogden J, Elenbaas B, Goodstal S

EMD Serono Research and Development Institute, Billerica, Massachusetts, USA (an affiliate of Merck KGaA, Darmstadt, Germany)

AACR Annual Meeting, 18–22 April 2015, Abstract No. 2603 (Poster Section 29)

Introduction

- The efficacy and tolerability of the MEK inhibitor pimasertib (Pim) and the hypoxia-activated prodrug evofosfamide (Evo; previously known as TH-302) combination were explored in pancreatic and biliary tract preclinical tumor xenograft models.
- These studies were based on the hypothesis that combination efficacy may occur by several possible mechanisms, including inhibition of DNA repair by Pim, increase of hypoxia by Pim, or by differential targeting of the oxic and hypoxic tumor compartments by Pim and Evo, respectively.
- Pim and Evo have each been tested in separate clinical trials in pancreatic cancer with gemcitabine (NCT01016483 and NCT01144455, respectively)[1,2] and, therefore, these data could provide the rationale for future clinical testing of this novel combination in pancreatic cancer.
- The combination was also tested in biliary tract cancer models (cholangiocarcinoma and gallbladder) based on the reported sensitivity of these tumor types to MEK inhibitors, their hypoxic nature, and the prevalence and high unmet need of these indications, particularly in Asia.

Objectives

- To assess the efficacy of Pim and Evo in combination in three pancreatic tumor xenograft models and a panel of 10 cholangiocarcinoma and six gallbladder patient-derived xenograft (PDX) models. In addition, we sought to determine if the scheduling of the two drugs influenced their efficacy.

Methods

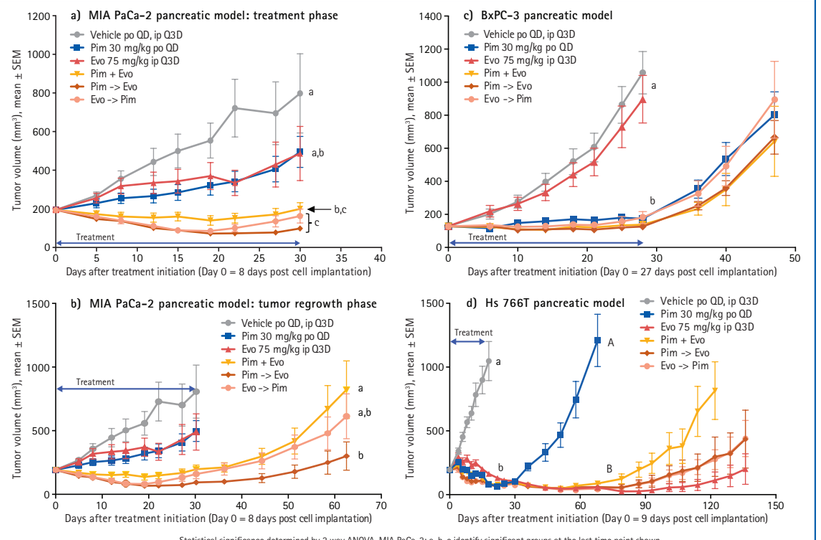
Tested models

- Pancreatic cancer cell line-derived xenograft (CDX) models
  - MIA PaCa-2, BxPC-3, Hs 766T.
- Biliary tract cancer patient-derived xenograft (PDX) models
  - 10 cholangiocarcinoma models
  - 6 gallbladder models.

Doses and schedules

- Pim: 30 mg/kg orally (po), every day (QD).
- Evo:
  - pancreatic: 75 mg/kg, intraperitoneally (ip), every 3 days (Q3D)
  - biliary tract: 60 mg/kg, ip, twice every week (2QW).

Figure 1. *In vivo* efficacy of combination of Evo with Pim in three pancreatic cancer xenograft models



Statistical significance determined by 2 way ANOVA. MIA PaCa-2: a, b, c identify significant groups at the last time point shown.
BxPC-3: a, b identify significant groups at Day 28. Hs 766T: a, b identify significant groups at Day 18; and A, B identify significant groups at Day 68

- Combination treatment schedules
  - pancreatic CDX models:
    - Evo + Pim: dosing simultaneously
    - Evo -> Pim: dose Evo 2 hours prior to Pim
    - Pim -> Evo: dose Pim 2 hours prior to Evo.
  - biliary tract PDX models:
    - in all PDX models, the combination schedule Pim -> Evo was used based on the results of the MIA PaCa-2 model.

Response criteria for PDX models using the %TV calculation

- **Tumor progression (PD, non-responder):** a tumor volume (TV) increase >73% at the end of the treatment compared to the TV at the start of treatment. This corresponds to a >20% increase across the longest diameter.
- **Tumor stasis/regression (responder):** a tumor volume increase ≤73% at the end of the treatment compared to the TV at the start of treatment. This corresponds to a ≤20% increase across the longest diameter (i.e. clinical RECIST response criteria).
- **Complete tumor regression (CR, responder):** non-palpable tumors.

Results

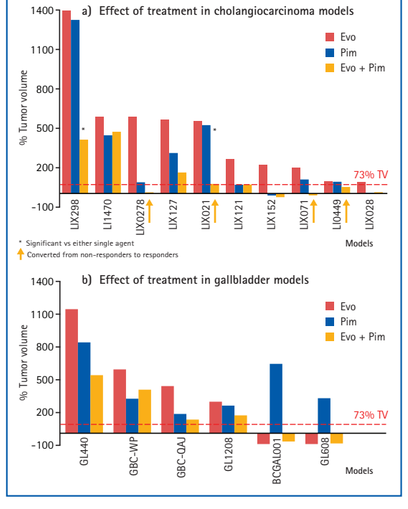
- Combination effects were observed in the MIA PaCa-2 model, and two out of three schedules showed significance ($p<0.05$) vs both monotherapies at the end of treament (**Figure 1a**).
- The schedule Pim -> Evo showed greater efficacy vs simultaneous administration in the tumor regrowth phase (**Figure 1b**).
- The BxPC-3 model is sensitive to Pim, but not Evo, and no combination effect was observed (**Figure 1c**).

Table 1. Results summary of treatment with Evo, Pim or the combination in 10 cholangiocarcinoma and six gallbladder PDX models

Cholangiocarcinoma	Evo	Pim	Evo + Pim
Total models	10	10	10
PD	10	7	3
Tumor stasis/ regression	0	3	7
CR	0	0	0
Overall response	0/10	3/10	7/10
p<0.05	0/10 vs vehicle	6/10 vs vehicle	8/10 vs vehicle; 2/10 vs single agents
Gallbladder	**Evo**	**Pim**	**Evo + Pim**
Total models	6	6	6
PD	4	6	4
Tumor stasis/ regression	0	0	0
CR	2	0	2
Overall response	2/6	0/6	2/6
p<0.05	2/6 vs vehicle	1/6 vs vehicle	3/6 vs vehicle and 0/6 vs single agents

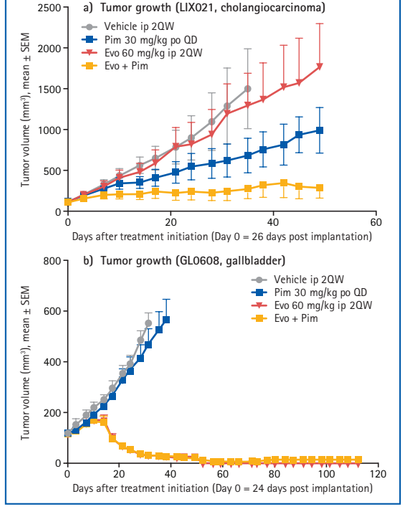
CR, complete response; Evo, evofosfamide; Pim, pimasertib; PD, progression of disease

Figure 2. *In vivo* efficacy of Evo, Pim and the combination in a) 10 cholangiocarcinoma and b) six gallbladder PDX models



- The Hs 766T model is more sensitive to Evo than Pim. No significant combination effects of adding Pim to Evo were observed ($p>0.05$; **Figure 1d**).
- Response results following treatment with Evo and Pim in cholangiocarcinoma and gallbladder models are shown in **Table 1**.
- None of the cholangiocarcinoma models were responders to Evo; three models were responders to Pim; seven were responders to the combination; the combination was statistically significant in two of the 10 models (**Figure 2a**).
- None of the gallbladder models were responders to Pim; two models had a complete response to Evo in all mice; no significant combination effects were observed (**Figure 2b**).
- No efficacy with Evo; tumor growth inhibition with Pim; tumor stasis was achieved with the combination in the cholangiocarcinoma model (**Figure 3a**).
- No efficacy with Pim; CRs with Evo in the gallbladder model (**Figure 3b**).

Figure 3. *In vivo* efficacy of Evo, Pim and the combination in the a) LIX021 cholangiocarcinoma model and b) GL0608 gallbladder model



Conclusions

- In pancreatic cancer models, the combination of Evo and Pim improved efficacy in MIA PaCa-2 but not BxPC-3 or Hs 766T, which are sensitive to Pim and Evo monotherapies, respectively.
- Cholangiocarcinoma PDX models are relatively sensitive to Pim monotherapy with 30% of responders at a clinically relevant dose (exposure) in 10 models, but these models were less sensitive to Evo monotherapy.
- Combination of Evo and Pim improved efficacy in the cholangiocarcinoma models, since four of seven non-responder models were converted to responders based on clinical RECIST criteria.
- Two out of the six gallbladder PDX models were highly sensitive to Evo monotherapy showing CRs. These gallbladder models were relatively resistant to Pim monotherapy. Combination of Evo and Pim had no benefit in the gallbladder models.
- Biomarkers tested so far did not identify hypoxia or other markers as being predictive of a combination benefit, although the sample set is too small to draw conclusions. Research on this Pim + Evo combination is continuing to better understand the mechanism and to identify predictive biomarkers.

References

1. Van Cutsem E, et al. Gastrointestinal Cancers Symposium, 15–17 January 2015 (Abstract 344).
2. Borad MJ, et al. J Clin Oncol 2014;55:7504 [Epub ahead of print].

Acknowledgments

This study was sponsored by Merck KGaA, Darmstadt, Germany. Editorial assistance was provided by Tawhid Ahmad, Bioscript, Macclesfield, UK and funded by Merck KGaA, Darmstadt, Germany. EMD Serono is an affiliate of Merck KGaA.

Disclosures

All authors on this poster are employees of EMD Serono, Billerica, MA, USA. Evofosfamide and pimasertib are currently under clinical investigation and have not been approved by any regulatory authority. Status: March 2015.