# Vascular Disruption Effects of MPC-6827

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## ABSTRACT

MPC-6827 is an investigational new drug that has recently completed Phase I clinical trials in advanced primary and metastatic tumors. MPC-6827 has been previously reported to potently inhibit tumor cell growth and survival *in vitro* and *in vivo*, with activity in xenograft models of mouse melanoma and human cancers of the ovary, breast, prostate, colon and pancreas. MPC-6827 has also been shown to compete with colchicine for binding to β-tubulin and to inhibit the formation of microtubules *in vitro* and in cell culture. We have recently begun to evaluate the potential of MPC-6827 to act as a vascular disrupting agent (VDA). VDAs target the tumor neovascular endothelium leading to disruption of tumor blood supply and subsequent tumor cell necrosis. In cell culture, MPC-6827 induced cytotoxicity in several primary endothelial cell types, including human umbilical vein, arterial, and microvessel endothelial cells, with $IC_{50}$ values from 1.8 to 3.2 nM. In human OVCAR-3 ovarian carcinoma xenografts in nude mice, a single intravenous treatment of MPC-6827 at 10 mg/kg induced dramatic vascular disruption and tumor cell necrosis within 24 hours. Based on these preliminary results, we conclude that the anti-tumor effects are likely to be mediated, at least in part, through a mechanism involving vascular disruption. We are currently studying the effects in the OVCAR-3 xenograft model in more detail and investigating other xenograft models.

*Data obtained since submission of abstract:*
VDAs have been limited in their efficacy due to the observation that the rim of the tumor survives treatment and will subsequently regrow. Therefore, a combination of standard cytotoxic therapy with a VDA has been proposed to increase efficacy. We have recently tested a single, suboptimal dose of MPC-6827 in combination with a single dose of carboplatin and found synergistic inhibition of OVCAR-3 human ovarian carcinoma xenograft growth. With the addition of these new findings to this poster, the authors have elected not to show the *in vitro* endothelial cell cytoxicity data cited in the original abstract.

## METHODS

For OVCAR-3 xenografts, female Crl:Nu/Nu-nuBR mice (Charles River Labs, Wilmington, MA) were implanted subcutaneously with $10^7$ cells in the right flank. Animals were housed by groups in Positive Individual Ventilation cages in flat-bottom cages with no more than ten mice per cage. Environmental controls were set to maintain a temperature between 65 and 75 ºF with a relative humidity of 30-70% in a 12:12 hour light:dark cycle. Animals were fed and watered *ad libitum*. Tumors were allowed to grow to approximately 100 $mm^3$ (Study 1) or 380 $mm^3$ (Study 3) and then mice were placed into test groups (N = 10). The mice were observed daily for mortality and signs of toxicity. Tumor growth was monitored externally using a caliper and volumes calculated using the formula [p/6 (width² x length)], in which width represents the smaller tumor diameter. Volume values were converted to percentage of original tumor size and group values averaged. Studies were completed when the first animal achieved a tumor volume > 1500 mm3. Statistical analysis of variance with unadjusted pair wise comparison was performed using SAS software (Cary, NC). These studies conformed to the recommendations set forth in the U.S. Public Health Service *Policy on Humane Care and Use of Laboratory Animals.*[1]

In Study 1, animals were treated with vehicle, 7.5 mg/kg MPC-6827 qwk x 3 *i.v.* or 30 mg/kg carboplatin qd x 5 *i.p.* In Study 2, mice with OVCAR-3 xenografts were treated with vehicle, combretastatin A-4 phosphate or MPC-6827. Animals were sacrificed 24 h later and tumors were fixed in formalin. Tissue sections were embedded in paraffin for storage, prior to Hematoxylin and Eosin Y (H & E) staining using standard techniques.[2] In Study 3, OVCAR-3 xenograft bearing mice were treated with a suboptimal single dose of 5 mg/kg MPC-6827 *i.v.* alone, a single dose of 60 mg/kg carboplatin *i.p.* alone, 5 mg/kg MPC-6827 *i.v.* followed 4 h later by 60 mg/kg carboplatin *i.p.*, or 60 mg/kg carboplatin *i.p.* followed 4 h later by 5 mg/kg MPC-6827 *i.v.*

[1] The U.S. Public Health Service *Policy on Humane Care and Use of Laboratory Animals*, Office of Laboratory Animal Welfare, National Institutes of Health, Department of Health and Human Services, Bethesda, MD 20892-7982

[2] Luna, L. Manual of Histologic Staining Methods of the Armed Forces Institute of Pathology, 3rd Edition. New York: McGraw-Hill Publisher; 1968.

## RESULTS

### STUDY 1

original tumor volume
= 106 ± 60 $mm^3$

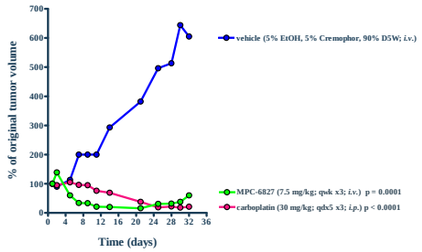
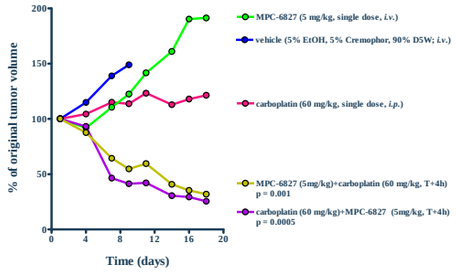



**Figure 1. Efficacy of multidose MPC-6827 or carboplatin in OVCAR-3 xenografts**

### STUDY 3

original tumor volume
= 383 ± 120 $mm^3$




**Response Evaluation Criteria in Solid Tumors (RECIST)**

**CR – disappearance**
**PR – partial response (> 30% decrease)**
**SD – stable disease (neither CR or PR criteria met)**
**PD – progressive disease (> 20% increase)**

| Vehicle (N = 8) | Carboplatin (N = 9) | MPC-6827 (N = 9) | Carboplatin + MPC-6827 (N = 7) | MPC-6827 + Carboplatin (N = 6) |
|---|---|---|---|---|
| PD – 8 | SD - 7<br>PD - 2 | PD - 7<br>SD - 1<br>PR - 1 | CR - 4<br>PR - 3 | CR - 1<br>PR - 5 |

**Figure 2. Efficacy of a single, suboptimal dose of MPC-6827 and/or carboplatin in OVCAR-3 xenografts**

### STUDY 2

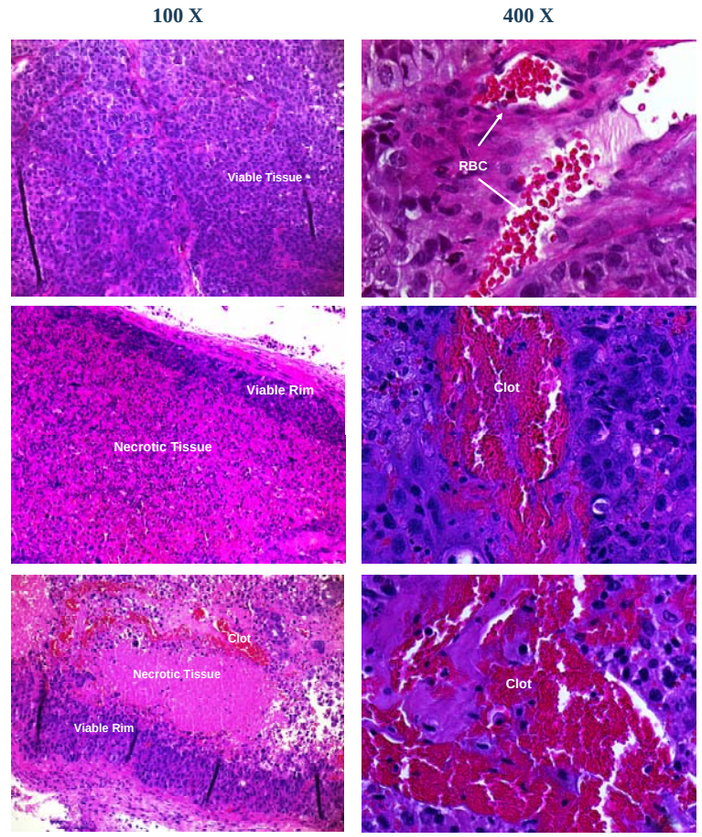



**Figure 3. H & E staining of human OVCAR-3 xenografts treated with vehicle, combretastatin A-4 P or MPC-6827**

## CONCLUSIONS

- Treatment of nude mice bearing OVCAR-3 xenografts resulted in rapid tumor vessel occlusion and massive tumor necrosis typical of vascular disrupting agents.
- MPC-6827 is equally effective as carboplatin on OVCAR-3 xenografts in Nu/Nu mice.
- MPC-6827 in combination with carboplatin synergistically delayed the growth of OVCAR-3 xenografts in nude mice.
- Partial responses were observed by RECIST in OVCAR-3 xenografts with a single low dose of MPC-6827 alone or in combination, but the combination led to complete responses.

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