Antiangiogenics are standard of care for clear cell carcinomas but outcomes in mPCR are not known. We present the clinical results of treatment antiangiogenics on patients (pts) with mPCR.
Material and Methods: An exhaustive retrospective monocentric review of the medical records of patients with mPCR treated with antiangiogenics in first or second line was performed. Papillary cell carcinoma diagnosis was pathologically established after surgery. Evaluation of the tumor response was done according to RECIST criteria, survival data were estimated using Kaplan-Meier method.
Results: A total of 30 pts (23 men, 77%), with a median age of 58 years [range: 29−77] has been analyzed. All underwent radical nephrectomy. At the diagnosis of mPCR, 20 pts (67%) and 5 pts (17%) had an ECOG performance status (PS) of 0 and 1 respectively. Twenty one pts (70%) had a single metastatic site. Metastatic sites were lung (n = 16, 53%), lymph node (n = 11, 37%), bone (n = 3, 10%), liver (n = 3, 10%) and other (n = 8, 27%). Thirteen pts (43%) were classified as intermediate and one as poor risk group according to Motzer criteria at the onset of first line therapy. After a median follow-up of 55.7 months, 13 pts (43%) were still alive and their median survival time was 38.2 months. Clinical outcomes for the first line are summarized in table 1. Five-teen pts received antiangiogenics as a second line. Partial response and SD were noted for 3 pts (20%) and for 12 pts (80%) respectively. Progression-free survival was 12.7 months.
Conclusions: Clinical benefit and survival of mPCR treated with antiangiogenics seem to be promising, but pathological classification of those tumors remains controversial. Reproductive criteria for diagnosis are necessary for valuable therapeutic evaluation.

Clinical outcomes of first-line for mPRC

	Partial response, n (%)	Stable disease, n (%)	Progression-free survival (months)
Cytokines (n = 15)	0	11 (73%)	6.8
Antiangiogenics (n = 6)	1 (16%)	4 (66%)	6.9
Chemotherapy (n = 9)	0	3 (33%)	2.6

Animal models

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Neurobehavioral properties of penclomedine (PEN) and derivatives

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Introduction: 4-Demethyl-4-cholesteryloxycarbonylpenclomedine (DM-CHOC-PEN) is a non-neurotoxic cholesteryl carbonate derivative of neurotoxic PEN developed by DEKK-TEC. DM-CHOC-PEN has begun clinical trials because of superior intracranial (IC) anticancer activity in gliomas (*vs*. other DM-PEN carbonates, carbamates and BCNU [AACR 48, Abst. 5614, 2007]), with no apparent neurotoxicity noted in animal studies. The current study was initiated to screen DM-CHOC-PEN in rats in a water maze to quantitate influences on memory and cognitive behavior.
Methods: The Morris water maze was modified to screen agents for memory and cognitive behavior. Adult female rats (5−10) were dosed IP once with therapeutic amounts of PEN and analogs and pyrimidines and compared vs. controls for learning/memory abilities after 1, 2, 3 & 24 h of dosing. The testing tank was 85×50 cm with 12 cm of water and a 15×15 cm wire pedestal rising 3 cm above the water. A monolayer of peanuts covered the water and pedestal. The time required for each rat to swim 29 cm & find the pedestal was compared. Each rat was tested six consecutive swims and the avg. and SD of the 1st & 6th trials were compared.
Results: PEN and 5-FU had the greatest impact on memory and learning with 65 & 50% impairment, resp., after 3 hr., with >50% for PEN at 24 h PEN – which continued for >5 days, despite normal appearances. 5-FU impairment reversed after 24 h. DM-CHOC-PEN demonstrated a *35% improvement* in memory and learning with no impairment of cognitive abilities noted. Gemicitabine demonstrated no impairment in memory/learning.
Conclusion: Any drug that is a pyrrole, pyridine or could form a pseudo-N-containing ring configuration with an available −N− could interact with or antagonize the hippocampal complex -NMDA receptor. The latter is a memory transmitter pathway that has a variety of neurotransmitter substrates – serine, glycine, N-methyl-D-aspartate, glutamate all of which can exist as pseudo-pyridine or pyrroles at the NMDA receptor. The interactions of PEN and 5-FU with the NMDA and phencyclidine (PCP) receptors and learning/memory will be discussed. DM-CHOC-PEN is a high energy carbonate, that in addition to being an effective anticancer agent for IC tumors (that localizes in IC tumor tissue) also improved memory and cognitive behavior in the rat model and serves as a springboard for new anticancer structures – carbonated aryl anticancer agents. The present described screen is easy to use and should be useful in screening new agents for behavioral modification properties.
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Hypoxic conditions increase hypoxia response element and vascular endothelial growth factor promoter reporter activity within the hollow fibre assay in vivo

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Background: The hollow fibre assay has been adopted by the NCI to facilitate short-term assessment of cancer drug efficacy in vivo. However, the current technique requires complete cell recovery and ex vivo outgrowth to determine cell numbers in conditions not reflective of the in vivo environment. We therefore aimed to develop a real-time imaging hollow fibre system in which cell viability and assessment of hypoxia can be quantified in vivo.
Material and Methods: The Flp-In system (Invitrogen) was used for the establishment of stable transfected cell lines – a Flp Recombination Target (FRT) site was randomly inserted into the host cell genome, and reporters were then inserted into the FRT site by recombination. Reporters were constructed by cloning a Far Red Fluorescent Protein gene (HcRed) into pcDNA5/FRT to track transfected cells either alone or followed by (i) three tandem hypoxia response elements (HRE) preceding a SV40 minimal promoter linked to a firefly luciferase gene, or (ii) a vascular endothelial growth factor (VEGF) promoter linked to firefly luciferase. Transfected cells were implanted into hollow fibres, cultured for 24 h, then subcutaneously embedded into MF1 nude mice to mimic tumour conditions. Fluorescence and luminescence (by intraperitoneal injection of 60 mg/kg D-Luciferin) were monitored over 14 days and imaged using an IVIS® 100 (Caliper Life Sciences).
Results: Cell lines transfected with HcRed alone (4e5 cells) displayed fluorescence detectable by the IVIS 100, whereas no fluorescence could be detected from cells transfected with a red fluorescent protein gene (DsRed). Cell lines stably transfected with the HRE-SV40 and VEGF promoter reporters displayed luciferase activity when exposed to hypoxic (1% oxygen) conditions in vitro in cell culture conditions and when loaded into hollow fibres. Upon implantation into mice within hollow fibres, HcRed fluorescence was detected in real-time and provided a means of monitoring cell viability. Using the HRE-SV40 reporter construct, luminescence intensity increased over time with increasing tumour size. Similarly, the VEGF promoter reporter also showed an increase in luminescence over time in response to the hypoxic environment.
Conclusions: The data validate the use of a Far Red Fluorescent Protein (HcRed) for quantifying cell viability, and HRE-SV40 and VEGF promoter reporters for monitoring hypoxic changes within hollow fibres in vivo. This model provides the basis for further investigations to assess short-term cellular responses to cancer drugs, and will define the need for second stage xenograft studies.

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Synergistic anti tumor effect of histone deacetylase inhibitor MS-275 in combination with interleukin 2 in a murine model of malignant melanoma

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Background: A high dosage of interleukin-2 (IL-2) is a standard treatment option at the National Cancer Institute in the USA for metastatic malignant melanoma patients. However, the toxicity and limited clinical benefits associated with IL-2 has limited its use. Histone deacetylase (HDAC) inhibitors have demonstrated antitumor activity in different tumor models including malignant melanoma, and also possess immunomodulatory properties.
In our study we tested the efficacy of a combination of IL-2 and HDAC inhibitor, MS-275, in a murine melanoma model.