Preclinical evaluation of novel treatment strategies in patient-derived xenograft models (PDX) of pancreatic cancer

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Background

Pancreatic cancer remains a lethal disease with only 3 – 8% of patients surviving 5 years after diagnosis of the tumor (WHO, 2012). Reasons for this poor situation are advanced and inoperable tumor stages at time of diagnosis and resistance to conventional therapies. One bottleneck in the development of novel therapies of this disease is the restricted availability of preclinical models of high clinical relevance.
Within the EU project "CAM-PaC" a comprehensive panel of twenty patient-derived PC xenografts (PDX) was established and used for the efficacy screening of new therapeutic options. Within this study, responders to the MPS-1 inhibitor BAY1161909, the Super Enhancer disrupting agent Minnelide and the MEK inhibitor Trametinib were identified and analyzed for potential biomarkers.

Conclusions

1) The TTK/MPS1 inhibitor BAY1161909 advances the efficacy of Abraxane

2) Both, Minnelide and Trametinib are restrictedly efficacious in PDX models of PDAC.

3) Comprehensive PDX libaries are a valuable tool for the effective screening of novel therapeutics or enhanced treatment settings

Tab1.: CAM-PAC Panel of PDX models of pancreatic cancer

PDX ID	Gender	Age at surgery	pT	pN	M	Stage	Histologic type	Mutations	Survival	Response to Gemcitabine (PDX)
12556	Male	67	3	1	0	IIB	PDAC	KRAS, TP53	929 days	PD
12558	Male	56	3	1	0	IIB	PDAC	KRAS	916 DAYS	PR
12559	Female	80	3	1	0	IIB	PDAC	KRAS, TP53, SMAD4, CDKN2A	189 days	PD
12560	Male	60	3	1	0	IIB	PDAC	KRAS	403 days	PD
12561	Male	48	3	0	0	IIA	PDAC	KRAS	360 days	PR
12650	Female	82	3	0	0	IIA	IPMN/PDAC	KRAS	NA	PD
12706	Female	82	3	0	0	IIA	IPMN/PDAC	KRAS	NA	SD
12707	Male	60	3	1	0	IIB	PDAC	KRAS	403 days	PD
12708	Female	56	3	1	0	IIB	PDAC	KRAS, APC, BRCA2, REV3L	503 days	PD
12709	Female	51	3	1	0	IIB	PDAC	KRAS, TP53, SMAD4, CDKN2A	710 days	SD
12911	Male	67	3	1	0	IIB	PDAC/clear cell	KRAS, SMAD4	NA	SD
12912	Male	67	3	0	0	IIA	PDAC	KRAS, ATM	825 days	PD
12975	Female	75	3	0	0	IIA	IPMN/PDAC	KRAS	230 days	PD
12976	Female	65	3	1	0	IIB	PDAC	KRAS, TP53	596 days	SD
14836*	Female	72	T4	Nx	M1 - lung	IV	PDAC	KRAS, TP53, SMAD4	42 days	SD**
14837*	Female	63	T4	Nx	M1 - lung	IV	PDAC	KRAS, TP53, SMAD5	417 days	SD**
14838*	Male	59	T4	Nx	M1 - liver	IV	PDAC	KRAS, TP53, SMAD6	23 days	PD**
14839*	Male	65	T4	Nx	M1 - liver, lung	IV	PDAC	KRAS, TP53, SMAD7	362 days	SD**
14840*	Male	53	T4	Nx	M1 - lung	IV	PDAC	KRAS, TP53, SMAD8	43 days	PD**
14841*	Female	83	T4	Nx	M1 - liver	IV	PDAC	KRAS, TP53, SMAD9	53 days	PR**

*established from circulating tumorigenic cancer stem cells isolated from peripheral blood using VAR2CSA coated magnetic beads
** models were tested for response to 3 cycles Gemcitabine+Abraxane+Cisplation

PD – progressive disease, SD – stable disease, PR – partial response (RECIST)

Methods

Maintenance of xenografts: Already established PDX were provided by UniVER and QMUL under sterile conditions. One vital piece of the tumor was transplanted subcutaneously into the flank of immunodeficient mice and engrafted tumors were transplanted into new recipients when a tumor volume of approx. 1cm³ was reached in the primary passage.
Therapeutic characterization: 3 to 10 NMRI:nu/nu mice with advanced subcutaneous tumors per group were treated with standard of care (SoC) and/or investigative test compounds according to clinically adapted protocols. Tumor growth inhibition was evaluated in comparison to control (T/C) and ranked according to modified RECIST criteria.

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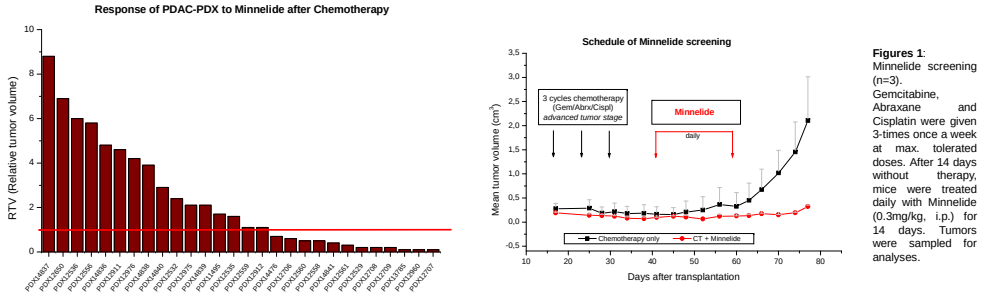
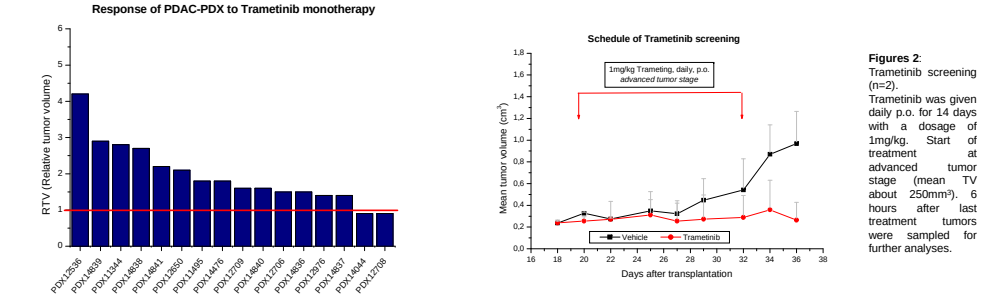
Triptolide Minnelide: moderate delay of tumor relapse when given second line after chemotherapy



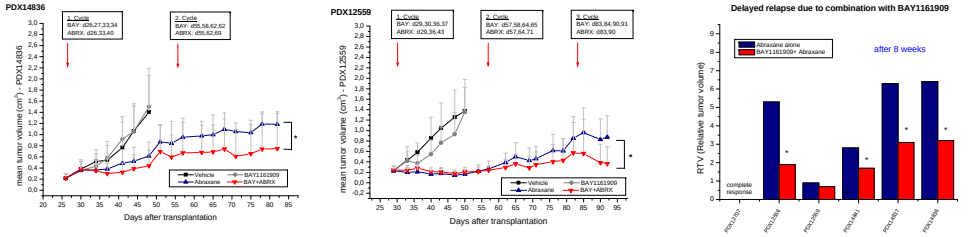
Figures 1: Minnelide screening (n=3). Gemcitabine, Abraxane and Cisplatin were given 3-times once a week at max. tolerated doses. After 14 days without therapy, mice were treated daily with Minnelide (0.3mg/kg, i.p.) for 14 days. Tumors were sampled for analyses.

MEK inhibitor Trametinib: marginal antitumoral activity after monotherapy in PDAC-PDX



Figures 2: Trametinib screening (n=2). Trametinib was given daily p.o. for 14 days with a dosage of 1mg/kg. Start of treatment at advanced tumor stage (mean TV about 250mm³). 6 hours after last treatment tumors were sampled for further analyses.

TTK/MPS1 inhibitor BAY1161909: delayed tumor relapse in combination with Abraxane



Figures 3: TKK/MPS1 inhibitor screening (n=10). BAY1161909 was given bid, p.o. with a dosage of 1.5mg/kg. One group was combined with 50mg/kg Abraxane once a week. Start of treatment at advanced tumor stage (mean TV about 250mm³). Tumors were sampled for further analyses.