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Randomised Phase II trial with an uPA inhibitor (WX-671) in patients with locally advanced non-metastatic pancreatic cancer

V. Heinemann[1], M. Ebert[2], T. Pinter[3], C. Mala[4], N. Neville[4], P. Bevan[4]

[1]Department of Internal Medicine III, Klinikum Großhadern, University of Munich, Germany; [2]Klinikum Rechts der Isar, Medical Dept. II, Munich, Germany; [3]Petz Aladar Megyei Oktató Kórház, Onkoradiológia, Gyor, Hungary; [4]WILEX, Munich, Germany

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INTRODUCTION

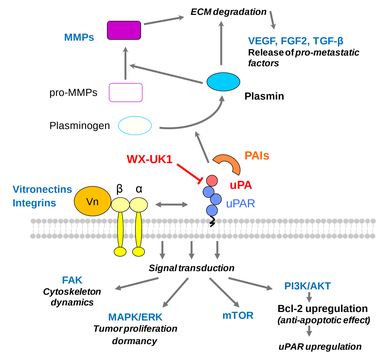
The uPA (urokinase- type plasminogen activator) system has various important roles in tumour biology:

- uPA/integrin –vitronectin interaction leads to reduction of tumour cell adhesion and increase in tumour cell migration
- uPA causes the release and activation of growth factors such as VEGF, bFGF leading to tumour cell growth
- uPA activates proteases (e.g. plasmin) leading to extracellular matrix degradation and cancer cell invasion
- uPA/uPAR interaction initiates intracellular signalling promoting tumour cell proliferation
- Elevated levels of uPA have been associated with poor prognosis in most common solid tumours.

uPA Inhibitors WX-671 and WX-UK1

- WX-UK1 is an uPA inhibitor effective in submicromolar range, previously evaluated in four Phase I studies.
- WX-671 (MESUPRON®) is an oral pro-drug of the active metabolite WX-UK1 which has been investigated in four Phase I studies and is currently in Phase II testing.

Figure 1: Role of the uPA system and the inhibitor WX-UK1



OBJECTIVES

Exploratory proof of concept study in 90 evaluable patients designed to

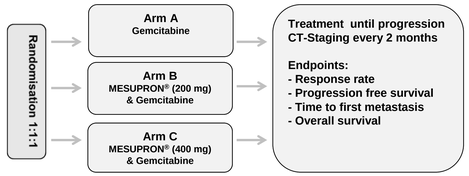
- evaluate the anti-tumour activity of WX-671 in combination with Gemcitabine
- assess the safety and tolerability of repeated daily dosing until disease progression
- explore pharmacokinetics in a subset of patients (n=6 per arm)
- determine potential effects of WX-671 on tumour marker (CA19-9) and uPA system related markers (D-Dimer) in blood

METHODS

STUDY DESIGN

- Phase II, randomised, three-arm, open-label proof-of-concept study
- Gemcitabine given in all arms at recommended dose of 1000 mg/m² as 30 min i.v. infusion once weekly for 7/8 weeks and then every 3/4 weeks
- Two different doses of WX-671 (200 or 400 mg) taken as a daily oral dose in the morning

Figure 2: Study Scheme



KEY ELIGIBILITY CRITERIA

- locally advanced, unresectable, non-metastatic, histological or cytologically proven pancreatic adeno-carcinoma
- no prior chemo- or radiotherapy, investigational, endocrine or biological therapy
- adequate performance status (ECOG performance ≤ 1), organ function and bone marrow reserve

RESULTS

- 95 patients accrued between Jul 2007 and Aug 2008
- Data collection was stopped in Feb 2010. One patient continued treatment under a protocol amendment until June 2010, contributing data until cycle 28 i.e. 112 weeks.
- Overall survival endpoint with 75% reported deaths was reached in Apr 2010

Table 1: Patient Baseline Characteristics

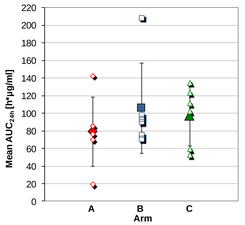
	All (n=95)	Arm A	Arm B	Arm C
Gender, number of patients				
Male	46 (48.8%)	14 (14.7%)	20 (21.1%)	12 (12.6%)
Female	49 (51.6%)	17 (17.9%)	11 (11.6%)	21 (22.1%)
Age, years				
Median	62	59	67	62
ECOG (%)				
0	17.9	16.1	12.9	24.2
1	82.1	83.9	87.1	75.8
Tumour localisation (%) *				
Head	87.4	80.6	90.3	90.9
Body	14.7	16.1	12.9	15.2
Tail	0.0	0.0	0.0	0.0
Periampullary	1.1	3.2	0.0	0.0

* *Subjects may have more than one localisation*

Table 2: Treatment Exposure (Gemcitabine)

	All	Arm A	Arm B	Arm C
Number of patients	93	30	30	33
Mean duration on study (weeks)	23.7	26.4	19.0	25.6
Mean cumulative dose (mg/m²)	16623	18180	13820	17755
Mean dose intensity (mg/m²/wk)	732.2	714.5	750.1	732.1

Figure 3: AUC_{24h} of dFdC + dFdU compared in all arms



Addition of WX-671 does not have a major impact on Gemcitabine pharmacokinetics.

The exposure to Gemcitabine was comparable in all three arms.

Table 3: Overview of Adverse Events (Safety Population)

Number of patients with	All	Arm A	Arm B	Arm C
Any AE	88 (94.6%)	28 (93.3%)	28 (93.3%)	32 (97.0%)
WX-671 related AE	30 (32.3%)	0	13 (43.3%)	17 (51.5%)
Gemcitabine related AE	70 (75.3%)	17 (56.7%)	25 (83.3%)	28(84.4%)
Any SAE	32 (34.4%)	7 (23.3%)	8 (26.7%)	17 (51.5%)
WX-671 related SAE	3 (3.2%)	0	1 (3.3%)	2 (6.1%)
Gemcitabine related SAE	6 (6.5%)	0	3 (10.0%)	3 (9.1%)

Figure 4: All AEs considered related and with incidence ≥ 10% in any arm

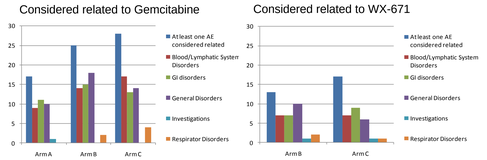
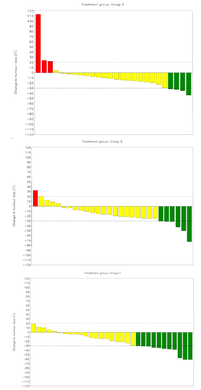


Table 4: Tumour Response – FAS Population

	All	Arm A	Arm B	Arm C
Number of patients	85	26	28	31
Overall response rate % (PR+CR) *	8.2	3.8	7.1	12.9
% Pts with PR as best response **	24.7	15.4	21.4	35.5

* *confirmed as per RECIST*
** *considering single reduction ≥ 30%*



Addition of WX-671 to standard treatment with Gemcitabine led to better disease control and more partial remissions.

All CTs were assessed centrally by an imaging core lab and by the same experienced independent reader.

Response endpoints were calculated for the full analysis set (FAS) which comprises all patients for which at least one follow up CT post baseline was available.

Table 5 : Progression Free Survival (radiologic)

	All	Arm A	Arm B	Arm C
Number of patients (PD/death)	71	21	24	26
Median PFS (weeks)	30.3	35.3	24.0	35.7
PFS rate at 6 months (%)	57.4	60.4	40.5	69.2
PFS rate at 12 months (%)	22.6	16.2	22.5	26.9

Figure 5: Kaplan Meier Plot

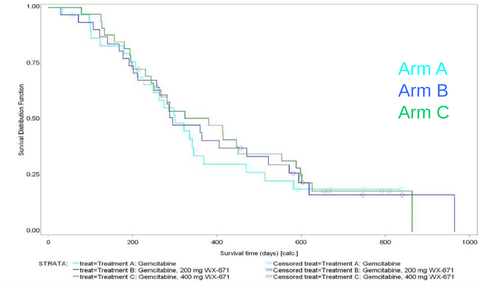


Table 6 : Overall Survival

	All	Arm A	Arm B	Arm C
Number of patients	75	23	25	27
Median OS (months)	10.6	9.9	9.7	12.5
OS rate at 6 months (%)	79.6	79.5	77.4	81.8
OS rate at 12 months (%)	42.1	33.9	40.7	50.6

CONCLUSIONS

The present study with WX-671 in combination with Gemcitabine demonstrated impressive anti-tumour activity when comparing Arm A vs. Arm C:

- Response rate increased from 3.8% to 12.9%
- 1 year PFS rate improved by 66%
- 1 year OS rate improved by 49%
- Median OS in months improved by 26%

The treatment did not cause any specific toxicities and was well tolerated for over 112 weeks of daily intake.

MESUPRON® is currently also being tested in a Phase II study in combination with Capecitabine in patients with metastatic breast cancer (NCT00615940).

ClinicalTrials.gov identifier: NCT00499265

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