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ABSTRACT

Background: PCSK145 is a synthetic 15-mer peptide which bears homology to Prostate Secretory Protein (PSP94). It subverts several functions and appears to work in animal models as an inhibitor of angiogenesis by rapid onset of binding to the laminin receptor in a 7H-and- α 7N-ratio fashion to downregulate ER, and to reduce plasma matrix metalloproteinase (MMP-9) levels, as well as the expression of MMP-9 within tumor. PCSK145 was evaluated previously in a dose-escalating study in the United Kingdom and was shown to be safe without toxicity and to exert a cytostatic effect on tumor growth. We confirmed safety in a phase I trial using two cohorts of 10 patients (pts) each which evaluated PCSK145 at 7.5 mg/m² 1x twice weekly versus 15mg/m² 1x weekly given for four weeks with four weeks off. Since that time, both cohorts have been accrued and a third cohort of 8 pts treated at 150mg/m² 1x weekly for 16 consecutive weeks to determine the maximum tolerated dose has also been completed.

Methods: Three cohorts of pts with CMPC with radiographic progression of disease despite multiple hormone manipulations and chemotherapy were studied. Two cohorts of 10 pts each compared 7.5mg/m² twice weekly with 15mg/m² weekly based on dosing schedules extrapolated from prior studies. In an attempt to determine the maximum tolerated dose, an additional cohort of 8 pts received 150mg/m² weekly for 16 consecutive weeks. For pts who derived benefit, additional cycles were permitted.

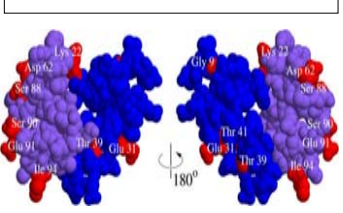
Results: PCSK145 was safe at all dose levels. There did not appear to be any difference in the pharmacologic profile between the 7.5mg/m² and 15mg/m² dosing schedules. Four patients from each of the 7.5mg/m², 15mg/m² and 150mg/m² dose cohorts received ≥ 2 more cycles of treatment, respectively. Of the 10 pts treated either the 7.5mg/m² or 15mg/m² cohorts, several pts were taken off study for anxiety due to rising PSA's in the absence of radiographic progression. One pt (with extensive pelvic adrenalectomy) treated at the 15mg/m² dose and 2 pts with bone metastases from the 7.5mg/m² twice weekly schedule have not shown radiographic progression since their initiation on study 22 months ago. The PSA doubling time (PSADT) was extended 1.5 to 2.4-fold in patients treated at the 15mg/m² dose and 2-5 fold in the 7.5mg/m² dose level, respectively. Of the 8 pts treated at 150mg/m² dose, two pts with bone metastases remain on study with stable bone scans for over one year. Pts treated at all dose-levels had precipitous declines in plasma MMP-9 levels while on drug which rose once the drug was discontinued.

Conclusions: PCSK145 was safe at all dose levels without toxicity. Though a phase I trial, pts with castrate metastatic disease to bone and/or lymph nodes who progressed despite prior treatment with hormones and chemotherapy have radiographically stable disease and lengthening of PSA doubling times for close to two years. These results were extended to pts with a natural history of patients who have failed prior treatment with hormones and/or chemotherapy. All dose levels were well-tolerated and there appeared to be an anti-tumor effect irrespective of the dose levels; 15mg/m² given weekly will likely be the dose for future phase III development.

BACKGROUND

PCSK145: •PCSK145 is a 15-mer synthetic peptide corresponding to peptide fragment 51 to 45 derived from the Prostate Secretory Protein (PSP94)

PSP94 (Prostate Secretory Protein)
 •Contains 94 amino acids, is hydrophilic, unglycosylated and rich in cysteine residues.
 •PSP94 - found in seminal plasma (mg/ml).
 •Synthesized mainly in the prostate and believed to be associated with normal cell growth.

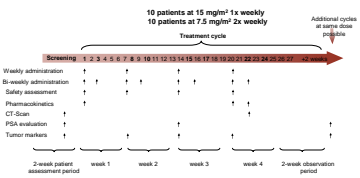


US Dosing Study

Objectives:
 •Evaluate 7.5 mg/m² - 2x weekly and 15 mg/m² - 1x weekly dosing schedules given 1x.

Secondary:
 •PSA and MMP-9 level changes
 •Pharmacokinetic parameters
 •Tumor response (radiographic/CTMRI assessments)

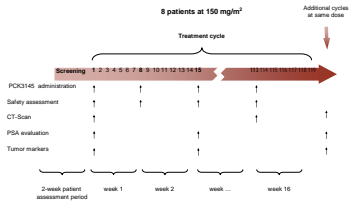
US dosing study Part I:



•Dose levels 15 mg/m² weekly and 7.5 mg/m² twice a week were transitioned from the UK trial into a North American patient population
 •Needed confirmation of the dose in an asymptomatic castrate metastatic prostate cancer patient population
 •The 5 mg/m² 3 times per week dose in the UK trial was showing the most relevant observations in terms of PSA reduction and MMP-9 normalization levels
 •Needed to do a transition from 3 times a week into a weekly administration in NA as the UK weekly data were not available back in summer 2004.

US Phase III dosing study amendment design

•To investigate the potential for pro-apoptotic effects for PCSK145 at a higher dose
 •Evaluate potential additional effects at 150mg/m² 1x weekly for 16 weeks



Patient Demographics

Patient Treatment History:

Treatments	7.5 and 15 mg/m ² doses	150 mg/m ² dose
Hormones	4	1
Hormones / Chemotherapy	2	
Prostatectomy / Hormones	2	
Radiotherapy / Hormones	3	
Prostatectomy / Radiotherapy / Hormones	2	
Prostatectomy / Hormones / Chemotherapy	3	
Radiotherapy / Hormones / Chemotherapy	6	3
Surgery / Radiotherapy / Hormones / Chemotherapy		4

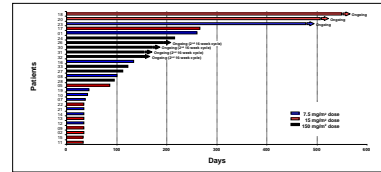
•Hormonal therapy included among others: Zoladex, Casodex, Lupron, Nilandron, etc.
 •Chemotherapy included among others: Taxotere, Mitoxantrone, Estramustine, etc.
 •Patient disease state (as per RECIST criteria)
 -Rising PSA
 -Radiographic metastasis (castrate)

Demographics:

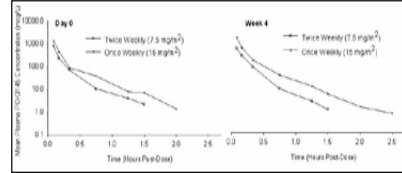
Total Patients Accrued:	32
No. Patients Evaluable:	20
No. Patients Inevaluable:	4
Currently Active:	8
OFF STUDY:	24
POD in Bone:	3
POD in Bone + Rising PSA:	5
POD in Soft Tissue:	1
Rising PSA:	6
POD in Bone, Soft Tissue and Rising PSA:	2
Symptomatic local progression in prostate (obstruction):	2

RESULTS

Patient Treatment Cycles



PK parameters



Toxicity

System/Organ Class	7.5 and 15mg/m ² cohorts				150mg/m ² cohort			
	1	2	3	4	1	2	3	4
Cardiac	0	0	0	0	0	0	0	0
Constipation	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0	0
Nausea	0	0	0	0	0	0	0	0
Neuropathy	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	0	0	0	0
Rhinitis	0	0	0	0	0	0	0	0
Syncope	0	0	0	0	0	0	0	0
Loss of Appetite/Weight Loss	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0
Stomach Pain	0	0	0	0	0	0	0	0
Upper and Lower Respiratory	0	0	0	0	0	0	0	0
Fever	0	0	0	0	0	0	0	0

Patients completing 2 + cycles of treatment Radiographic assessments

Patient	Date	Dose schedule - 2x per week (7.5mg/m ²)				Dose schedule - 1x weekly (15mg/m ²)			
		Pre-treatment	DT (days)	DT (days)	DT (days)	Pre-treatment	DT (days)	DT (days)	DT (days)
01	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
02	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
03	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
04	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
05	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
06	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
07	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
08	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
09	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
10	7.2	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
11	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
12	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
13	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
14	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
15	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
16	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
17	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
18	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
19	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
20	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
21	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
22	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
23	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
24	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
25	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
26	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
27	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
28	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
29	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
30	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
31	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
32	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
33	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
34	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
35	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
36	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
37	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
38	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
39	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
40	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
41	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
42	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
43	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
44	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
45	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
46	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
47	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
48	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
49	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
50	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
51	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
52	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
53	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
54	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
55	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
56	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
57	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
58	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
59	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
60	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
61	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
62	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
63	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
64	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
65	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
66	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
67	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
68	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
69	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
70	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (days)	DT (days)	DT (days)
71	150	Day-7	SD-38	SD-46	SD-119	Pre-treatment	DT (