Activity of the VEGFR/KIT tyrosine kinase inhibitor cediranib (AZD2171) in alveolar soft part sarcoma

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Introduction

- Alveolar soft part sarcoma (ASPS) is a rare entity making up <1% of soft tissue sarcomas (STS)
- It is usually indolent but with a high incidence of metastatic disease, usually to the lungs, but also to unusual sites such as the brain
- Metastases have been known to become dormant
- Response to conventional systemic treatment is poor

Biology of ASPS

- Associated with t(X;17)(p11;q25) translocation resulting in ASPL-TFE3 fusion protein which activates MiT (Microphthalmia transcription factor) resulting in over-expression of MET
- MET is receptor for hepatocyte growth factor (HGF)
  - Cell survival
  - Adhesion
  - Invasion and migration
  - Angiogenesis
- Is dormancy due to inhibition of angiogenesis

Cediranib in ASPS

- This is a preliminary report of the activity of cediranib (AZD2171, RECENTIN™) in seven patients with ASPS
  - Cediranib is a highly potent and selective VEGF signalling inhibitor with activity against all three VEGF receptors and additional activity versus KIT
  - Early clinical data show that cediranib had encouraging antitumour activity across a broad range of tumours[1]

1. Drevs J *et al. J Clin Oncol* 2007;25:3045–3054

Methods

- Efficacy and tolerability data were collected for seven patients with ASPS
  - One was treated in a Phase II randomized trial of cediranib ± prophylactic antihypertensive therapy[1,*]
  - Six were treated in a Phase II study in patients with imatinib-refractory gastrointestinal stromal tumours (GIST) or other STS[†]
- Cediranib was administered orally, once daily at an initial dose of 45 mg/day
- Response was assessed according to Response Evaluation Criteria in Solid Tumours (RECIST)

*Study code 2171IL0038; †Study code 2171IL0046
1. Langenberg M *et al. J Clin Oncol* 2008:26(15S):asbt 3555

Patient characteristics

Median age, years (range)	39 (26–49)
Sex, male/female	4/3
Race, Caucasian/Oriental	6/1
Baseline WHO performance status	
0	3
1	4
Histology	
ASPS	7

- All patients had pulmonary metastases and two had additional sites of disease (brain, bone, intra-abdominal) at study entry

WHO, World Health Organization

Treatment with cediranib 45 mg/day was well tolerated

- Adverse events were generally CTC grade 1–2 and manageable
- The most frequently reported adverse events were fatigue (n=6), diarrhoea (n=5), stomatitis (n=4), headache (n=3) and hypertension (n=3)
  - All were considered cediranib related* except for headache and two incidences of fatigue

*Adverse events were defined as causally related if in the investigator's opinion there was a reasonable possibility that the event may have been caused by cediranib
CTC, Common Terminology Criteria

Adverse events reported in in ≥1 patient

	CTC grade			
Adverse event	1	2	3	All grades
Fatigue	4	2	0	6
Diarrhoea	4	1	0	5
Stomatitis	2	0	2	4
Headache	1	1	0	3*
Hypertension	1	2	0	3
Anorexia	1	1	0	2
Dysgeusia	2	0	0	2
Dysphonia	2	0	0	2
Musculoskeletal pain	0	2	0	2
PPE syndrome	1	1	0	2
Pharyngolaryngeal pain	1	0	1	2
Pyrexia	1	1	0	2
Viral infection	1	1	0	2

*CTC grade is missing for one instance of headache
CTC, Common Terminology Criteria; PPE, palmar–plantar erythrodysaesthesia (hand–foot) syndrome

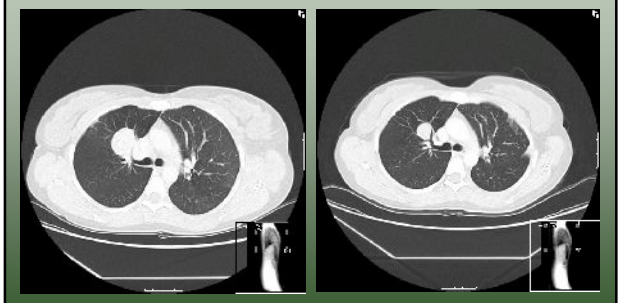
Best objective response

Best response	Investigator assessment	RECIST validated data
Partial response	5	4
Minor response*		2
Stable disease	2	1
Progressive disease		

*A reduction in maximum tumour diameter of ≥10% and <30%

- As of October 2008, five patients remain on treatment with a median (range) duration of 35 weeks (26–49)

Young woman with alveolar soft part sarcoma on VEGFR inhibitor cediranib August 2006 to June 2008. Disease in axilla and lungs



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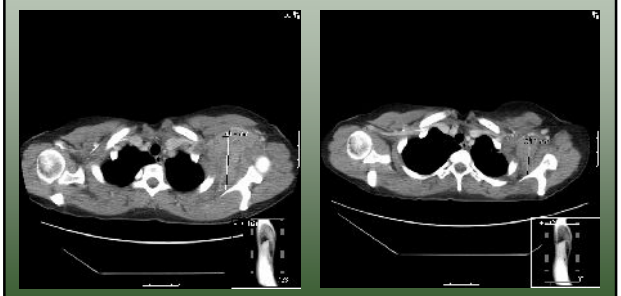
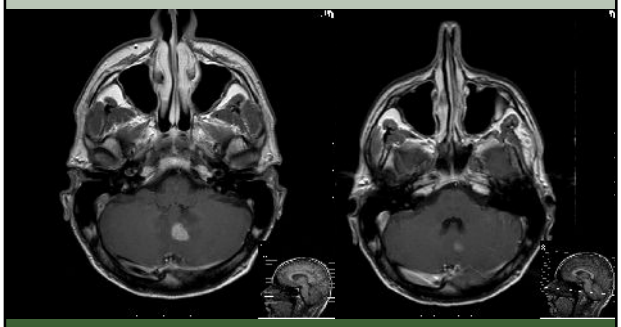


28 year old man, slowly progressive lung disease, several operations for resection of brain metastases, on cediranib since December 2007



November 2007 September 2008

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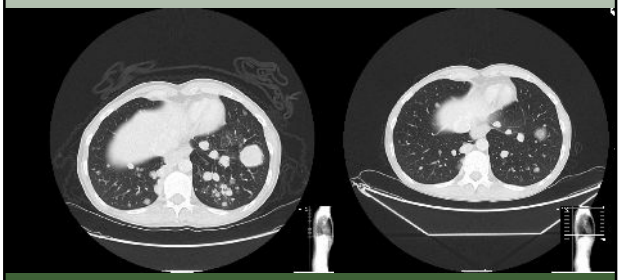
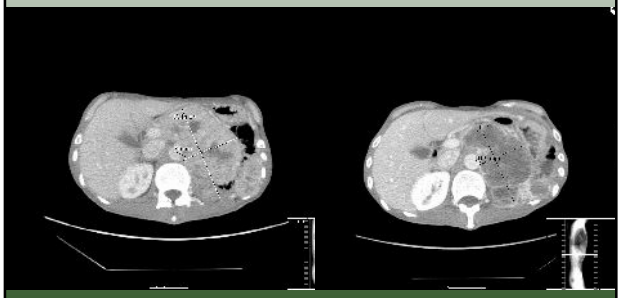


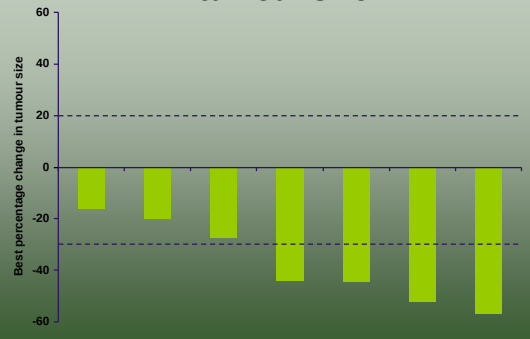
November 2007 September 2008

50 year old man with history of multiple pulmonary metastasectomies, started cediranib December 2006, developed symptoms from unsuspected brain metastases March 2008, requiring surgery and RT, and came off trial



December 2006 February 2007

Waterfall plot of best change in tumour size



Each bar represents one patient
Tumour size is the sum of the longest diameters of the target lesions
Reference lines indicate boundaries for partial response (-30%) and progressive disease (20%)

Conclusions

- There is currently no effective systemic treatment for patients with advanced ASPS
- These data demonstrate the exciting preliminary activity and safety of chronic administration of cediranib in this disease
- Further investigation is warranted