CIRCCa: (Cediranib In Recurrent Cervical Cancer)

A randomised double blind phase II trial of carboplatin-paclitaxel plus cediranib versus carboplatin-paclitaxel plus placebo in metastatic/recurrent cervical cancer

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Aim

- Results of standard chemotherapy for metastatic or relapsed cervical cancer poor:
  - RR - 20-30%
  - Survival < 1 year
- High tumour angiogenesis/high VEGF levels adverse prognostic factors
- Cediranib is a potent oral tyrosine kinase inhibitor of VEGF receptors 1,2 & 3

Methods

Eligibility:

- Histologically proven metastatic or relapsed cervix cancer unsuitable for radiotherapy or surgery
- No previous chemotherapy except cisplatin given along with radiotherapy as primary treatment

Major Exclusions:

- Bowel obstruction
- Active bleeding
- Fistula
- Significant proteinuria
- Uncontrolled hypertension

Methods

Design

Randomised double-blind phase II. Patients randomised (1:1) to:-

Cediranib 20mg daily or matched **Placebo**

in combination with Carboplatin AUC5 + Paclitaxel 175mg/m² 3 weekly (max 6 cycles) and then until progression/lack of tolerability

Primary Endpoint

Progression free survival (PFS)

Secondary Endpoints

- Change in plasma VEGFR-2 (from baseline to 28 days after chemotherapy start)
- Response to chemotherapy (using RECIST1.1 criteria)
- Overall survival (OS)
- Toxicity (assessed using NCI CTCAE v4.0)
- Quality of Life (assessed using EORTC QLQ-C30 and CX24)

Power

80% chance (20% 1-sided) of detecting a 60% increase in median PFS from 4 to 6.4 months

Patients

69 patients (35 Placebo and 34 Cediranib)

13% local relapse only

30% extra pelvic disease only

57% both

Treatment delivery

79% completed 6 cycles of chemotherapy

22% on Placebo arm

17% on Cediranib arm

} discontinued study drug for treatment related reasons

Results

	Median PFS (wks)	80% CI
Cediranib (A)	35	(32-38)
Placebo (P)	30	(29-31)

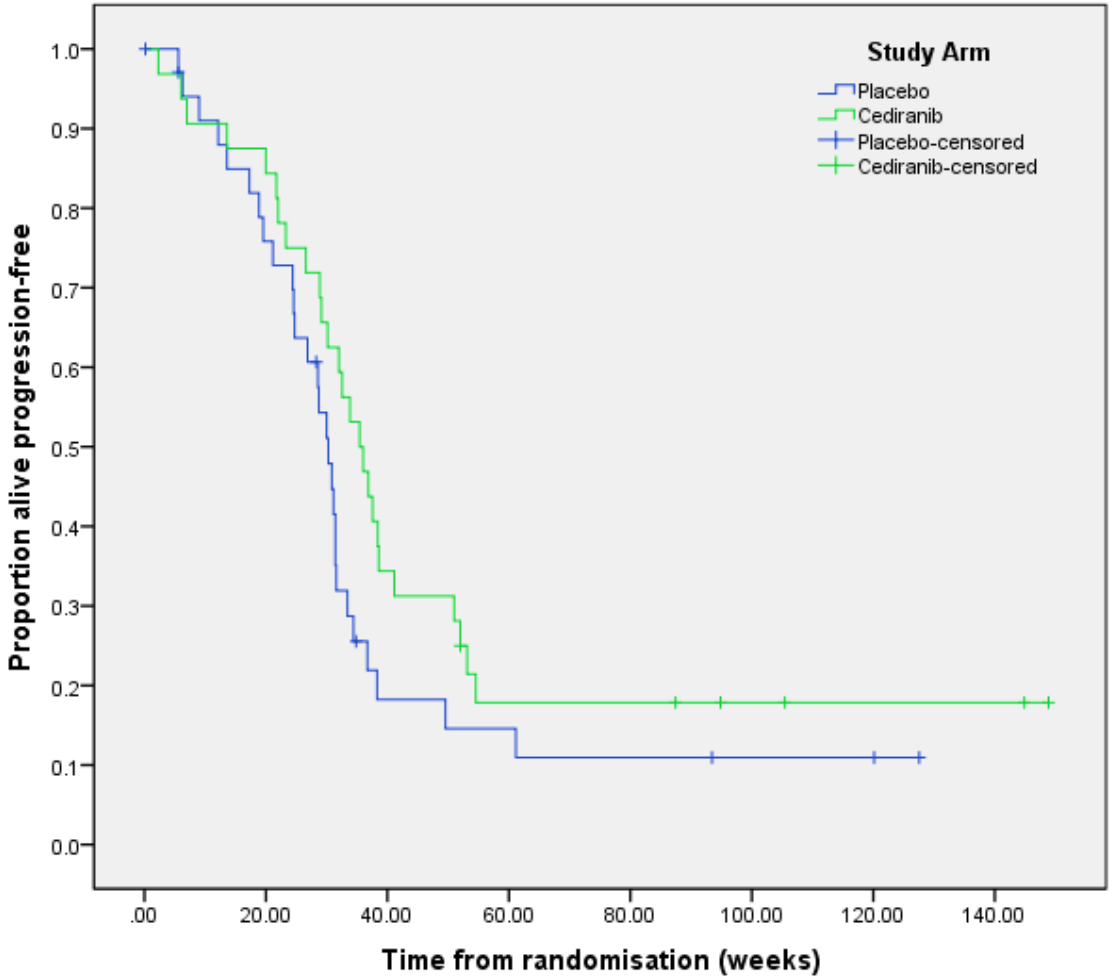
HR[1] A/P 0.61 (80% CI 0.41 – 0.89) P (1-sided) = 0.046

	Median OS (wks)	80% CI
Cediranib (A)	59	(50-75)
Placebo (P)	63	(55-80)

HR[1] A/P 0.93 (80% CI 0.64 – 1.36) P (1-sided) = 0.401

1. Estimated HR adjusted for stratification factors

Results



Patients at risk

Week	0	20	40	60	80	100	120	140
Placebo	35	25	5	4	3	2	2	0
Cediranib	34	27	11	5	5	3	2	2

Results

Response Rate

	CR	PR	Overall (80% CI)
Cediranib	3 (9.4%)	18 (56.3%)	66% (53%-77%)
Placebo	0 (0.0%)	13 (41.9%)	42% (30%-55%)

P (1-sided) = 0.030

Median change in log_{10} VEGFR-2 from baseline at 28 days

Cediranib -0.036 (iqr* -.097 to .048, n=18)

Placebo 0.067 (iqr .016 to .134, n=22)

*interquartile range

P (1-sided) = <0.001

Toxicity

	Cediranib		Placebo
Diarrhoea *(Grade 2/3/4)*	50%		18%
		P= 0.005	
Hypertension *(Grade 2/3/4)*	34%		12%
		P= 0.038	
Neutropenia *(Grade 3/4)*	31%		9%
		P= 0.019	
Overall AE *(Grade 2/3/4)* during study drug only period	19%		9%
		P= 0.240	

No treatment related deaths

Further analysis

- Individual patient correlation with response/fall in VEGFR-2 levels
- Correlation with other biomarkers

Conclusion

- PFS, inhibition of VEGF-2 receptor and response rate significantly increased in Cediranib arm.

- This was accompanied by a manageable increase in diarrhoea, hypertension and neutropenia.