A phase II study evaluating the safety and anti-tumour activity of avelumab and cetuximab in recurrent/metastatic squamous cell carcinomas

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Background

Patients with recurrent or metastatic squamous cell carcinoma (SCC) have low response rates to second line therapies, including PD-1 inhibitors nivolumab and pembrolizumab, representing an area of unmet clinical need. Cetuximab has modest activity as a single agent but potentiates the activity of radiotherapy in locally advanced head & neck SCC (HNSCC) and chemotherapy in recurrent or metastatic HNSCC. Cetuximab initiates Natural killer cell antibody-dependent cell-mediated cytotoxicity, resulting in an anti-tumour immune response and the potential to augment the activity of PD-1/PD-L1 inhibition.

Methodology

This was a randomised phase II trial preceded by a safety run-in phase. Entry for the safety run-in required histologically confirmed incurable recurrent or metastatic (R/M) SCC of any body site with: measurable disease by RECIST v1.1, unless by PD-L1 expression; no previous treatment with cetuximab for R/M disease; WHO performance status of 0 or 1. Prior therapy with anti-PD-1, anti-PD-L1 or anti-PD-L2 was excluded. Patients with undifferentiated carcinomas, nasopharyngeal or sino-nasal cancers were excluded. Previous treatment with an investigational agent, monoclonal antibody therapy, chemotherapy, targeted small molecule therapy or radiotherapy was required to have ended prior to trial entry. Patients received avelumab 10 mg/kg + cetuximab 500 mg/m² intravenously every 2 weeks, for up to 1 year. Primary endpoint was occurrence of dose-limiting toxicity within 42 days of treatment starting, graded using CTCAE v5. Secondary endpoints were objective response (ORR) and disease control rate (DCR) at 6 and 12 months using iRECIST. 16 patients were recruited to the safety run-in from 2 sites across the UK between July 2018 and October 2019. Due to funding constraints the trial did not progress to the randomised phase of the trial.

Trial Design

Eligible patients:
- Recurrent/metastatic, SCC
- No prior cetuximab for metastatic/recurrent disease
- Measurable disease
- No contra-indications for immunotherapy

Register patient

Cycle 1 – DLT assessment period
- Day 1
  - Cetuximab 500 mg/m² given IV over ~3 hours
- Day 15
  - Cetuximab 10 mg/kg given IV over ~3 hours, followed by Avelumab 10 mg/kg given IV over ~1 hour

Cycle 2 – DLT assessment period to day 34
- Days 3, 8, 15
  - Cetuximab 500 mg/m² given IV over ~2 hours, followed by Avelumab 10 mg/kg given IV over ~1 hour

All other cycles (up to 1 year of treatment)
- Days 3, 8, 15
  - Cetuximab 500 mg/m² given IV over ~2 hours, followed by Avelumab 10 mg/kg given IV over ~1 hour

Completion of treatment visit

Follow up for safety
- every 38 days for up to 90 days after last dose of treatment

Follow up for disease assessment
- every 3 months up to end of year 2 or PD

Baseline characteristics (n=16)

| Age (in years) | Median 58 years (range 34-88) |
| Sex | Male 12, Female 4 |
| Site of primary | Head and Neck 12, Penile 1, Anal 1, Cervical 1, Skin 1, Oesophagus 0, Vulval SCC 1 |
| Extent of Relapse | Local recurrence 9, Lung 8, Liver 0, Bone 1, Nodal 4, Other 3 |
| WHO status | 0 5, 1 11 |
| Smoking status | Ex-smoker 10, Current smoker 1, Never smoker 5 |

Results

Toxicity

➢ No patients experienced dose-limiting toxicities.
➢ No Treatment related deaths. Grade 3 Adverse Events were seen in 4 patients; Grade 5 in 3 patient. None were related to trial treatment.
➢ Grade 1/2 rash, related to treatment, but manageable, was seen in 11 patients.

Response

Patients evaluable for response by iRECIST (n= 11*)

| Complete response | 2 (1 CR in lymph nodes) (18%) |
| Partial response | 4 (36%) |
| Stable disease | 4 (36%) |
| Progressive disease | 1 (9%) |

Duration of follow up and response

Conclusion

Avelumab + cetuximab is safe and tolerable and demonstrates promising efficacy in recurrent or metastatic squamous cell carcinoma patients