# Phase 2a, open-label, multi-dose study of the anti-kappa monoclonal antibody, MDX-1097, in relapsed kappa-chain restricted multiple myeloma with stable measurable disease

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## INTRODUCTION

The majority of multiple myeloma (MM) patients initially show responses to biological agents such as the immunomodulatory drugs (IMiDs; thalidomide, lenalidomide and pomalidomide) and the proteasome inhibitor bortezomib, however re-emergence of active disease is invariable. Therefore, more effective and tolerable therapeutic approaches are required for MM.

In this context we have developed a monoclonal antibody, MDX-1097, that binds to a tumour specific antigen, kappa myeloma antigen (KMA), which consists of membrane associated κFLC that is not bound to immunoglobulin heavy chain[1-3]. KMA is expressed on malignant plasma cells present in the bone marrow of patients with kappa restricted MM (κMM) and human myeloma cell lines. A human tissue cross-reactivity study of MDX-1097 binding confirmed the specificity for KMA as no off target binding was observed. Both in vitro and ex vivo studies have demonstrated that the anti-tumor activity of MDX-1097 is mediated via antigen dependent cellular cytotoxicity (ADCC) and this effect is augmented in combination with the IMiDs[4].

Previously a phase I, open-label, single ascending dose study was conducted in κMM patients to determine the safety, tolerability, maximum tolerated dose (MTD) and biologically relevant dose of MDX-1097. No DLTs were reported and the MTD was not reached up to the highest dose of 10 mg/kg. At all dose levels MDX-1097 was detectable in serum for up to 15 days post-infusion and no soluble antigen sink was observed. No conventional disease responses were observed, however, one patient with light chain only κMM treated at the highest dose level showed a sustained decrease in serum κFLC levels of ≥50% for 3 months post infusion. A second patient in the 3mg/kg cohort had resolution of bone pain and activity of MM on 18FDG-PET scanning[5].

Based on the positive safety, pharmacokinetic and efficacy data at 10 mg/kg a Phase 2a multi-dose study of MDX-1097 was carried out.

## OBJECTIVES

**Primary Objective:** To assess the efficacy of MDX-1097 in previously treated MM subjects with stable measurable disease.

**Secondary Objectives:**

To characterize the safety and tolerability of MDX-1097, including acute and chronic toxicities.

To evaluate the multiple-dose pharmacokinetics of MDX-1097.

To evaluate the immunogenicity of MDX-1097.

To assess duration of response in the Follow Up Phase.

## METHODS

The study followed a Simon two-stage minimax design, with >1 response needed in the first 13 patients to expand the study. Responses were evaluated by IMWG guidelines (Durie et al, 2006). Eligible patients were administered MDX-1097 at 10mg/kg by a 90 minute intravenous infusion weekly for 8 weeks (ie. a total of 8 doses at 10mg/kg). Efficacy and safety data included vital signs, physical examination, ECG, haematology assessments, clinical chemistry, C-reactive protein, β2 microglobulin, immunoglobulin quantification, urinalysis, and creatinine clearance. Patients entering the study demonstrated stable measurable disease for >3 months prior to study entry and were allowed to continue existing maintenance therapy for MM including lenalidomide or thalidomide and low dose steroids throughout the trial. This study was conducted in accordance with ICH-GCP recommendations.

## RESULTS

A total of 19 patients completed the study. The 8 weekly doses of 10 mg/kg MDX-1097 were completed by all patients and were well tolerated. The overall incidence of adverse events (AEs) are summarised in Table 1.

The evaluation of best overall disease response is shown in Table 2.

**Table 1. Summary of Adverse Events**

| | Number of Patients (%) with Adverse Events [Number of Adverse Events] 10 mg/kg MDX-1097(N=19) |
|---|---|
| **All treatment emergent adverse events** | |
| Grade 1 | 15 (78.9%) [56] |
| Grade 2 | 14 (73.7%) [24] |
| Grade 3 | 4 (21.1%) [4] |
| Grade 4 | 0 |
| Total | 18 (94.7%) [84] |
| **Possibly, probably, or definitely related adverse events** | |
| Grade 1 | 6 (31.6%) [27] |
| Grade 2 | 6 (31.6%) [10] |
| Grade 3 | 1 (5.3%) [1] |
| Grade 4 | 0 |
| Total | 9 (47.4%) [38] |
| **Patients discontinued due to adverse events** | |
| Total | 0 |
| **Patients with dose limiting toxicities** | |
| Total | 0 |
| **Patients with serious adverse events** | |
| Total | 3 (15.8%) [3] |

Grade 1 and 2 AEs considered to be related to MDX-1097 included fatigue (3 patients) and infusion related reactions (4 patients). Grade 3 AEs of complete heart block, pneumonia and anaemia were considered unrelated to MDX-1097. One Grade 3 AE of acute pancreatitis occurred 58 days after completing MDX-1097 therapy and was considered possibly related to treatment by the Investigator. The independent Data Monitoring Committee reviewed the data and concluded that the event was unlikely to be related to study drug. There were no emergent dose limiting toxicities on study and no patients were discontinued due to adverse events.

**Table 2. Evaluation of Best Overall Disease Response**

| | Number of Patients (%) with Response 10 mg/kg MDX-1097 | |
|---|---|---|
| Response | Per-protocol Population (N=18) | All Patients Population (N=19) |
| Stringent complete response | 0 | 0 |
| Complete response | 0 | 0 |
| Very good partial response | 1 (5.6%) | 1 (5.3%) |
| Partial response | 1 (5.6%) | 2 (10.5%) |
| Minimal response | 3 (16.7%) | 3 (15.8%) |
| Stable disease | 10 (55.6%) | 10 (52.6%) |
| Disease progression | 2 (11.1%) | 2 (10.5%) |
| Not evaluable | 1 (5.6%) | 1 (5.3%) |

In the Per-protocol Population a VGPR and a PR were observed in two patients both of whom had been on maintenance lenalidomide for > 18 months. The All Patients Population included a patient with rapidly progressive κ light chain MM on no other therapy who did not meet the eligibility criteria but nevertheless received 8 doses of MDX-1097 and achieved a PR lasting >6 months.

## SUMMARY

- The best overall disease response was a VGPR for 1 patient, PR for 2 patients, MR for 3 patients, SD for 10 patients and PD for 2 patients. The VGPR is presently ongoing after 6 months.
- Multiple IV doses of 10 mg/kg MDX-1097 were well tolerated. There were no dose limiting toxicities and no patients were discontinued due to adverse events.
- Fatigue and mild infusion-related reactions were the most frequently reported drug-related adverse events.
- Multiple IV doses of 10 mg/kg MDX-1097 had no effect on serum biochemistry, haematology and urinalysis laboratory evaluations, vital signs, 12-lead ECGs and physical examinations.
- MDX-1097 had a low volume of distribution which suggests the antibody is confined to the blood and extracellular fluid spaces. The mean terminal half-life following the final 10 mg/kg dose was 315 hours (~13 days).
- During the study 8 of the 19 patients (42%) had ongoing medication for treatment of their multiple myeloma (26% lenalidomide, 26% dexamethasone, 16% thalidomide, 5% cyclophosphamide). The addition of MDX-1097 did not alter the safety profile of these other drugs.

## CONCLUSION

In this Phase 2a trial MDX-1097 showed favourable pharmacokinetics, an excellent safety profile and demonstrable activity against κ light chain-restricted MM. A randomised trial exploring lenalidomide with or without MDX-1097 for relapsed/refractory MM will commence in late 2013.

**REFERENCES**

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