Clinical outcomes and survival of patients with myeloma and lymphoma enrolled into phase I clinical trials

The primary objectives of phase 1 trials are typically to assess the safety and tolerability of investigational agents and to determine the recommended phase 2 dose. They are not generally statistically powered to assess efficacy (Peppercorn, 2006; Kimmelman, 2017). However results from first-in-human studies for haematological cancers have been used in applications to regulatory authorities for fast-track approval designation. These patients typically have no standard treatment options, but meet strict trial eligibility criteria. Whilst trials are reported individually, outcomes once patients stop trial therapy is generally not collected [except overall survival (OS)], the assumption being that most receive supportive care alone. In solid cancers, prognostic scores at trial entry have been proposed which may aid patient selection (Horstmann *et al*, 2005; Arkenau *et al*, 2008; Wheler *et al*, 2012); however this has not been investigated for haematology patients entering phase 1 trials.

We therefore investigated the outcomes of patients with haematological malignancies treated in phase 1 trials at a large specialist haematology centre. The primary and secondary objectives were to assess OS, adverse events and subsequent treatment. Exploratory objectives were to identify potential predictive markers of outcome. Patients with histologically proven relapsed/refractory myeloma or lymphoma enrolled onto a phase I or I/II trial between March 2012 and February 2017 that had at least one dose of the study drug were included. Toxicity was assessed and graded by National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). Informed consent for participation in the relevant trial, approved by the UK Health Research Authority was obtained. Statistical methods were as described in Appendix S1.

Eleven trials (six myeloma, five lymphoma, two-first-in-human) recruited between 2012 and 2017. These included monoclonal antibodies (two trials) and small molecule inhibitors (9 trials), of which four were combinations. Sixty-eight patients were recruited to at least one trial, eight onto two and each entry was considered a separate event (total 76 patient trial episodes). Baseline characteristics are given in Table I. Forty-three patients had myeloma and 25 had lymphoma [diffuse large B cell lymphoma (DLBCL), $n = 12$; indolent lymphoma, $n = 9$, including one enrolled on a second trial for transformed DLBCL; Hodgkin lymphoma, $n = 2$; Adult T cell leukaemia/lymphoma, $n = 1$; and T cell lymphoma, $n = 1$). Of the 76 patient trial episodes, 65 discontinued treatment by data cut-off. This was due to disease progression ($n = 41$) and 'lack of efficacy' (investigator decision for stable disease, $n = 3$); toxicity ($n = 7$), four mandated by the trial protocol (including 3 dose-limiting toxicities), and three due to patient decision; three completed the set number of treatments on protocol. Ten came off study to undergo autologous stem cell transplantation (ASCT) and one came off due to revision of the histological diagnosis (Figure S1). No toxicity-related deaths occurred.

After a median follow-up of 17 months [95% confidence interval (CI) 7–27] the median OS was 24 months (95% CI 14–35) (myeloma: 31 months, lymphoma: 6 months) with a 2-year OS of 47% (Fig 1A, B). Fifty-four patients discontinued their trial (exluding those with planned ASCT), of which 33 recieved further therapy [another trial (8, 24%) or off-trial (25, 76%)], 9 recieved supportive care only and outcomes are unkown for 12. Of the 33 having further treatment, those that responded to their trial treatment (≥partial response) appeared to have a better OS than those that did not, suggesting more sensitive disease (Fig 1C).

Exploratory analyses (Fig 1D–F) revealed no difference in OS according to age > or <65 years (World Health Organization definition of elderly), however survival was inferior for those ≥75 years vs. <75 years (3 vs. 24 months, $P = 0{\cdot}045$). The number of prior lines of therapy was not associated with survival. In univariate analysis, raised lactate dehydrogenase (LDH) at trial entry was associated with a worse outcome, however haemoglobin <100 g/l or albumin <35 g/l was not significant. Multivariable analysis for haemoglobin ≥100 g/l, albumin ≥35 g/l, LDH ≤225 iu/l, age and disease type were significantly associated with outcome (except for haemoglobin), with disease type [Hazard ratio (HR) 5·1 95% CI 1·7–15·6, $P = 0{\cdot}004$] and LDH (HR 3·6 95% CI 1·4–9·4, $P = 0{\cdot}008$) having the largest HR. OS did not differ for those with Grade 3/4 toxicity related to the trial agent compared to those who did not. Patients who had a dose interruption of greater than a week had a median survival of 51 months compared to 16 months, $P = 0{\cdot}03$. This may be artefactual due to the longer exposure time on treatment for the patients that responded.

Phase 1 trials are important for the development of novel agents for cancers. The American Society of Clinical Oncology (ASCO) policy statement emphasised the therapeutic role of phase 1 trials in cancer (Weber *et al*, 2017). As with our cohort, ASCO commented that many patients enrolled onto

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Table I. Patient Characteristics at trial entry, length of time on trial, overall response rate and toxicities.

	Overall	Myeloma	Lymphoma	*P* value
Total number of patients	76	48	28	
Sex (male/female)	44/32	22/26	22/6	0·008
Age at trial entry (years)	59 (31–80)	60 (41–75)	59 (31–80)	0·81
Time from diagnosis to trial entry (months)	45 (2–199)	55 (12–199)	24 (2–140)	0·001
Number of lines of prior therapy	3 (1–8)	3 (1–7)	4 (1–8)	0·11
Time on trial (months)	4 (0·5–24)	5 (0·5–24)	2 (0·5–20)	<0·0001
Number of cycles on trial	5 (0·5–27)	6 (0·5–27)	2 (0·5–27)	0·001
Patients with dose interruptions > 1 week	26	18	8	0·43
Patients with dose modification	23	20	3	0·004
Patients with Grade 1/2 AEs due to IMP	67	43	24	0·4
Patients with Grade 3/4 AEs due to IMP	26	12	14	0·03
Overall response rate (%) (achieved PR or better)	53	69	25	<0·0001

AEs, adverse events; IMP, investigational medicinal product; PR, partial response.
All value reported as number or median (range) unless otherwise noted.

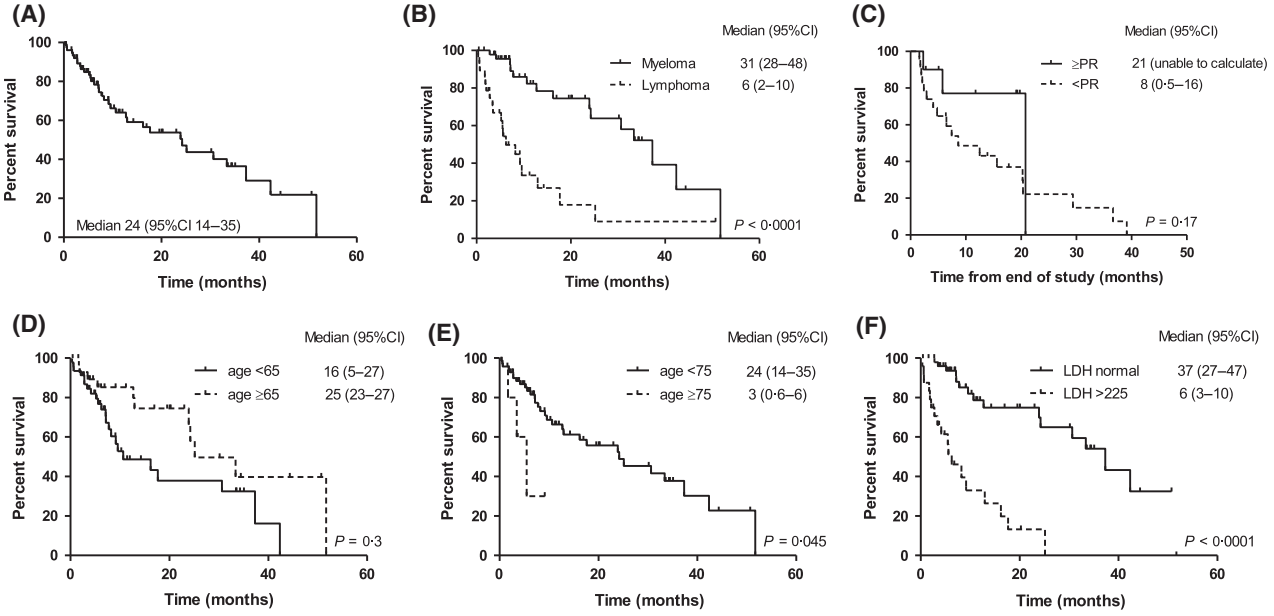

Fig 1. Overall survival in (A) the whole cohort, (B) split by disease sub-type, (C) in patients who went on to have further treatment after trial split by response in trial, (D) age above and below 65 years, (E) age above and below 75 years and (F) according to LDH above and below upper limit of normal.

these trials go on to have further therapy, challenging the paradigm that phase 1 trials are offered to patients with no other options except palliation. The longer survival of myeloma patients compared to those with lymphoma reflects the difference in disease biology (half had high grade disease). However, the efficiacy of novel agents and the ability to effectively salvage these patients with subsequent therapies is likely to be contributory to better outcomes for both groups. Whilst age >75 years was associated with inferior survival, fraility analysis was not collected in these studies, which may provide more useful information. Both LDH and albumin were independent prognostic indicators in this cohort and may be helpful to guide trial participation discussions. However larger prospective studies are required to validate this.

In conclusion, the survival of patients with myeloma and lymphoma enrolled onto early phase trials were better than expected. This may be partly due to patient selection, but probably also reflects improvements in the efficacy and tolerability of new therapies under evaluation. These included monoclonal antibodies and other immunotherapies showing promise. This data provides further evidence that pateints can derive clinical benefit from experimental agents and we recommend that suitable patients should be considered for phase 1 trials. Importantly, a significant number of patients

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were able to receive further treatment, including other clinical trials, following completion of the phase 1 study, signyfiing that many continue to retain a good performance status and organ function at this stage.

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Conflicts of Interest

WT received honoraria from Roche and Gilead. DE, CN, EMP, KLY, KMA, AK and RP declare no potential conflict of interest.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Supplementary methods.

Fig S1. Consort diagram summarising reasons patients came off trial.

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