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Daratumumab, cyclophosphamide, bortezomib and dexamethasone for non-transplant eligible myeloma (AMaRC 03-16)

Tracking no: ADV-2023-012539R2

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Abstract:
In newly diagnosed transplant-ineligible patients with myeloma, daratumumab has improved outcomes when added to the standard of care regimens. In a randomized trial, we tested whether similar improvements would be seen when daratumumab was added to the bortezomib, cyclophosphamide and dexamethasone (VCD) regimen. Non-transplant eligible patients with untreated myeloma were randomized to receive VCD or VCD plus daratumumab (VCDD). 121 patients were randomized, 57 in the VCD arm and 64 in the VCDD arm. Baseline characteristics were balanced between the two arms. The median PFS was 16.8m (95%CI 15.3 - 21.7m) and 25.8m (95%CI 19.9 - 33.5) in the VCD and VCDD arms, respectively (HR 0.67, log-rank test p=0.066). In a pre-planned analysis, the estimated PFS at fixed time-points post-randomization demonstrated significantly improved PFS for the daratumumab containing arm from 18 months onwards. The proportions of patients who were progression free at the following time points were: 18 months, 48% vs 68% (p=0.0002); 24 months, 36% vs 52% (p=0.0001); and 30 months, 27% vs 41% (p<0.0001) in the VCD and VCDD arms, respectively. The best overall response and VGPR rate were significantly better in the daratumumab arm (65% vs 86%, p=0.007 and 28% vs 52%, p=0.009) for the VCD and VCDD arms, respectively. Seventy-two percent of the VCDD patients completed the 9 cycles of induction therapy with no grade 3 or 4 peripheral neuropathy adverse events. This study supports VCDD as an option for the initial treatment of non-transplant eligible patients with myeloma. Australian and New Zealand Clinical Trials Registry (ACTRN12617000202369). https://www.anzctr.org.au/

Conflict of interest: COI declared - see note

COI notes: PM is a member of Advisory Boards for Amgen, BMS, Janssen, Caelum, EUSA, Pfizer, SkylineDx and Takeda (no personal fees received) and has received research funding from Janssen and Pfizer. JR is a current equity holder in Novartis AG and Alcon and has received research funding from Abbvie. WJ is a member of Advisory Boards for BMS, Astra Zenica, Janssen and Amgen and has performed consultancy work for Celgene. HQ is a member of Advisory Boards and has performed consultancy work for Amgen, Sanofi, Celgene, Karyopharm, GSK, Janssen, BMS, Antengene, Takeda and CSL and has received research funding from Amgen, Sanofi, Celgene, Karyopharm, GSK and BMS. PC has performed consultancy for Amgen, Astra Zenica, CSL, Janssen, Novartis and Roche and has received research funding from Janssen, Novartis, Roche and BMS. SG has performed consultancy work for Janssen, Celgene, Amgen, Takeda, BMS and Pfizer. NW is a member of Advisory Boards for Amgen. AS has performed consultancy for Celgene, Amgen, BMS, Takeda and STA, has been on the Speaker's Bureau for Celgene, Janssen and Takeda and has received research funding from Celgene, Amgen Janssen, BMS and Takeda. SL, EL, KT, TC, CWB, FK, IK, HW, PJH and NH declare no competing financial interests.

Preprint server: No;

Author contributions and disclosures: PM, JR and AS designed the trial. PM and JR were responsible for overall trial conduct, analysis and writing of the manuscript. WJ, HQ, PC, SG, SL, EL, KT, TC, CW-G, FK, NW, IK, HW, PJH, MFL, NH and AS contributed to patient care and accrual and review of the manuscript. All authors had access to the primary clinical trial data.

Non-author contributions and disclosures: No;

Agreement to Share Publication-Related Data and Data Sharing Statement: Deidentified individual participant data that underlie the reported results may be made available after publication of all study related manuscripts via the AMaRC trial office. Proposals for access should be sent to the corresponding author and will be reviewed by the AMaRC Steering Committee. The study protocol is included as a data supplement available with the online version of this article.

Clinical trial registration information (if any): Australian and New Zealand Clinical Trials Registry (ACTRN12617000202369). https://www.anzctr.org.au/

Title page

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Short title: VCD vs VCD+dara for transplant ineligible myeloma

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Data Sharing Statement:

For original deidentified data, please contact the corresponding author.

Deidentified individual participant data that underlie the reported results may be made available after publication of all study related manuscripts via the AMaRC trial office. Proposals for access should be sent to the corresponding author and will be reviewed by the AMaRC Steering Committee. The study protocol is included as a data supplement available with the online version of this article.

Text word count: 3133

Abstract word count: 244

Number of figures: 5

Number of tables: 4

Number of references: 31

Key points

- the addition of daratumumab to the VCD chemotherapy backbone provides deeper hematological responses and improved PFS

Abstract

In newly diagnosed transplant-ineligible patients with myeloma, daratumumab has improved outcomes when added to the standard of care regimens. In a randomized trial, we tested whether similar improvements would be seen when daratumumab was added to the bortezomib, cyclophosphamide and dexamethasone (VCD) regimen. Non-transplant eligible patients with untreated myeloma were randomized to receive VCD or VCD plus daratumumab (VCDD). 121 patients were randomized, 57 in the VCD arm and 64 in the VCDD arm. Baseline characteristics were balanced between the two arms. The median PFS was 16.8m (95%CI 15.3 – 21.7m) and 25.8m (95%CI 19.9 – 33.5) in the VCD and VCDD arms, respectively (HR 0.67, log-rank test p=0.066). In a pre-planned analysis, the estimated PFS at fixed time-points post-randomization demonstrated significantly improved PFS for the daratumumab containing arm from 18 months onwards. The proportions of patients who were progression free at the following time points were: 18 months, 48% vs 68% (p=0.0002); 24 months, 36% vs 52% (p=0.0001); and 30 months, 27% vs 41% (p<0.0001) in the VCD and VCDD arms, respectively. The best overall response and VGPR rate were significantly better in the daratumumab arm (65% vs 86%, p=0.007 and 28% vs 52%, p=0.009) for the VCD and VCDD arms, respectively. Seventy-two percent of the VCDD patients completed the 9 cycles of induction therapy with no grade 3 or 4 peripheral neuropathy adverse events. This study supports VCDD as an option for the initial treatment of non-transplant eligible patients with myeloma. Australian and New Zealand Clinical Trials Registry (ACTRN12617000202369). https://www.anzctr.org.au/

Introduction

Treatment regimens for elderly patients with myeloma require agents that are both effective and well tolerated. Doses and schedules that are deliverable to transplant-eligible patients are often associated with excess non-hematological toxicity resulting in premature treatment discontinuation and poor efficacy, outcomes that worsen with increasing frailty[1]. Daratumumab has proven to be an ideal treatment for elderly patients due to its anti-myeloma activity and safety profile. Daratumumab, when added to standard of care regimens in relapsed and untreated myeloma, has consistently demonstrated significant improvements in response rates, induction of MRD negative responses resulting in prolonged progression-free survival (PFS) and overall survival (OS) while proving highly tolerable with minor increases in overall regimen toxicity [2-7]. In the setting of newly diagnosed non-transplant eligible patients with myeloma, this benefit of daratumumab was seen when added to the bortezomib, melphalan and prednisolone (VMP) and, lenalidomide and dexamethasone backbones[3, 6].

However, in many jurisdictions the VMP regimen is not widely used with the combination of bortezomib, cyclophosphamide and dexamethasone (VCD) being favoured due to concerns about genotoxicity of melphalan and difficulty of dosing melphalan in renal impairment[8]. VCD has been widely used as initial therapy in elderly populations despite a lack of prospective studies in this population with the majority of publications being in the transplant eligible setting[9-11]. Whether daratumumab improves outcomes in transplant-ineligible patients with newly diagnosed myeloma treated with VCD remains to be tested.

In this report, we present the results of a randomized, Phase 2 trial of a dose-modified VCD regimen suitable for use in elderly patients with or without daratumumab for the treatment of newly diagnosed myeloma in patients who are not eligible for autologous stem cell transplantation.

Methods

Trial design

This was a prospective, multi-centre, open-label, response adapted randomized phase 2 trial of VCD induction compared to VCD and daratumumab (VCDD) induction followed by daratumumab maintenance until disease progression or toxicity. Subjects were enrolled between August 2017 and December 2019 at 18 sites throughout Australia. The study was approved by a nationally approved human research ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonisation - Good Clinical Practice guidelines. All participants gave written informed consent. This study was registered under the Australian and New Zealand Clinical Trials Registry (ACTRN12617000202369).

Patients

Patients had newly diagnosed myeloma and were not considered candidates for high-dose chemotherapy with autologous stem cell transplantation due to either age >65 years or the presence of comorbidities. No prior treatment was permitted with the exception of short course corticosteroids (maximum total 160mg dexamethasone or equivalent) or radiotherapy. Patients needed to have an Eastern Cooperative Oncology Group performance status of 0 to 2 and any degree of renal impairment, including dialysis dependence, was allowed. Exclusions from trial eligibility included: AL amyloidosis, monoclonal gammopathy of uncertain significance or smouldering myeloma; ≥ Grade 3 peripheral neuropathy or Grade 2 neuropathy with pain; and cancer within the prior two years (exceptions were squamous cell and basal-cell carcinomas of the skin, carcinoma in situ of the cervix, Stage 1 prostate cancer). High-risk cytogenetics were defined as the presence of del(17p) and/or t(4;14) and/or t(14;16).

Treatments

VCD consisted of nine cycles (cycle length 35 days) of subcutaneous bortezomib (1.3 mg/m2 on days 1, 8, 15 and 22), oral cyclophosphamide (300mg/m2 on days 1, 8, 15 and 22) and oral dexamethasone (20 mg on days 1, 8, 15 and 22). This schedule of bortezomib was based on a phase 3 GIMEMA (Gruppo Italiano Malattie Ematologiche dell'Adulto) trial where delivery of weekly bortezomib for four weeks for nine five-week cycles significantly reduced neurotoxicity without impacting efficacy[12]. VCDD consisted of VCD plus intravenous daratumumab (16 mg/kg on days 1, 8, 15 and 22 of cycles 1 and 2, days 1 and 15 of cycles 3 to 6, and day 1 of cycles 7 to 9, followed by daratumumab maintenance 16 mg/kg every 4 weeks until progression). The following medications were administered within one hour of daratumumab administration to mitigate the risk of infusion reactions: oral paracetamol (1000mg), oral or intravenous diphenhydramine (25-50mg or equivalent), oral dexamethasone (using the treatment dosing), and optional oral montelukast (10mg). Anti-viral prophylaxis, anti-bacterial prophylaxis and bisphosphonates were mandatory and given according to individual institutional protocols.

Assessments and end points

Response was assessed by the IMWG response criteria[13] with the exception that for patients with disease not measurable by serum monoclonal immunoglobulin, the serum FLC assay was used to assess response in preference to urine Bence Jones proteinuria[14]. A 24 hour urine was only used to assess response in patients whose disease was not measurable by either serum protein electrophoresis (paraprotein <10g/L) or serum FLC (involved FLC ≥100mg/L and abnormal FLC ratio) but was still required to define complete response. Daratumumab interference for patients with a

small residual IgG kappa band running in the same position as the original paraprotein was not resolved and was classified as a very good partial response (VGPR). Response assessments were performed at the end of each cycle of VCD and every 3 months thereafter until disease progression. Minimal residual disease (MRD) was assessed in a central laboratory by multiparameter 8 colour flow cytometry[15] on bone marrow aspirate samples collected in patients achieving VGPR or better after nine cycles of VCD(D). MRD negative status was set at a threshold of 1 myeloma per 10^{-5} white cells). Patients in whom samples were found to be either MRD positive, of insufficient quality or were not assessed were considered to be MRD positive. Adverse events were graded in according to the NCI CTCAE (version 4).

The primary end point was progression-free survival (PFS), defined as the time from randomization to either disease progression or death. Secondary end points were the overall response rates, MRD, overall survival, safety and toxicity, and global health status as measured by the patient reported outcome instrument, EORTC QLQ-C30[16].

Statistical analysis of the primary endpoint

The trial was designed to utilise a response adaptive randomization (RAR) strategy; after a 'burn-in' period of 1:1 randomized allocation of the first 30 patients to the two study arms, RAR was to be used to preferentially assign patients to the study arm that appeared to be superior as assessed by the VGPR rate after four cycles of therapy and regular updating of a model for the relationship between this short-term response endpoint and PFS (details are provided in the Supplementary Protocol). After the trial had commenced, the Trial Management Committee reviewed the timeliness for reports of the short-term response endpoint and ultimately decided not to "switch on" RAR due to delays in reporting coupled with an acceleration in the accrual rate. Consequently, the comparison of PFS between the treatment arms is based on conventional statistical methods rather than a model-based approach that would have attempted to account for deviations from a 1:1 randomization and that relied on an assumed model for a relationship between the response endpoint and PFS. This report uses conventional confidence intervals for responses rates and hazard ratios.

The log-rank test was used to compare the PFS distributions of the two treatment arms. In anticipation of non-proportional hazards and either early or late differences between the treatment arms in their PFS, three comparisons of PFS between the arms were planned and conducted at 6, 12 and 18 months from randomization. To account for multiplicity of comparisons, a Bonferroni adjustment to the alpha-level of each test was implemented, namely a comparison between the treatment arms at one of these time points was judged to be statistically significant if the associated p-value was $\leq \alpha/m$ where $\alpha=0.05$ and $m=3$; the threshold for statistical significance was accordingly 0.0167. Exploratory univariate and multivariate analyses of PFS and OS used Cox proportional hazards regression models to examine associations with treatment arm and the following baseline covariates: age dichotomised at 75 years, R-ISS stage, CKD-EPI 2021 eGFR categories, gender, ECOG performance status, frailty (two levels - frail and non-frail and three levels, frail, intermediate and fit) and cytogenetic risk (standard and high). A landmark analysis was used to assess the impact of post-treatment initiation outcomes (response rate, MRD) on PFS.

Sample size

A total sample size of n=120 patients was selected based on simulations of the trial design and the intended model-based analysis (details are provided in the Supplementary Protocol). With the selected sample size, the false positive (i.e. Type I) error rate was controlled below 5% and the

(Bayesian) power exceeded 80% when the hazard ratio was 0.5 (e.g. median PFS = 24 and 48 months in the VCD and VCDD treatment arms respectively).

The study was approved by a nationally approved human research ethics committee (Alfred Hospital Ethics Committee) on 28 April 2017

Results

Patient and treatment characteristics

A total of 129 patients were randomized but 8 did not commence any trial therapy, 6 from the VCD arm and 2 from the VCDD arm. The following modified intent-to-treat analysis is based on 121 patients, 57 in the VCD arm and 64 in the VCDD arm, who commenced protocol therapy. The disposition of patients through the study is shown in Figure 1.

Baseline characteristics are presented in (Table 1). Median age was 75 years (range, 62-91yrs) with 18% being ≥80 years of age and 31% were female. ECOG performance status was 0 (43%), 1 (36%), ≥2 (19%) and unknown (2%). ISS stage was 1 (21%), 2 (50%), 3 (29%) and 1 unknown. R-ISS stage was I (12%), II (70%), III (10%) and unknown (8%). 16% were known to have high-risk cytogenetics. Disease characteristics were generally balanced between the two arms although there was slightly less advanced stage disease (5.3% vs 14.1%) and high-risk cytogenetics (12.3% vs 18.8%) in the VCD arm compared to the VCDD arm. The median follow-up (by Reverse Kaplan-Meier) is 44.7 months.

Efficacy

Median PFS for the entire cohort was 21.7 months (95%CI, 17.7 – 26.3 months) and was 16.8 months (95%CI 15.3 – 21.7 months) and 25.8 months (95%CI 19.9 – 33.5 months) in the VCD and VCDD arms, respectively (HR 0.67, log-rank test p=0.066). In a pre-planned analysis, the estimated PFS at specific fixed time-points post-randomization demonstrated significantly improved PFS for the daratumumab containing arm from 18 months onwards. The proportions of patients who were progression free at the following time points were: 18 months, 48% vs 68% (p=0.0002); 24 months, 36% vs 52% (p=0.0001); and 30 months, 27% vs 41% (p<0.0001) in the VCD and VCDD arms, respectively.

Subgroup analyses of PFS (Figure 3) demonstrated what appeared to be a significant difference favouring the VCDD treatment arm in the younger age group (p=0.042; HR = 0.508, 95% CI: 0.265 to 0.975) but not in the older age group (p=0.533; HR = 0.834, 95% CI: 0.474 to 1.470). In the younger age group (age < 75 years) median PFS was 16.3 months (95% CI: 10.3 – 26.5 months) and 29.8 months (95% CI: 18.7 – Not Reached) in the VCD and VCDD treatment arms respectively. In the older age group (age 75 years or more) median PFS was 19.0 months (95% CI: 15.0 – 28.5 months) and 23.0 months (95% CI: 17.7 – 31.6 months) in the VCD and VCDD treatment arms respectively. In R-ISS stage 2 patients, the stage with the largest number of patients, there was evidence of a difference favouring VCDD patients (p=0.010; HR = 0.512, 95% CI: 0.308 to 0.851). There was also an apparent difference in the small group of stage 3 patients (p=0.053; HR = 0.202, 95% CI: 0.040 to 1.024). In all subgroups, there was an apparent benefit of daratumumab with estimates of HR consistently < 1.

The best achieved overall response rate was 65% in the VCD arm and 86% in the VCDD arm (p=0.007, Table 2). The rate of ≥ VGPR was significantly improved by daratumumab (28% in VCD arm vs 52% in VCDD arm, P=0.009). Because assays to differentiate daratumumab from residual monoclonal IgG kappa bands were not available in the study, we were not able to accurately assess the impact of daratumumab on complete response (CR) rates. As a result, CR rates remained low in both arms (4% vs 6%, p=0.488). MRD assessment by flow cytometry was hampered by delays in transporting samples to the central laboratory caused by the COVID-19 pandemic which disproportionately affected the VCDD arm. At the end of induction, 11 of 16 patients achieving VGPR

in the VCD arm and 16 of 33 patients achieving VGPR in the VCDD arm had a successful MRD analysis performed. Thus, in the modified intent-to-treat analysis set, 5% of patients in the VCD group compared to 16% of patients in the VCDD arm were flow MRD negative (p=0.066). In a landmark analysis, achievement of flow MRD negativity did not impact on PFS (p=0.255).

Follow-up remains immature to adequately assess for any overall survival differences between the arms (Figure 4). Median OS is estimated to be 58.7 months (95%CI, 47.0 – NA months) in the VCD arm and "not reached" (95%CI, 41.7 – NA months) in the VCDD arm (P=0.392).

Safety

In all, 61% and 78% of patients in the VCD and VCDD groups, respectively, completed all nine cycles of planned induction. Twenty-six percent and 13% completed four or less induction cycles and, 12% and 8% completed five to eight cycles of induction, respectively.

In the VCD group, 82% of the patients had at least one adverse event reported in comparison to 89% in the VCDD treatment arm (Figure 5). There was one Grade 5 adverse event (Other infection) in the VCDD arm. The reporting period, which included the COVID-19 era, was significantly longer for the VCDD group where adverse events continued to be reported during daratumumab maintenance which continued until disease progression. The most common adverse events of any grade were: pain (47% in the VCD group and 48% in the VCDD group), nausea and vomiting (26% and 25% respectively), diarrhoea (21% and 25% respectively), peripheral neuropathy (18% and 28% respectively), fatigue and lethargy (23% and 20% respectively), lower limb oedema (16% and 22%) and upper respiratory tract infections (11% and 27%). Pneumonia occurred in 5% of VCD patients and 11% of VCDD patients. Adverse events reported as "OTHER" while moderately frequent (25% and 39% in the VCD and VCDD arms respectively) but did not exceed Grade 2.

Drug-related adverse events leading to permanent treatment discontinuation occurred in 7% and 3% of patients in the VCD and VCDD arms respectively and adverse events that required a temporary interruption to treatment occurred in 28% and 38% respectively (Table 3). Serious adverse events occurred in 25% of the patients in the VCD treatment arm and 29% in the VCDD arm. There were six early deaths within six months from randomization, one in the VCD arm (respiratory failure n=1) and 5 in the VCDD arm (progressive disease n=2, infection n=3).

Discussion

The addition of daratumumab to the VCD regimen improves the chance of deeper responses (VGPR or better) in elderly patients with myeloma. While there is a trend to daratumumab improving PFS, the primary endpoint of the trial was not met which may be related to the sample size not being large enough to detect a significant difference between the arms. It is also possible that imbalances in disease characteristics between the two treatment arms, such as greater advanced stage disease (14.1% vs 5.3%) and high-risk cytogenetics (18.8% vs 12.3%) in the VCDD arm, could have impacted the primary endpoint analysis. However, in a pre-planned analysis, daratumumab was clearly superior when assessed for PFS benefit at delayed time points after 12 months. The magnitude of improvement in PFS with VCDD versus VCD in this study is slightly less than that observed in randomized trials of daratumumab added to bortezomib-based chemotherapy backbones: the hazard ratio of PFS benefit was 0.50, 0.43 and 0.67 in the ALCYONE[6], OCTANS [17] and our study, respectively. In the context of these other randomized studies there is clear evidence that daratumumab added to bortezomib-based regimens improves PFS in the initial therapy of non-transplant eligible patients with myeloma. While these are active combinations, the most impressive outcomes with daratumumab in the initial treatment of elderly patients with myeloma, both in terms of PFS and OS, have been seen with the lenalidomide and dexamethasone backbone where the addition of daratumumab resulted in a 5-year PFS and OS of 52.5% and 66.3%, respectively[3].

The median PFS of 25.8 months reported in our study appears less than that reported in other trials of daratumumab with bortezomib-based backbones (Table 4). Although cross-study comparisons should be interpreted with caution, this could relate to our study containing an older, more frail population which included patients with severe renal failure and comorbidities. The benefit of daratumumab on PFS was consistent across several subgroups examined with the possible exception of older age. Because of our trial design, we could not determine the presence or degree of benefit associated continuing with daratumumab beyond the initial induction. We observed that the benefit of daratumumab was more pronounced in patients less than 75 years of age than in older patients. Similar trends were seen in the ALCYONE[6] or MAIA[3] trials although the reasons for this lesser relative efficacy have not been explained. It could relate to increased infectious toxicity, especially respiratory tract infections, seen with the addition of daratumumab. The elderly may not tolerate such infections as well as younger patients leading to dose delay or modification, early therapy cessation associated with loss of disease control or, premature death. Such an effect was seen in newly diagnosed, fit, elderly patients where a recent trial reported increased rates of infections leading to death when daratumumab was added to the carfilzomib, lenalidomide and dexamethasone regimen[18]. Otherwise, consistent with other randomized trials of chemotherapy with or without daratumumab, the benefit of daratumumab was seen in adverse disease stages, high-risk cytogenetics, poor performance status and renal impairment subgroups.

Similar to other trials (Table 4) we saw an improvement in the overall hematological response rate with the addition of daratumumab (65% vs 86%) which included a near doubling of deeper responses (VGPR or better 28% vs 52%). Assessment of minimal residual disease was impacted by the COVID-19 pandemic. As a result, while the MRD negative rate on an intent-to-treat basis was tripled in the daratumumab arm (5% in the VCD arm and 16% in the VCDD arm), similar to that seen the ALCYONE trial[6] (6% vs 22% in the VMP and VMP + dataumumab groups, respectively), this difference was not statistically different (p=0.066). Possibly related to the small number of successful MRD specimens, and in contrast to the ALCYONE trial[6], MRD negativity did not predict PFS.

An important issue in the treatment of elderly patients with myeloma is the tolerability and deliverability of the therapy. The improved tolerability of weekly compared to twice weekly

bortezomib in the context of the VMP regimen has been well described[19] and the ALCYONE trial[6] used bi-weekly bortezomib for cycles 1-2 followed by weekly bortezomib for cycles 3-9 in the VMP regimen in recognition of the difficulty of delivering twice weekly bortezomib schedules to the elderly. In the context of the VCD regimen, weekly delivery of bortezomib has been reported in transplant eligible populations[20-23] but there have only been a few small retrospective reports of a weekly VCD regimen for the initial treatment of elderly patients[24, 25]. The schedule of VCD in our trial, utilising four weekly bortezomib doses in a 5-week cycle, proved highly tolerable in spite of the elderly and frail population. Approximately 80% of patients in the VCDD arm completed the planned nine cycles of induction with an all grade peripheral neuropathy rate of 28% with no grade 3 or 4 events. Infective adverse events appeared more common in the daratumumab arm, particularly upper respiratory tract infections (27% vs 11%) and pneumonia (11% vs 5%) which is in keeping with other studies of daratumumab in myeloma[3, 6]. The extended safety monitoring in the VCDD treatment arm which continued throughout maintenance likely accounts for a proportion of the apparently higher infection rates in the daratumumab arm, but this finding mandates close respiratory tract infection monitoring in patients treated with daratumumab and also argues for prospective trials of infection prophylaxis strategies.

In summary, in the initial treatment of elderly, frail patients with myeloma, the addition of daratumumab to this VCD chemotherapy backbone provides deeper hematological response rates and improved PFS from 18 months onwards, although at the expense of increased infectious toxicity. Daratumumab, lenalidomide and dexamethasone remains the current standard of care due to a superior efficacy and toxicity profile. In jurisdictions where this combination is not reimbursed, however, this study supports VCDD, along with daratumumab-VMP as alternate regimens for the initial treatment of non-transplant eligible patients with myeloma.

Acknowledgements

The authors wish to thank the patients and their families and trial coordinators at the sites for their dedication to the study. We also wish to acknowledge the work of the AMaRC Trial Centre Project and Data Managers (Flora Yuen, Nina Byard, Ivy Deng, Khoa Le).

The study was supported with funding and supply of daratumumab for Janssen. Otherwise Janssen had no role in the study design, conduct, analysis or manuscript preparation.

Authorship contributions

PM, JR and AS designed the trial. PM and JR were responsible for overall trial conduct, analysis and writing of the manuscript. WJ, HQ, PC, SG, SL, EL, KT, TC, CW-G, FK, NW, IK, HW, PJH, MFL, NH and AS contributed to patient care and accrual and review of the manuscript. All authors had access to the primary clinical trial data.

Disclosure of Conflicts of Interest

PM is a member of Advisory Boards for Amgen, BMS, Janssen, Caelum, EUSA, Pfizer, SkylineDx and Takeda (no personal fees received) and has received research funding from Janssen and Pfizer. JR is a current equity holder in Novartis AG and Alcon and has received research funding from Abbvie. WJ is a member of Advisory Boards for BMS, Astra Zenica, Janssen and Amgen and has performed consultancy work for Celgene. HQ is a member of Advisory Boards and has performed consultancy work for Amgen, Sanofi, Celgene, Karyopharm, GSK, Janssen, BMS, Antengene, Takeda and CSL and has received research funding from Amgen, Sanofi, Celgene, Karyopharm, GSK and BMS. PC has performed consultancy for Amgen, Astra Zenica, CSL, Janssen, Novartis and Roche and has received research funding from Janssen, Novartis, Roche and BMS. SG has performed consultancy work for Janssen, Celgene, Amgen, Takeda, BMS and Pfizer. NW is a member of Advisory Boards for Amgen. AS has performed consultancy for Celgene, Amgen, BMS, Takeda and STA, has been on the Speaker's Bureau for Celgene, Janssen and Takeda and has received research funding from Celgene, Amgen Janssen, BMS and Takeda. SL, EL, KT, TC, CWB, FK, IK, HW, PJH and NH declare no competing financial interests.

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Table 1. Patient Characteristics

	VCD	VCDD
n	57	64
Age		
Median (range) - yrs	75.4 (62 – 89)	75.9 (64 – 91)
Distribution – no (%)		
< 70 years	8 (14.0)	9 (14.1)
≥ 70 years and < 75 years	16 (28.1)	20 (31.3)
≥ 75 years and < 80 years	24 (42.1)	22 (34.4)
≥ 80 years	9 (15.8)	13 (20.3)
Gender (% male)	59.7%	76.6%
ECOG Performance Status – n (%)		
0	26 (45.6)	26 (40.6)
1	20 (35.1)	24 (37.5)
≥ 2	10 (17.5)	13 (20.4)
Not known	1 (1.8)	1 (1.6)
Revised-ISS Stage – n (%)		
Stage 1	6 (10.5)	8 (12.5)
Stage 2	44 (77.2)	41 (64.1)
Stage 3	3 (5.3)	9 (14.1)
Not known	4 (7.0)	6 (9.4)
Cytogenetics		
Standard risk	43 (75.4)	42 (65.6)
High risk	7 (12.3)	12 (18.8)
Not known	7 (12.3)	10 (15.6)
Renal function		
Median eGFR	65.2mls/min	75.2mls/min
Distribution – n (%)		
≥ 60 mls/min	34 (59.6)	42 (65.6)
≥ 45 and < 60 mls/min	9 (15.8)	12 (18.8)
≥ 30 and < 45 mls/min	13 (22.8)	6 (9.4)
< 30 mls/min	1 (1.8)	4 (6.2)
IMWG Frailty Score – n (%)		
Frail	11 (19.3)	13 (20.3)
Intermediate	23 (40.4)	22 (34.4)
Fit	23 (40.4)	29 (45.3)

ECOG, Eastern Oncology Cooperative Group; ISS, International staging system; eGFR, estimated glomerular filtration rate; IMWG, International Myeloma Working Group

Table 2. Best responses to therapy

	VCD (n=57)		VCDD (n=64)		
	%	95% CI	%	95% CI	P-value
Overall response (PR or better)	64.91	51.13, 77.09	85.94	74.98, 93.36	0.007
CR/sCR	3.51	0.43, 12.11	6.25	1.73, 15.24	0.488
≥VGPR	28.07	16.97, 41.54	51.56	38.73, 64.25	0.009
MR	10.53	3.96, 21.52	6.25	1.73, 15.24	0.394
SD	12.28	5.08, 23.68	0.00	0.00, 5.60	0.004
PD	1.75	0.04, 9.39	0.00	0.00, 5.60	0.287
MRD Negative[1]	5.26	1.10, 14.62	15.63	7.76, 26.86	0.066

VCD, bortezomib, cyclophosphamide and dexamethasone; VCDD, VCD and daratumumab; CR, complete response; VGPR, very good partial hematological response; MR, minimal response; SD, stable disease; PD, progressive disease; MRD, minimal residual disease

[1] Patients not known to be MRD negative, with a missing value, either through a missing or suboptimal sample, are assumed to be MRD positive.

Table 3. Summary of adverse events

AE summary, n (%)	**VCD (n=57)**	**VCDD (n=64)**
Any AE	47 (82.5)	57 (89.1)
Grade ≥3 AE	23 (40.4)	32 (50.0)
Grade ≥4 AE	4 (7.0)	10 (15.6)
Therapy-related AE	37 (64.9)	47 (73.4)
Grade ≥3 TR-AE	13 (22.8)	21 (32.8)
Grade ≥4 TR-AE	2 (3.5)	8 (12.5)
Daratumumab-related AE		34 (53.1)
Grade ≥3 DR-AE		14 (21.9)
Grade ≥4 DR-AE		6 (9.4)
Drug-related AE leading to permanent discontinuation	4 (7.0)	2 (3.1)
Drug-related AE leading to dose interruption/delay	16 (28.1)	24 (37.5)
Any SAE	14 (24.6)	19 (29.7)
Fatal SAE	0 (0.0)	1 (1.6)
Therapy-related fatal SAE	0 (0.0)	1 (1.6)

Table 4. Trials of daratumumab with bortezomib-based chemotherapy in newly diagnosed non-transplant eligible patients with myeloma

	ALCYONE[6]		OCTANS[17]		VCDD		LYRA[26]
n	706		220		121		48
Median age	71yrs		69yrs		75yrs		66yrs
Age ≥ 75yr	30%		15%		50%		21%
ECOG ≥ 2	25%		17%		18%		8%
ISS stage							
Stage 1	19%		25%		19%		33%
Stage 2	42%		44%		46%		33%
Stage 3	38%		30%		27%		33%
High-risk FISH	16%		22%		16%		43%
eGFR <30mls/min	Excluded		0.50%		4%		Not stated
Therapy	VMP	Dara+VMP	VMP	Dara+VMP	VCD	VCDD	VCDD
Response							
ORR	74%	91%	78%	88%	65%	75%	83%
≥VGPR	50%	71%	43%	74%	32%	52%	70%
MRD negative	6%	22%	7%	30%	5%	16%	Not stated
Median PFS	19.3m	36.4m	18.2m	>18.2m	18.9m	25.8m	>36m

ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; FISH, fluorescent in-situ hybridization cytogenetics; eGFR, estimated glomerular filtration rate; VMP, bortezomib, melphalan and prednisolone; Dara+VMP, daratumumab and VMP; VCD, bortezomib, cyclophosphamide and dexamethasone; VCDD, VCD and daratumumab; ORR, overall response rate; VGPR, very good partial response; MRD, minimal residual disease; PFS, progression-free survival

Figure legends

Figure 1. Consort diagram. Patient disposition until the end of cycle 9

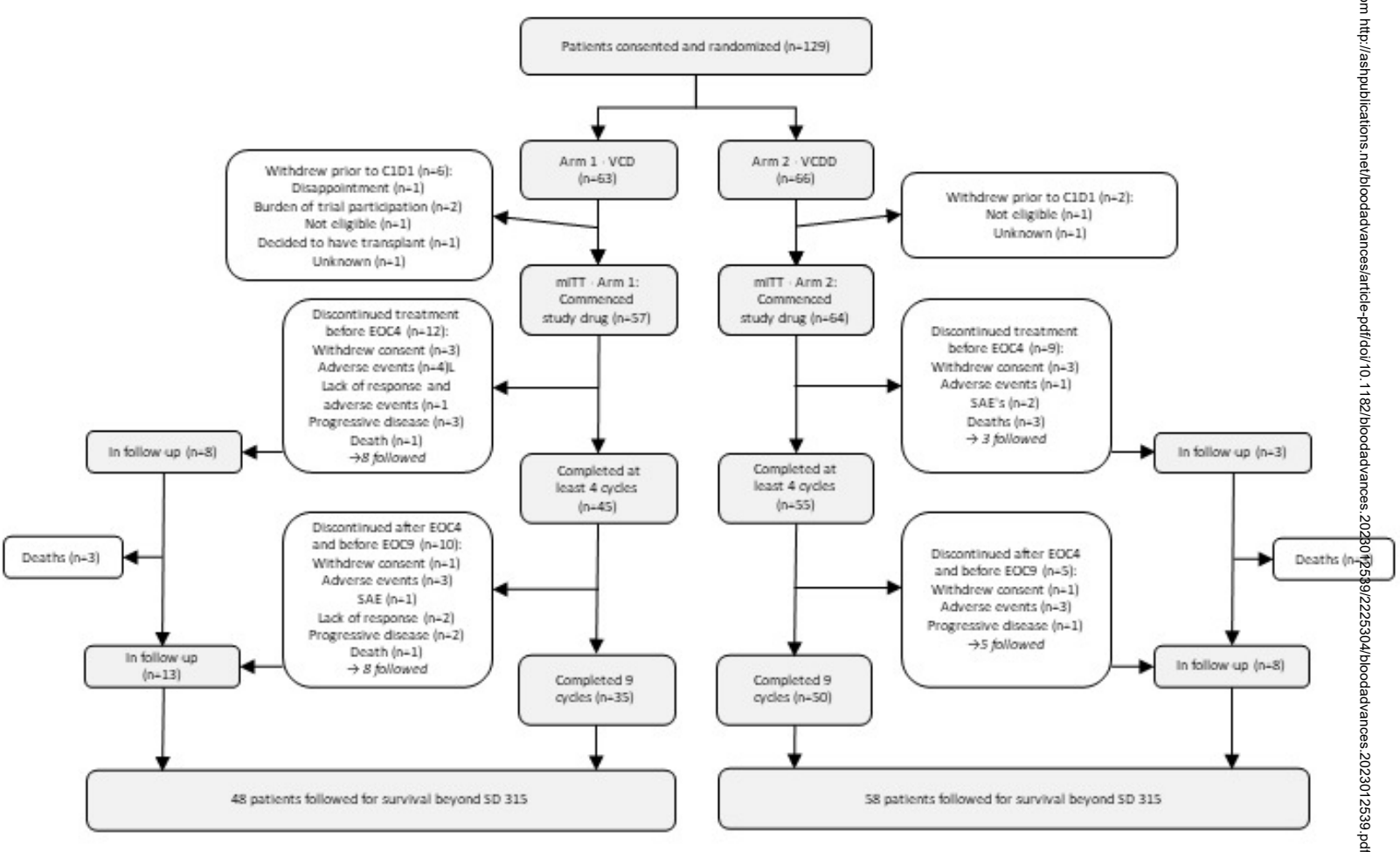
Figure 2. Progression-free survival by treatment arm

Figure 3. Subgroup analysis of progression-free survival

Figure 4. Overall survival by treatment arm

Figure 5. Adverse events according to treatment arm.

Figure 1



C1D1 = Cycle 1, Day 1; SD = Study Day (SD 1 = C1D1); mITT = modified Intention-To-Treat; EOC4 = End Of Cycle 4; EOC9 = End Of Cycle 9; SAE = Serious Adverse Event.

Figure 2

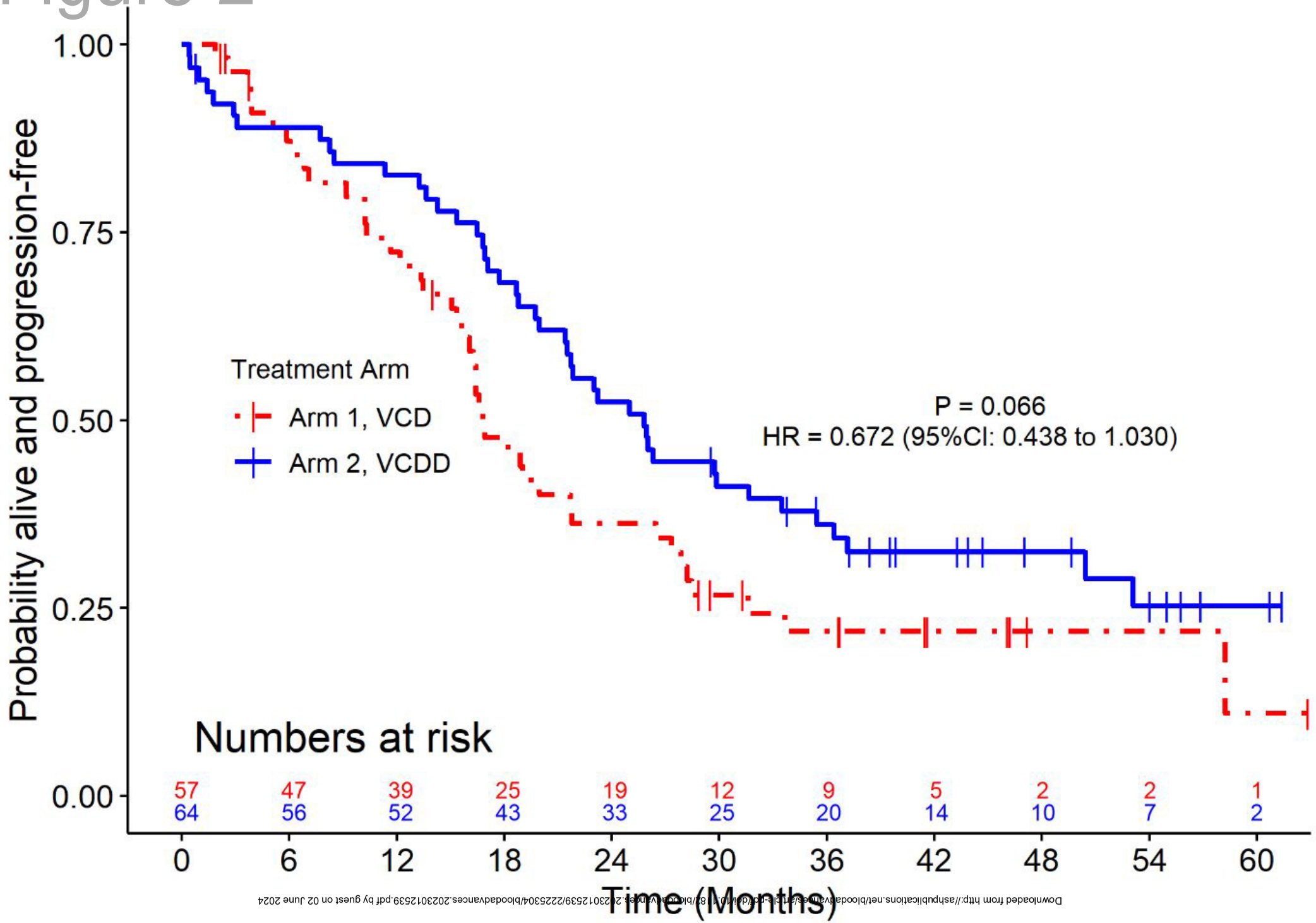


Figure 3

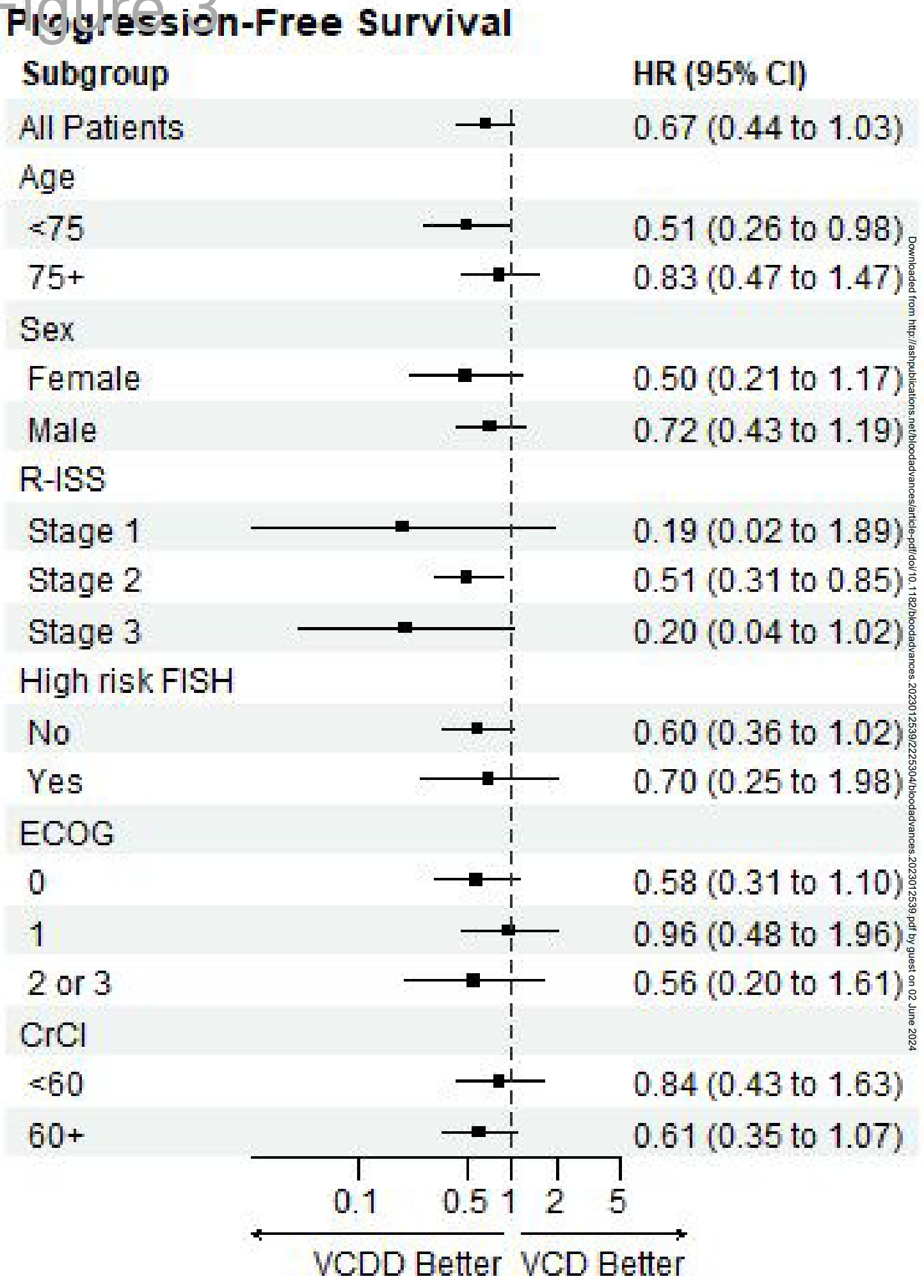


Figure 4

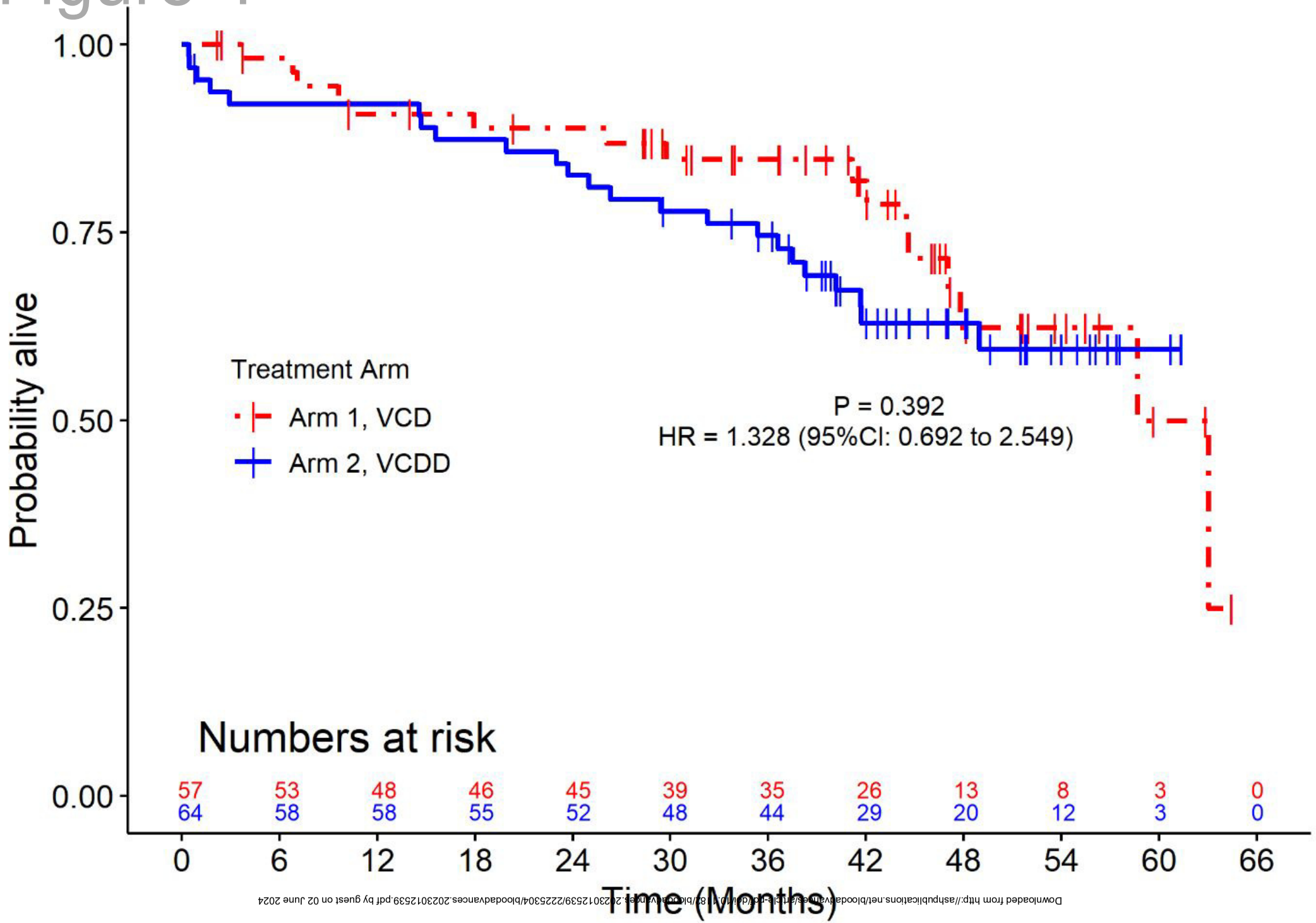
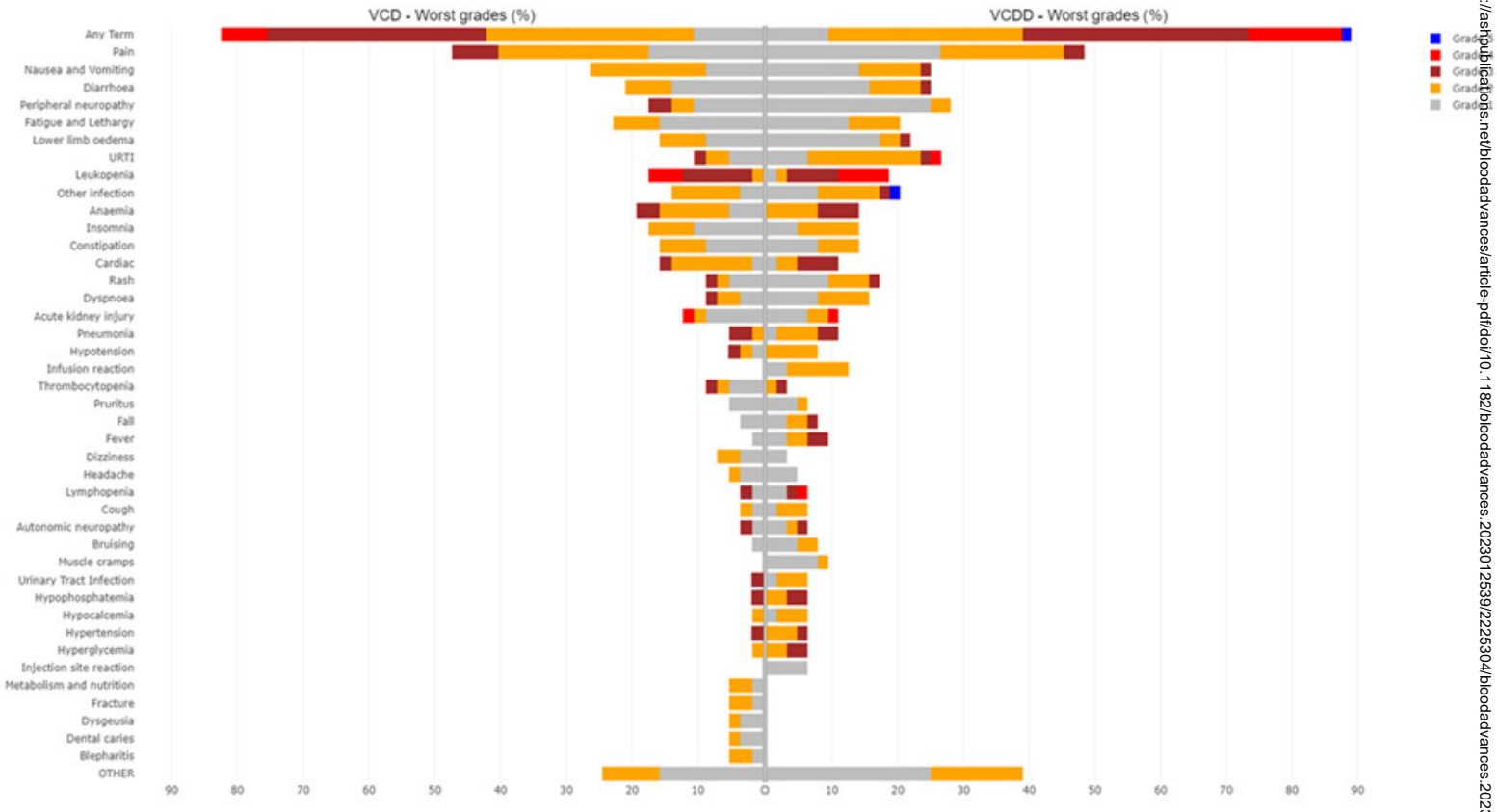


Figure 5



URTI denotes upper respiratory tract infection.

[1]Adverse events that occurred in at least 5% of the patients in either treatment arm, regardless of relationship to study drug, are listed.