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STEM CELL TRANSPLANTATION (R MAZIARZ, SECTION EDITOR)

Should Overall Survival Remain an Endpoint for Multiple Myeloma Trials?

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Abstract

Purpose of Review While the traditional gold standard for demonstrating clinical benefit of a therapy has been to show prolongation of overall survival (OS), there are multiple factors which can hinder the use of OS as a primary endpoint in randomized clinical trials (RCTs). Here, we analyze recent myeloma RCTs and evaluate the issues relevant to current and future myeloma RCT design.

Recent Findings A review of recent phase III RCTs that led to approval of new agents/combinations reveals that none were designed with OS as the primary endpoint, but instead utilized time to progression (TTP) or progression-free survival (PFS). These studies illuminate the inherent difficulties of designing trials with the primary endpoint of OS/PFS in a disease characterized by increasingly prolonged survival times, availability of effective salvage therapies, and competing events such as co-morbid conditions.

Summary Alternative primary endpoints other than OS or PFS need to be developed for future myeloma RCTs. Validated surrogate endpoints with novel clinical trial designs will help improve the feasibility of conducting comparative clinical trials in a timely manner.

Keywords Multiple myeloma · Overall survival · Primary endpoint · Clinical trial

Introduction

With the introduction of the immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and more recently monoclonal antibodies, the survival of patients with multiple myeloma has steadily improved over the past several decades [1]. Traditionally, the gold standard for demonstrating true clinical benefit of a therapy or intervention has been to show prolongation of overall survival (OS) with a favorable risk-to-benefit ratio and impact on health-related quality of life (HRQoL). However, there are multiple practical factors which hinder the routine use of OS as a primary endpoint in clinical trials, including the need for large numbers of patients, prolonged follow-up, and the confounding effects of crossover/post-progression therapies. For some malignancies such as myeloma, the steady approval of new agents and combinations over the past decade has ensured the availability of multiple lines of effective salvage therapies. There is an increasingly important need to define surrogate endpoints that are associated with clinical benefit yet can be reached in a timely manner to allow for rapid translation into the clinic. Here, we provide an overview of the use of different endpoints in oncology and then focus on lessons learned from phase III studies performed in myeloma. We review the recent literature focused on developing novel endpoints in myeloma and discuss the implications for the design of future studies.

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Overview of Clinical Trial Endpoints in Oncology

In the early 1980s, the Food and Drug Administration (FDA) primarily approved drugs based on objective overall response rate (ORR). However, following discussions with the Oncologic Drugs Advisory Committee, the FDA indicated that oncology drug approval should be based on more direct evidence of clinical benefit, including improvements in OS, HRQoL, tumor-related symptoms, and/or physical functioning [2]. It was noted that ORR may not predict these types of clinical benefits. Since that time, several endpoints have become accepted as surrogates for clinical benefit, including disease-free survival (DFS) and relief of tumor-specific symptoms. In 1992, Subpart H was added to the new drug application (NDA) regulations in order to create an accelerated approval process. This process was created to allow patients with life-threatening diseases earlier access to therapies that have evidence of benefit but do not yet meet the standard for regular approval. In this context, the accelerated approval is often based on surrogate endpoints such as DFS, time to progression (TTP), or ORR [3].

Historically, in phase III randomized clinical trials (RCTs), OS has been the gold standard endpoint for demonstrating clinical benefit. OS time does not rely upon surveillance schedules, methods of monitoring, number/location of lesions, or interpretation of patient symptoms, scans, or blood work to draw conclusions concerning disease response. However, a RCT utilizing OS as its primary endpoint usually requires several years of follow-up and large sample sizes. Interpretation of the trial results may become difficult as patients who did not receive the investigational agent in the RCT may receive it later in their disease course or as part of the crossover portion of the RCT. Other potential confounders include variations in supportive care and post-progression therapies over the course of the trial and competing causes of death. Analysis of survival data fails to consider whether the survival period consists of patients receiving multiple lines of therapy in an effort to prolong survival or whether the patient is suffering from a co-morbid condition that will be the eventual cause of death.

TTP and progression-free survival (PFS) are commonly used as primary endpoints in RCTs. Although these studies generally utilize consensus guidelines for determining response (e.g., RECIST criteria for solid tumors, International Myeloma Working Group criteria for myeloma [4]), investigator subjectivity can still be a confounding factor and it is preferable to utilize a blinded external review committee to adjudicate responses. While a study might demonstrate a statistically significant treatment benefit in TTP/PFS, it may not translate to a clinically meaningful OS benefit. TTP and PFS have been proposed as surrogate endpoints for OS. A surrogate endpoint is an outcome measure where changes induced by a treatment intervention reflect changes in the clinical endpoint (such as OS) and reliably predict whether clinically meaningful changes in the clinical endpoint will occur [5]. Fleming and Powers provide insight into why a putative surrogate endpoint may fail to reliably reflect changes in the clinical endpoint [5]. The use of TTP and PFS as surrogate endpoints for OS should be limited to situations where studies have been conducted to validate the association between prolongation in TTP/PFS and a clinically meaningful prolongation in OS. Cartier et al. performed a meta-analysis of 21 myeloma RCTs (14 first-line, 4 maintenance, and 3 relapsed/refractory) using trial-level data [6••]. They found a moderate-to-strong positive correlation between hazard ratios for treatment effects for PFS and OS and advocate that patient-level data be used to validate these findings.

PFS has also been suggested as a possible surrogate for health-related quality of life (HRQoL). However, there has been little work done in this area for myeloma. In a recent study by Kovic et al., a systematic review was performed evaluating 38 randomized oncology studies to determine whether PFS is associated with HRQoL [7]. This study included only one myeloma RCT, and the authors ended up removing this study as an outlier in their analysis. As noted by Freidlin et al., progression in hematological malignancies is often determined by changes in laboratory measures that may not be accompanied by deleterious effects on HRQoL [8].

Phase III RCTs in Multiple Myeloma

A summary of key phase III myeloma studies involving PIs, IMiDs, or other novel agents is provided in Table 1. The majority of these studies changed the standard of care and/or led to the subsequent approval of new agents or combinations. Notably, none of these RCTs were designed with OS as its primary endpoint; rather, the majority used TTP or PFS as the primary endpoint. Whether prolongation of PFS was associated with prolongation of OS in these studies was variable. The interpretation of the impact of the experimental arm/combination on the prolongation of OS is confounded by the large percentage of patients randomized to the standard treatment arm who switch to the experimental arm at disease progression or when PFS findings are released. As OS is a secondary endpoint in many trials, there is often no a priori plan for the number of deaths needed to have sufficient power to detect a pre-specified survival advantage with the experimental regimen. OS findings are often reported when PFS findings are first reported and the early OS findings may not hold or will change with longer follow-up.

In the pooled analysis of two phase III RTCs comparing lenalidomide/dexamethasone to placebo/dexamethasone in relapsed/refractory patients, 48% of patients on the placebo arm received lenalidomide-based therapy after unblinding of the studies (following findings of the first interim analyses of each respective study) or after disease progression [26]. With a median

Table 1 Summary of recent phase III RCTs in myeloma

Study	Patient population	*n*	Randomization	Primary endpoint	OS outcomes
SWOG S0777 [9]	ND	525	RVD vs RD induction	PFS 43 vs 30 months; $p = 0.0018$	Median 75 vs 64 months; $p = 0.025$
GIMEMA-MMY-3006 [10•, 11]	ND TE	480	VTD vs TD (induction, transplant, consolidation)	CR/nCR rate after induction 31% vs 11%, $p < 0.001$	Median: NR vs 110 months; $p = 0.007$
IFM2009 [12]	ND TE	700	Consolidation with single ASCT vs RVD	PFS 50 vs 36 months; $p < 0.01$	4 years, 81 vs 82%
StaMINA [13]	ND TE	758	Single ASCT vs single ASCT + RVD consolidation vs double ASCT	PFS 38 months, 52.2 vs 56.7 vs 56.5%	38 months, 83.4 vs 85.7 vs 82.0%
VISTA [14, 15]	ND TI	682	VMP vs MP	TTP 24.0 vs 16.6 months; $p < 0.001$	Median 56.4 vs 43.1 months, $p < 0.001$
FIRST [16, 17]	ND TI	1623	RD continuous vs RD18 vs MPT	PFS 25.5 vs 20.7 vs 21.2 months	Median 59.1 vs 62.3 vs 49.1 months
HOVON87/NMSG18 [18]	ND TI	668	MPT-T vs MPR-R	PFS 20 vs 23 months; $p = 0.12$	4 years, 52% vs 56%; $p = 0.13$
ECOG E1A06 [19]	ND TI	306	MPT-T vs MPR-R	PFS 21.0 vs 18.7 months; $p = 0.186$	Median 52.6 vs 47.7 months; $p = 0.476$
GIMEMA RV-2009 [20]	ND TE	524	First: ASCT vs MPR; second: R maintenance vs observation	PFS from R1, 43.0 (ASCT) vs 22.4 (MPR) months; $p < 0.001$	4 years, 81.6 vs 65.3%; $p = 0.02$
RV-MM-EMN-441 [21]	ND TE	389	First: ASCT vs CRD; second: maintenance with R vs RP	PFS from R1, 43.3 (ASCT) vs 28.6 (CRD) months; $p < 0.001$	4 years, 86% vs 73%; $p = 0.04$
EMN02/HO95 [22]	ND TE	1266	First: ASCT vs VMP; second: VRD consolidation vs none	PFS from R1 3 years, 66% (ASCT) vs 57.5% (VMP)	Not reported
CALGB 100104 [23•, 24]	Post-ASCT maintenance	460	R vs placebo maintenance	TTP 57.3 vs 28.9 months; $p < 0.0001$	Median 113.8 vs 84.1 months; $p = 0.0004$
IFM 2005–02 [25]	Post-ASCT maintenance	614	R vs placebo maintenance	PFS 41 vs 23 months; $p < 0.001$	4 years, 73% vs 75%; $p = 0.7$
MM-009 and MM-010 [26–28]	R/R	704	RD vs placebo-D	TTP 13.4 vs 4.6 months; $p < 0.001$	Median 38.0 vs 31.6 months; $p = 0.045$
APEX [29, 30]	R/R	669	V vs D	TTP 6.2 vs 3.5 months, $p < 0.001$	Median 29.8 vs 23.7 months; $p = 0.027$
A.R.R.O.W. [31]	R/R	478	Once vs twice weekly KD	PFS 11.2 vs 7.6 months; $p = 0.0029$	Median: NR vs NR; $p = 0.214$
ENDEAVOR [32, 33]	R/R	929	KD vs VD	PFS 18.7 vs 9.4 months; $p < 0.0001$	Median 47.6 vs 40 months; $p = 0.01$
POLLUX [34]	R/R	569	Dara-RD vs RD	PFS: NR vs 18.4 months; $p < 0.001$	Median: NR vs 20.3 months; $p = 0.0534$
CASTOR [35]	R/R	498	Dara-VD vs VD	PFS: NR vs 7.2 months; $p < 0.001$	Median: NR vs NR; HR 0.77, $p = 0.30$
ASPIRE [36, 37]	R/R	729	KRD vs RD	PFS 26.3 vs 17.6 months; $p = 0.0001$	Median 48.3 vs 40.4 months; $p = 0.0045$
TOURMALINE-MM1 [38]	R/R	722	IRD vs RD	PFS 20.6 vs 14.7 months; $p = 0.01$	Median: NR vs NR
ELOQUENT-2 [39]	R/R	646	Elo-RD vs RD	PFS 19.4 vs 14.9 months; $p < 0.001$	Median: NR vs NR
PANORMA-1 [40, 41]	R/R	768	Pano-VD vs VD	PFS 12.0 vs 8.1 months; $p < 0.0001$	Median 40.3 vs 35.8 months; $p = 0.51$
OPTIMISMM [42]	R/R	559	PVD vs VD	PFS 11.2 vs 7.1 months; $p < 0.0001$	Not reported

ASCT, autologous stem cell transplant; *CRD*, cyclophosphamide/lenalidomide/dexamethasone; *D*, dexamethasone; *Dara-VD*, daratumumab/bortezomib/dexamethasone; *Dara-VMP*, daratumumab/bortezomib/melphalan/prednisone; *Dara-RD*, daratumumab/lenalidomide/dexamethasone; *Elo-RD*, elotuzumab/lenalidomide/dexamethasone; *IRD*, ixazomib/lenalidomide/dexamethasone; *KD*, carfilzomib/dexamethasone; *MP*, melphalan/prednisone; *MPR*, melphalan/prednisone/lenalidomide; *MPT*, melphalan/thalidomide/prednisone; *ND*, newly diagnosed; *NR*, not reached; *Pano-VD*, panobinostat/bortezomib/dexamethasone; *PVD*, pomalidomide/bortezomib/dexamethasone; *R*, lenalidomide; *R1*, first randomization; *RD*, lenalidomide/dexamethasone; *RP*, lenalidomide/prednisone; *RVD*, lenalidomide/bortezomib/dexamethasone; *T*, thalidomide; *TE*, transplant eligible; *TI*, transplant ineligible; *VD*, bortezomib/dexamethasone; *VMP*, bortezomib/melphalan/prednisone; *KRD*, carfilzomib/lenalidomide/dexamethasone; *R/R*, relapsed refractory; *VTD*, bortezomib/thalidomide/dexamethasone

follow-up of 48 months for surviving patients, the addition of lenalidomide to dexamethasone significantly improved PFS ($p < 0.001$) and overall survival ($p = 0.045$). In APEX, a phase III RCT comparing bortezomib to dexamethasone in relapsed/refractory patients, 62% of the patients randomized to dexamethasone crossed over to receive bortezomib at time of disease progression [29, 30]. The study was halted at the first interim analysis when the superiority of bortezomib was demonstrated in terms of TTP and OS. Although an OS advantage (HR = 0.57, $p = 0.001$) was seen, the median length of follow-up for those patients still alive was only 8.3 months. This type of post-progression treatment information is not available from some of the more recent studies, but presumably, a significant number of patients randomized to doublet therapies instead of triplet therapies (e.g., those individuals in the lenalidomide/dexamethasone arms of the POLLUX (evaluating the addition of daratumumab [34]) or ASPIRE (evaluating the addition of carfilzomib [36, 37]) trials) later received the novel agent in question with a subsequent line of therapy.

Within the last several years, a number of RCTs in both the newly diagnosed or post-transplant settings have had sufficient follow-up to report median OS data in one or both treatment arms. These findings have provided the field with new benchmarks to judge clinical benefit, necessitating the next generation of RCTs to be longer in duration and/or larger in sample size. For example, CALGB 100104, which randomized patients to either lenalidomide or placebo maintenance following autologous stem cell transplant (ASCT), reported a median OS of 9.5 years and 7.0 years for the lenalidomide arm and placebo arm, respectively [23•]. In this trial, OS time began at the start of ASCT, which was typically 6–12 months after initiation of induction therapy. The GIMEMA-MMY-3006 study, which randomized patients to triple therapy with VTD (bortezomib, thalidomide, dexamethasone) vs doublet therapy with TD (thalidomide, dexamethasone) as induction/consolidation around tandem ASCT, reported a median OS of 9.9 years for the TD arm, but the median has not yet been reached for the VTD arm [10•]. In the relapsed/refractory setting, a number of recent phase III RCTs have demonstrated the superiority of triplet over doublet combinations, where the median OS durations of the triplet arms have either been in the 4-year range [32, 33, 36, 37] or have not yet been reached [34, 35, 38, 39].

In aggregate, these studies highlight the difficulty of planning future prospective phase III RCTs in myeloma with OS as the primary endpoint. When planning such trials, there is often a trade-off between the number of patients that can be enrolled per year and the minimum length of follow-up once enrollment is terminated to ensure there is sufficient number of events to assess the primary endpoint with adequate power. The question often arises whether the duration of the study is too long such that by the time the data are mature, the primary aim may no longer be clinically relevant. The planned SWOG S1803 study is an example of a study which may be hindered by many of these issues. This study is a phase III RCT comparing lenalidomide to daratumumab + lenalidomide maintenance therapy post-ASCT. MRD status is evaluated after 2 years of maintenance. Maintenance therapy is continued for patients who are MRD positive. For patients who are MRD negative, there is a randomization to either continuing or discontinuing maintenance therapy. This study has been designed with OS as the primary objective and powered to compare a median OS of 10 years in the lenalidomide arm to 15.7 years in the combination arm. To achieve this endpoint, 950 patients will need to be accrued over an estimated 6 years, and accounting for dropout, 1100 patients will need to be enrolled. The study has been designed to include a number of interim analyses to evaluate for futility, and there are plans to report earlier endpoints such as the 2-year MRD negativity rate 1 year after all patients are randomized as well as PFS. However, given the very large numbers of patients required, the prolonged enrollment period, and the expected median PFS of the control arm (4.8 years based on CALGB 100104 [23•]), even the earlier endpoints are predicted to be reported at a minimum of 8 years after the start of the study. Given the rapid rate at which the myeloma therapeutic landscape is evolving and other studies such as the randomized phase II study GRIFFIN study which has already completed enrollment and evaluates lenalidomide vs daratumumab + lenalidomide maintenance post-transplant [43], it is possible that by the time the S1803 study is completed, the primary question will no longer be clinically relevant.

As noted in Table 1, nearly all recent phase III studies have used TTP or PFS as the primary endpoint. The IFM 2009 study has provided a new benchmark for PFS in the newly diagnosed, transplant-eligible setting. In this study, 700 newly diagnosed patients were enrolled between 2010 and 2012 and received RVD (lenalidomide, bortezomib, dexamethasone) induction followed by randomization to consolidation with ASCT or RVD. The estimated median PFS was 4.2 years and 3.0 years for the ASCT and RVD arms, respectively [12]. Median OS has not yet been reached for either arm in this study. The StaMINA study is another example that highlights the numbers of patients and duration of follow-up required to evaluate PFS as a primary endpoint in the newly diagnosed setting. This study enrolled 758 patients between 2010 and 2013 and randomized them in equal numbers to single ASCT, tandem ASCT, or single ASCT plus RVD consolidation [13]. This study has required a prolonged follow-up and median PFS numbers have not yet been reported. Thus, the issues of sample size and study duration associated with planning a RTC where OS is prolonged are also present when planning a RTC in a disease setting with a prolonged PFS time. Another issue that arises in planning the analytic approach to be taken when PFS is the primary endpoint is the extent to which competing events prior to disease progression (such as

death due to co-morbid conditions, development of second primary malignancies, or initiation of alternative therapies) may be present in order to avoid biased estimates of effect.

Phase II Studies in Myeloma

Historically, the most common primary endpoint for phase II studies in the relapsed/refractory setting has been the ORR, typically defined as partial response (PR) or better. With the increasing number of salvage therapy options and identification of molecular subtypes with varying prognoses, it is becoming more difficult to determine appropriate benchmarks for determining whether an agent or combination is promising in a given patient population. For example, Vogl et al. conducted a phase II study assessing whether the ORR with the combination of selinexor and dexamethasone in patients with either quad-refractory (defined as refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide) or penta-refractory (quad-refractory plus refractory to anti-CD38 monoclonal antibody) disease was at most 15% against the alternative hypothesis that it was 30% [44]. The observed ORR in this study was 21%. The authors noted that in retrospect, given the lack of suitable comparators with penta-refractory patients, they should have set their threshold at 10% [44].

A number of studies have reported that the achievement of deeper responses (e.g., very good partial response (VGPR) or complete response (CR)) is associated with improved survival outcomes (reviewed in [45]). Several recent phase II studies have as their primary endpoint VGPR + CR rate [46–48] or CR or stringent CR (sCR) rates (NCT02874742, NCT03012880, NCT03012880). However, it is evident that not all patients who achieve CR or sCR have equivalent outcomes. This heterogeneity is in part due to the presence of minimal residual disease (MRD). A recent meta-analysis of studies which evaluated MRD status in myeloma patients who had achieved a CR revealed that MRD negativity was associated with increased PFS and OS compared to MRD positivity [49•].

MRD as an Endpoint in Myeloma Studies

MRD assessment by either flow cytometry or next-generation sequencing (NGS) was incorporated into the International Myeloma Working Group (IMWG) response criteria in 2016 [4]. Currently, these response criteria specify that a minimum sensitivity of 1×10^{-5} be utilized; however, increasingly, a sensitivity of 1×10^{-6} is becoming a standard of care. The prognostic significance of MRD negativity has been confirmed across the spectrum of myeloma, including newly diagnosed transplant-eligible patients undergoing ASCT, newly diagnosed transplant-ineligible patients, patients receiving maintenance therapy, and relapsed/refractory patients (reviewed in [50]). These findings have raised the question as to whether MRD may be a surrogate endpoint for OS. Currently, MRD is considered a prognostic biomarker, defined as a biomarker that can help identify patients at higher risk of adverse disease-related outcomes. In contrast, response biomarkers are defined as being dynamic assessments that show a biological response has occurred in a patient receiving a therapeutic intervention [51].

Validation studies are needed to demonstrate that a change in MRD status reliably predicts a meaningful change in OS. An assay that is reliable, reproducible, and validated for detection of MRD and a cut point for defining negativity are important pieces in the validation process. The clonoSEQ assay, which evaluates MRD by NGS, was recently given de novo designation by the FDA for the detection and monitoring of MRD in myeloma patients (https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm622004.htm). Next steps encompass both individual- and trial-level validations. In planning these validation studies, Kemp et al. point out that care must be given to minimizing measurement error, evaluation bias, attribution bias, or informative censoring which may weaken the association between the potential surrogate and the clinical endpoint [52].

Innovative Clinical Trial Design Strategies

Clinical trial methodology has had to adapt to the changing landscape of limited patient numbers, lower and lower event rates with standard treatments, multiple investigational agents/treatment strategies to be evaluated, costs of trial conduct, and the assessment of multiple clinical and correlative hypotheses. Seamless phase II/III clinical trial designs have been proposed where a number of investigational agents are evaluated and the most promising is then brought forward to be compared to the standard treatment [53]. Multi-arm, multi-stage (MAMS) clinical trial designs were proposed when the objective is to compare a number of investigational treatments to the standard treatment [54]. Pre-planned interim analyses are conducted to determine which experimental treatments should continue until their pre-specified maximum sample size is attained. Treatments that lack sufficient activity can be replaced with new investigational agents.

Insights into the molecular genetic aberrations that drive cancer growth have led to the identification of molecular subtypes within a given primary cancer that have heterogeneous clinical outcomes. Novel agents/treatment strategies are being developed and tested on a limited number of individuals with a given molecular cancer subtype. The umbrella trial design typically involves a set of enrichment trials for patients with a single type of cancer but with different genomic alterations [55]. In contrast, basket clinical trials have been proposed to assess the impact of an investigational agent on cancers with a specific mutation rather than conducting a clinical trial in each specific primary tumor

site [55]. Thus, the validation of surrogate endpoints, coupled with the incorporation of novel clinical trial designs, will enable future comparative clinical trials to be conducted in a timely manner.

Conclusions and Future Directions

The efficacy of the current standard-of-care combinations as well as those containing investigational agents, coupled with the availability of multiple lines of effective salvage regimens, has translated to prolonged OS times for myeloma patients. Moving forward, the detection of clinically significant OS differences will therefore require not only increasingly larger numbers of patients and prolonged follow-up periods but also understanding of the post-progression treatment patterns and competing risks. Thus overall, the conduct of large RCTs with OS, or even PFS as the primary endpoint, is becoming increasingly less feasible in myeloma. While MRD status may prove to be a suitable surrogate endpoint for survival, with the advantage of providing an earlier readout for studies, the identification of molecular subsets of myeloma and the development of therapies specific for those subsets will require novel trial designs that extend beyond the traditional RCT approach.

Compliance with Ethical Standards

Conflict of Interest Sarah Holstein reports serving as an advisory board member for Celgene, Takeda, and Adaptive Biotechnologies and as a consultant for Celgene and GlaxoSmithKline, outside the submitted work. Vera Suman declares no potential conflicts of interest. Philip McCarthy reports receiving honoraria from Bristol-Myers Squibb, Celgene, Sanofi-Aventis, Takeda, and Binding Site and research funding from Celgene and has served on advisory committees/review panels/board membership for Bristol-Myers Squibb, Celgene, Sanofi-Aventis, Takeda, Binding Site, and Karyopharm outside the submitted work.

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- • Of importance
- •• Of major importance

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