RESEARCH ARTICLE

Randomized Controlled Trials versus Single Cohort Studies in Relapse Refractory Multiple Myeloma

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DEDICATION:
This work is dedicated to Dr. Tina Sampalis MD, PhD (1961 – 2020)
Innovator in breast oncology.

Abstract

Background:

The Randomized Controlled Trial (RCT) is considered the gold-standard for the evaluation of treatment efficacy. For rare or end stage cancers for which there are no effective treatments, or the number of patients is sparse, the use of RCTs for the assessment of efficacy and safety may be difficult. In these circumstances the single cohort study (SC) can be considered as an alternative to the RCT.

Purpose:

The purpose of this study was to compare the measures of efficacy as assessed with estimates of the Overall Response Rate (ORR) or Overall Survival (OS) obtained in RCT and SC studies that evaluate the same treatments for Relapse Refractory Multiple Myeloma (RRMM). The study also compared the estimates of ORR and OS ratios between treatments estimated in RCTs and extrapolated in SCs for the same treatments of RRMM.

Methods:

The study utilized data from 42 RCTs and 47 SCs assessing 18 different treatment protocols for RRMM that were identified through a MEDLINE search.

Results:

The results showed that there were no material differences in the demographics of patients enrolled in RCTs and SCs. The estimates of ORR and OS obtained in RCTs and SCs were comparable. Statistically significant Intra-Class Correlation Coefficient (ICC = 0.618, P = 0.027) was observed for ORR and for OS (ICC = 0.734; P = 0.014) indicating good agreement between RCTs and SCs.

Treatment effect size as measured by the ORR and OS ratios (new treatment / control) was ascertained directly from RCTs and extrapolated for SCs based on the control ORR and OS observed in RCTs. There was agreement between RCTs and SCs with respect to the magnitude and direction of the ORR ratios (91% of the studies) and the OS ratios (75% of the studies). With respect to the conclusion regarding the relative efficacy of the new treatment versus the control, there was agreement between RCTs and SCs for 8/11 treatments based on ORR ratios and for 6 / 8 based on OS ratios.

Conclusions:

The results of this study have shown that for RRMM single cohort studies can be used to assess the efficacy of new treatments, given that sufficient data are available on controls treatments used as standard of care. The results may have implications for the evaluation of treatments of rare and advanced cancers as well as other conditions.

1 Background:

The Randomized Controlled Trial RCT has been considered as the gold-standard for the evaluation of treatment efficacy and is the single most frequently used source of evidence in the approval of new treatments[1]. The theoretical advantages of RCT include the minimization of bias primarily through the process of randomization and blinding of treatment allocation. With randomization it is expected that the compared treatment groups are comparable with respect to known and unknown confounders. Blinding of the health care provider and the patient with respect to treatment allocation is expected to reduce placebo effect and bias in the ascertainment of treatment outcomes.

In recent years, there has been an increased realization that the classical RCT paradigm may not be the ideal source of evidence for the assessment of therapeutic effectiveness and safety as it applies to the real world[2-4]. Recruitment of highly selected patients that are treated in university – academic institutions under very rigid and strict protocols compromise the validity of the results to the general population and the real – world – setting.

In many cases, especially with regard to the management of chronic conditions, real-world evidence (RWE) studies can be deployed to assess the real – life effectiveness and safety of marketed treatments and compare these to the expectations generated by the registrational RCTs. Post marketing studies can be prospective or retrospective in direction and can employ single cohort or multiple cohort designs. Real – world treatment and safety gaps can be assessed with a well-designed and executed post marketing program. The Post Marketing Program results can then be used to design and test interventions aimed at optimizing real – life effectiveness and safety of approved treatments. However, the implementation of post marketing assessment of real – life effectiveness and safety are applicable for chronic conditions for which treatment and survival of the patient is expected to span over several years or decades.

With respect to end – stage cancer the use of RCTs for the assessment of efficacy and safety under ideal conditions with subsequent post marketing assessment of real – world effectiveness and safety is not as easily applied. Due to the limited number of eligible patients available, RCTs in late – stage cancers carry very long recruitment periods and hence approval of treatment is delayed substantially with high resource and financial costs[5]. Consequently, a considerable number of patients may be either deprived of an effective treatment or may be subjected to treatments that are not beneficial. The societal costs of these delays can be significant[6].

The single cohort study (SC) can be considered as an alternative to the RCT for the evaluation of the efficacy / effectiveness and safety of new treatments for end – stage cancer.The criticism of single cohort studies is primarily based on the lack of a control / comparator group and the possibility of placebo effect and ascertainment bias. With respect to end-stage cancer, the use of concurrent control groups may not be practical or ethical given that in most cases the patients will have been unsuccessfully treated with all the available protocols under standard of care. Some stakeholders, such as NICE, a UK-based health technology assessment agency, published recommendations on indirect treatment comparisons between single arm trials (controlling for patient characteristics) and implicitly recognized that RCTs may not always be possible or even optimal for healthcare decision-making[7]. This suggests

an alternative approach in utilizing data from published studies for estimating the therapeutic effect of the control / comparator treatments.

Bias in ascertaining outcomes and placebo effect can be significant in single cohort open label studies when the outcomes assessed are "soft" such as subjective clinical assessments or patient reported outcomes. In the assessment of cancer treatment however, the use of objective outcomes such as Overall Response Rate (ORR), Overall Survival (OS) and Progression Free Survival (PFS) greatly diminish, if not eliminate, the concern of outcome ascertainment bias.

Observational or open label SC studies when designed and conducted properly, have certain advantages over RCTs. Generalization to the real – life setting is easier for SCs given appropriate study sample selection. This is because, typically, selection of patients for SCs is not based on the same stringent criteria that are applied in RCTs. This allows for better emulation of the routine clinical practice rather than the experimental setting that drives patient selection for RCTs.

The cost of SCs is considerably lower than that of RCTs with the difference being primarily due to the lower sample size requirements and related shorter study duration[8]. More specifically, for the same effect size, power and significance levels, the sample size requirements for SC are approximately ¼ of that for RCT (Figure 1). As a result, the results of SCs can become available with less delays allowing for a more expedited conclusion regarding effectiveness and safety of the treatment. As a result, approval of the drug can be decided with fewer patients unnecessarily exposed to non – beneficial treatments.

The critical question to be addressed is whether the results obtained in SCs can be considered as strong enough evidence to make decisions regarding treatment effectiveness and whether, the RCT results would lead to a different decision. There is, therefore, a need for the quantitate comparison of the therapeutic efficacy estimates obtained in RCTs and SCs assessing the same treatments in comparable patient populations. The other dimension of this question goes beyond the absolute estimate of treatment efficacy and is concerned with relative effectiveness. That is, whether the difference between the experimental treatment and a comparator/control observed in RCTs is similar to what would have been obtained if the effectiveness observed for the experimental treatment in a SC would have been compared indirectly to a comparator control using data from other published studies.

The current study aims to address these questions.

2 Objectives:

1. To compare the estimates of ORR and OS obtained in RCTs and SCs assessing the same treatments for Relapse Refractory Multiple Myeloma (RRMM).
2. To compare the relative therapeutic effectiveness estimated in RCTs and SCs for the treatment of RRMM, as measured by the ratio and difference in ORR and OS rates between experimental and comparator/control treatments.

3 Methods:

The study was based on data extracted from published literature. For the first phase, the MEDLINE database was searched using the

following criteria: *((((Randomized clinical trial)OR random)) AND multiple myeloma) AND ((relapsed) OR refractory).* This search yielded 167 articles, which were then sequentially numbered and identified by an RCT Identification Number (RCT ID#). The following exclusion criteria were then applied yielding a final set of 61 randomized clinical trials:

- The study was not related to Multiple Myeloma (MM) or evaluated MM in combination with other diseases such as leukemia.
- Patients were newly diagnosed, or the study was based on a combination of new and relapsed patients.
- The study was a Systematic Review, Metanalysis, reported the results of previous studies or the pooled results of other studies.
- Outcomes reported did not include ORR or OS.
- Sequence of different drug combinations was examined.
- Hematopoietic cell transplantation (HCT) was included in the treatment.
- The study compared different doses or routes of administration of the same drug.
- Non-English articles or abstracts.

For the second phase of the search, Single Cohort studies assessing any of the 18 protocols used as experimental or control arms in the selected RCTs were identified. The following key words were used in the MEDLINE search: *((((((Single-Arm) OR Single Arm)) OR nonrandomized)) AND multiple myeloma) AND ((relapsed) OR refractory) + RCT treatmentprotocols.* This search yielded 47 Single Cohort studies evaluating the same treatment protocols as those evaluated in the selected RCTs.

In the final selection process, another 19 RCTs were excluded because SCs assessing the treatments were not identified. Hence a total of 42 RCTs and 47 SCs (Table 2) assessing 18 treatments for RRMM (Table 1) were included in the first part of the study (Figure 2).

For the second part of the study a total of 11 RCTs were included for which the experimental treatment was also assessed in a SC. A total of 10 treatments were included in the second part of the study (Table 6).

For each treatment, the weighted average was used to estimate the aggregate age, percent male, ORR and OS rates. When ORR rates were reported by the authors the reported estimates were used for the calculation of the aggregate. When ORR rates were not reported, the following definition was used to estimate the ORR: Complete Response or Partial Response. The time frame for all outcomes was set at 12 months. When the 12-month rates were reported, these were used in the analysis. When 12-month estimates were not reported these were extrapolated from Kaplan Meier curves when reported by the authors.

For the first part of the study the Intraclass Correlation Coefficient (ICC) was used to assess the agreement between the ORR and OS estimates in RCTs and SCs for the same treatment.In the second part of the study the aim was to assess the differential effectiveness as assessed by the ratio and absolute difference in ORR and OS of the experimental treatment to a comparator. For RCTs, the comparator was the treatment used as a control in the study. For SCs, the aggregate effectiveness markers – specifically ORR and OS – were compared to the estimates reported for the same comparator in RCTs evaluating the same treatment. The Kappa statistic was used to assess the agreement between RCTs and SCs

with respect to the direction of the effect and the statistical significance of the ORR ratio, the OS ratio, the difference in ORR and the difference in OS.

Using the RCT results as the criterion "gold standard", sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall agreement for the direction, statistical significance, and the conclusion regarding acceptability of the treatment were estimated. For this analysis, acceptable treatment was defined as one where a statistically significant and positive effect of the experimental treatments was observed.

4 Results:

Table 3 describes the RCTs and SCs used in the first part of the study by treatment. These results show that there were no differences in the age and gender between patients enrolled in RCTs and those enrolled in SCs.

The results in Table 4 and Figure 3 show that there is good agreement between the ORR rates reported in RCTs and SCs with an ICC of 0.618 (P = 0.027). The highest discrepancy between the RCT – ORR and the SC – ORR was observed for treatments #10 (Botezomib + Doxorubicin), #9 (Botezomib + Vorinostat) and #4 (Carfizomib + Lenalidomide + Dexamethasone). However, there were only one RCT and one SC assessing each one of these treatments. The results also show that for 9 of the 18 treatments the 95% CI of the RCT – ORR and the SC – ORR overlap.

The results in Figure 4 show that the absolute difference between RCT – ORR and SC – ORR increases with higher RCT – ORR estimates. In fact, these results show that for lower RCT – ORR estimates, the SC – ORR is higher than the RCT – ORR and the direction of the difference reverses with higher RCT – ORR estimates. The estimated RCT – ORR was higher than SC – ORR for 10 of the 18 treatments, equal for one and lower for 7. Statistically significant difference between RCT – ORR and SC – ORR was observed for 9 (50%) of the 18 treatments and specifically for 3 (42%) out of the 7 for which the SC – ORR was higher and for 6 (60%) out of the 10 for which the RCT – ORR was higher.

With respect to OS, the results summarized in Table 5 and Figure 5 show that for the 12 treatments with reported OS, there is very good agreement between the RCT – OS and the SC - OS rates with an ICC of 0.736 (P = 0.014). The highest difference between RCT – OS and SC – OS was observed for treatment # 9 ((Botezomib + Vorinostat)). The RCT – OS was higher than that reported in SC for 11 (92%) of the 12 treatments. Statistically significant differences between RCT – OS and SC – OS were observed for 6 (50%) of the 12 treatments; and, specifically for the one treatment where the SC – OS was higher and for 5 (45%) of the11 treatments for which the RCT – OS was higher. The difference between RCT – OS and SC – OS increased with higher estimated of RCT-OS (Figure 6).

The second part of the study was focused on comparing the differential effectiveness of active (experimental) treatments and comparators (controls) as estimated in RCTs and SCs for the treatments listed in Table 6. The results summarized in Table 7 show that the ORR ratio (ORR Experimental / ORR Control) as estimated in RCT and extrapolated for the same treatment and comparator for SCs were in the same direction and similar as indicated by overlapping 95% CI for 10 of the 11 RCT-SC pairs. The exception was for RCT ID# 57 [9] comparing thalidomide as active drug to dexamethasone as the control.

Similar results were observed when

comparing the difference (d) in ORR rates reported in RCTs and extrapolated to the SCs of the same treatment. These results summarized in Table 7 and Figure 8 show that for the majority of the RCT – SC pairs, specifically 7 (63%) of the 11, the 95% CI of the difference in ORR estimated in RCTs and SCs overlap, and that the direction is the same in 10 (91%) of the 11.

As with the ORR ratio, the RCT – SC pair comparing thalidomide (active) to dexamethasone (control), the difference in ORR (ORR Experimental - ORR Control) was in favor of the control in the RCT and in favor of the active treatment in the SC. For RCT – SC pairs # 107[10] and # 108[11] comparing dexamethasone as the control to lenalidomide + dexamethasone and # 33[12] comparing dexamethasone (control) to dexamethasone + pomalidomide, the 95% CI of the difference in ORR do not overlap indicating a statistically significant difference in estimated effect size (Figure 8).

The data in Table 8 summarize the OS ratio (OS Experimental / OS Control) and difference (OS Experimental - OS Control) between experimental and control treatments as reported in RCTs and extrapolated in SCs. These results show that for 6 (75%) of the 8 RCT – SC pairs the 95% CI of the OS ratios estimated in the RCT and SC overlapped. For RCT ID# 33[12] comparing dexamethasone (control) to dexamethasone + pomalidomide the results of the RCT favored the control arm and the opposite was true for the SC. For RCT ID# 32[13] comparing bortezomib as the control, to bortezomib + Vorinostat, the RCT results showed no difference between control and experimental treatment while the SC estimate favored the control arm. For both of these RCT-SC pairs, the 95% CI of the OS ratios did not overlap indicating statistically significantly different estimated effects (Figure 9).

The results for the difference (d) in OS between active and control treatments as reported in RCTs and extrapolated to SCs are summarized in Table 8 and Figure 10. These results show that for 5 (63%) of the 8 RCT – SC pairs with OS data, the 95% CI of the OS differences overlapped. For RCT ID#32[13] comparing bortezomib (control) to bortezomib + vorinostat, the SC results favored the control arm while the RCT results would indicate no difference. For RCT ID# 108[11] comparing dexamethasone (control) to dexamethasone + lenalidomide, the RCT results favor the control arm while the SC results would be in the opposite direction in favor of the active treatment. For RCT ID# 107[10] also comparing dexamethasone (control) to dexamethasone + lenalidomide, the RCT and SC results are in the same direction; however, the effect size is significantly larger in the SC.

Based on the ORR ratio estimates the RCT would conclude a positive treatment effect for the experimental group in 9 of the RCT-SC pairs, of which 6 (67%) were statistically significant. For 2 pairs, the RCT results were negative and non-significant. As per the SC results, a positive effect for the experimental group would have been observed in 10 of the pairs, of which 5 (50%) were statistically significant. For one pair the RCT results were negative and non-significant while the SC results were positive and statistically significant. For another pair, the RCT and the SC results were negative and non-significant (Table 9a). The kappa statistic for these pairs was 0.554 (P = 0.011) for direction and significance of the effect and 0.621 (P = 0.026) for direction of the effect only. These results suggest good agreement between RCT and SC with respect to the ORR ratio.

The assumption used in the subsequent analyses was that acceptance of a treatment would require a positive and statistically significant result. Based on the ORR ratio, a positive recommendation would be indicated for the RCTs in 6 pairs and for the SC in 5. Using the RCT results as the gold standard, the SC results have a sensitivity of 67%, specificity of 80%,PPV of 80%, NPV of 67% and agreement of 73% (Table 9b). In 2 of the 3 pairs where there was discordance between the RCT and SC based conclusion, the SC results would indicate non-acceptance of the treatment and the RCT was positive, the opposite being true for the remaining one pair.

Based on the ORR difference between active and comparator treatments there were 9 pairs for which the RCT results were positive of which 6 (67%) were also statistically significant. Conversely as per the SC, there were 10 positive results of which 4 (40%) were statistically significant. There was one pair in which both the RCT and SC results were negative and non – significant and another in which the RCT result was negative and non-significant, but the SC would yield a positive and significant finding (Table 10a). For this outcome, the kappa statistic for the directions and difference was 0.429(P = 0.038) indicating modest agreement and 0.600 (P = 0.064) for the direction only indicating good agreement.

The treatment acceptance conclusions according to the ORR difference between the active and comparator treatments are summarized in Table 10b. These results show that a positive recommendation for acceptance of the treatment would be indicated by the RCT in 6 (55%)and by the SC in 4 (36%) of the 11 RCT – SC pairs. The SC would confirm 3 of the 6 positive RCT results for a sensitivity of 50%, and 4 of the 5 negative RCT results for a specificity of 80%. The PPV, NPV and agreement values are 75%, 57% and 64% respectively. For the majority (3/4) of the discordant pairs, the RCT would conclude a positive recommendation while the SC would not concur. The opposite is true for one pair in which the SC would conclude a positive and the RCT a negative recommendation.

There were 8 RCT – SC pairs reporting OS as a measure of treatment effectiveness. In 6 (75%) of these 8 pairs, the RCT had a positive result with statistical significance achieved in 3 (50%); while the SC had a positive result in 4 (50%) of which 3 (75%) were also statistically significant (Table 11a). For the 2 pairs with non – significant and negative RCT results, the SC results were negative and significant for 1 and positive and significant for the other. There was poor agreement with respect to direction and significance of the OS – ratio results as indicated by a kappa of 0.167 (P = 0.365); while the agreement for direction alone was good as indicated by a kappa of 0.621 (P = 0.026) (Table 11a) was 67%, NPV

The treatment acceptance results based on the OS ratio are summarized in Table 11b. Among the 8 pairs, the RCT results would indicate positive recommendation in 3 (38%) and the SC in 3 (38%) as well; both the RCT and SC would yield positive recommendations in 2 of the 3. For this outcome sensitivity was 67%, specificity was 80%, PPV was 80% and agreement was 75%. There were 2 discordant pairs, one in each direction (Table 11b).

The results in Table 12a show that for the OS difference between experimental and control treatments as a measure of effectiveness, the RCT results were positive for 7 (87.5%) of the 8 pairs of which 3 (43%) were statistically significant. For the SC

results 3 (75%) of the 4 (50%) positive results were also statistically significant. However, there was concordance between RCT and SC for the 3 positive and significant results. For the 4 pairs with positive but non – significant results according to the RCT, the SC would yield negative and non – significant findings. For one pair, the SC results were positive and non – significant while the RCT result was negative and non – significant. The kappa statistics were poor for both directions and significance (kappa = 0.149; P = 0.428) and direction alone (kappa = 0.250; P = 0.285).

The results in Table 12b show that there is high agreement between RCT and SC in the conclusion regarding acceptance of the treatment based on the difference in OS.

5 Discussion:

The aim of the current study was to determine whether the evidence generated in single cohort prospective studies, can be used to reach valid and reliable decisions regarding the approval of new treatments. The theoretical concerns with such an approach are predominantly based on bias that would exaggerate the treatment effect, and lead to ineffective or potentially harmful treatments to be approved and incorporated in routine clinical practice. With randomization, inclusion of a control group and blinding of treatment allocation as the cornerstone attributes of the Randomized Controlled Trial (RCT) the methodology has been hailed as the gold standard for the evaluation of new treatments. This is based on the expectation that through these design features, selection, confounding, and ascertainment bias are eliminated[1].

Recently, the dogma of the RCT as the gold standard for treatment evaluation has been challenged by many authors [2-4]. The challenge is primarily based on the limited generalizability of the RCT results to the real-life setting. This limited generalizability is due to the highly selected patient populations enrolled, patient management and treatment taking place in highly specialized institutions under very strict protocols that enhance patient follow up and improve compliance at levels that are not reproducible in real – life. Self – selection of physicians and of patients participating in RCTs is another factor compromising external validity of the results.

Well-designed observational and RWE studies, such as single cohort designs, could potentially generate evidence of treatment effectiveness and safety beyond the RCT, with results that are more generalizable to the real – life setting [3 4 14 15]. The concern that observational studies may over-estimate the treatment effect has been refuted by several authors that have shown that observational studies show similar effects qualitatively and quantitatively to those reported in RCTs [3 4 8 14-16] Conversely, there is evidence to suggest that the therapeutic efficacy and patient outcomes reported in RCTs are often better than those of observational studies and hence in the real – life setting [17-20]. In addition to the Hawthorne effect, the inclusion of highly selected patients with potentially better prognosis or responsiveness to treatment and the participation of highly specialized academics and clinicians may explain this phenomenon. Consequently, the results observed in RCTs are not always reproducible in the real-life setting, where treatment benefits may be lower than those anticipated based on the registrational clinical trials.

A solution to this problem would be the incorporation of well-designed

interventional single cohort studies, synthetic controls trials or pragmatic trials in the decision process for approval of new treatments. This solution would of course be pertinent to rare diseases and cancers for which the RCT process would not be possible or optimal.

The analyses conducted in the current study have been implemented in a logical sequence to empirically address the question as to whether SCs can be used instead of RCTs in the assessment of new treatments. RRMM was selected as the paradigm of a disease with limited treatment options, and for which the expedited assessment and decision regarding the effectiveness of new treatments would be beneficial to all health care stakeholders, including patients, physicians, the pharmaceutical industry, and payers.

The first analysis was aimed at assessing whether there is a quantitative (effect size) and qualitative (direction) difference between the effectiveness estimates obtained in RCTs and SCs assessing treatments for RRMM. This analysis showed that overall, there is concurrence between RCTs and SCs in the estimates of treatment response and survival for the same treatment protocols. The results of the analyses showed that with respect to the direction and the size of the effect, there is agreement between SCs and RCTs. However, as the magnitude of ORR and OS became higher, the difference between SC and RCT increased with the RCTs producing higher values. This observation is in line with those reported by others [17-20] and can be explained by the highly selected patients and stringent protocol driven treatment by highly specialized physicians at university centers.

The important observation from this analysis is that when there was disagreement between RCTs and SCs, and the effects were larger and hence more clinically relevant, the SCs are more likely to produce lower estimates of treatment effects when compared to RCT. Conversely, the SC estimates of effectiveness were higher when compared to RCTs for when the treatment effect were lower. This would suggest that in these cases, the lack of adequate clinical significance would most likely lead to non – acceptance of the treatment. Hence, the likelihood of ineffective treatments being approved based on the results of an SC study is low. The conclusion from this analysis is that the results of SCs could be considered as adequate,and even conservative proxies of the treatment effects that would be observed in RCTs.

The second analysis focused on the comparative effectiveness of treatments. In this analysis, the SC effectiveness of the new treatment would be compared to control/comparator effectiveness data derived from published literature, and more specifically published RCTs. In this model, the aggregate effectiveness estimates for the new treatment observed in SCs would be statistically compared to the aggregate effectiveness estimates of the comparators that were used in RCTs assessing the same new treatments. The results of these analyses showed that overall, there were acceptable agreements between RCTs and SCs with respect to the direction and statistical significance of the comparative effectiveness of new treatments and controls. The conclusion from these analyses is that properly designed SC studies, using comparator data derived from published RCTs, would be an acceptable replacement to a full RCT. Furthermore, this approach would most likely lead to fewer positive results, thus minimizing the likelihood of spurious findings in favor of ineffective treatments.

Ultimately, the decision for accepting /

approving a new treatment is based at a minimum on the demonstration of a statistically significant benefit over the comparators. The final analyses of the study focused on this point. Specifically, the final analyses were based on the assumption that a positive recommendation for acceptance/approval of a new treatment would require at the minimum a positive and statistically significant difference from the comparator. The precise question is whether based on this criterion, the results of a SC study using aggregate data for comparator effectiveness from published RCTs would result in the same conclusion for acceptance of the new treatment as that of the RCTs. The results of the analyses showed very good to excellent agreement on the conclusion regarding recommendation for acceptance of a new treatment between RCTs and SCs. Once again, in the cases of discordance, the SC results would be more conservative and would not support recommendation for approval whereas the RCT conclusion would support approval of less effective treatments.

A potential weakness of the current study is the fact that it was based on published literature and not primary data collection. However, only published data can be used to compare the results of already completed and reported SCs and RCTs. As with all reviews and syntheses of published data, the effect of publication bias must be taken into consideration when interpreting the results of this study.

Another potential limitation of the study is the fact that the sample was limited to treatments for which at least one RCT and one SC were published. This would eliminate treatments for which only RCTs or only SCs were conducted and reported. The aim of this study was to provide a simple and direct comparison of results obtained in RCTs and SCs for the same treatment and this can only be achieved using the methodology employed. Alternative methods such as network meta-analysis can be employed to produce indirect comparisons of treatments. However, these more complicated analytical methods would detract from the simple interpretation of the results of the study. The current methodology while being non – complicated is also easily reproducible and has adequately addressed the relevant research question.

The strengths of the current study include the comprehensive literature search that was aimed at reducing possible selection bias. The review of the articles and retrieval of readily available data describing "hard outcomes", specifically ORR and OS, by health professionals and experienced researchers reduces the possibility of ascertainment bias. Given the universally accepted definitions of ORR and OS in RRMM, there is no possibility of between study variability in the interpretation and ascertainment of these outcomes. This supports strong internal validity of our analyses.

The current study has implications on our approach to the approval of treatments for certain cancers as well as rare or orphan diseases with unmet needs. This research can be expanded to other diseases to improve and validate the generalizability of the results. From a regulatory perspective, there would be a need for the expansion of the current mindset to pursue the development of strict guidelines defining the conditions under which single cohort interventional studies can be considered for approval of new treatments. Guidance on the design and criteria for assessment of the results of these single cohort studies must also be developed and applied. Improvements in the methodology of single cohort studies aimed at enhancing internal

and external validity must become an important focus of epidemiologists and biostatisticians. Finally, in many cases development of innovative programs that would generate evidence to support decisions regarding the approval of new drugs must be considered. These innovative programs may include single cohort studies, pragmatic trials and perhaps confirmatory and smaller randomized controlled trials, among other designs. Implementation of such programs can significantly expedite the approval process with substantial benefits to all health care stakeholders.

6 Conclusion:

The current study has demonstrated strong agreement between RCTs and SCs assessing treatments for RRMM. The results support the paradigm of considering approval of new treatments for RRMM on the basis of well-designed programs of interventional SCs. The deployment of follow – up observational studies to confirm the conclusions if the interventional SCs regarding acceptance of the treatment is necessary. While the results suggest that SCs are a reasonable option for the assessment of new treatments, this should not be interpreted to suggest that RCTs should not be conducted when possible. Post approval randomized or pragmatic trials would be essential in confirming the results obtained in single cohort studies. This is in line with the fact that decisions regarding the acceptance and continued use of marketed treatments must be made on the basis of accumulation of evidence from all possible sources. This would follow a model of ongoing evaluation where decisions can be altered as evidence is generated, rather than one with terminal/final decision points based on a small number of registrational RCTs.

An important comment warrants mention at this point. The current study and learned opinion in the literature support the potential use of *well – designed* SC interventional and observational studies for the assessment of new treatments, when RCTs may not be the ideal solution, due to practical or ethical reasons. The key term in this statement is "well designed" which must be taken seriously. This means that all measures must be taken to design and execute these studies in a way that reliability and validity are optimized. Unlike RCTs, for which the protocols and execution of the studies follow well known guidelines and templates, the single cohort studies have more complex considerations for the prevention of bias and misinterpretation of the results. Multi- disciplinary teams comprised of epidemiologists, clinicians and biostatisticians must be involved in all aspects of these studies. Industry sponsors of these studies must also take all necessary measures to ensure integrity and validity of the results by assigning their execution to scientists and organizations with adequate and documented expertise and experience.

TABLES AND FIGURES

Table 1. List of Treatments in Included Studies:

Treatment Number	Drug Names			
1	Vincristine	Doxorubicin	Interferon alpha	Dexamethasone
2	Vincristine	Doxorubicin	Dexamethasone	
3	Carfilzomib	Lenalidomide	Dexamethasone	
4	Melphalan	Arsenic trioxide	Ascorbic acid	
5	Elotuzumab	Lenalidomide	Dexamethasone	
6	Bortezomib	Panobinostat	Dexamethasone	
7	Bortezomib	Thalidomide	Dexamethasone	
8	Bortezomib	Dexamethasone		
9	Bortezomib	Vorinostat		
10	Bortezomib	Doxorubicin		
11	Pomalidomide	Dexamethasone		
12	Lenalidomide	Dexamethasone		
13	Carfilzomib	Dexamethasone		
14	Thalidomide	Dexamethasone		
15	Thalidomide	Interferon alpha		
16	Bortezomib			
17	Carfilzomib			
18	Thalidomide			

Table 2. Listing of Studies Included

	RCT						SC						
Treatment Number	Author	Year	N	% Male	Duration of Follow Up (median) months	months*	Treatment Number	Author	Year	N	% Male	Duration of Follow Up (median) months	months*
1E	Gertz MA [21]	1995	23	65%	12		1	Young RI [22]	1997	12	75%	N/A	6 NOC
2C	Friedenberg WR [23]	2006	65	62%	31.1		2	Browman GP [24]	1992	38	59%	N/A	N/A
2C	Sonneveld P [25]	2001	41	49%	49								
2C	Mineur P [26]	1998	62	64%	N/A	4 DOT							
2C	Gertz MA [21]	1995	24	71%	12								
2C	Phillips JK [27]	1995	22	50%	N/A	72 MOS							
2C	Dalton WS [28]	1995	63	54%	N/A	48 MOS							
3E	Stewart AK [29]	2015	396	54%	32.3		3	Wang M [30]	2013	84	57%	24.4	
							3	Niesvizky R [31]	2013	40	55%	N/A	7.2 DOT
4C	Sharma M [32]	2012	20	40%	36		4	Berenson JR [33]	2006	65	N/A	12	
5E	Lonial S [34]	2015	321	N/A	24.5		5	Lonial S [35]	2012	28	N/A	16.4	
							5	Richardson PG [36]	2015	36	56%	37	
6E	San-Miguel JF [37]	2014	387	52%	N/A	5 DOT	6	San-Miguel JF [38]	2013	15	73%	N/A	5.3 DOT
							6	Richardson PG [39]	2013	55	53%	N/A	4.6 DOT
7E	Garderet L [40]	2012	135	64%	30		7	Pineda-Roman M [41]	2008	85	61%	46	
8E	Jagannath S [42]	2004	12	35%	26.1		8	Ozaki S [43]	2016	47	45%	21.6	
8C	Hjorth M [44]	2012	67	64%	N/A	3.5 DOT	8	Bao L [45]	2008	13	43%	9.5	
8C	Dimopoulos MA [46]	2016	465	49%	11.1								
8C	San-Miguel JF [37]	2014	381	54%	5.59								
8C	Jakubowiak A [47]	2016	75	49%	11.7								
9E	Dimopoulos M [13]	2013	317	60%	14.1		9	Siegel DS [48]	2016	142	61%	N/A	3 DOT
10E	Orlowski RZ[49]	2007	324	58%	N/A	3.5 DOT	10	Orlowski RZ [50]	2005	22	45%	36	
11E	San Miguel J [12]	2013	302	60%	10		11	Lacy MQ [51]	2009	60	60%	N/A	7 NOC
11E	Richardson PG [52]	2014	113	55%	14.2		11	Ichinohe T [53]	2016	36	44%	N/A	5.5 DOT
							11	Dimopoulos MA [54]	2015	302	N/A	15.4	
							11	Sehgal K [55]	2015	20	60%	N/A	5.1 DOT

Table 2. Listing of Studies Included

	RCT						SC						
Treatment Number	Author	Year	N	% Male	Duration of Follow Up (median) months	months*	Treatment Number	Author	Year	N	% Male	Duration of Follow Up (median) months	months*
							11	Leleu X [56]	2013	43	N/A	22.8	
							11	Lacy MQ [57]	2011	35	60%	9.7	
12E	Weber DM [10]	2007	177	60%	17.6		12	Hou J [58]	2013	187	62%	15.2	
12E	Dimopoulos M [11]	2007	176	59%	16.4		12	Alegre A [59]	2012	63	62%	13.4	
12C	Dimopoulos MA [60]	2016	283	N/A	13.5		12	Richardson PG [61]	2006	102	63%	31	
12C	Moreau P [62]	2016	362	56%	14.6								
12C	Lonial S [34]	2015	325	59%	24.5								
12C	Stewart AK [29]	2015	396	59%	31.5								
13E	Dimopoulos MA [46]	2016	464	52%	11.9		13	Berenson JR [63]	2016	104	58%	N/A	7.7 DOT
							13	Lendvai N [64]	2014	42	43%	18.4	
14E	Hjorth M [44]	2012	67	41%	N/A	5.1 DOT	14	Murakami H [65]	2007	66	41%	15	
14C	Garderet L [40]	2012	134	62%	30								
14C	Offidani M [66]	2007	47	60%	24								
15E	Chiou TJ [67]	2007	16	81%	N/A	3.34 DOT	15	Mileshkin L [68]	2003	75	61%	18	
16E	Richardson PG [69]	2005	315	56%	8.3		16	Petrucci MT [70]	2013	126	57%	N/A	7 NOC
16C	Orlowski RZ [71]	2015	144	59%	24.5		16	Hainsworth JD [72]Hainsworth JD [72]	2008	40	53%	24	
16C	Hellmann A [73]	2011	17	50%	N/A	2.7 DOT	16	Richardson PG [74]	2006	202	60%	23	
16C	Dimopoulos M [13]	2013	320	58%	14.2		16	Mikhael JR [75]	2009	638	55%	N/A	3.75 DOT
16C	White D [76]	2013	53	57%	13.3		16	Jagannath S [77]	2008	26	35%	65	
16C	Orlowski RZ [49]	2007	322	54%	N/A	3.5 DOT							
16C	Jagannath S [42]	2004	14	35%	26.1								
17E	Hájek R [78]	2016	157	61%	N/A	4.08 DOT	17	Herndon TM [79]	2013	266	58%	N/A	4 NOC
							17	Jagannath S [80]	2012	46	54%	N/A	2.5 DOT
							17	Siegel DS [81]	2012	266	58%	N/A	3 DOT
							17	Vij R [82]	2012	35	51%	13.4	
							17	Vij R [83]	2012	70	44%	13.8	

Table 2. Listing of Studies Included

	RCT						SC						
Treatment Number	Author	Year	N	% Male	Duration of Follow Up (median) months	months*	Treatment Number	Author	Year	N	% Male	Duration of Follow Up (median) months	months*
							17	Lendvai N [64]	2014	44	43%	18.4	
							17	Watanabe T [84]	2016	40	45%	N/A	6 NOC
18E	Kropff M [9]	2012	122	46%	N/A	7 NOC	18	Neben K [85]	2002	83	73%	17	
18C	Chiou TJ [67]	2007	12	92%	8		18	Uppal G [86]	2005	26	69%	N/A	8 DOT
							18	Decaux O [87]	2012	120	52%	N/A	12 DOT
							18	Murakami H [88]Murakami H [88]	2009	37	38%	N/A	4 DOT
							18	Hattori Y [89]	2008	56	64%	48	
							18	Mileshkin L [68]	2003	75	61%	18	
							18	Yakoub-Agha I [90]	2012	195	46%	N/A	60 MOS
							18	Singhal S [91]	1999	84	62%	13	

*If duration of follow-up was not available, first the median of duration of treatment (DOT) was reported. If DOT was not available, considering each cycle of treatment is roughly equal to 1 month, the median number of cycles (NOC) was translated into months and then reported. Finally, if there was no other data, the maximum time in Kaplan Myer OS diagram (MOS) was reported.
E= Experimental Arm; C=Control Arm; RCT = Randomized Controlled Trial, SC = Single Cohort Study

Table 3. Description of RCTs and SCs by Treatment

Treatment number	RCT						SC					
	Reference	N	Age (Years)	Male %	ORR	OS	Reference	N	Age (years)	Male %	ORR	OS
1	[21]	23	68	0.65	0.30	0.30	[22]	12	61.00	0.75	0.50	
Aggregate 1	[21]	23	68	0.65	0.30	0.30	[22]	12	61.00	0.75	0.50	
2	[23]	65	65	0.62	0.29	0.55	[24]	38	62.10	0.59	0.29	
2	[25]	41	63	0.49	0.49	0.55						
2	[26]	62	62	0.64	0.22	0.66						
2	[21]	24	64	0.71	0.25	0.35						
2	[27]	22	64	0.50	0.40	0.50						
2	[28]	63	64	0.54	0.41	0.48						
Aggregate 2	[21]-[23], [25]-[28]	277	64	0.59	0.34	0.54	[24]	38	62.10	0.59	0.29	
3	[29]	396	64	0.54	0.87	0.73	[30]	84	61.50	0.57	0.69	
3							[31]	40	61.50	0.55	0.63	
Aggregate 3	[29]	396	64	0.54	0.87	0.73	[30], [31]	124	61.50	0.56	0.67	
4	[32]	20	60	0.40	0.85		[33]	65	66.00		0.26	0.65
Aggregate 4	[32]	20	60	0.40	0.85		[33]	65	66.00	0.00	0.26	0.65
5	[34]	321	67		0.79		[35]	28	60.00		0.82	
5							[36]	36	60.60	0.56	0.76	

Table 3. Description of RCTs and SCs by Treatment

Treatment number	RCT						SC					
	Reference	N	Age (Years)	Male %	ORR	OS	Reference	N	Age (years)	Male %	ORR	OS
Aggregate 5	[34]	321	67		0.79		[35], [36]	54	60.34	0.56	0.79	
6	[37]	387	63	0.52	0.61	0.80	[38]	15	62.00	0.73	0.73	
6							[39]	55	61.00	0.53	0.35	0.60
Aggregate 6	[37]	387	63	0.52	0.61	0.80	[38], [39]	70	61.21	0.57	0.43	0.60
7		135	60	0.64	0.87	0.71	[41]	85	60.00	0.61	0.63	0.68
Aggregate 7	[40]	135	60	0.64	0.87	0.71	[41]	85	60.00	0.61	0.63	0.68
8	[42]	12	60	0.35	0.50		[43]	47	75.00	0.45	0.49	0.70
8	[44]	67	71	0.64	0.63	0.42	[45]	13	65.00	0.43	0.62	
8	[13 46]	465	65	0.49	0.62							
8	[37]	381	63	0.54	0.55	0.80						
8	[47]	75	65	0.49	0.63	0.74						
Aggregate 8	[37], [42], [44], [46], [47],	1000	64	0.53	0.62	0.74	[43], [45]	60	72.83	0.45	0.52	0.70
9		317	61	0.60	0.56	0.85	[48]	142	63.00	0.61	0.11	0.32
Aggregate 9	[13]	317	61	0.60	0.56	0.85	[48]	142	63.00	0.61	0.11	0.32
10	[49]	324	61	0.58	0.44	0.85	[50]	22	59.00	0.45	0.73	

Table 3. Description of RCTs and SCs by Treatment

Treatment number	RCT						SC					
	Reference	N	Age (Years)	Male %	ORR	OS	Reference	N	Age (years)	Male %	ORR	OS
Aggregate 10	[49]	324	61	0.58	0.44	0.85	[50]	22	59.00	0.45	0.73	
11	[12]	302	64	0.60	0.31	0.55		60	66.00	0.60	0.63	
11	[52]	113	64	0.55	0.33	0.60	[53]	36	65.00	0.44	0.42	
11							[54]	302	64.00		0.35	0.55
11							[55]	20	61.00	0.60	0.45	0.62
11							[56]	43	60.00		0.35	0.58
11							[57]	35	61.00	0.60	0.29	0.34
Aggregate 11	[12], [52]	415	64	0.59	0.32	0.56	[51], [53]- [57]	151	63.64	0.56	0.39	0.54
12	[10]	177	64	0.60	0.61	0.88	[58]	187	60.00	0.62	0.48	
12	[11]	176	63	0.59	0.60	0.78	[59]	63	62.00	0.62	0.78	
12	[60]	283	65		0.76	0.76	[61]	102	60.00	0.63	0.17	0.78
12	[62]	362	66	0.56	0.72							
12	[34]	325	66	0.59	0.66							
12	[29]	396	65	0.59	0.67	0.82						
Aggregate 12	[29], [34], [10], [11], [60], [62]	1719	65	0.58	0.68	0.81	[58], [59], [61]	352	60.36	0.62	0.44	0.78
13	[46]	464	65	0.52	0.77	0.82	[63]	104	68.50	0.58	0.77	
13							[64]	42	63.00	0.43	0.55	0.55

Table 3. Description of RCTs and SCs by Treatment

Treatment number	RCT						SC					
	Reference	N	Age (Years)	Male %	ORR	OS	Reference	N	Age (years)	Male %	ORR	OS
Aggregate 13	[46]	464	65	0.52	0.77	0.82	[63], [64]	146	66.92	0.54	0.71	0.55
14	[44]	67	71	0.41	0.55	0.66	[65]	66	64.50	0.41	0.64	0.74
14	[40]	134	63	0.62	0.72	0.85						
14	[66]	47	66	0.60	0.59	0.72						
Aggregate 14	[40], [44], [66]	248	66	0.56	0.65	0.77	[65]	66	64.50	0.41	0.64	0.74
15	[67]	16	64	0.81	0.19	0.62	[68]	75	64.00	0.61	0.28	0.56
Aggregate 15	[67]	16	64	0.81	0.19	0.62	[68]	75	64.00	0.61	0.28	0.56
16	[69]	315	62	0.56	0.38	0.80	[70]	126	67.00	0.57	0.40	
16	[71]	144	61	0.59	0.47	0.85	[72]	40	69.00	0.53	0.55	0.75
16	[73]	17	65	0.50	0.70		[74]	202	60.00	0.60	0.27	0.60
16	[13]	320	63	0.58	0.41	0.82	[75]	638	62.70	0.55	0.67	
16	[76]	53	65	0.57	0.51		[77]	26	60.00	0.35	0.38	0.81
16	[49]	322	62	0.54	0.41	0.80						
16	[42]	14	60	0.35	0.38							
Aggregate 16	[42], [13], [49], [69],[71], [73], [76]	1185	62	0.56	0.42	0.81	[70], [72] [74], [75], [77]	1032	62.87	0.55	0.55	0.64
17	[78]	157	63	0.61	0.19	0.48	[79]	266	63.00	0.58	0.23	

Table 3. Description of RCTs and SCs by Treatment

Treatment number	RCT						SC					
	Reference	N	Age (Years)	Male %	ORR	OS	Reference	N	Age (years)	Male %	ORR	OS
17							[80]	46	63.50	0.54	0.17	
17							[81]	266	63.00	0.58	0.24	0.58
17							[82]	35	63.00	0.51	0.17	
17							[83]	70	66.00	0.44	0.35	0.85
17							[64]	44	63.00	0.43	0.55	0.56
17							[84]	40	66.00	0.45	0.23	
Aggregate 17	[78]	157	63	0.61	0.19	0.48	[64], [79]- [84]	767	63.46	0.55	0.26	0.63
18	[9]	122	63	0.46	0.18	0.82	[85]	83	59.00	0.73	0.42	0.86
18	[67]	12	62	0.92	0.50	0.55	[86]	26	53.50	0.69	0.62	
18							[87]	120	66.00	0.52	0.32	0.48
18							[88]	37	63.00	0.38	0.35	
18							[89]	56	57.00	0.64	0.39	
18							[68]	75	64.00	0.61	0.28	0.55
18							[90]	195		0.46	0.60	0.73
18							[91]	84		0.62	0.32	0.60
Aggregate 18	[67], [9]	134	63	0.50	0.21	0.80	[68], [85] -[91]	676	61.79	0.56	0.43	0.65

Aggregate calculated as the weighted average.
RCT = Randomized Controlled Trial, SC = Single Cohort Study

Table 4. ORR by Treatment and Study Design:

Treatment Number	–RCT - ORR					SC - ORR					RCT-ORR – SC-ORR		
	Reference	n	ORR	95% CI		Reference	n	ORR	95% CI		ORR RCT - ORR SC	95% CI	
				Lower	Upper				Lower	Upper		Lower	Upper
15	[67]	16	0.19	0.02	0.36	[68]	75	0.28	0.18	0.38	-0.092	-0.29	0.11
17	[78]	157	0.19	0.13	0.25	[64], [79]-[84]	767	0.26	0.22	0.29	-0.065	-0.13	0.00
18	[67], [9]	134	0.21	0.14	0.28	[68], [85]-[91]	676	0.43	0.39	0.46	-0.218	-0.30	-0.14
1	[21]	23	0.30	0.13	0.47	[22]	12	0.50	0.26	0.75	-0.200	-0.50	0.10
11	[12], [52]	415	0.32	0.27	0.36	[51], [53]-[57]	496	0.39	0.35	0.43	-0.074	-0.14	-0.01
2	[21]-[23], [25]-[28]	277	0.34	0.28	0.39	[24]	38	0.29	0.15	0.43	0.046	-0.10	0.19
16	[42], [13], [49], [69],[71], [73], [76]	1185	0.42	0.39	0.44	[70], [72] [74], [75], [77]	1032	0.55	0.52	0.58	-0.130	-0.17	-0.09
10	[49]	324	0.44	0.39	0.49	[50]	22	0.73	0.56	0.90	-0.290	-0.47	-0.11
9	[13]	317	0.56	0.51	0.62	[48]	142	0.11	0.06	0.16	0.449	0.37	0.52
6	[40]	387	0.61	0.56	0.66	[38], [39]	70	0.43	0.32	0.54	0.179	0.06	0.30
8	[37], [42], [44], [46], [47]	1000	0.62	0.59	0.65	[43], [45]	60	0.52	0.39	0.64	0.108	-0.02	0.23
14	[40], [44], [66]	248	0.65	0.59	0.71	[65]	66	0.64	0.52	0.75	0.013	-0.11	0.14
12	[29], [34], [10], [11], [60], [62]	1719	0.68	0.66	0.70	[58], [59], [61]	352	0.44	0.39	0.49	0.239	0.18	0.29
13	[46]	464	0.77	0.73	0.81	[63], [64]	146	0.71	0.63	0.78	0.063	-0.02	0.15
5	[34]	321	0.79	0.75	0.83	[35], [36]	64	0.79	0.69	0.88	0.004	-0.10	0.11
4	[32]	20	0.85	0.71	0.99	[33]	65	0.26	0.16	0.36	0.590	0.41	0.77
7	[40]	135	0.87	0.81	0.93	[41]	85	0.63	0.53	0.73	0.240	0.13	0.35
3	[29]	396	0.87	0.84	0.90	[30], [31]	124	0.67	0.59	0.75	0.202	0.11	0.29

Data are presented in ascending order of ORR-RCT
ORR = Overall Response Rate, RCT = randomized Controlled Trial, SC = Single Cohort Study, CI = Confidence Interval

Table 5. OS by Treatment and Study Design:

Treatment Number	–RCT - OS					SC - OS					RCT-OS – SC-OS		
	Reference	n	OS	95% CI		Reference	n	OS	95% CI		OS RCT - OS SC	95% CI	
				Lower	Upper				Lower	Upper		Lower	Upper
17	[78]	157	0.48	0.40	0.56	[64], [81], [83]	380	0.63	0.58	0.68	-0.147	-0.24	-0.06
11	[12], [52]	415	0.56	0.52	0.61	[54]-[57]	400	0.54	0.49	0.59	0.025	-0.04	0.09
15	[67]	16	0.62	0.41	0.84	[68]	75	0.56	0.45	0.67	0.064	-0.17	0.30
7	[40]	135	0.71	0.63	0.79	[41]	85	0.68	0.58	0.78	0.030	-0.09	0.15
8	[37], [44], [47]	523	0.74	0.70	0.78	[43]	47	0.70	0.57	0.83	0.040	-0.09	0.17
14	[40], [44], [66]	248	0.77	0.72	0.82	[88]	66	0.74	0.64	0.84	0.033	-0.08	0.15
18	[67], [9]	134	0.80	0.73	0.86	[68], [85], [87], [90], [91]	557	0.65	0.61	0.69	0.145	0.07	0.22
6	[40]	387	0.80	0.76	0.84	[39]	55	0.60	0.47	0.73	0.200	0.07	0.33
12	[10], [11], [60]	1032	0.81	0.78	0.83	[61]	102	0.78	0.70	0.86	0.028	-0.05	0.11
16	[13], [49], [69],[71]	1101	0.81	0.79	0.84	[72] [74], [77]	268	0.64	0.59	0.70	0.170	0.11	0.23
13	[46]	464	0.82	0.79	0.85	[64]	42	0.55	0.41	0.69	0.270	0.12	0.42
9	[13]	317	0.85	0.81	0.89	[48]	142	0.32	0.24	0.40	0.530	0.44	0.62

Data are presented in ascending order of OS-RCT
OS = Overall Survival Rate, RCT = randomized Controlled Trial, SC = Single Cohort Study, CI = Confidence Interval

Table 6. RCT and SC Studies Included in Part 2

RCT#[1]	Author	Year	Control Treatment			SC Treatment Number	Active Treatment			
112	Chiou TJ [67]	2007	Thalidomide			15	Thalidomide	Interferon alpha		
57	Kropff M [9]	2012	Dexamethasone			18	Thalidomide			
110	Orlowski RZ [49]	2007	Bortezomib			10	Bortezomib	Doxorubicin		
148	Gertz MA [21]	1995	Vincristine	Doxorubicin	Dexamethasone	1	Vincristine	Doxorubicin	Interferon alpha	Dexamethasone
132	Jagannath S [42]	2004	Bortezomib			8	Bortezomib	Dexamethasone		
32	Dimopoulos M [13]	2013	Bortezomib			9	Bortezomib	Vorinostat		
31	Richardson PG [52]	2014	Pomalidomide			11	Pomalidomide	Dexamethasone		
130	Richardson PG [69]	2005	Dexamethasone			16	Bortezomib			
108	Dimopoulos M [11]	2007	Dexamethasone			12	Lenalidomide	Dexamethasone		
107	Weber DM [10]	2007	Dexamethasone			12	Lenalidomide	Dexamethasone		
33	San Miguel JF [12]	2013	Dexamethasone			11	Pomalidomide	Dexamethasone		

SC Treatment Number as listed in Table 1

[1] RCT# refers to the sequentially numbered RCTs that were identified in the initial MEDLINE database search as described in section 3: Methods.

Table 7. Estimated Effect Size (ORR-Ratio) by Treatment and Study Design

RCT#	Control		Active		ORR Ratio: RCT			SC		ORR Ratio: SC			Difference(d) in RCT - ORR			Difference (d) in SC - ORR		
	ORR	N	ORR	N	RR	95% CI		ORR	N	RR	95% CI		d	95% CI		d	95% CI	
112	0.50	12	0.19	16	0.38[a]	0.12	1.21	0.44	352	0.88[a]	0.49	1.57	-0.31[a]	-0.65	0.03	-0.06[a]	-0.35	0.23
57	0.25	126	0.18	122	0.72[a]	0.44	1.17	0.73	22	2.92[d]	1.97	4.33	-0.07[a]	-0.17	0.03	0.48[d]	0.28	0.68
110	0.41	322	0.44	324	1.07[c]	0.90	1.28	0.44	352	1.07[c]	0.90	1.28	0.03[c]	-0.05	0.11	0.03[c]	-0.04	0.10
148	0.25	24	0.30	23	1.20[c]	0.47	3.05	0.43	676	1.72[c]	0.86	3.46	0.05[c]	-0.21	0.31	0.18[c]	0.00	0.36
132	0.38	14	0.50	12	1.32[c]	0.55	3.16	0.55	1032	1.45[c]	0.74	2.83	0.12[c]	-0.26	0.50	0.17[c]	-0.09	0.43
32	0.41	320	0.56	317	1.38[d]	1.17	1.63	0.52	60	1.28[c]	0.97	1.69	0.16[d]	0.08	0.23	0.11[c]	-0.02	0.25
31	0.18	108	0.33	113	1.83[d]	1.13	2.96	0.50	12	2.78[d]	1.39	5.56	0.15[d]	0.04	0.26	0.32[d]	0.03	0.61
130	0.18	336	0.38	330	2.11[d]	1.62	2.76	0.28	75	1.56[d]	1.01	2.39	0.2[d]	0.13	0.27	0.10[c]	-0.01	0.21
108	0.24	175	0.60	176	2.51[d]	1.88	3.35	0.39	496	1.63[d]	1.22	2.16	0.36[d]	0.27	0.46	0.15[d]	0.07	0.23
107	0.20	176	0.61	177	3.07[d]	2.23	4.22	0.39	496	1.96[d]	1.43	2.69	0.41[d]	0.32	0.50	0.19[d]	0.12	0.26
33	0.10	153	0.31	302	3.10[d]	1.87	5.13	0.11	142	1.10[c]	0.56	2.14	0.21[d]	0.14	0.28	0.01[c]	-0.06	0.08

Data are presented in ascending order of RR-RCT for ORR
ORR = Overall Response Rate, RR = Relative Rate (ORR Active/ORR Control), RCT = Randomized Controlled Trial, SC = Single Cohort Study, Difference (d) = ORR Active - ORR Control
a=Negative + Not Statistically Significant (P ≥ 0.05); b = Negative and Statistically Significant (P < 0.05);
c=Positive + Not Statistically Significant (P ≥ 0.05); d = Positive and Statistically Significant (P < 0.05);

Table 8. Estimated Effect Size (OS) by Treatment and Study Design

RCT#	Control		Active		OS Ratio: RCT			SC		OS Ratio: SC			Difference(d) in –RCT - OS			Difference (d) in –SC - OS		
	OS	N	OS	N	RR	95% CI		OS	N	RR	95% CI		d	95% CI		d	95% CI	
33	0.38	153	0.20	302	0.53[a]	0.39	0.71	0.54	400	1.42[d]	1.14	1.77	-0.18[b]	-0.27	-0.09	0.01[c]	-0.29	0.31
32	0.65	320	0.65	317	1.00[a]	0.89	1.12	0.32	142	0.49[b]	0.38	0.63	0.00[a]	-0.07	0.07	-0.15[b]	-0.23	-0.07
57	0.8	126	0.82	122	1.03[c]	0.91	1.16	0.65	557	0.81[b]	0.73	0.90	0.02[c]	-0.08	0.12	-0.33[b]	-0.42	-0.24
31	0.56	108	0.6	113	1.07[c]	0.86	1.34	0.50	12	0.89[a]	0.49	1.61	0.04[c]	-0.09	0.17	-0.06[b]	-0.36	0.24
112	0.55	12	0.63	16	1.15[c]	0.61	2.16	0.56	75	1.02[c]	0.59	1.76	0.08[c]	-0.29	0.45	-0.02[b]	-0.10	0.06
130	0.66	336	0.8	330	1.21[d]	1.10	1.33	0.64	268	0.97[a]	0.86	1.09	0.14[d]	0.07	0.21	0.54[d]	0.44	0.64
107	0.22	176	0.49	177	2.23[d]	1.62	3.06	0.78	102	3.55[d]	2.64	4.77	0.27[d]	0.17	0.37	0.56[d]	0.46	0.66
108	0.24	175	0.65	176	2.71[d]	2.04	3.60	0.78	102	3.25[d]	2.45	4.31	0.41[d]	0.32	0.50	0.16[d]	0.07	0.25

Data are presented in ascending order of RR-RCT for OS
OS = Overall Survival Rate, RR = Relative Rate (OS Active/OS Control), RCT = Randomized Controlled Trial, SC = Single Cohort Study, Difference (d) = OS Active - OS Control
a=Negative + Not Statistically Significant (P ≥ 0.05); b = Negative and Statistically Significant (P < 0.05); c=Positive + Not Statistically Significant (P ≥ 0.05); d = Positive and Statistically Significant (P < 0.05);

Table 9a. Agreement Between RCT and SC for ORR Ratio

			ORR Ratio: SC			
			Negative		Positive	
			Non - Significant	Significant	Non - Significant	Significant
ORR Ratio: RCT	Negative	Non-Significant	1			1
		Significant				
	Positive	Non-Significant			3	
		Significant			2	4

Kappa for direction and statistical significance: 0.554 (P = 0.011)
Kappa for direction: 0.621 (P = 0.026)

ORR = Overall Response Rate,
ORR Ratio = ORR Active/ORR Control
RCT = Randomized Controlled Trial, SC = Single Cohort Study,Non – Significant: P ≥ 0.05; Significant: P < 0.05

Table 9b. Agreement Between RCT and SC for Treatment Acceptability on the basis of ORR Ratio

		ORR Ratio: SC Acceptance		
		Yes	No	Total
ORR Ratio: RCT Acceptance	Yes	4	2	6
	No	1	4	5
	Total	5	6	11

ORR = Overall Response Rate,
ORR Ratio = ORR Active/ORR Control
RCT = Randomized Controlled Trial, SC = Single Cohort Study,
Acceptance Criteria: Yes = Positive and Statistically Significant (P < 0.05) ORR Ratio; Else = No

Table 10a. Agreement Between RCT and SC for ORR Difference

			ORR Difference (d): SC			
			Negative		Positive	
			Non - Significant	Significant	Non - Significant	Significant
ORR Difference (d): RCT	Negative	Non-Significant	1			1
		Significant				
	Positive	Non-Significant			3	
		Significant			3	3

Kappa for direction and statistical significance: 0.429 (P = 0.038)
Kappa for direction: 0.600 (P = 0.064)

ORR = Overall Response Rate,
Difference (d) = ORR Active - ORR Control
RCT = Randomized Controlled Trial, SC = Single Cohort Study,Non – Significant: P ≥ 0.05; Significant: P < 0.05

Table 10b. Agreement Between RCT and SC for Treatment Acceptability based on ORR Difference

		ORR Difference: SC Acceptance		
		Yes	No	Total
ORR Difference: RCT Acceptance	Yes	3	3	6
	No	1	4	5
	Total	4	7	11

ORR = Overall Response Rate,
ORR Difference = ORR Active - ORR Control
RCT = Randomized Controlled Trial, SC = Single Cohort Study,
Acceptance Criteria: (Yes = Positive and Statistically Significant (P < 0.05) ORR Difference; Else = No)

Table 11a. Agreement Between RCT and SC for OS Ratio

			OS Ratio: SC			
			Negative		Positive	
			Non - Significant	Significant	Non - Significant	Significant
OS Ratio: RCT	Negative	Non-Significant		1		1
		Significant				
	Positive	Non-Significant	1	1	1	
		Significant	1			2

Kappa for direction and statistical significance: 0.167 (P = 0.365)
Kappa for direction: 0.621 (P = 0.026)

OS = Overall Survival Rate,
OS Ratio = OS Active/OS Control,
RCT = Randomized Controlled Trial, SC = Single Cohort StudyNon – Significant: P ≥ 0.05; Significant: P < 0.05

Table 11b. Agreement Between RCT and SC for Treatment Acceptability on the basis of OS Ratio

		OS Ratio: SC Acceptance		
		Yes	No	Total
OS Ratio: RCT Acceptance	Yes	2	1	3
	No	1	4	5
	Total	3	5	8

OS = Overall Survival Rate,
OS Ratio = OS Active/OS Control
RCT = Randomized Controlled Trial, SC = Single Cohort Study,
Acceptance Criteria: (Yes = Positive and Statistically Significant (P < 0.05) OS Ratio; Else = No)

Table 12a. Agreement Between RCT and SC for OS Difference

			OS Difference (d): SC			
			Negative		Positive	
			Non - Significant	Significant	Non - Significant	Significant
OS Difference (d): RCT	Negative	Non-Significant			1	
		Significant				
	Positive	Non-Significant	4			
		Significant				3

Kappa for direction and statistical significance: 0.149 (P = 0.428)
Kappa for direction: 0.250 (P = 0.285)

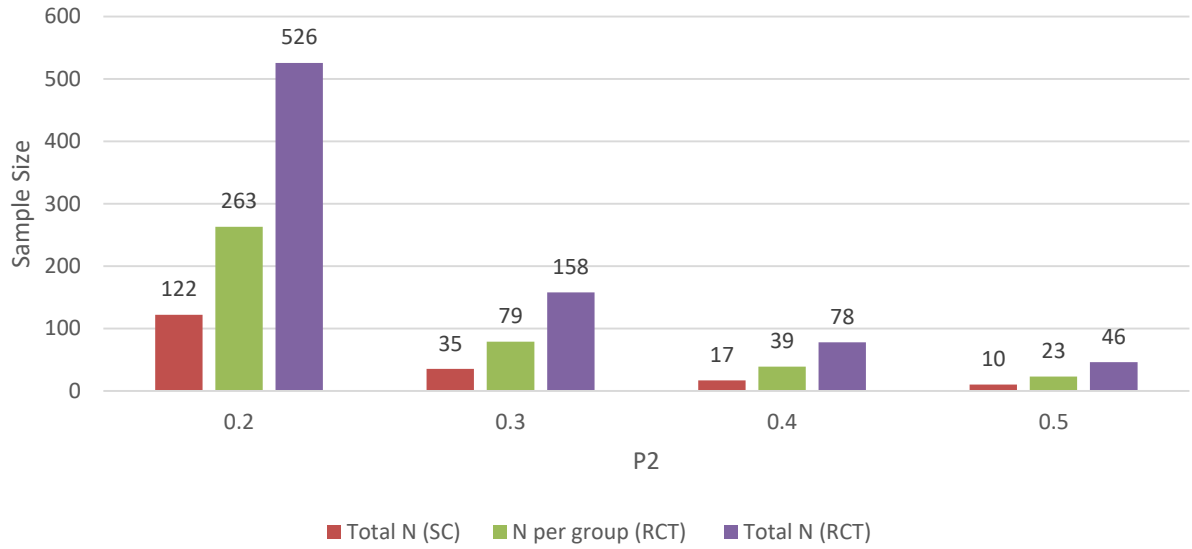
OS = Overall Survival Rate,
OS Difference (d) = OS Active - OS Control
RCT = Randomized Controlled Trial, SC = Single Cohort StudyNon – Significant: P ≥ 0.05; Significant: P < 0.05

Table 12b. Agreement Between RCT and SC for Treatment Acceptability based on OS Difference

		OS Ratio: SC Acceptance		
		Yes	No	Total
OS Ratio: RCT Acceptance	Yes	3	0	3
	No	0	5	5
	Total	3	5	8

OS = Overall Survival Rate,
OS Difference = OS Active - OS Control
RCT = Randomized Controlled Trial, SC = Single Cohort Study,
Acceptance Criteria: (Yes = Positive and Statistically Significant (P < 0.05) OS Difference; Else = No)

Figure 1. Sample Size Requirements
P1 = 0.10; Power = 0.90; Alpha = 0.05



P1 = Outcome rate in one group; P2 = Outcome rate in the comparator; Sample size is estimated to detect a difference between P1 and P2 with 90% Power (β = 0.10) at 5% Significance (α = 0.05).

Figure 2. Selection of Clinical Trials

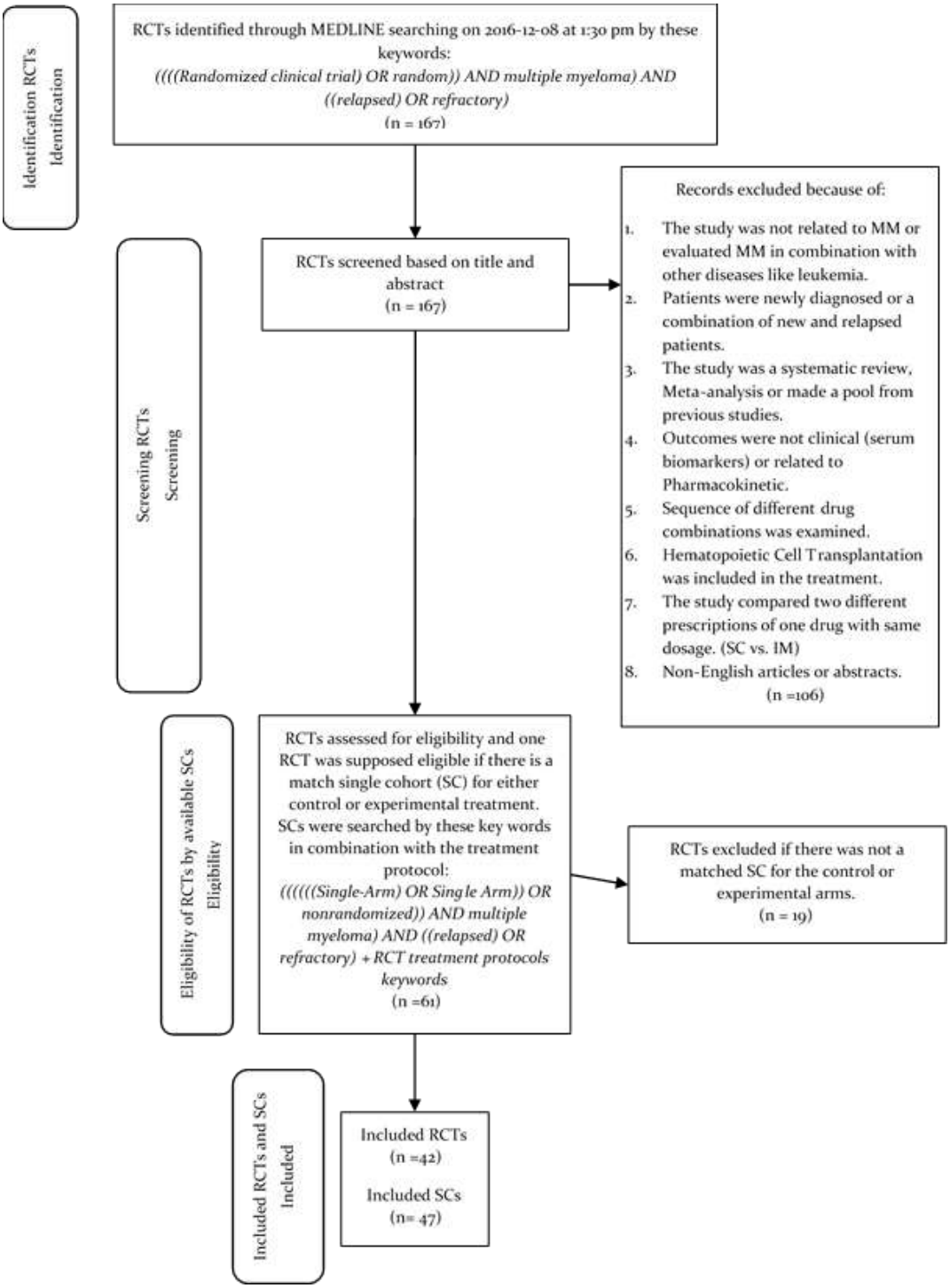
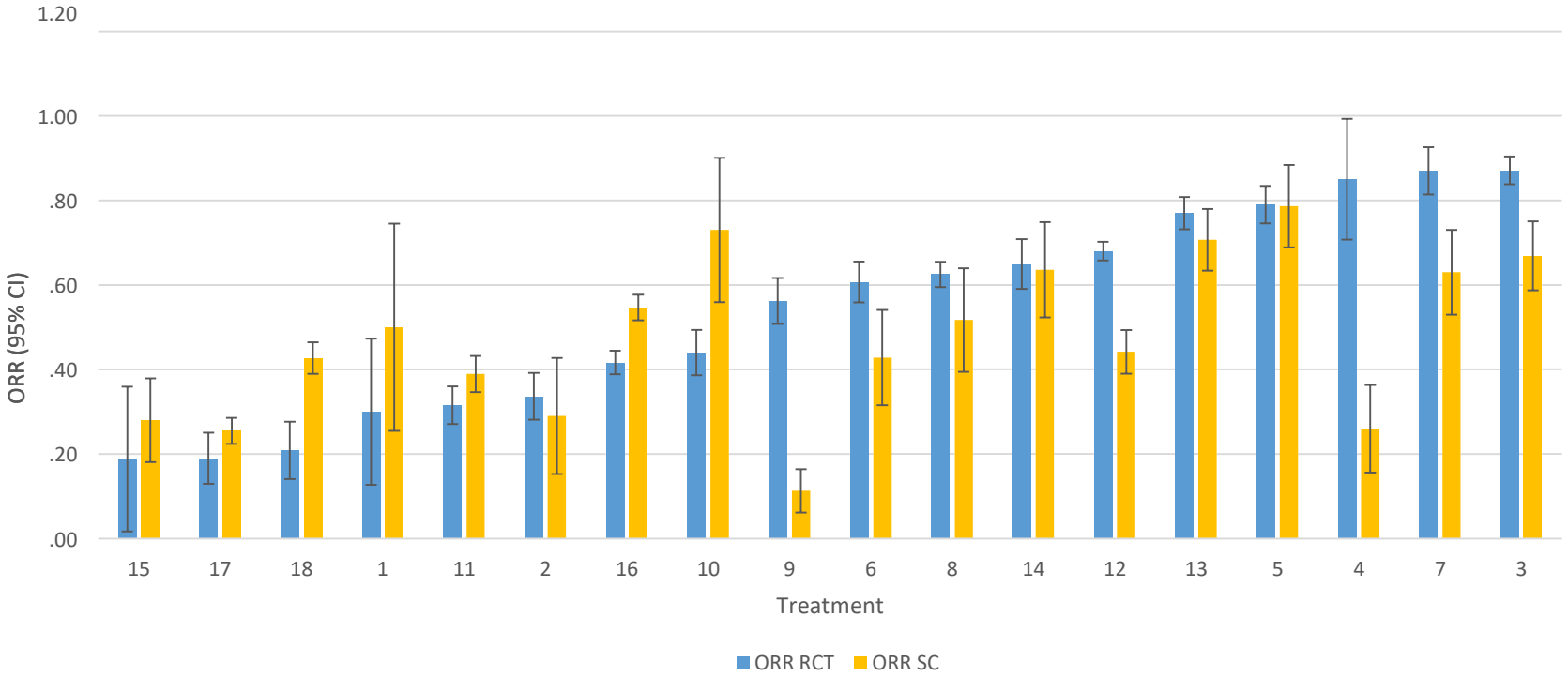
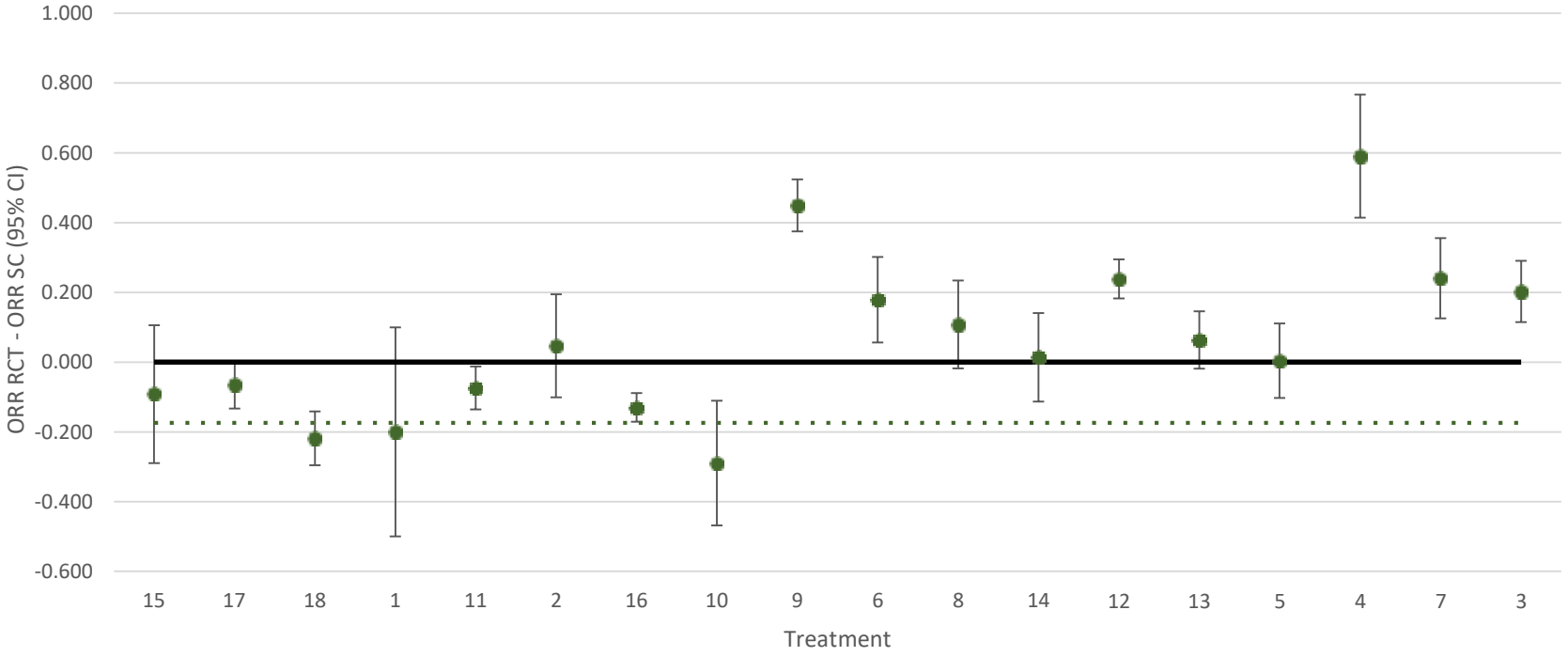


Figure 3. ORR by Treatment and Study Type



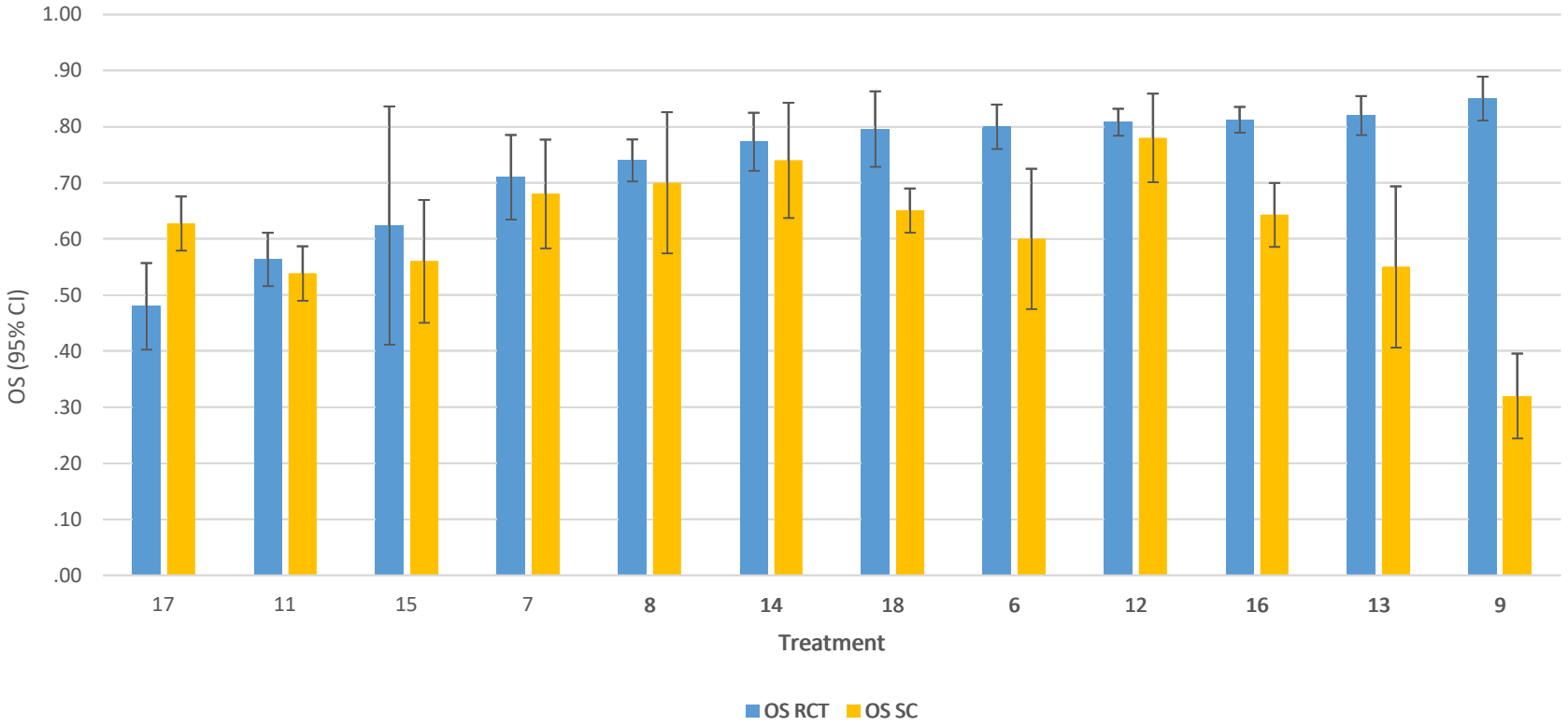
ORR = Overall Response Rate; RCT = Randomized Controlled Trial; SC = Single Cohort Study; CI = Confidence Intervals

Figure 4.: Difference (d) Between RCT - ORR and SC - ORR by Treatment



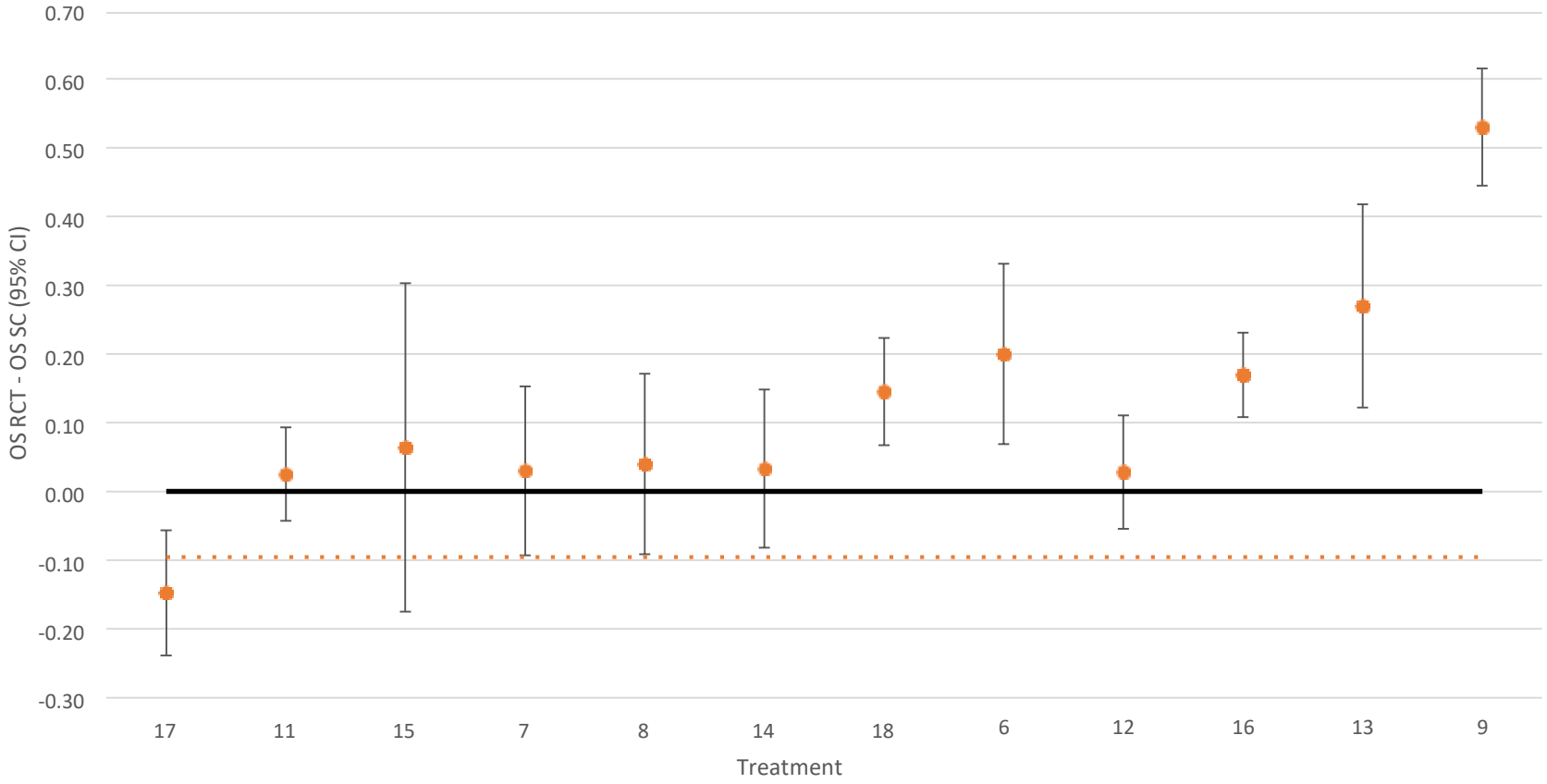
ORR = Overall Response Rate; RCT = Randomized Controlled Trial; SC = Single Cohort Study; Difference (d) = ORR $_{RCT}$ – ORR $_{SC}$; CI = Confidence Interval

Figure 5.: OS by Treatment and Study Type



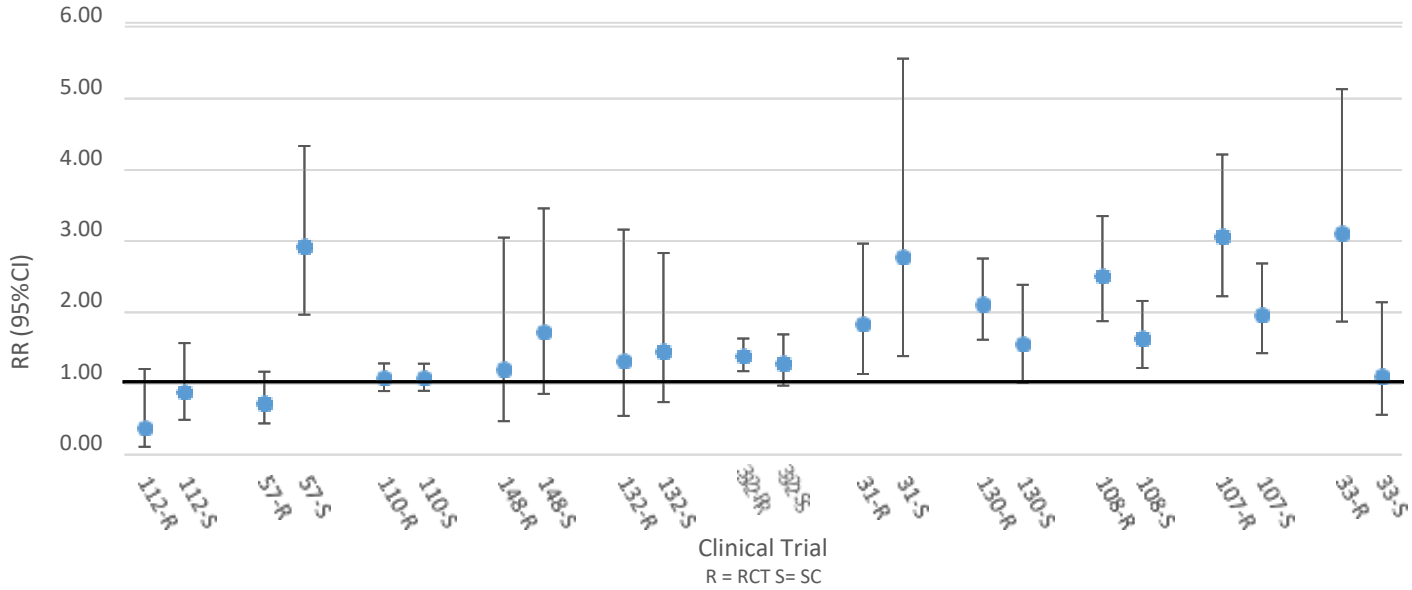
OS = Overall Survival; RCT = Randomized Controlled Trial; SC = Single Cohort Study; CI = Confidence Intervals

Figure 6. Difference (d) Between RCT-OS and SC-OS by Treatment



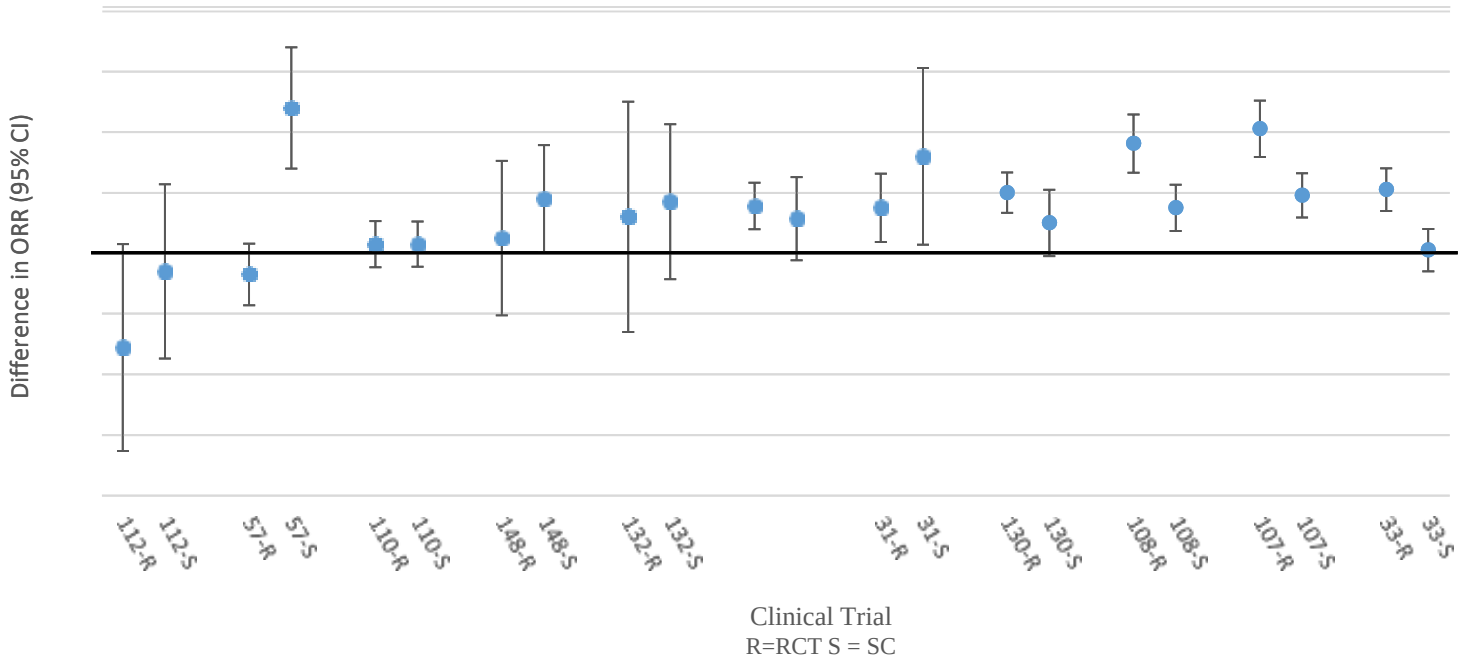
OS = Overall Survival; RCT = Randomized Controlled Trial; SC = Single Cohort Study; Difference (d) = OS $_{RCT}$ – OS $_{SC}$; CI = Confidence Interval

Figure 7. ORR Relative Rates by Clinical Trial and Design



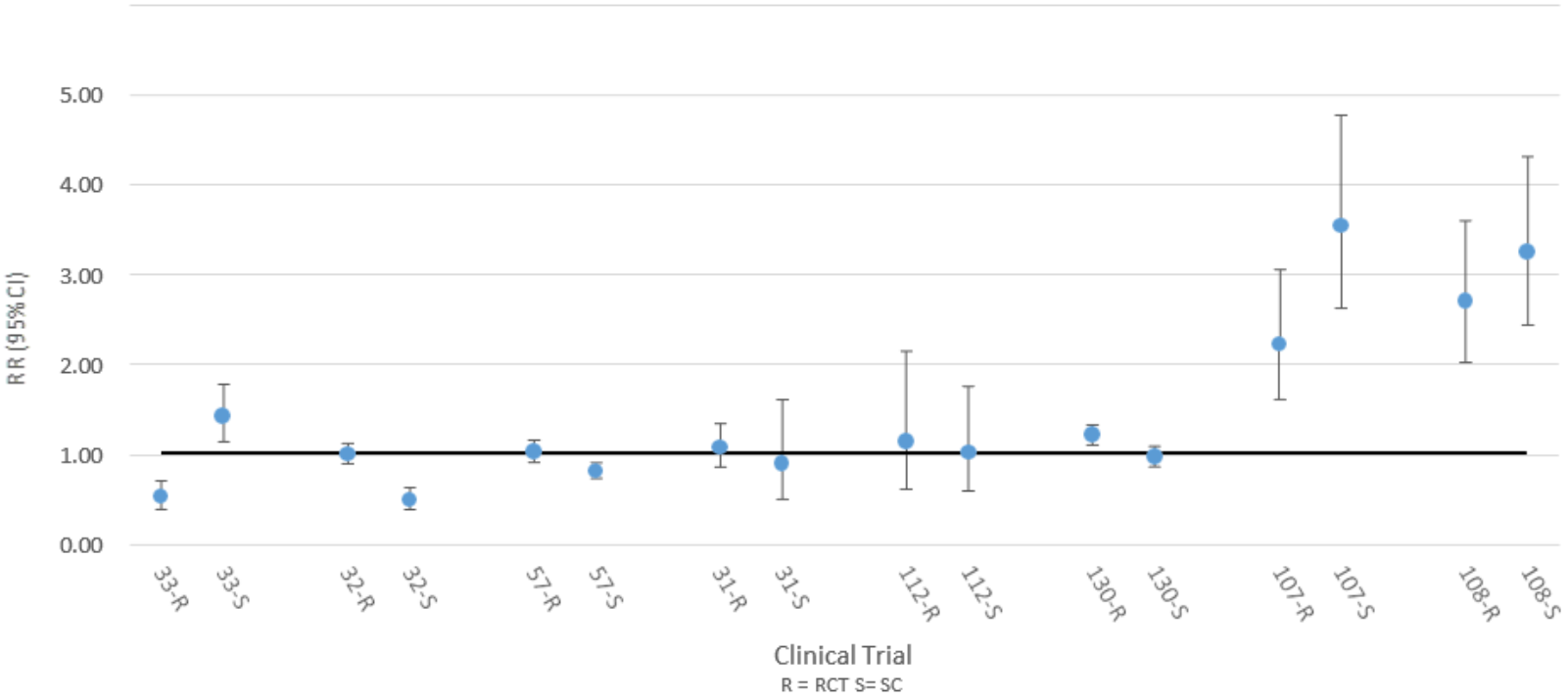
ORR = Overall Response Rate; RR = Relative Rate = ORR $_{Active}$ / ORR $_{Control}$; RCT = Randomized Controlled Trial; SC = Single Cohort Study; CI = Confidence Intervals

Figure 8. Difference (d) in ORR Between RCT and SC



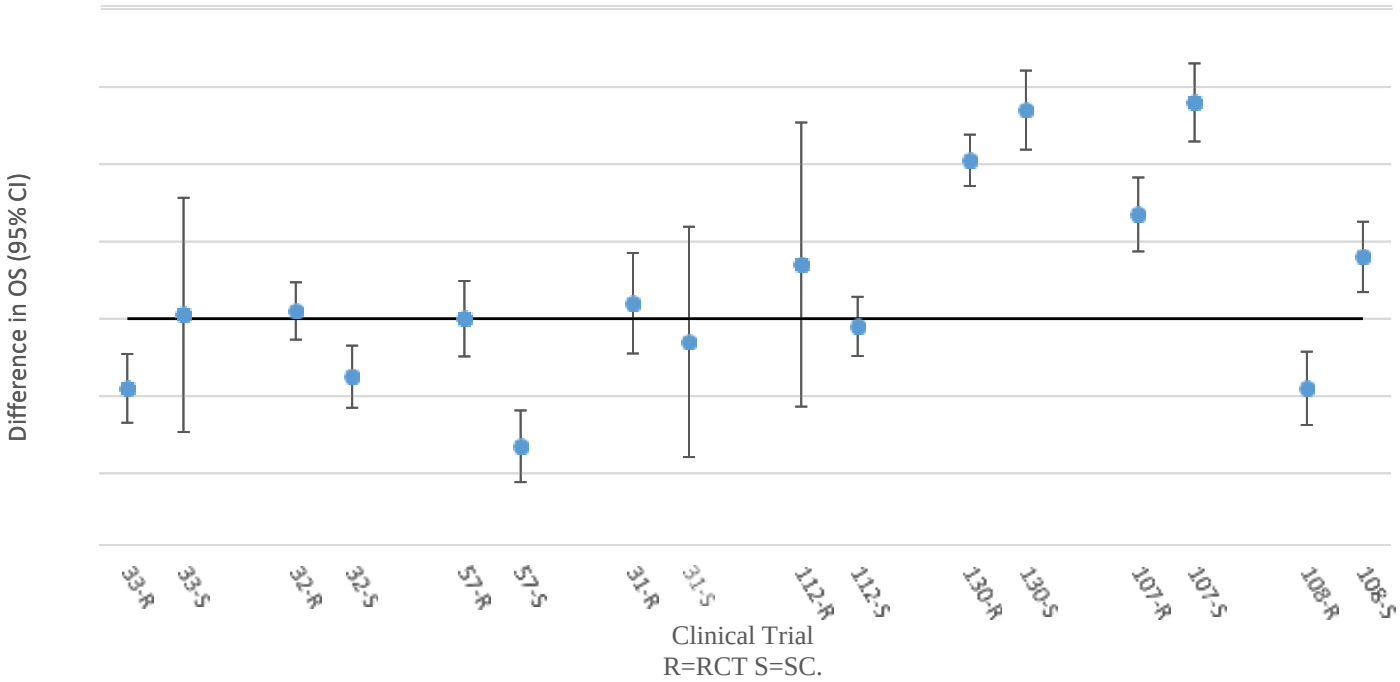
ORR = Overall Response Rate; Difference (d) ORR $_{Active}$ - ORR $_{Control}$; RCT = Randomized Controlled Trial; SC = Single Cohort Study; CI = Confidence Intervals

Figure 9. OS Relative Rates by Clinical Trial and Design



OS = Overall Survival Rate; RR = Relative Rate = OS_{Active} / $OS_{Control}$; RCT = Randomized Controlled Trial; SC = Single Cohort Study; CI = Confidence Intervals;

Figure 10. Difference (d) Between RCT and OS



OS = Overall Survival Rate; Difference (d) OS $_{Active}$ - OS $_{Control}$; RCT = Randomized Controlled Trial; SC = Single Cohort Study; CI = Confidence Intervals;

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