Relationship between overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) in clinical trials of patients with Mantle Cell Lymphoma (MCL)

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BACKGROUND

Mantle cell lymphoma (MCL)

- Mantle cell lymphoma (MCL) is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma (NHL)
- MCL accounts for approximately 6% of all incident NHL cases in the United States and about 5% to 7% of all lymphomas in Europe, with an annual incidence of 1 per 200,000
- Given the low incidence rate, randomized trials evaluating long-term outcomes in this disease are limited
- There is a need to understand if proximal surrogate outcomes such as overall tumor response (ORR) may be associated with longer-term survival outcomes in this disease

Study objective

- To estimate the relationship between outcomes in trials of MCL:
  1. The relationship of ORR with progression-free survival (PFS)
  2. The relationship of ORR with overall survival (OS)
  3. The relationship of PFS with OS

Methods

Identification of clinical trial data for analysis

- A search strategy was implemented in Medline, EMBASE and Evidence-based Medicine Reviews as well as hematology and oncology-focused conference proceedings.
  - The search strategy and screening criteria were based on PICO (patients, interventions, comparators and outcomes) criteria
  - Studies were included that were randomized controlled trials for patients with MCL that included tumor response data as well as at least one longer-term outcome (progression-free or overall survival [PFS or OS])
  - There were no restrictions placed on the line of therapy received or the specific intervention or comparator investigated

Statistical analysis plan

- Data were extracted and verified from the publications, including ORR, PFS and OS. Where hazard ratios (HR)/standard error data were not available for PFS or OS, the Kaplan Meier curve was digitized using WebPlotDigitizer to obtain this information
- In accordance with NICE guidelines, the difference in ORR between treatment groups was evaluated for its association with the HR for the differences in time to event outcomes between treatment groups within identified trials
- Multiple approaches were undertaken to evaluate the association between outcomes:
  - Bivariate random effects meta-analysis models with non-informative prior, Wishart prior, and product normal formulation, which include heterogeneity for both target and surrogate endpoint, as well as Pearson product (r) correlation
  - Correlation statistics were generated using R and JAGS

STUDIES INCLUDED

A total of 14 studies were identified and included in this analysis

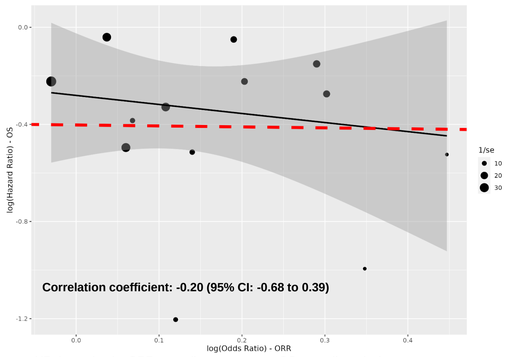
Table 1: Studies reporting ORR with PFS and/or OS

Publication	Data reported	Study design
Forstpointner, 2004[1]	ORR + PFS; n=48	RCT: FCM vs FCM-R
GLGLSG[2]	ORR + OS, n=95	RCT: FCM vs FCM-R
GLGLSG_2006[3]	ORR + OS, n=86	RCT: CHOP vs MCP
Jurczak_2018[4]	ORR + PFS/OS, n=89	RCT: Temsirolimus (2 doses)
Lenz_2005[5]	ORR + PFS/OS, n=122	RCT: R-CHOP vs CHOP
LYM-3002[6]	ORR + PFS/OS, n=487	RCT: R-CHOP vs VR-CAP
MCL-002 (Sprint)[7]	ORR + PFS/OS, n=254	RCT: Lenalidomide vs investigator choice
NCTN E1411[8]	ORR + PFS, n=359	RCT: BVR vs BR
OPTIMAL trial[9]	ORR + PFS/OS, n=108	RCT: Temsirolimus vs investigator choice
Rule, 2011[10]	ORR + PFS/OS, n=370	RCT: R-FC vs FC
Rule, 2013[11]	ORR + PFS/OS, n=46	RCT: Bortezomib-CHOP vs CHOP
Rummel, 2015[12]	ORR + PFS/OS, n=47	RCT: Bendamustine-R vs fludarabine-R
Ray Study[13]	ORR + PFS/OS, n=280	RCT: Ibrutinib vs Temsirolumus
Klein-Nelemans[14]	ORR + OS, n=532	RCT: R-CHOP vs R-FC

ORR: overall response rate; PFS: progression-free survival; OS: overall survival; RCT: randomized controlled trial; FCM: fludarabine, cyclophosphamide, mitoxantrone; R=rituximab; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; CAP: cyclophosphamide, doxorubicin, prednisone; BVR: bendamustine, bortezomib, rituximab; FC: fludarabine, cyclophosphamide

Relationship: ORR and OS

Figure 2. Relationship between the differences in ORR as measured by log odds ratio and change in OS as measured by log hazard ratio

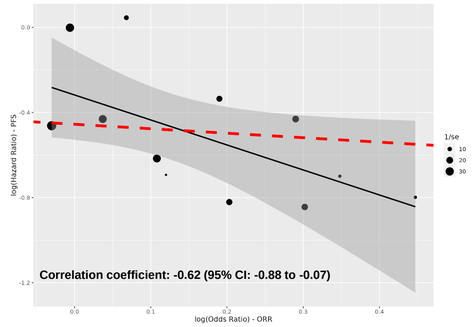


HR: hazard ratio; ORR: overall response rate; OS: overall survival

Note: Red line represents the bayes estimate; black line is weighted regression

RELATIONSHIP: ORR AND PFS

Figure 1. Relationship between differences in ORR as measured by log odds ratio and change in PFS as measured by log hazard ratio

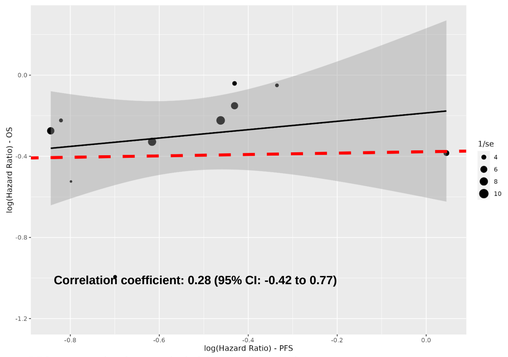


HR: hazard ratio; ORR: overall response rate; PFS: progression-free survival

Note: Red line represents the bayes estimate; black line is weighted regression

Relationship: PFS and OS

Figure 3. Relationship between changes in PFS and OS as measured by log hazard ratio



PFS: progression-free survival; OS: overall survival

Note: Red line represents the bayes estimate; black line is weighted regression

CONCLUSIONS

- A moderate relationship was identified between ORR and PFS.
- There was no clear relationship between differences between study arms for ORR and the difference observed in OS, nor between differences in PFS and OS.
  - While both ORR and PFS occur within the treatment period of clinical trials, OS occurs later, and can be influenced by future events.
  - Therefore, the lack of a direct relationship between ORR and survival events with less temporal proximity is not unexpected.
  - Findings should be interpreted with caution due to the small number of studies.
  - Should additional studies become available, an assessment by line of therapy may clarify these relationships.
- Assessment of the use of ORR may not translate to longer-term outcomes beyond PFS in MCL
  - OS is likely impacted by events following the initial response to treatment that could not be accounted for in this study

Results

- A total of 14 studies were identified in the literature (Table 1)
- PFS and ORR data were reported for 2,196 patients in 12 trials; OS and ORR data reported for 2,015 patients in 13 trials
- Pearson correlation statistics demonstrated the strongest relationship between ORR and logPFS (r = -0.62; 95% CI: -0.88 to -0.07) (Figure 1)
- The relationship between ORR and logOS (r = -0.20; 95% CI: -0.68 to 0.39) and logPFS and logOS (r = 0.28; 95% CI: -0.42 to 0.77) were low. (Figure 2)
- Bayesian bivariate analyses were limited by the lack of individual patient-level data and trial-to-trial variability.

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