

Improved survival for dose-intensive chemotherapy in primary mediastinal B-cell lymphoma: a systematic review and meta-analysis of 4,068 patients

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Data Supplement

Supplementary Table 1: Other Clinical Characteristics and Demographic Information

| Characteristic | n, % |
|--------------------------------|------------|
| Median age, range (n = 335) | 35, 16-78 |
| Female gender (n = 335) | 183, 54.6% |
| Stage (n = 335) | |
| I - II | 303, 90.4% |
| III-IV | 32, 9.5% |
| B-symptoms (n= 335) | 126, 37.6% |
| Bulky Disease (n= 335) | 186, 55.5% |
| LDH > ULN (n= 335) | 224, 66.9% |
| Extranodal disease (n= 95) | 34, 35.8% |
| Pleural Effusion (n = 188) | 58, 30.9% |
| Pericardial Effusion (n = 188) | 44, 23.4% |

Includes 5 publications that did not divide clinical characteristic based on treatment regimen. One of these 5 publications (Binkley et al) only analyzed Stage I/II PMBCL patients, hence the heavily weighted stage I/II disease.

Supplementary Table 2: Pediatric Clinical Characteristics and Demographic Information

| Pediatric Characteristic | n, % |
|-------------------------------------|----------------|
| Median age (years), range (n = 173) | 15.4, 1.4-19 |
| Mean age (years), range (n = 116) | 15.5, 1.4-21.7 |
| Female gender (n = 289) | 158, 54.7% |
| Stage (Ann Arbor, n = 88) | |
| I - II | 50, 56.8% |
| III-IV | 38, 43.2% |
| Stage (Murphy/St Jude, n = 201) | |
| II | 1, 0.5% |
| III | 178, 88.6% |
| IV | 1, 0.5% |
| NR | 21, 10.4% |

| | |
|--------------------------------------|-----------|
| Bulky Disease (n= 101) | 73, 72.3% |
| LDH \geq 2x ULN (n= 173) | 88, 50.9% |
| Subdiaphragmatic Involvement (n= 88) | 25, 28.4% |
| Bone Marrow Involvement (n = 259) | 3, 1.2% |
| CNS Involvement (n = 97) | 2, 2.1% |

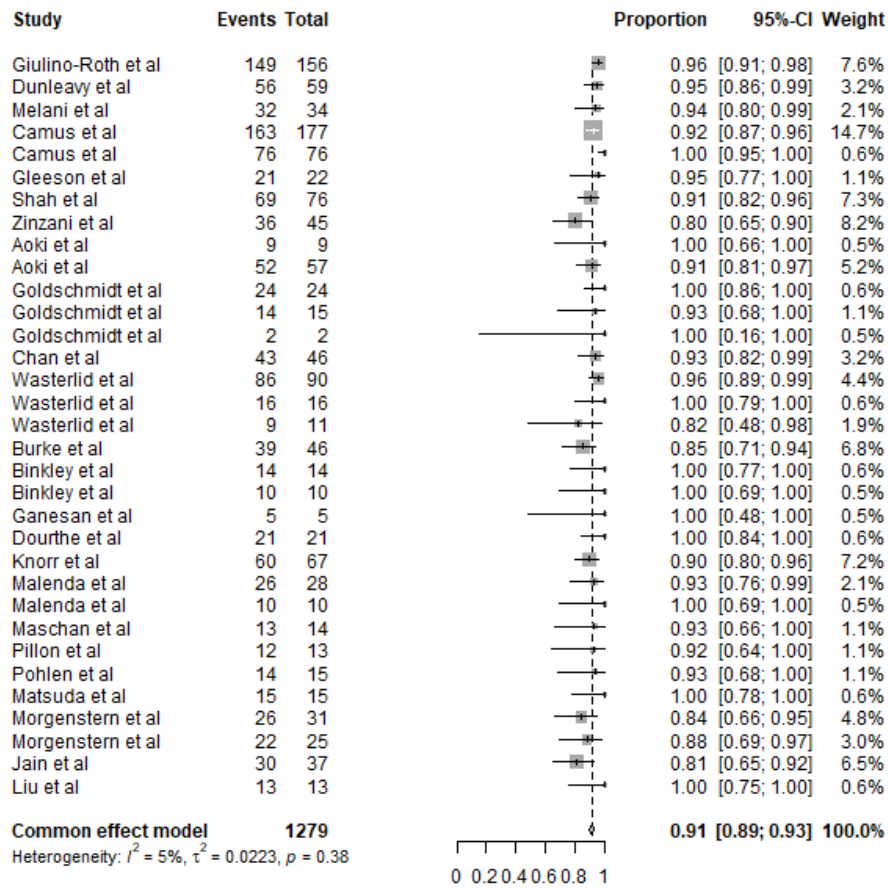
Includes 6 pediatric only publications. Pediatric patients that were included in analyses with adults, that had information reported for specific CIT regimens is included within the main text.

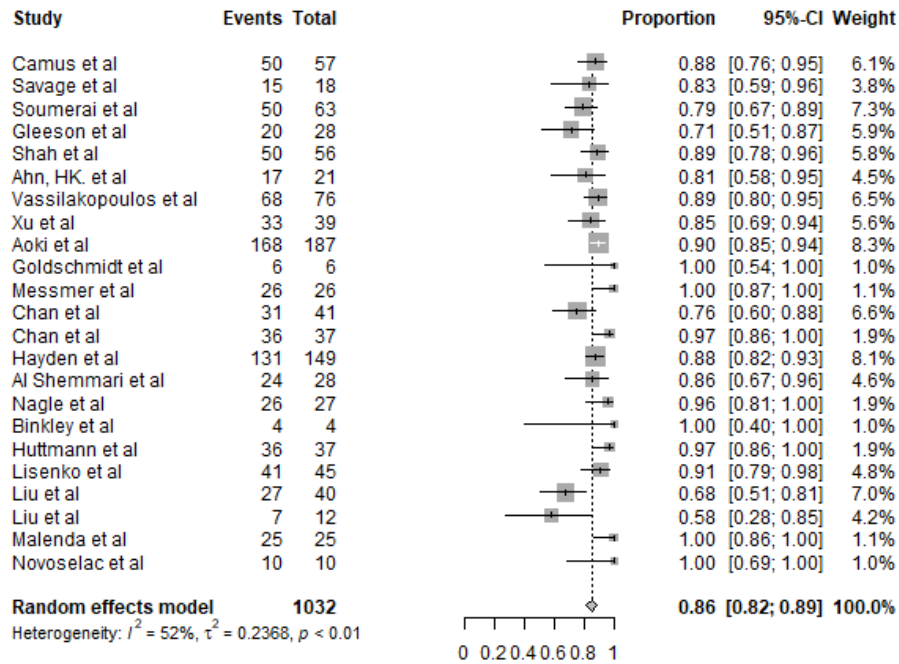
Supplementary Table 3. Meta-regression analysis statistics for each outcome

| Outcomes | Treatments | Statistics | Estimation | P-value | CI.lower | CI.upper |
|----------------------------------|--------------------------------------|-----------------|------------|---------|----------|----------|
| Overall Survival | Dose intensive vs. Standard approach | Intercept | 0.88 | <0.01 | 0.84 | 0.93 |
| | | Follow up years | -0.01 | <0.01 | -0.02 | -0.01 |
| | | Treatment | 0.08 | <0.01 | 0.04 | 0.13 |
| | da-EPOCH-R vs. R-CHOP21 | Intercept | 0.93 | <0.01 | 0.88 | 0.98 |
| | | Follow up years | -0.01 | 0.19 | -0.02 | <0.01 |
| | | Treatment | 0.03 | 0.25 | -0.02 | 0.07 |
| Event Free Survival | Dose intensive vs. Standard approach | Intercept | 0.7 | <0.01 | 0.47 | 0.93 |
| | | Follow up years | -0.02 | 0.12 | -0.06 | 0.01 |
| | | Treatment | 0.19 | 0.01 | 0.04 | 0.34 |
| | da-EPOCH-R vs. R-CHOP21 | Intercept | 0.73 | <0.01 | 0.56 | 0.89 |
| | | Follow up years | 0.01 | 0.46 | -0.02 | 0.03 |
| | | Treatment | 0.08 | 0.19 | -0.04 | 0.21 |
| Progression Free Survival | Dose intensive vs. Standard approach | Intercept | 0.75 | <0.01 | 0.68 | 0.82 |
| | | Follow up years | <0.01 | 0.24 | -0.01 | <0.01 |
| | | Treatment | 0.13 | <0.01 | 0.05 | 0.2 |
| | da-EPOCH-R vs. R-CHOP21 | Intercept | 0.78 | <0.01 | 0.65 | 0.9 |
| | | Follow up years | 0.01 | 0.63 | -0.02 | 0.03 |
| | | Treatment | 0.07 | 0.18 | -0.03 | 0.17 |
| Radiation Received | Dose intensive vs. Standard approach | Intercept | 0.53 | <0.01 | 0.41 | 0.66 |
| | | Treatment | -0.24 | <0.01 | -0.41 | -0.08 |
| | da-EPOCH-R vs. R-CHOP21 | Intercept | 0.55 | <0.01 | 0.4 | 0.7 |
| | | Treatment | -0.42 | <0.01 | -0.64 | -0.19 |

| Outcomes | Treatments | Statistics | Estimation | P-value | CI.lower | CI.upper |
|--|--------------------------------------|-----------------|------------|---------|----------|----------|
| Overall Survival for rituximab-only patients | Dose intensive vs. Standard approach | Intercept | 0.93 | <0.01 | 0.89 | 0.98 |
| | | Follow up years | -0.01 | 0.16 | -0.02 | <0.01 |
| | | Treatment | 0.04 | 0.03 | <0.01 | 0.07 |

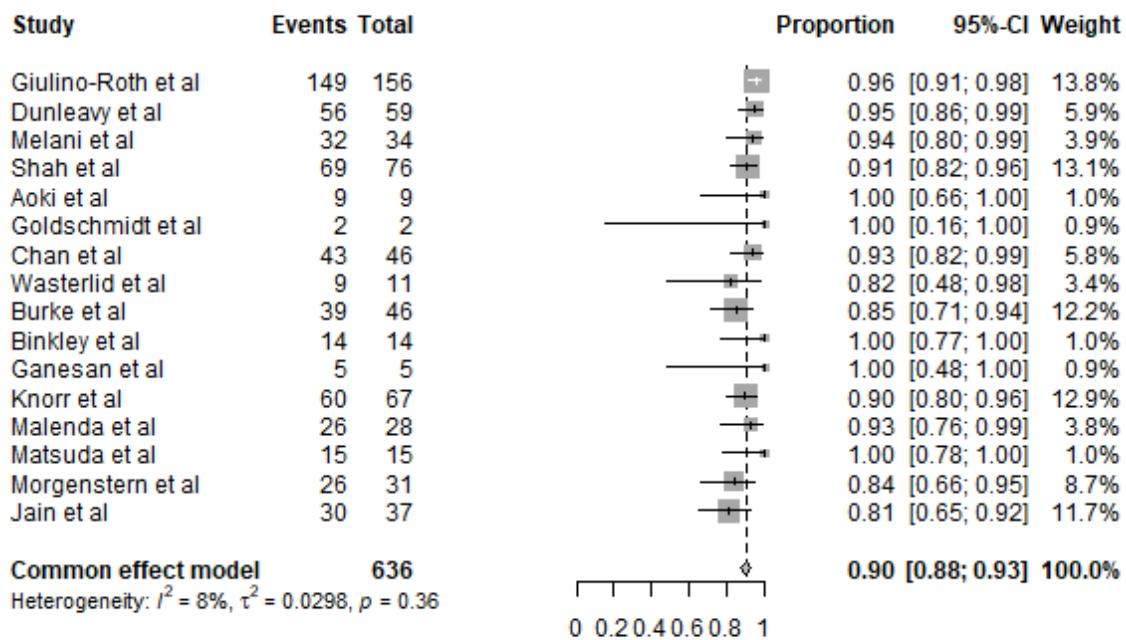
Supplementary Figure 1: Overall Survival, Rituximab-DI-CIT versus R-CHOP-21

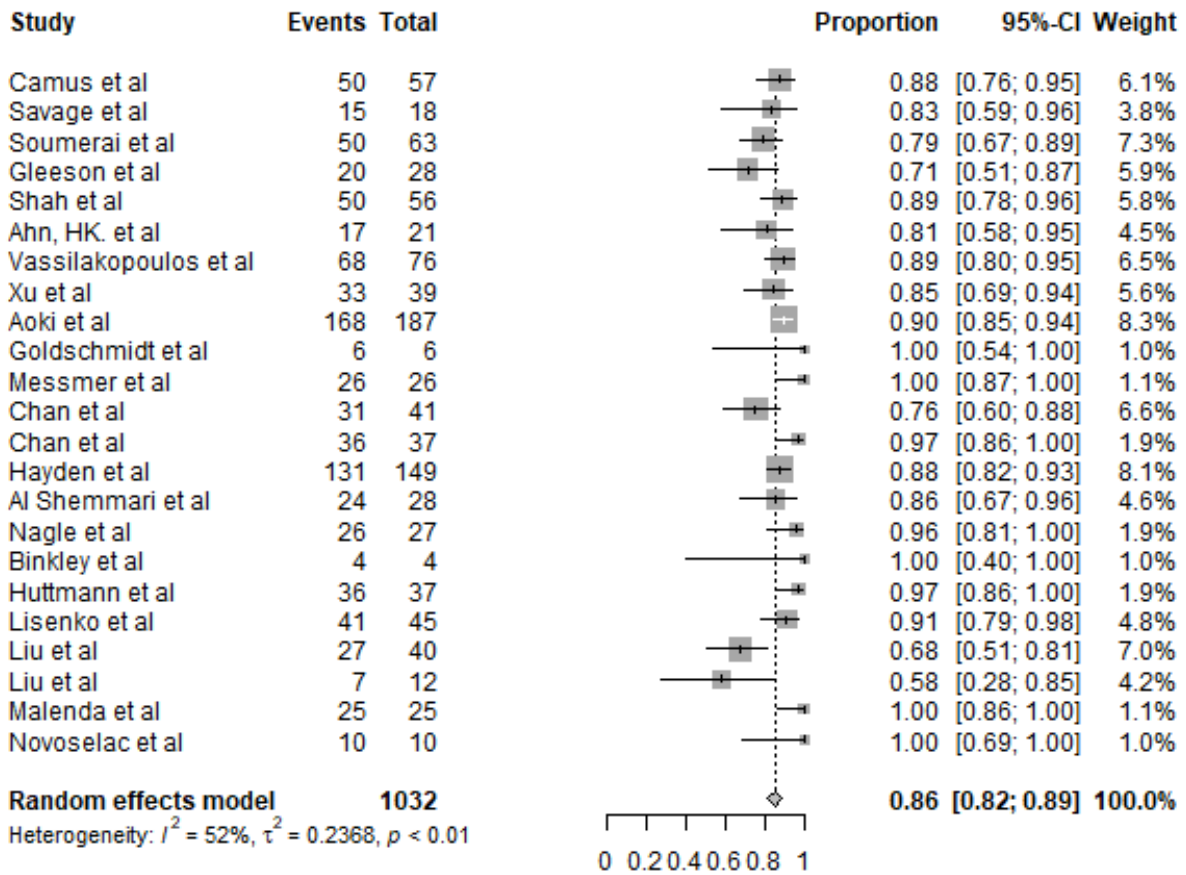




Overall survival of studies that used rituximab containing treatment protocols. Forest plot top = rituximab-DI-CIT. Forest plot bottom = R-CHOP-21.

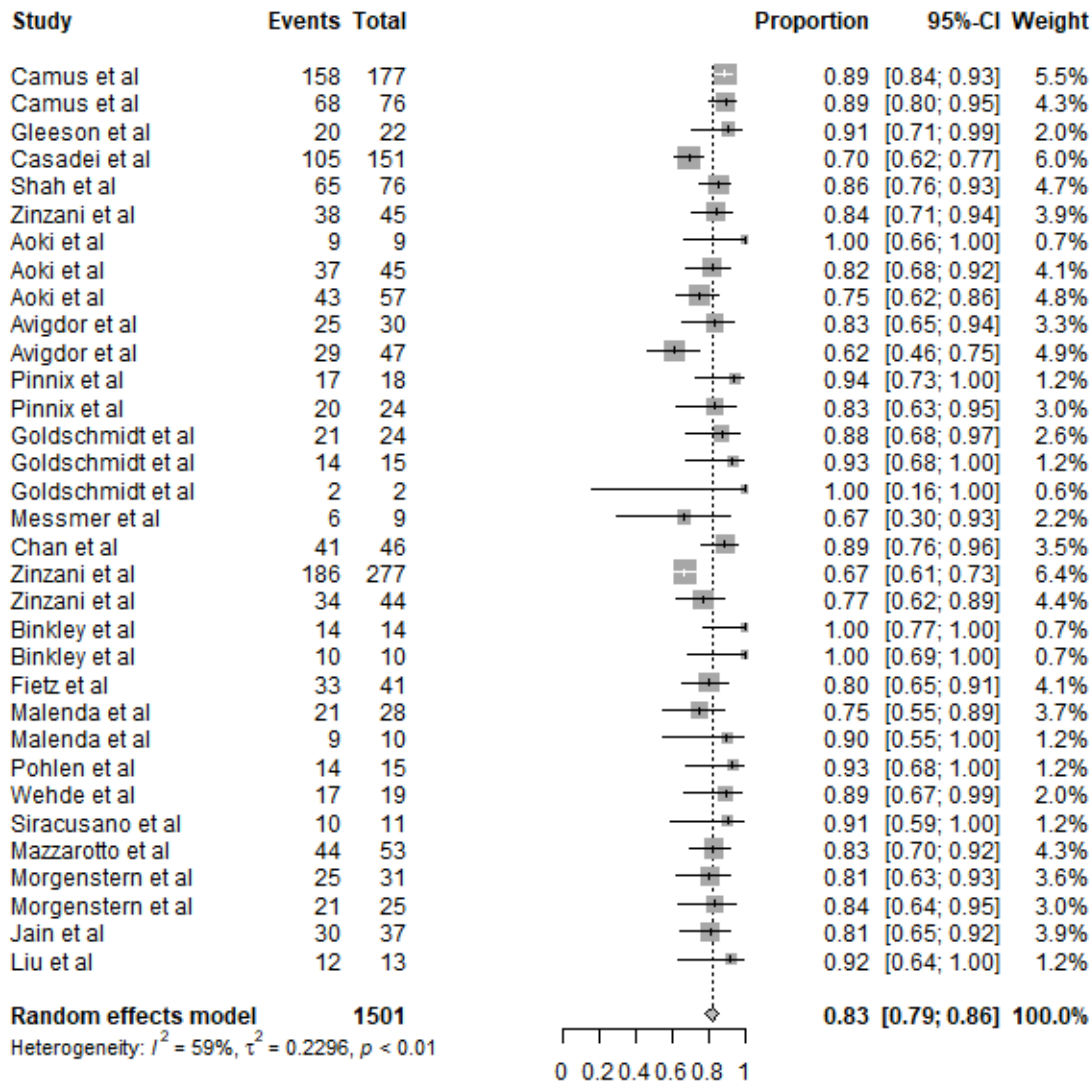
Supplementary Figure 2: Overall Survival, da-EPOCH-R versus R-CHOP-21

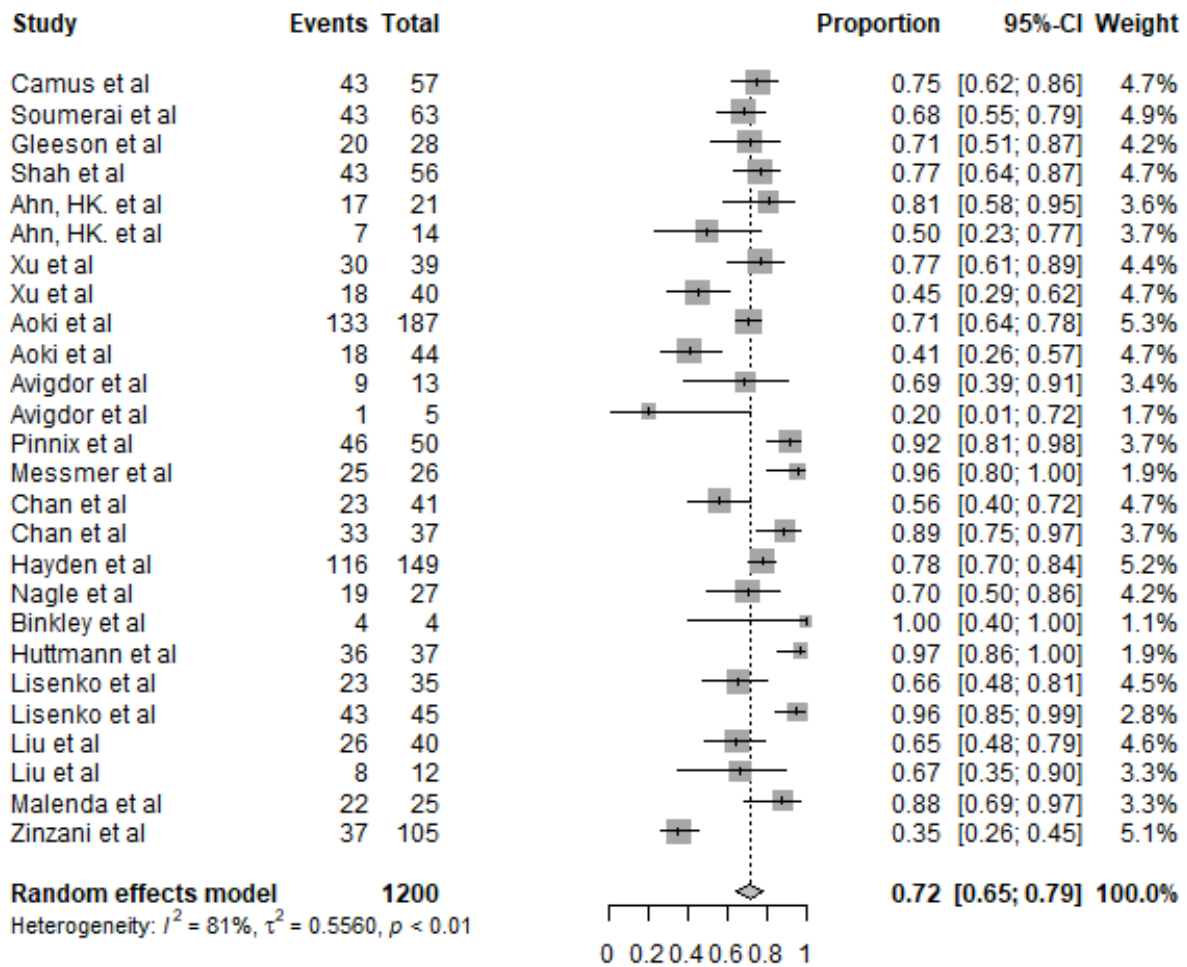




Overall survival of studies that used only da-EPOCH-R and R-CHOP-21 treatment protocols. Forest plot top = da-EPOCH-R. Forest plot bottom = R-CHOP-21

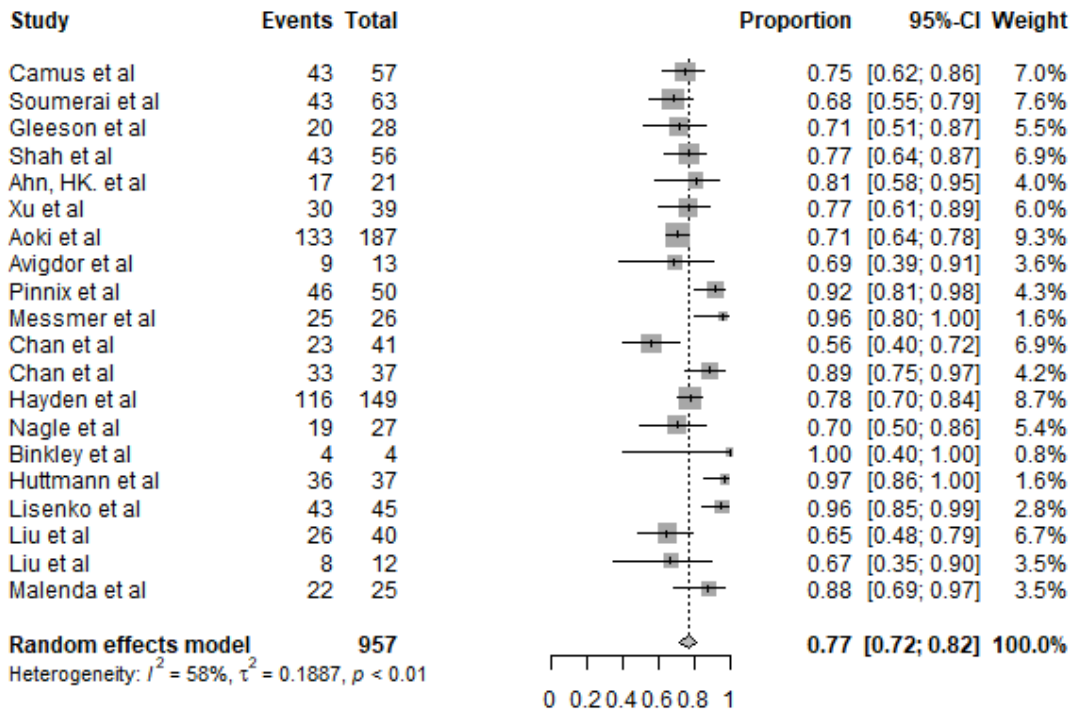
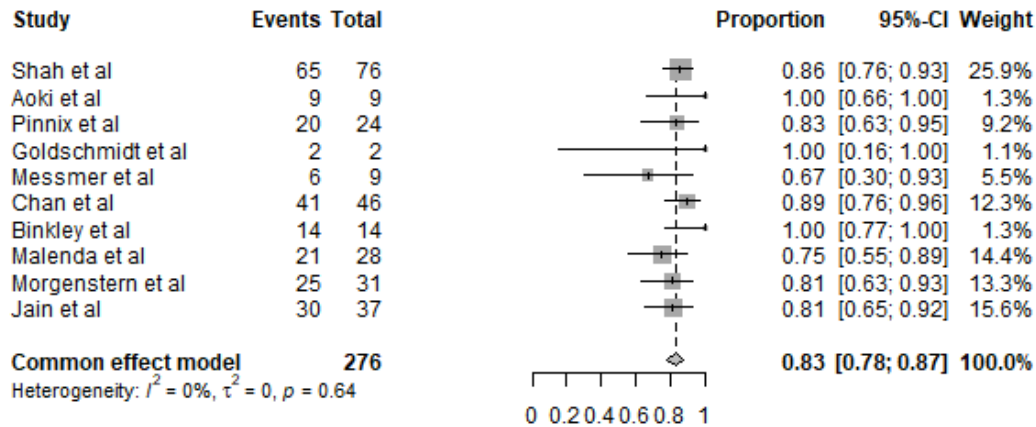
Supplementary Figure 3: Progression Free Survival, DI-CIT versus S-CIT





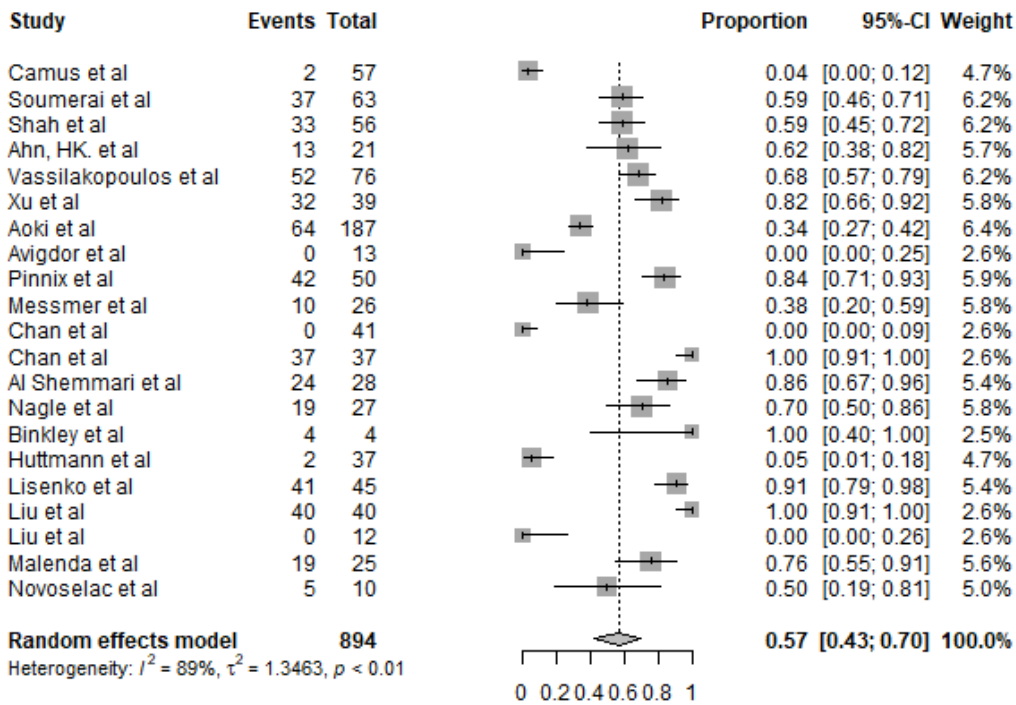
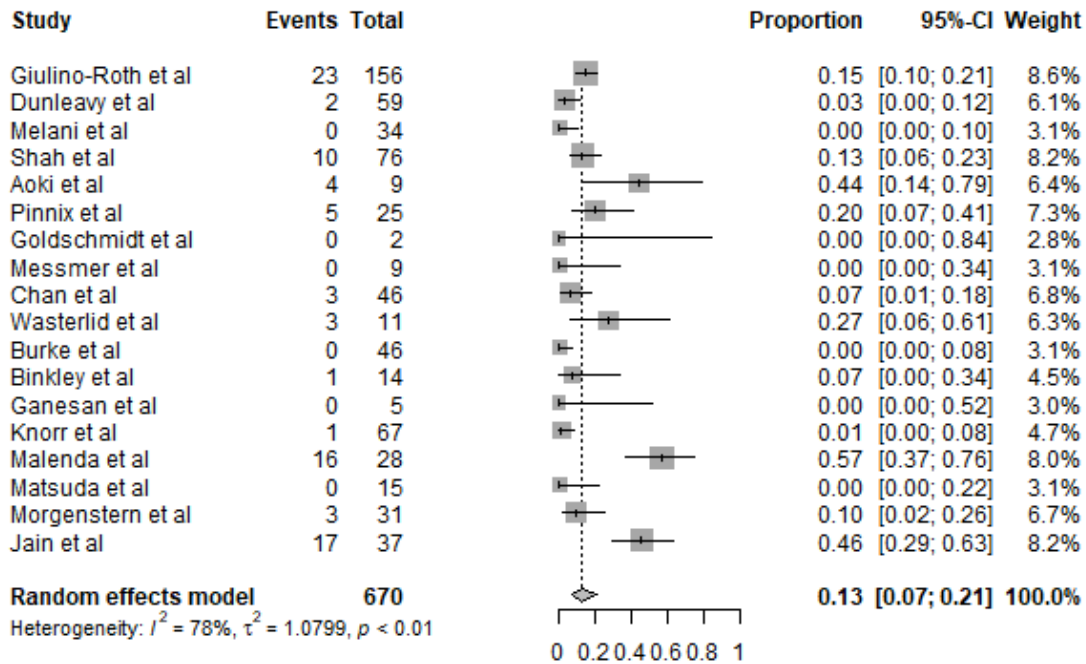
Progression free survival of DI-CIT versus S-CIT treatment protocols. Forest plot top = DI-CIT. Forest plot bottom = S-CIT

Supplementary Figure 4: Progression Free Survival, da-EPOCH-R versus R-CHOP-21



Progression free survival of studies that used only da-EPOCH-R and R-CHOP-21 treatment protocols. Forest plot top = da-EPOCH-R. Forest plot bottom = R-CHOP-21

Supplementary Figure 5: Consolidative Mediastinal Radiation, da-EPOCH-R versus R-CHOP-21



Consolidative mediastinal radiation administered to patients of studies that used only da-EPOCH-R and R-CHOP-21 treatment protocols. Forest plot top = da-EPOCH-R. Forest plot bottom = R-CHOP-21

PMBCL Systematic Review and Meta-Analysis Search Strategies

| | | |
|---|---|----------------|
| Ovid MEDLINE(R) ALL 1946 to February 15, 2022 | | |
| Date Searched | 2/16/22 | |
| Concept | Search String | Results |
| 1 | primary mediastinal B-cell lymphoma*.ti,ab,kf. OR PMBL.ti,ab,kf. OR PMBCL.ti,ab,kf. OR primary mediastinal large B-cell lymphoma*.ti,ab,kf. OR PMLBCL.ti,ab,kf. | 713 |
| 2 | (mediastin* ADJ3 (cancer* OR neoplasm* OR tumor* OR lymphoma*)).ti,ab,kf. OR Mediastinal Neoplasms/ OR (Mediastinum/ AND Neoplasms/) | 17,669 |
| 3 | (B cell ADJ2 Lymphoma*).ti,ab,kf. OR (B-cell ADJ2 Lymphoma*).ti,ab,kf. OR Lymphoma, B-Cell/ OR Lymphoma, Large B-Cell, Diffuse/ | 56,287 |
| 4 | (frontline ADJ2 therap*).ti,ab,kf. OR (frontline ADJ2 treatment*).ti,ab,kf. OR (treatment ADJ2 naive).ti,ab,kf. OR (therapy ADJ2 naive).ti,ab,kf. OR (first-line ADJ2 treatment*).ti,ab,kf. OR (first-line ADJ2 therap*).ti,ab,kf. OR EPOCH-R.ti,ab,kf. OR da-EPOCH-R.ti,ab,kf. OR dose-adjusted-EPOCH-R.ti,ab,kf. OR dose adjusted EPOCH R.ti,ab,kf. OR bleomycin.ti,ab,kf. OR Blenoxane.ti,ab,kf. OR cyclophosphamide.ti,ab,kf. OR Cytosan.ti,ab,kf. OR doxorubicin.ti,ab,kf. OR Adriamycin.ti,ab,kf. OR etoposide.ti,ab,kf. OR Vepesid.ti,ab,kf. OR hydroxydaunorubicin.ti,ab,kf. OR leucovorin.ti,ab,kf. OR methotrexate.ti,ab,kf. OR Otrexup.ti,ab,kf. OR Rasuvo.ti,ab,kf. OR Xatmep.ti,ab,kf. OR RediTrex.ti,ab,kf. OR prednisone.ti,ab,kf. OR Deltasone.ti,ab,kf. OR Prednicot.ti,ab,kf. OR predniSONE.ti,ab,kf. OR Intensol.ti,ab,kf. OR Sterapred.ti,ab,kf. OR Rayos.ti,ab,kf. OR vincristine.ti,ab,kf. OR oncovin.ti,ab,kf. OR Vincasar.ti,ab,kf. OR rituximab.ti,ab,kf. OR Rituxan.ti,ab,kf. OR vindesine.ti,ab,kf. OR Eldisine.ti,ab,kf. OR Enison.ti,ab,kf. OR R-CHOP-14.ti,ab,kf. OR R-CHOP.ti,ab,kf. OR R-ACVBP.ti,ab,kf. OR MACOP-B.ti,ab,kf. OR VACOP-B.ti,ab,kf. OR R-CHOP-21.ti,ab,kf. OR Antineoplastic Combined Chemotherapy Protocols/ OR Antibodies, Monoclonal, Murine-Derived/ OR Bleomycin/ OR Cyclophosphamide/ OR Doxorubicin/ OR Etoposide/ OR Leucovorin/ OR Methotrexate/ OR Prednisone/ OR Rituximab/ OR Vincristine/ OR Vindesine/ | 443,075 |
| Combo | (1 OR (2 AND 3)) AND 4 | 376 |
| Limits | None | |

| | | |
|--------------|--|-----|
| Total | | 376 |
|--------------|--|-----|

| Ovid Embase Classic+Embase 1947 to 2022 February 15 | | |
|---|--|---------|
| Date Searched | 2/16/22 | |
| Concept | Search String | Results |
| 1 | primary mediastinal B-cell lymphoma*.ti,ab,kf. OR PMBL.ti,ab,kf. OR PMBCL.ti,ab,kf. OR primary mediastinal large B-cell lymphoma*.ti,ab,kf. OR PMLBCL.ti,ab,kf. OR primary mediastinal B cell lymphoma/ | 1,853 |
| 2 | (Mediastin* ADJ3 (cancer* OR neoplasm* OR tumor* OR lymphoma*)).ti,ab,kf. OR Mediastinum Tumor/ OR Mediastinum Cancer/ OR Mediastinum Metastasis/ OR (Mediastinum/ AND exp Neoplasm/) | 30,627 |
| 3 | (B cell ADJ2 Lymphoma*).ti,ab,kf. OR (B-cell ADJ2 Lymphoma*).ti,ab,kf. OR B cell lymphoma/ OR diffuse large B cell lymphoma/ OR centroblastic lymphoma/ OR immunoblastic lymphoma/ OR plasmablastic lymphoma/ | 79,533 |
| 4 | (frontline ADJ2 therap*).ti,ab,kf. OR (frontline ADJ2 treatment*).ti,ab,kf. OR (treatment ADJ2 naive).ti,ab,kf. OR (therapy ADJ2 naive).ti,ab,kf. OR (first-line ADJ2 treatment*).ti,ab,kf. OR (first-line ADJ2 therap*).ti,ab,kf. OR EPOCH-R.ti,ab,kf. OR da-EPOCH-R.ti,ab,kf. OR dose-adjusted-EPOCH-R.ti,ab,kf. OR dose adjusted EPOCH R.ti,ab,kf. OR bleomycin.ti,ab,kf. OR Blenoxane.ti,ab,kf. OR cyclophosphamide.ti,ab,kf. OR Cytosan.ti,ab,kf. OR doxorubicin.ti,ab,kf. OR Adriamycin.ti,ab,kf. OR etoposide.ti,ab,kf. OR Vepesid.ti,ab,kf. OR hydroxydaunorubicin.ti,ab,kf. OR leucovorin.ti,ab,kf. OR methotrexate.ti,ab,kf. OR Otrexup.ti,ab,kf. OR Rasuvo.ti,ab,kf. OR Xatmep.ti,ab,kf. OR RediTrex.ti,ab,kf. OR prednisone.ti,ab,kf. OR Deltasone.ti,ab,kf. OR Prednicot.ti,ab,kf. OR predniSONE.ti,ab,kf. OR Intensol.ti,ab,kf. OR Sterapred.ti,ab,kf. OR Rayos.ti,ab,kf. OR vincristine.ti,ab,kf. OR oncovin.ti,ab,kf. OR Vincasar.ti,ab,kf. OR rituximab.ti,ab,kf. OR Rituxan.ti,ab,kf. OR vindesine.ti,ab,kf. OR Eldisine.ti,ab,kf. OR Enison.ti,ab,kf. OR R-CHOP-14.ti,ab,kf. OR R-CHOP.ti,ab,kf. OR R-ACVBP.ti,ab,kf. OR MACOP-B.ti,ab,kf. OR VACOP-B.ti,ab,kf. OR R-CHOP-21.ti,ab,kf. OR cyclophosphamide plus doxorubicin plus etoposide plus prednisolone plus vincristine/ OR cyclophosphamide plus doxorubicin plus prednisolone plus rituximab plus vincristine/ OR cyclophosphamide plus doxorubicin plus etoposide plus | 966,381 |

| | | |
|---------------|---|-------|
| | prednisolone plus rituximab plus vincristine/ OR exp combination chemotherapy/ OR antineoplastic monoclonal antibody/ OR Bleomycin/ OR Cyclophosphamide/ OR Doxorubicin/ OR Etoposide/ OR Folinic Acid/ OR Methotrexate/ OR Prednisone/ OR Rituximab/ OR Vincristine/ OR Vindesine/ | |
| | (1 OR (2 AND 3)) AND 4 | 1,291 |
| Limits | | |
| Total | | 1,291 |

| Ovid EBM Reviews - Cochrane Central Register of Controlled Trials January 2022 | | |
|--|---|---------|
| Date Searched | 2/16/22 | |
| Concept | Search String | Results |
| 1 | primary mediastinal B-cell lymphoma*.ti,ab,kw. OR PMBL.ti,ab,kw. OR PMBCL.ti,ab,kw. OR primary mediastinal large B-cell lymphoma*.ti,ab,kw. OR PMLBCL.ti,ab,kw. | 142 |
| 2 | (Mediastin* ADJ3 (cancer* OR neoplasm* OR tumor* OR lymphoma*)).ti,ab,kw. OR Mediastinal Neoplasms/ OR (Mediastinum/ AND Neoplasms/) | 436 |
| 3 | (B cell ADJ2 Lymphoma*).ti,ab,kw. OR (B-cell ADJ2 Lymphoma*).ti,ab,kw. OR Lymphoma, B-Cell/ OR Lymphoma, Large B-Cell, Diffuse/ | 2,548 |
| 4 | (frontline ADJ2 therap*).ti,ab,kw. OR (frontline ADJ2 treatment*).ti,ab,kw. OR (treatment ADJ2 naive).ti,ab,kw. OR (therapy ADJ2 naive).ti,ab,kw. OR (first-line ADJ2 treatment*).ti,ab,kw. OR (first-line ADJ2 therap*).ti,ab,kw. OR EPOCH-R.ti,ab,kw. OR da-EPOCH-R.ti,ab,kw. OR dose-adjusted-EPOCH-R.ti,ab,kw. OR dose adjusted EPOCH R.ti,ab,kw. OR bleomycin.ti,ab,kw. OR Blenoxane.ti,ab,kw. OR cyclophosphamide.ti,ab,kw. OR Cytoxan.ti,ab,kw. OR doxorubicin.ti,ab,kw. OR Adriamycin.ti,ab,kw. OR etoposide.ti,ab,kw. OR Vepesid.ti,ab,kw. OR hydroxydaunorubicin.ti,ab,kw. OR leucovorin.ti,ab,kw. OR methotrexate.ti,ab,kw. OR Otrexup.ti,ab,kw. OR Rasuvo.ti,ab,kw. OR Xatmep.ti,ab,kw. OR RediTrex.ti,ab,kw. OR prednisone.ti,ab,kw. OR Deltasone.ti,ab,kw. OR Prednicot.ti,ab,kw. OR predniSONE.ti,ab,kw. OR Intensol.ti,ab,kw. OR Sterapred.ti,ab,kw. OR Rayos.ti,ab,kw. OR vincristine.ti,ab,kw. OR oncovin.ti,ab,kw. OR Vincasar.ti,ab,kw. OR rituximab.ti,ab,kw. OR Rituxan.ti,ab,kw. OR vindesine.ti,ab,kw. OR Eldisine.ti,ab,kw. OR Enison.ti,ab,kw. OR R-CHOP-14.ti,ab,kw. OR R-CHOP.ti,ab,kw. OR R- | 70,363 |

| | | |
|--------------------|--|----|
| | ACVBP.ti,ab,kw. OR MACOP-B.ti,ab,kw. OR VACOP-B.ti,ab,kw. OR R-CHOP-21.ti,ab,kw. OR Antineoplastic Combined Chemotherapy Protocols/ OR Antibodies, Monoclonal, Murine-Derived/ OR Bleomycin/ OR Cyclophosphamide/ OR Doxorubicin/ OR Etoposide/ OR Leucovorin/ OR Methotrexate/ OR Prednisone/ OR Rituximab/ OR Vincristine/ OR Vindesine/ | |
| Combination | (1 OR (2 AND 3)) AND 4 | 93 |
| Limits | | |
| Total | | 93 |

| Web of Science Core Collection | | |
|--------------------------------|--|---------|
| Date Searched | | |
| Concept | Search String | Results |
| 1 | TS=("primary mediastinal B-cell lymphoma*" OR PMBL OR PMBCL OR "primary mediastinal large B-cell lymphoma*" OR PMLBCL) | 1,018 |
| 2 | TS=(Mediastin* NEAR/3 (cancer* OR neoplasm* OR tumor* OR lymphoma*)) | 6,613 |
| 3 | TS=((B cell NEAR/2 Lymphoma*) OR (B-cell NEAR/2 Lymphoma*)) | 52,299 |
| 4 | TS=((frontline NEAR/2 therap*) OR (frontline NEAR/2 treatment*) OR (treatment NEAR/2 naive) OR (therapy NEAR/2 naive) OR (first-line NEAR/2 treatment*) OR (first-line NEAR/2 therap*) OR "EPOCH-R" OR "da-EPOCH-R" OR "dose-adjusted-EPOCH-R" OR "dose adjusted EPOCH R" OR bleomycin OR Blenoxane OR cyclophosphamide OR Cytosan OR doxorubicin OR Adriamycin OR etoposide OR Vepesid OR hydroxydaunorubicin OR leucovorin OR methotrexate OR Otrexup OR Rasuvo OR Xatmep OR RediTrex OR prednisone OR Deltasone OR Prednicot OR predniSONE OR Intensol OR Sterapred OR Rayos OR vincristine OR oncovin OR Vincasar OR rituximab OR Rituxan OR vindesine OR Eldisine OR Enison OR "R-CHOP-14" OR "R-CHOP" OR "R-ACVBP" OR "MACOP-B" OR "VACOP-B" OR "R-CHOP-21") | 358,049 |
| Combination | (1 OR (2 AND 3)) AND 4 | 352 |
| Limits | | |
| Total | | 352 |