## Supplementary Material

### Supplementary Table 1: Search strategy

<table>
<thead>
<tr>
<th>Search Steps</th>
<th>Search Fields</th>
<th>MEDLINE</th>
<th>EMBASE</th>
<th>Cochrane registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 &quot;dose intensity&quot; OR &quot;dose reduction&quot; OR &quot;reduced dose&quot; OR &quot;miniCHOP&quot;</td>
<td>text words (including MeSH)</td>
<td>title, abstract, keywords</td>
<td>title, abstract, keywords</td>
<td></td>
</tr>
<tr>
<td>2 &quot;DLBCL&quot; OR &quot;diffuse large B cell lymphoma&quot; OR &quot;diffuse large B-cell lymphoma&quot;</td>
<td>text words (including MeSH)</td>
<td>title, abstract, keywords</td>
<td>title, abstract, keywords</td>
<td></td>
</tr>
<tr>
<td>3 1 AND 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: miniCHOP: dose attenuated CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone); DLBCL: diffuse large B-cell lymphoma; MeSH: medical subject headings
Supplementary Table 2: CASP analysis of studies included in the analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Did the study address a clearly focused issue?</th>
<th>Was the cohort recruited in an acceptable way?</th>
<th>Was the exposure accurately measured to minimize bias?</th>
<th>Have the authors identified all important confounding factors?</th>
<th>Have they taken account of the confounding factors in the design and/or analysis?</th>
<th>Was the follow-up of subjects complete enough?</th>
<th>How precise are the results?</th>
<th>Do you believe in the results?</th>
<th>Can the results be applied to the local population?</th>
<th>Do the results of this study fit with other available evidence?</th>
<th>What are the implications of this study for practice?</th>
<th>Total score (/5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terada et al</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear</td>
<td>Yes</td>
<td>Unclear/3</td>
</tr>
<tr>
<td>Hirakawa et al</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
<td>Unsure</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear/4</td>
</tr>
<tr>
<td>Carson et al</td>
<td>Yes</td>
<td>No</td>
<td>Unsure</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear/1</td>
</tr>
<tr>
<td>Ha et al</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Low</td>
<td>Yes</td>
<td>Unclear/3</td>
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<tr>
<td>Vidal et al</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
<td>Unsure</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear/4</td>
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<tr>
<td>Juul et al</td>
<td>No</td>
<td>Yes</td>
<td>Unsure</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
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<td>Unclear/3</td>
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<tr>
<td>Morth et al</td>
<td>No</td>
<td>No</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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</tr>
<tr>
<td>Eyre et al</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Długosz-Danecka et al</td>
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<td>No</td>
<td>Unclear</td>
<td>No</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Unclear/3</td>
</tr>
<tr>
<td>Nagata et al</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
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<tr>
<td>Hwang et al</td>
<td>Yes</td>
<td>Yes</td>
<td>Unsure</td>
<td>Unclear</td>
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<td>Yes</td>
<td>Yes</td>
<td>Low</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear/3</td>
</tr>
<tr>
<td>Lee et al</td>
<td>Yes</td>
<td>No</td>
<td>Unsure</td>
<td>Unclear</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear/3</td>
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</table>
Supplementary Table 3: Overview of the studies in the elderly population age > 70, based on dose intensity and outcomes analysis

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Papers</th>
<th>RDI cut off</th>
<th>Univariable OS impact</th>
<th>Univariable PFS impact</th>
<th>Multivariable OS impact</th>
<th>Multivariable PFS impact</th>
<th>Adjustment performed for ECOG and comorbidity</th>
<th>Cause-specific survival used for OS estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70</td>
<td>Ha et al.</td>
<td>60%</td>
<td>Pts ≥70 years only RDI &lt;60%: HR 0.45, 95% CI (0.21-0.97), p =0.04</td>
<td>Not done</td>
<td>Pts ≥70 years only RDI ≥60%: HR 1.597, 95% CI (0.607-4.202), p=0.343</td>
<td>Not done</td>
<td>B symptoms, Stage ≥3, ECOG PS ≥2, LDH&gt;ULN, EN sites ≥2, IPI ≥3, BM involvement, Bulky tumor</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Vidal et al.</td>
<td>90%</td>
<td>Dose (cycle 1 [H], continuous variable), for every 10% increase: HR 0.80, p &lt;0.0001, 95% CI (0.72-0.88)</td>
<td>Not done</td>
<td>Calculated individually for Cycle 1 of [C], [H], and for cycles 1+2 for [C], [H] [Dose[C]<em>{cycle 1} ] (for every 10% dose increase): HR 0.77, 95% CI (0.64-0.92), p&lt;0.005 [Dose[C]</em>{cycle 1+2} ] (for every 10% dose increase): HR 0.76, 95% CI (0.60-0.96), p&lt;0.019 [Dose[H]<em>{cycle 1} ] (for every 10% dose increase): HR 0.81, 95% CI (0.70-0.94), p&lt;0.005 [Dose[H]</em>{cycle 1+2} ] (for every 10% dose increase): HR 0.79, 95% CI (0.65-0.96), p&lt;0.018</td>
<td>Not done</td>
<td>ECOG 0-1 vs. ≥2; age ≥80 years; gender; IPI, Hb, and albumin</td>
<td>No</td>
</tr>
<tr>
<td>Study</td>
<td>Percentage</td>
<td>IDI ≥80%</td>
<td>OS: SHR 0.35, p&lt;0.001, 95% CI (0.35-0.58)</td>
<td>PFS: SHR 0.50, p&lt;0.001, 95% CI (0.39-0.64)</td>
<td>SHR: 1.80, p =0.004, 95% CI (1.21-2.67)</td>
<td>CIR: Age: 70-79 years</td>
<td>Additional Factors</td>
<td>Conclusion</td>
</tr>
<tr>
<td>------------------</td>
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</tr>
<tr>
<td>Eyre et al.</td>
<td>80%</td>
<td>IDI ≥80%</td>
<td></td>
<td>CIR: Age: 70-79 years</td>
<td></td>
<td>Age, stage, ECOG PS ≥2, LDH, albumin, gender, B-symptoms, EN &gt;1,</td>
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<tr>
<td>≥75</td>
<td>Juul et al.</td>
<td>Full dose</td>
<td>≥80%, KM analysis for OS 75-79 years: p = 0.068</td>
<td>MVA for R ± CHOP/CHOEP (ref) vs. less intensive t/t</td>
<td>75-79 years: OS, HR 1.54, 95% CI (1.04-2.30)</td>
<td>Not done</td>
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<tr>
<td>≥80</td>
<td>Eyre et al.</td>
<td>Not done</td>
<td>CIR: Age ≥80 years IDI &lt;80% SHR: 1.40 95% CI (0.95-2.07), p=0.09</td>
<td>Not done</td>
<td>CIR: Age ≥80 years IDI &lt;80% SHR: 1.48 95% CI (0.96-2.29), p=0.078</td>
<td>Age, stage, ECOG PS ≥2, LDH, albumin, gender, B-symptoms, EN &gt;1,</td>
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<tr>
<td></td>
<td>(subgroup analysis)</td>
<td>80%</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
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<tr>
<td></td>
<td>Juul et al.</td>
<td>Full dose</td>
<td>≥80%, KM analysis for OS 80-84 years: p = 0.414</td>
<td>MVA for R ± CHOP/CHOEP (ref) vs. less intensive t/t</td>
<td>80-84 years: OS, HR 1.39, 95% CI (1.01-1.91)  ≥ 85 years: OS, HR 1.04, 95% CI (0.69-1.58)</td>
<td>Not done</td>
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<tr>
<td></td>
<td>(subgroup analysis)</td>
<td>80%</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>age, sex, IPI, CCI score</td>
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<tr>
<td>Vidal et al.</td>
<td>90%</td>
<td>Not done</td>
<td>Delivered dose of [H]&lt;90%: OS, HR 0.88, 95% CI (0.74-1.06), p = 0.16</td>
<td>Delivered dose of [C]&lt;90%: OS, HR</td>
<td>Not done</td>
<td>Age, gender, IPI, Hb, albumin</td>
<td></td>
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<tr>
<td></td>
<td>(subgroup analysis)</td>
<td>90%</td>
<td>Not done for the subgroup of ≥ 80 years</td>
<td>Not done</td>
<td>Not done</td>
<td>No</td>
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<tr>
<td>Study</td>
<td>RDI/C%</td>
<td>Methodology</td>
<td>OS 1-yr Rate</td>
<td>HR (CIR)</td>
<td>95% CI</td>
<td>p</td>
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<tr>
<td>Carson et al.</td>
<td>85%</td>
<td>KM, and log-rank for OS comparison</td>
<td>Not done</td>
<td>Not done</td>
<td></td>
<td>p = 0.16</td>
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<tr>
<td></td>
<td></td>
<td>1-yr OS rate: RDI ≥85% - 59%</td>
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<tr>
<td></td>
<td></td>
<td>RDI &lt;85% - 70%; (Log-rank p=0.029), HR not provided</td>
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</tr>
<tr>
<td>Lee et al.</td>
<td>50%</td>
<td>KM analysis: tARDI &gt;50% vs. ≤50%</td>
<td>Not done</td>
<td>tARDI (10%): HR 0.889, 95% CI (0.809-0.975), p=0.013</td>
<td>Not done</td>
<td>albumin, CCI score, IPI score</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2yr OS = 61.8% vs. 50.8%, p=0.030</td>
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</tr>
</tbody>
</table>

**Abbreviations:**
- OS: Overall survival; PFS: Progression-free survival; MVA: multivariable analysis; UVA: univariable analysis
- C: Cyclophosphamide; H: Doxorubicin; O: Vincristine; P: Prednisone; R: Rituximab; THP-ADM: tetrahydropyranyladriamycin;
- IPI – International prognostic index; CCI: Charlson Comorbidity Index; LDH: Lactate dehydrogenase; ULN: Upper limit of normal; EN: extranodal disease; PS: performance status
- SHR: sub-hazard ratio
- IDI – Intended dose intensity = Average delivered dose [C+H] in cycle 1, expressed as a % relative to the standard dose.
- RDI - Relative Dose Intensity (varies by study design). See table 2 for details on the derivation of RDI.
- tARDI: total average RDI used in Lee et al. Haematologica 2020
- CIR: Cumulative Incidence of Relapse