**Supplementary Appendix**

Supplement to: Thurner L, Ziepert M, Berdel C et al.

Radiation and Dose-Densification of R-CHOP in aggressive B-cell lymphoma with intermediate prognosis: the UNFOLDER study

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Table S2: UNFOLDER Protocol Amendments

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Version | Date of version | Date of approval by the Ethics Committee of the Medical Council of Saarland | Date of activation | Changes |
| Initial version | 3.1 | 15 September 2004 | 02 October 2004 | - | - |
| Amendment 1 | 3.2 | 27 June 2005 | 18 August 2005 | - | - |
| Supplement | 3.2.1 | 28 September 2005 | 07 October 2005 | 02 January 2006  (start of recruitment) | Change of patient informed consent form |
| Supplement | 3.2.2 | 06 February 2006 | 02 March 2006 | 06 April 2006 | I.th. CNS prophylaxis also for patients with Burkitt and Burkitt-like lymphoma, addition of rate of secondary neoplasia as secondary endpoint, clarification and editorial changes |
| Amendment 2 | 4.0 | 22 November 2012 | 25 February 2013 | 08 May 2013 | Closure of the two treatment arms (R-CHOP-21, R-CHOP-14) without radiotherapy for patients with bulky disease and/or extranodal involvement, abandonement of i.th. CNS prophylaxis, introduction of prophylactic irradiation of contralateral testis in case of testicular lymphoma, clarification and editorial changes |

Table S3: Demographics for patients qualifying and not qualifying for radiotherapy

|  |  |  |  |
| --- | --- | --- | --- |
|  | qualifying for  radiotherapy | not qualifying for radiotherapy | UNFOLDER |
| (n=467) | (n=228) | (n=695) |
| Male  Female | 261 (56%)  206 (44%) | 142 (62%)  86 (38%) | 403 (58%)  292 (42%) |
| Age, median (range) | 44 (18, 60) | 50 (18, 60) | 47 (18, 60) |
| Serum lactate dehydrogenase > than upper limit of normal | 211 (45%) | 82 (36%) | 293 (42%) |
| Eastern Cooperative Oncology Group Performance status > 1 | 2 (0.4%) | 1 (0.4%) | 3 (0.4%) |
| Stage III/ IV | 165 (35%) | 131 (57%) | 296 (43%) |
| Age-adjusted International Prognostic Index  0\*  1  2 | 94 (20%)  368 (79%)  5 (1%) | 17 (7%)  208 (91%)  3 (1%) | 111 (16%)  576 (83%)  8 (1%) |
| Stage I  II  III  IV | 122 (26%)  180 (39%)  47 (10%)  118 (25%) | 37 (16%)  60 (26%)  77 (34%)  54 (24%) | 159 (23%)  240 (35%)  124 (18%)  172 (25%) |
| Extralymphatic involvement. | 242 (52%) | 82 (36%) | 324 (47%) |
| Extralymphatic involvement > 1 | 88 (19%) | 25 (11%) | 113 (16%) |
| Bulk ≥ 7·5 cm | 357 (76%) | 39 (17%) | 396 (57%) |
| B symptoms\*\* | 118 (25%) | 34 (15%) | 152 (22%) |
| Bone marrow involvement | 22 (5%) | 19 (8%) | 41 (6%) |
| Reference pathology available | 449 (96%) | 206 (90%) | 655 (94%) |
| DLBCL | 396 (88%) | 161 (78%) | 557 (85%) |
| PMBCL\*\*\* | 131 (29%) | 5 (2%) | 136 (21%) |
| Follicular lymphoma IIIb | 9 (2%) | 10 (5%) | 19 (3%) |
| Follicular lymphoma III° + DLBCL | 14 (3%) | 22 (11%) | 36 (6%) |
| Burkitt‘s lymphoma | 3 (1%) | 3 (1%) | 6 (1%) |
| Burkitt-like | 3 (1%) | 0 (0%) | 3 (0.5%) |
| Aggressive marginal zone lymphoma | 1 (0.2%) | 4 (2%) | 5 (1%) |
| Grey zone lymphoma | 3 (1%) | 0 (0%) | 3 (0·5%) |
| B-cell, NOS | 1 (0.2%) | 2 (1%) | 3 (0·5%) |
| B-cell, unclassified (techn. insufficient mat.) | 7 (2%) | 0 (0%) | 7 (1%) |
| Other, not B-cell | 12 (3%) | 4 (2%) | 16 (2%) |

\*10 (4/6) IPI=0 without bulk \*\*4 (3/1) missing values \*\*\* Subtype of DLBCL

Bone marrow is counted as extralymphatic; spleen and Waldeyers ring are counted as lymphathic

DLBCL: diffuse large B-cell lymphoma, PMBCL: primary mediastinal B-cell lymphoma, NOS: not otherwise specified

Table S4: Sites of extralymphatic involvements

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Localisation | qualifying for radiotherapy (n=467) | | | | not qualifying for radiotherapy (n=228) | |
| R-CHOP-21  (n=81) | R-CHOP-14  (n=81) | R-CHOP-21 +radiotherapy  (n=155) | R-CHOP-14 +radiotherapy  (n=150) | R-CHOP-21  (n=114) | R-CHOP-14  (n=114) |
| Bone marrow | 3 (4%) | 5 (6%) | 8 (5%) | 6 (4%) | 13 (11%) | 6 (5%) |
| Lung | 2 (2%) | 3 (4%) | 9 (6%) | 8 (5%) | 4 (4%) | 4 (4%) |
| Liver | 0 (0%) | 1 (1%) | 1 (1%) | 3 (2%) | 2 (2%) | 2 (2%) |
| Skeletal\* | 11 (14%) | 9 (11%) | 20 (13%) | 18 (12%) | 4 (4%) | 1 (1%) |
| Pleura | 2 (2%) | 5 (6%) | 5 (3%) | 3 (2%) | 0 (0%) | 1 (1%) |
| Pericard | 1 (1%) | 1 (1%) | 5 (3%) | 5 (3%) | 0 (0%) | 0 (0%) |
| CNS | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Stomach | 5 (6%) | 2 (2%) | 8 (5%) | 4 (3%) | 1 (1%) | 4 (4%) |
| Small intestine | 5 (6%) | 0 (0%) | 5 (3%) | 5 (3%) | 4 (4%) | 11 (10%) |
| Colon | 1 (1%) | 0 (0%) | 2 (1%) | 3 (2%) | 4 (4%) | 2 (2%) |
| Orbita | 0 (0%) | 0 (0%) | 0 (0%) | 3 (2%) | 0 (0%) | 0 (0%) |
| Paranasal sinuses | 1 (1%) | 3 (4%) | 4 (3%) | 5 (3%) | 0 (0%) | 1 (1%) |
| Main nasal cavity | 2 (2%) | 1 (1%) | 2 (1%) | 3 (2%) | 1 (1%) | 0 (0%) |
| Mouth region | 4 (5%) | 2 (2%) | 4 (3%) | 5 (3%) | 1 (1%) | 0 (0%) |
| Tongue | 0 (0%) | 1 (1%) | 2 (1%) | 2 (1%) | 0 (0%) | 0 (0%) |
| Salivary glands | 1 (1%) | 1 (1%) | 1 (1%) | 4 (3%) | 1 (1%) | 0 (0%) |
| Thyroid gland | 2 (2%) | 3 (4%) | 2 (1%) | 3 (2%) | 2 (2%) | 4 (4%) |
| Mammary gland | 0 (0%) | 0 (0%) | 6 (4%) | 3 (2%) | 0 (0%) | 0 (0%) |
| Peritoneum | 0 (0%) | 2 (2%) | 1 (1%) | 1 (1%) | 1 (1%) | 0 (0%) |
| Pancreas | 0 (0%) | 1 (1%) | 1 (1%) | 1 (1%) | 1 (1%) | 0 (0%) |
| Kidney | 2 (2%) | 1 (1%) | 1 (1%) | 2 (1%) | 0 (0%) | 2 (2%) |
| Adrenal gland | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 2 (2%) | 2 (2%) |
| Urinary bladder | 0 (0%) | 0 (0%) | 2 (1%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Testes | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 6 (5%) | 4 (4%) |
| Ovary | 0 (0%) | 0 (0%) | 1 (1%) | 1 (1%) | 5 (4%) | 1 (1%) |
| Uterus | 2 (2%) | 0 (0%) | 1 (1%) | 3 (2%) | 1 (1%) | 0 (0%) |
| Skin | 1 (1%) | 1 (1%) | 5\*\* (3%) | 2 (1%) | 2 (2%) | 0 (0%) |
| Soft tissues | 9 (11%) | 15 (19%) | 22 (14%) | 17 (11%) | 5\*\*\* (4%) | 7 (6%) |
| Ascites | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 1 (1%) | 0 (0%) |
| Other | 5\*\*\*\* (6%) | 2 (2%) | 4 (3%) | 4 (3%) | 2 (2%) | 1 (1%) |

\*13 (1/3/5/2/1/1) with cranial and caudal skeletal involvement

\*\*1 with two skin involvements

\*\*\*1 with two soft tissues involvements

\*\*\*\*1 with two other involvements

Table S5: Primary pathology

|  |  |  |  |
| --- | --- | --- | --- |
|  | qualifying for radiotherapy | not qualifying for radiotherapy | UNFOLDER |
| (n=467) | (n=228) | (n=695) |
| DLBCL\* | 431 (92%) | 190 (83%) | 621 (89%) |
| Follicular lymphoma III°b | 5 (1%) | 8 (4%) | 13 (2%) |
| Follicular lymphoma III° + DLBCL | 13 (3%) | 20 (9%) | 33 (5%) |
| Burkitt‘s lymphoma | 0 (0%) | 1 (0.4%) | 1 (0·1%) |
| Burkitt-like | 0 (0%) | 1 (0.4%) | 1 (0·1%) |
| Aggressive marginal zone lymphoma | 1 (0·2%) | 2 (1%) | 3 (0·4%) |
| B-cell, NOS | 17 (4%) | 6 (3%) | 23 (3%) |

DLBCL: diffuse large B-cell lymphoma, NOS: not otherwise specified

\* including primary mediastinal B-cell lymphoma (PMBCL).

Table S6: Causes of death

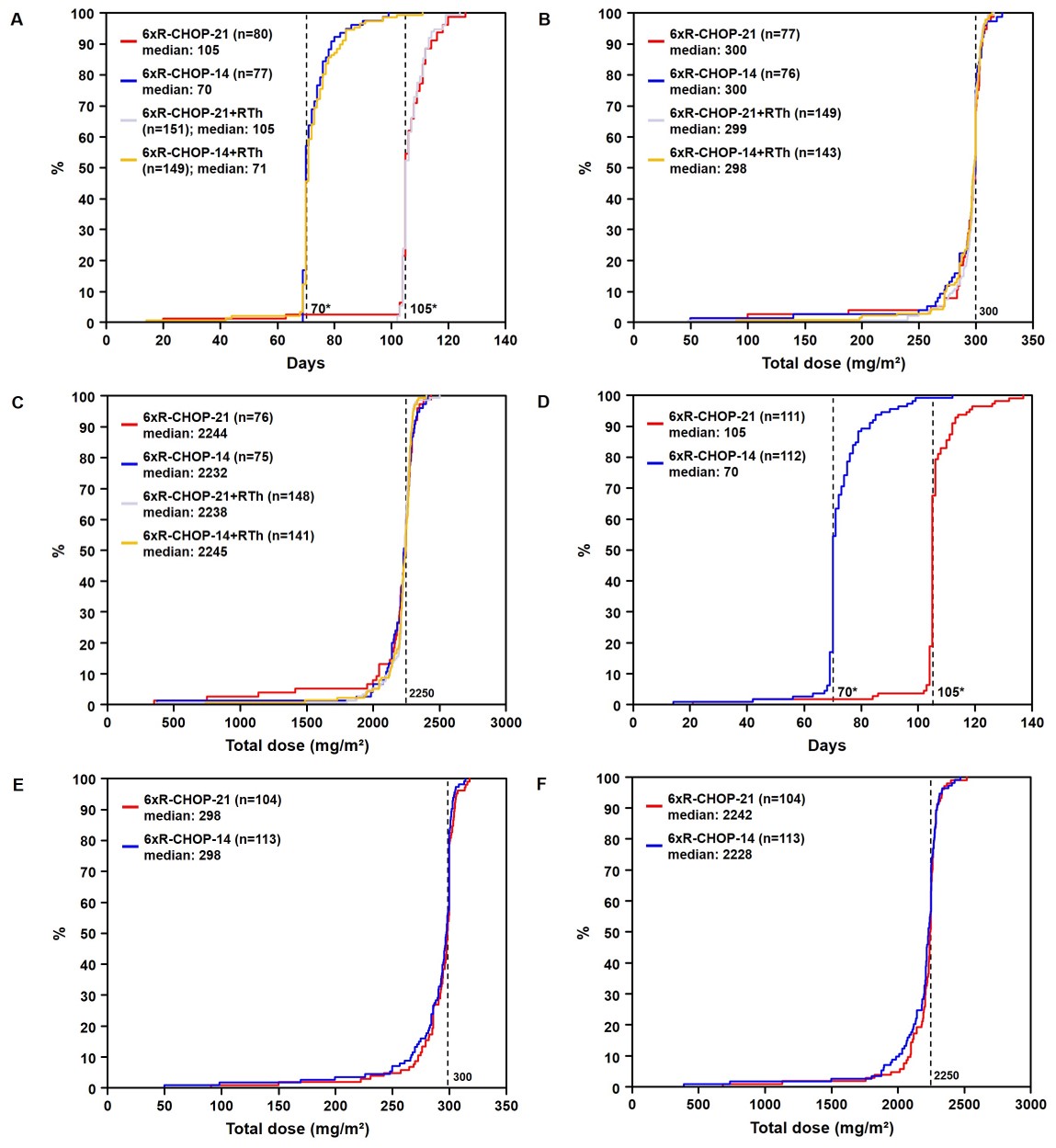
|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | qualifying for radiotherapy (n=467) | | | | not qualifying for radiotherapy (n=228) | |
| R-CHOP-21  (n=81) | R-CHOP-14  (n=81) | R-CHOP-21 + radiotherapy  (n=155) | R-CHOP-14 + radiotherapy  (n=150) | R-CHOP-21  (n=114) | R-CHOP-14  (n=114) |
| Lymphoma related | 4 | 4 | 9 | 10 | 8 | 3 |
| Related to study treatment# | 0 | 1 | 2 | 0 | 0 | 1 |
| Secondary neoplasia | 2 | 0 | 2 | 1 | 1 | 2 |
| Concomitant diseases | 0 | 1 | 1 | 0 | 1 | 2 |
| Other\* | 1 | 1 | 0 | 0 | 0 | 3 |
| Unknown | 0 | 0 | 1 | 0 | 0 | 0 |
| Total (patients died) | 7 (9%) | 7 (9%) | 15 (10%) | 11 (7%) | 10 (9%) | 11 (10%) |

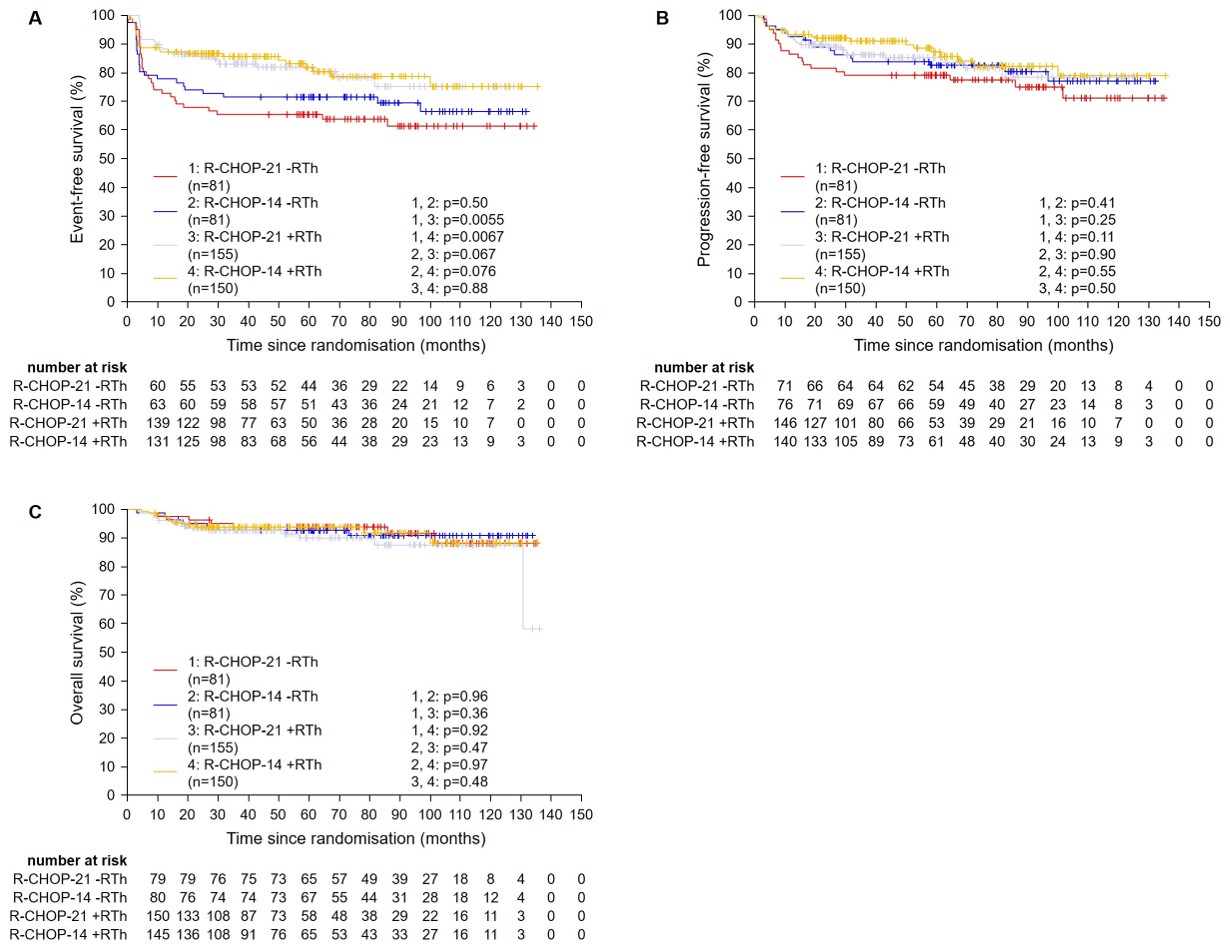
# all deaths related to study treatment were related to R-CHOP chemotherapy

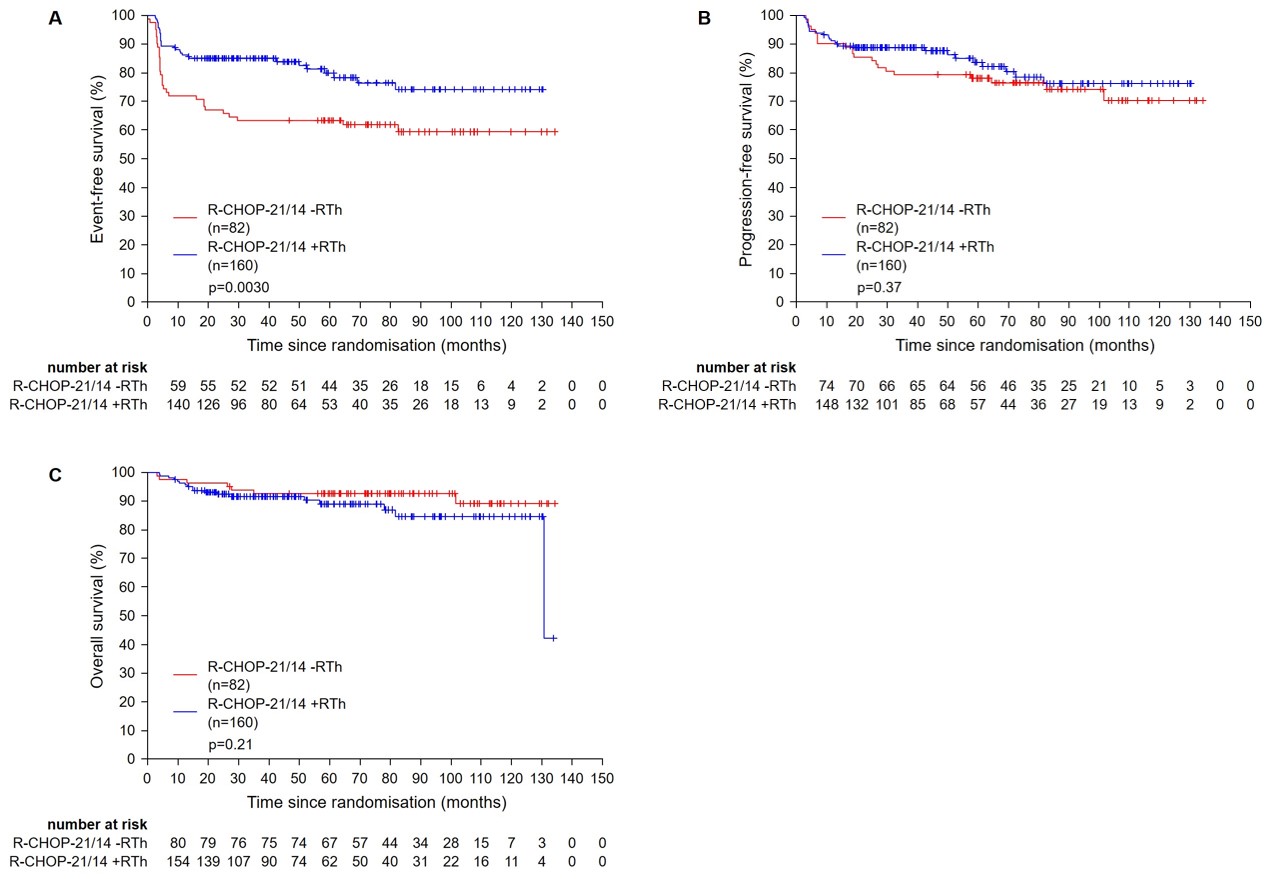
\* sudden cardiac arrest, traffic accident, suicide, cardiogenic shock during percutaneous coronary intervention, liver failure

Table S7: Secondary neoplasia

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | qualifying for radiotherapy (n=467) | | | | not qualifying for radiotherapy (n=228) | |
| R-CHOP-21  (n=81) | R-CHOP-14  (n=81) | R-CHOP-21 + radiotherapy  (n=155) | R-CHOP-14 + radiotherapy  (n=150) | R-CHOP-21  (n=114) | R-CHOP-14  (n=114) |
| Breast cancer | 1 | 1 | - | 1 | 1 | - |
| Lung cancer | - | - | 1 | 1 | 2 | 2 |
| Head and neck cancer | 1 | - | 1 | - | - | 1 |
| Renal cell carcinoma | - | - | - | - | - | 1 |
| Prostate cancer | - | - | 1 | 1 | - | 1 |
| Rectal cancer | - | - | - | - | 1 | - |
| Gastric cancer | - | - | 1 | - | - | - |
| Cholangiocellular-Carcinoma | - | - | 1 | - | - | - |
| Neuroendocrine tumor of ileum  Neuroendocrine carcinoma of the gastro-intestinal tract | 1 | -  - | -  - | 1  - | -  - | -  - |
| MALT-lymphoma | - | - | 1 (ocular adnexis) | - | - | 1 (parotic gland) |
| Basal cell carcinoma | - | - | - | - | 1 | - |
| Malignant Melanoma | 1 | - | - | - | - | - |
| Multiple Myeloma | - | - | - | - | - | 1 |
| Rhabdomyosarcoma | - | - | 1 | - | - | - |
| Liposarcoma | - | - | - | - | - | 1 |
| Gastrointestinal stroma tumor | - | - | - | - | 1 | - |
| Hodgkin‘s Lymphoma | - | - | - | - | 1 | - |
| Acute myeloid leukemia | - | - | - | - | 1 | - |
| Total | 4 (5%) | 1 (1%) | 7 (4%) | 4 (3%) | 8 (7%) | 8 (7%) |

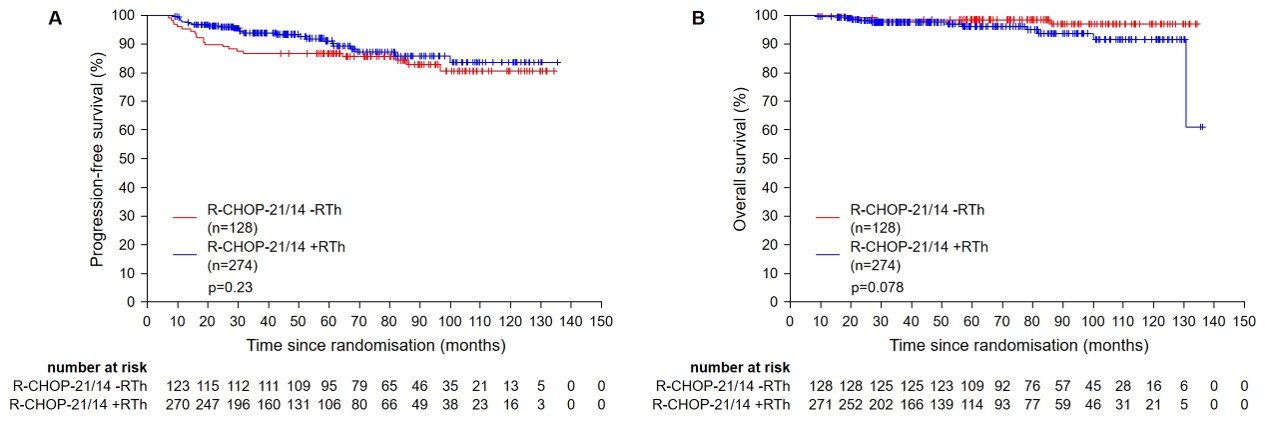
**Supplementary Figure S1: Total duration of CHOP chemotherapy, absolute dose of doxorubicin, and rituximab.** Graphs show total duration of CHOP chemotherapy in patients qualifying for radiotherapy (A), absolute dose of doxorubicin in patients qualifying for radiotherapy (B), absolute dose of rituximab in patients qualifying for radiotherapy C) and total duration of CHOP chemotherapy in patients not qualifying for radiotherapy (D), absolute dose of doxorubicin in patients not qualifying for radiotherapy (E), absolute dose of rituximab in patients not qualifying for radiotherapy (F).

**Supplementary Figure S2. EFS, PFS, and OS according to therapy arms**. Graphs show EFS (A), PFS (B) and OS (C) in patients qualifying for radiotherapy according to therapy arms.

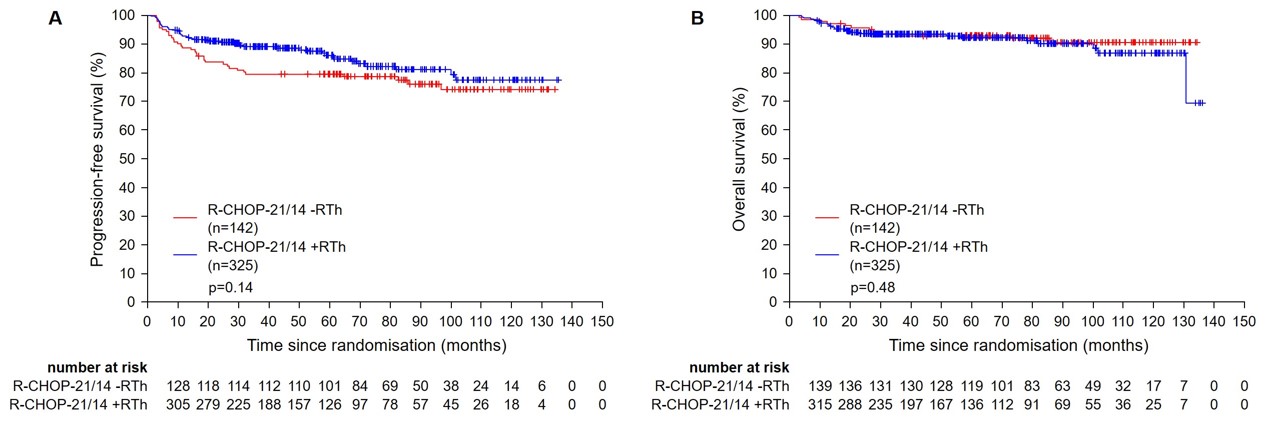


**Supplementary Figure S3. EFS, PFS, and OS in patients qualifying for radiotherapy with extralymphatic involvement.**

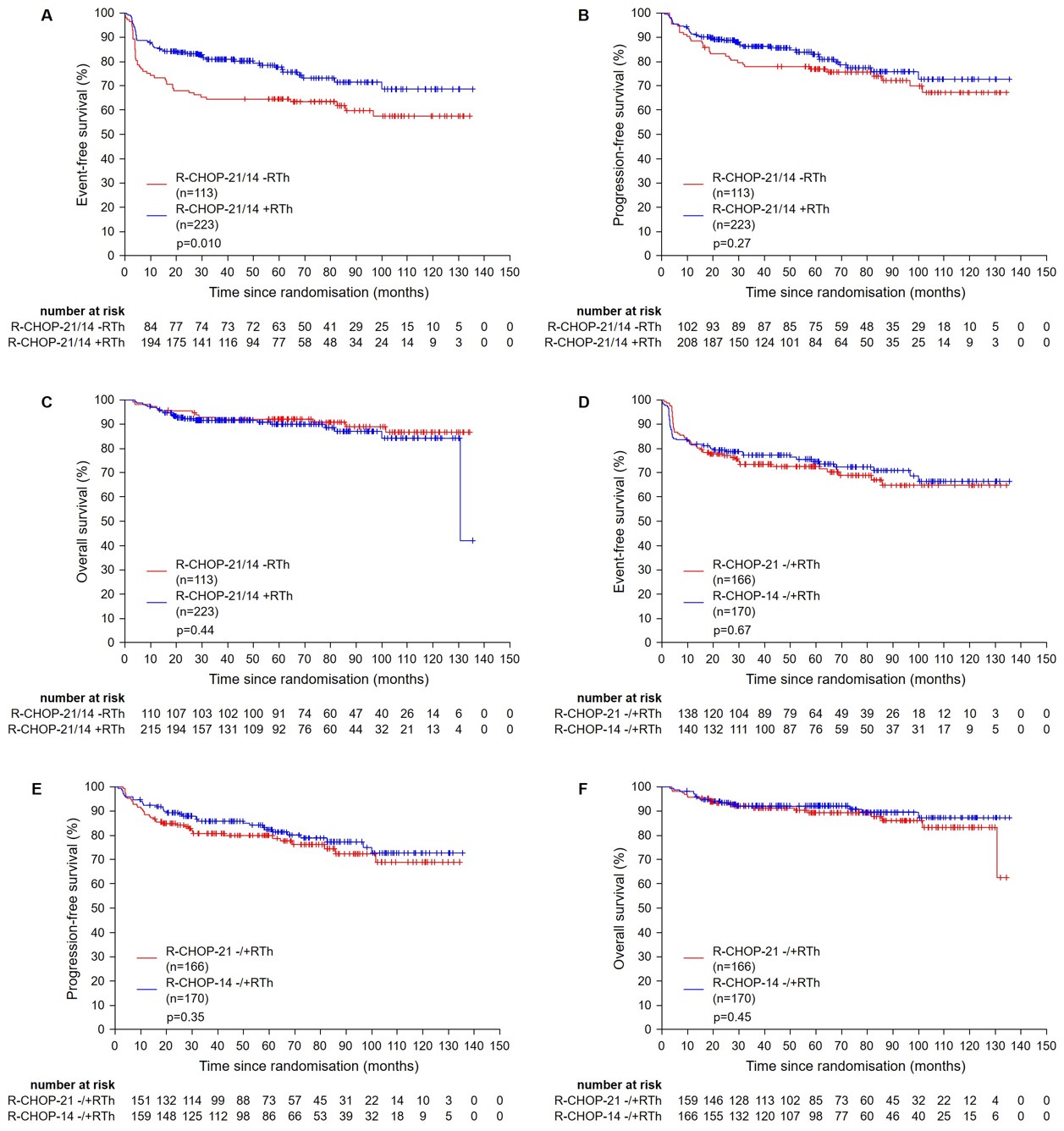
Graphs show EFS (A), PFS (B), and OS (C) according to radiotherapy - or observation-arm.



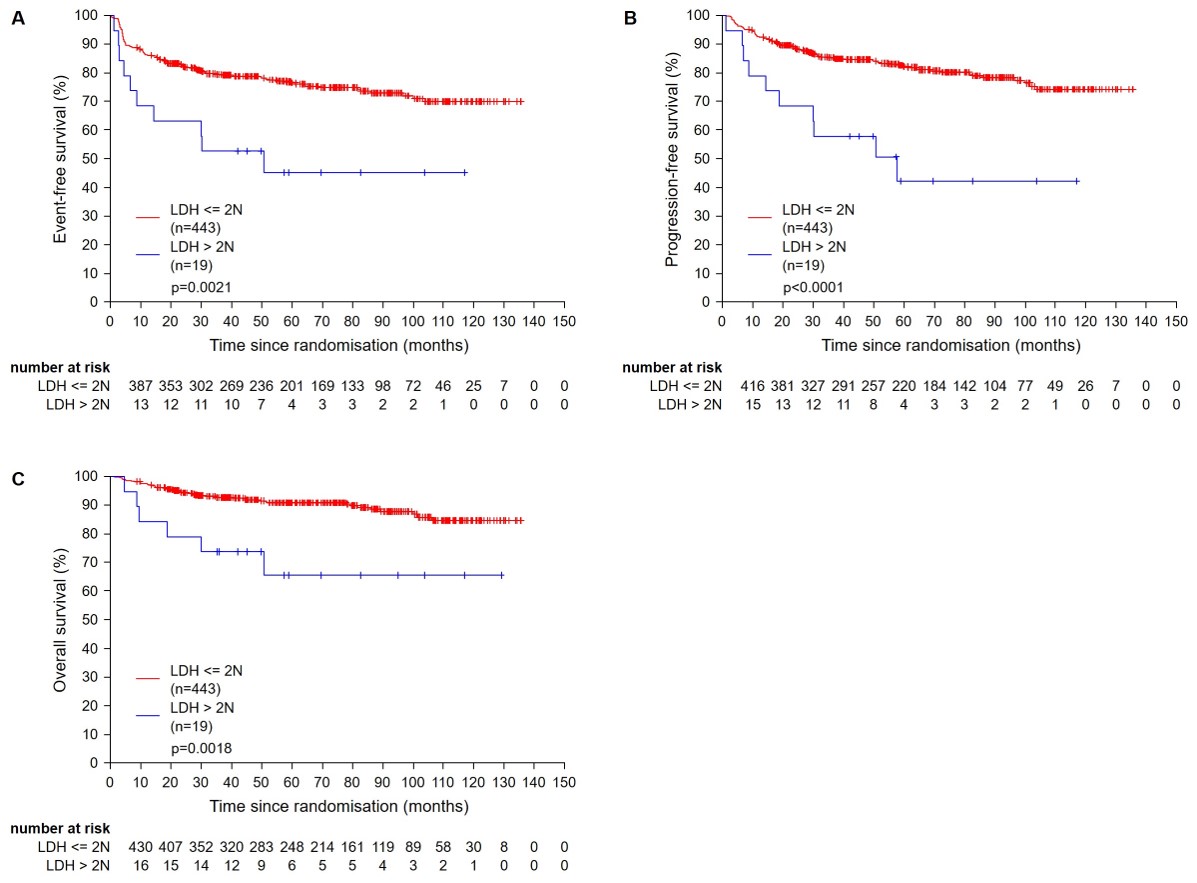
**Supplementary Figure S4. PFS and OS for patients qualifying for radiotherapy, who achieved a CR/CRu after R-CHOP chemotherapy.** Graphs show PFS (A) and OS (B).



**Supplementary Figure S5. PFS and OS for patients qualifying for radiotherapy as treated analysis.** Graphs show PFS (A) and OS (B).



**Supplementary Figure S6. EFS, PFS, and OS according to radiotherapy- or observation-arm and R-CHOP-14 or R-CHOP21 arm** **for non- primary mediastinal B-cell lymphoma patients qualifying for radiotherapy.** Graphs showEFS (A), PFS (B), and OS (C) according to radiotherapy- or observation-arm and EFS (D), PFS €, and OS (F) according to R-CHOP-14 or R-CHOP21 arm.



**Supplementary Figure S7: EFS, PFS, and OS for non- primary mediastinal B-cell lymphoma and aaIPI 1 patients according to LDH.** Graphs showEFS (A), PFS (B), and OS (C) according to LDH > twice the upper limit of normal [LDH <= twice the upper limit of normal compared to LDH > twice the upper limit of normal］.

**Ein Bild, das Diagramm enthält.

Automatisch generierte Beschreibung**

**Supplementary Figure S8: Event- free, progression-free, and overall survival for patients with bulky disease according to treatment arm.** Graphs showEFS (A), PFS (B), and OS (C) in patients qualifying for radiotherapy according to therapy arms.