Rituximab (MabThera®) for the treatment of paediatric patients with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL)

General information

Drug description	Indication
monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes	Rituximab in combination with chemotherapy is indicated for the treatment of paediatric patients (aged ≥6 months to <18 years old) with previously untreated advanced stage CD20 positive diffuse large B-cell lymphoma (DLBCL), Burkitt lymphoma (BL)/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or Burkitt-like lymphoma (BLL)

Current treatment [1]

- multi-agent combination chemotherapy with or without immunotherapy → chemotherapy of six weeks to eight months duration, depending on the stage of disease
- enrolment in a clinical trial

Regulatory status

EMA [2]

Approval status for this indication: March 2020

Other indications:

- NHL:
  - indicated for the treatment of previously untreated adult pts with stage III-IV follicular lymphoma in combination with chemotherapy.
  - maintenance therapy is indicated for the treatment of adult follicular lymphoma pts responding to induction therapy.
  - monotherapy is indicated for treatment of adult pts with stage III-IV follicular lymphoma who are chemoresistant or are in their second or subsequent relapse after chemotherapy.
  - indicated for the treatment of adult pts with CD20 positive diffuse large B cell non-Hodgkin's lymphoma in combination with CHOP chemotherapy.
  - in combination with chemotherapy is indicated for the treatment of paediatric pts (aged ≥6 months to <18 years old) with previously untreated advanced stage CD20 positive DLBCL, BL/Burkitt leukaemia (mature B-cell acute leukaemia) (BAL) or BLL.
- CLL
  - in combination with chemotherapy is indicated for the treatment of pts with previously untreated and relapsed/refractory CLL. Only limited data are available on efficacy and safety for pts previously treated with monoclonal antibodies including rituximab or pts refractory to previous rituximab plus chemotherapy.
- Rheumatoid arthritis
  - in combination with methotrexate is indicated for the treatment of adult pts with severe active rheumatoid arthritis who have had an inadequate response or intolerance to other DMARD including one or more (TNF) inhibitor therapies.
- GPA and MPA
  - in combination with glucocorticoids, is indicated for the treatment of adult pts with severe, active GPA and MPA
- Pemphigus vulgaris
  - indicated for the treatment of pts with moderate to severe pemphigus vulgaris

FDA [3]

Approval status for this indication: -

Other indications: rituximab is indicated for the treatment of:

- Adult pts with NHL:
  - relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
  - previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy.
  - non-progressing (including stable disease), low-grade, CD20positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
  - previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone) (CHOP) or other anthracycline-based chemotherapy regimens.
- Adult pts with CLL:
  - previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide
- Rheumatoid arthritis in combination with methotrexate in adult pts with moderately-to severely-active rheumatoid arthritis who have inadequate response to one or more TNF antagonist therapies
- GPA (Wegener's Granulomatosis) and MPA in adult and paediatric pts 2 years of age and older in combination with glucocorticoids
- Moderate to severe pemphigus vulgaris in adult pts

Costs

MabThera® 500 mg concentrate for solution for infusion = € 1,516.43 (ex-factory price) [4]
Assuming an average BSA of 1.22 m^2 (children at the age of ~7 years; median age of trial patients was 7-8 years)→ 375 mg/m^2 of rituximab → 1.22m^2: ~457.5 mg → **€1,387.6/dose**

Study characteristics

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
NA	328	rituximab + LMB	LMB	EFS	Multicentre, single arm study, open-label	-	Genentech, Inc. Roche	EPAR [5]

<table>
<tr><th colspan="3">Efficacy (I vs. C)</th><th colspan="3">Safety (I vs. C)</th></tr>
<tr><td colspan="3">EFS: 1-year rate estimates of 94.2% (95% CI, 88.5% - 97.2%) in the intervention arm vs. 81.5% (95% CI, 73.0% - 87.8%) in the control arm → HR 0.33 (95% CI, 0.14 - 0.79) (~1 year median follow-up)
CR: intervention 94.0% (95% CI, 88.8% - 97.2%) versus control 93.6% (95% CI, 88.2% - 97.0%)
OS: median OS not reached, hazard ratio for death 0.36 (95% CI, 0.16 - 0.81); estimated 3-year OS rates → intervention 95.1% (95% CI, 90.5% - 97.5%) versus control 87.3% (95% CI, 81.2% - 91.6%)</td><td colspan="3">The safety profile of rituximab in paediatric patients (aged ≥ 6 months to < 18 years old) with previously untreated advanced stage CD20 positive DLBCL/BL/BAL/BLL was generally consistent in type, nature and severity with the known safety profile in adult NHL and CLL patients. Addition of rituximab to chemotherapy did result in an increased risk of some events including infections (including sepsis) compared to chemotherapy only.</td></tr>
<tr><td colspan="6">Risk of bias (study level)</td></tr>
<tr><td>Adequate generation of randomisation sequence</td><td>Adequate allocation concealment</td><td>Blinding</td><td>Selective outcome reporting unlikely</td><td>Other aspects which increase the risk of bias</td><td>Risk of bias</td></tr>
<tr><td colspan="6">Unclear, since the information is solely based on the EPAR from the EMA website [5]</td></tr>
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Abbreviations: BAL=Burkitt leukaemia (mature B-cell acute leukaemia), BL=Burkitt lymphoma, BLL=Burkitt-like lymphoma, CLL= chronic lymphocytic leukaemia, CR=complete response, CYVE=CYtarabine (Aracytine, Ara-C), VEposide (VP16), DLBCL=diffuse large B-cell lymphoma, EFS= event free survival (defined as the occurrence of progressive disease, relapse, second malignancy, death from any cause, or non-response as evidenced by detection of viable cells in residue after the second CYVE course, whichever occurs first), EMA=European Medicines Agency, EPAR=European Public Assessment Reports, FDA=Food and Drug Administration, HR=hazard ratio, LMB= Lymphome Malin B chemotherapy (corticosteroids, vincristine, cyclophosphamide, high-dose methotrexate, cytarabine, doxorubicin, etoposide and triple drug [methotrexate/cytarabine/ corticosteroid] intrathecal therapy), n=number, NA=not available, NHL= Non-Hodgkin's Lymphoma, OS=overall survival, pts=patients, QoL=quality of life

References:

[1] Termuhlen AM, Gross TG. UpToDate - Overview of non-Hodgkin lymphoma in children and adolescents,. In: UptoDate, Park JR, Rosmarin AG, editors.2020.
[2] European Medicines Agency (EMA). MabThera. 2020 [cited 31.03.2020]; Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/mabthera.
[3] U.S.Food and Drug Administration (FDA). Rituxan. Label information. [cited 30.03.2020]; Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103705s5461lbl.pdf.
[4] Apotheker-Verlag. Warenverzeichnis Online. [2020-02-18]; Available from: https://warenverzeichnis.apoverlag.at/.
[5] European Medicines Agency. EPAR - SUMMARY OF PRODUCT CHARACTERISTICS RITUXIMAB. 2020 [cited 30.03.2020]; Available from: https://www.ema.europa.eu/en/documents/product-information/mabthera-epar-product-information_en.pdf.