Improving outcome for patients with Burkitt lymphoma

Igor Aurer
University Hospital Centre Zagreb
And
Medical School, University of Zagreb
Croatia

DISCLOSURES

- Research support and funding
  - Roche, Pfizer, Gilead
- Honoraria
  - Roche, Takeda, Johnson&Johnson, Amgen, Teva
- Advisory board
  - Roche, Celgene
- Speakers bureau and expert testimony
  - none

The man behind the name

It is better to read a little and ponder a lot than to read a lot and ponder a little.

Denis Parsons Burkitt

THE BRITISH JOURNAL OF SURGERY

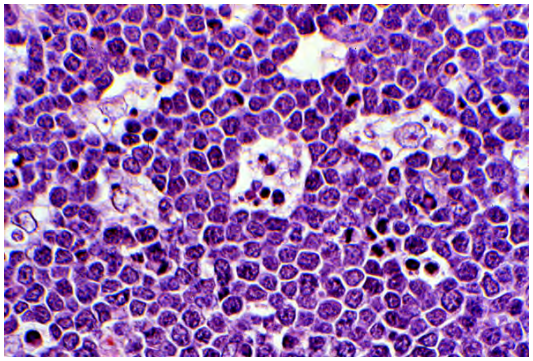
A SARCOMA INVOLVING THE JAWS IN AFRICAN CHILDREN

By DENIS BURKITT

GEOGRAPHICAL DISTRIBUTION

CLINICAL FEATURES

Burkitt lymphoma



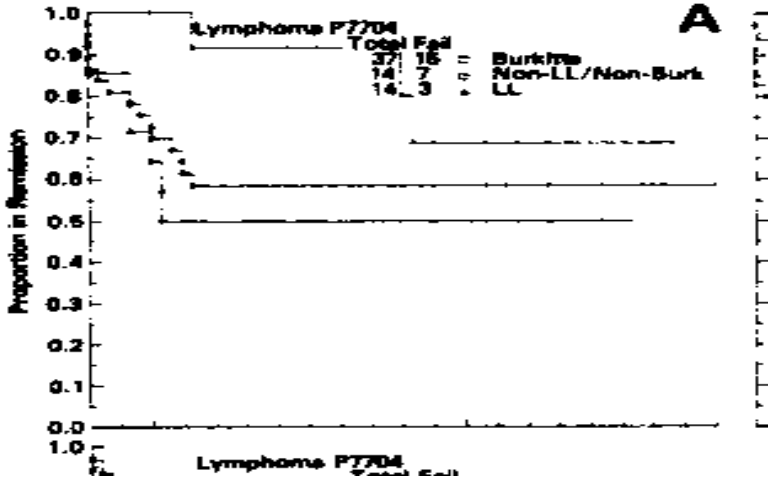
- Rare B-NHL (1-2%), typically affecting children and young adults
- Endemic, sporadic, immunodeficieny-associated
- Monomorphic medium-sized transformed cells with extremely short doubling time
- Immunophenotype: strong mIgM, CD10+, BCL6+, BCL2-, TdT-, Ki67 > 90% (≥99%)
- Cytogenetics: Ig-MYC +, BCL2-, BCL6-
- Frequent extranodal and leukemic presentation
- Genetically relatively stable

Diagnosis and classification

- Elder days
  - ALL – L3;
  - high-grade NHL, small-noncleaved cells
- New age
  - Burkitt lymphoma / leukemia vs.
    - Burkitt-like NHL (REAL)
    - DLBCL (WHO 2004)
    - B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and BL (aka grey-zone) (WHO 2008)

Treatment

- Elder days
  - ALL – L3 — ALL type th
  - high-grade NHL, small-noncleaved cells — CHOP-like th
- Intermediate phase — HD-MTX based th



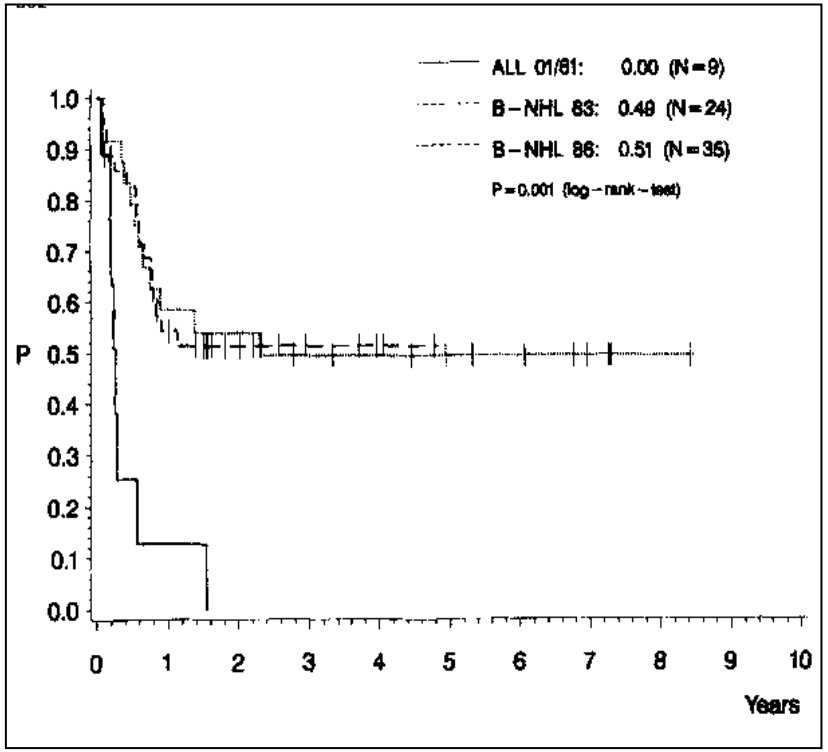
Magrath et al, Blood 63:1102, 1984
Ramirez et al, Cancer Chemother Pharmacol 3:103, 1979

- New age — HD-MTX+R based th

Improvements in results

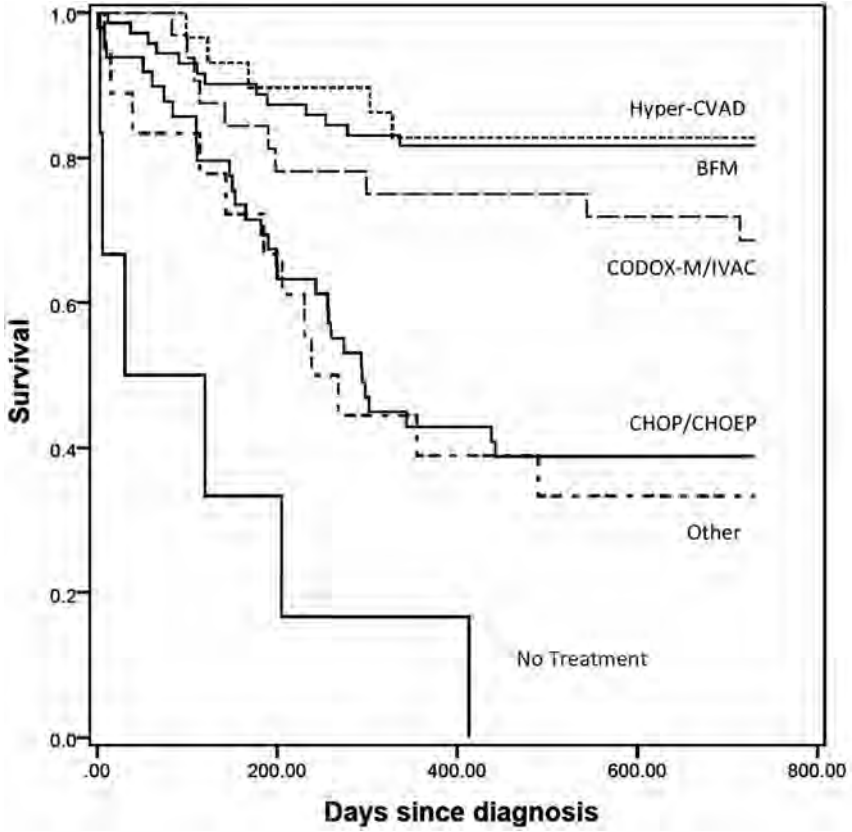
overall survival

Burkitt leukemia



Hoelzer et al. Blood 1996; 87:495

Burkitt lymphoma



Wästerlid et al. Ann Oncol 2013;24:1879-1886

(some pts. also received rituximab)

What about rituximab?

Retrospective comparisons

some find improvement in OS

(reviewed in Wildes et al 2014)

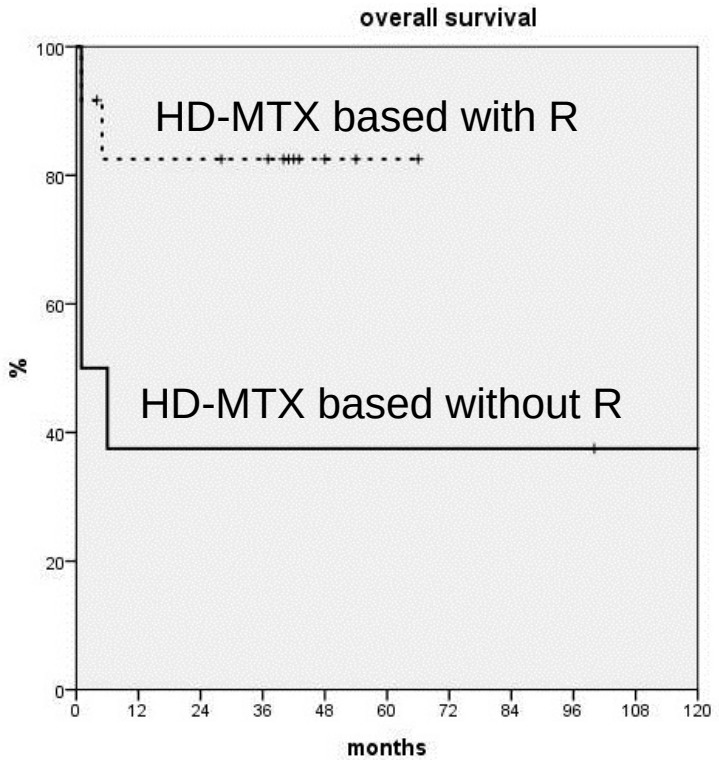
some don't

(Todeschini et al 2012, Wasterlid et al 2011&2013, Kojima et al 2014)

Question uninteresting, toxicity of rituximab negligible, price acceptable, probably useful

therefore

use it!



Dujmović et al, Acta Haematol, 2013

Which HD-MTX based regimen?

Countries of origin

- USA- Stanford, Hyper-CVAD, CALGB
- UK – CODOX-M/IVAC
- F – LMB
- D – B-NHL 86, B-NHL 2002

- CALGB = B-NHL 86 with increased Ara-C dose

HD-MTX based regimens

Dose intensity (mg/m^2/3 wks)

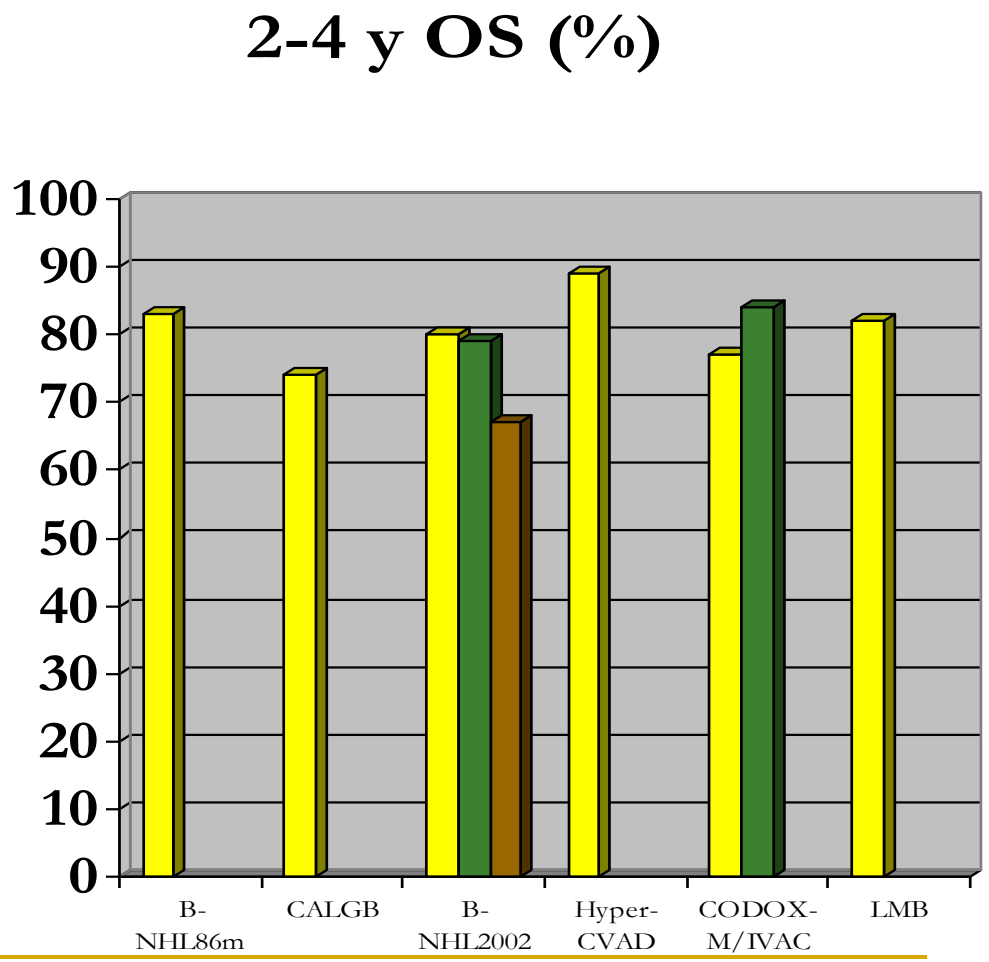
	Hyper-CVAD	CODOX-M/ IVAC	B-NHL 86m	CALGB	B-NHL 2002
cyclophosphamide	900	800	500	500	333
ifosfamide	0	3750	2000	2000	1333
MTX	500	1500	1500	1500	1500
Ara-C	6000	4000	300	1000	1533
vincristine*	2	1	2	2	1.67
vindesine*	0	0	0	0	1.67
etoposide	0	0	100	80	167
teniposide	0	0	0	0	67
doxorubicin	25	25	25	25	17

* total dose

R-HD-MTX based regimens

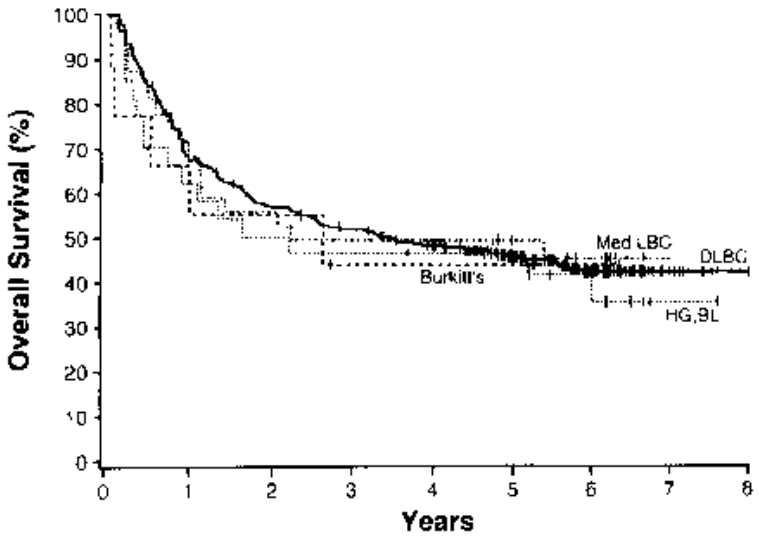
Outcomes

- Modified B-NHL 86
  - 3y OS 83% (Dujmović et al 2012)
- CALGB
  - 4y OS 74% (Rizzieri et al 2014)
- B-NHL 2002
  - 3y OS 80% (Hoelzer et al 2014)
  - 2y OS 79% (Ribera et al 2013)
  - 3y OS 67% (Intermesoli et al 2013)
- Hyper-CVAD
  - 3y OS 89% (Thomas et al 2006)
- CODOX-M/IVAC
  - 2y OS 77% (Barnes et al 2011)
- ibid + liposomal dox & HD-R
  - 2y OS 84% (Evens et al 2013)
- LMB
  - 3y-OS 82% (Ribrag et al 2012)



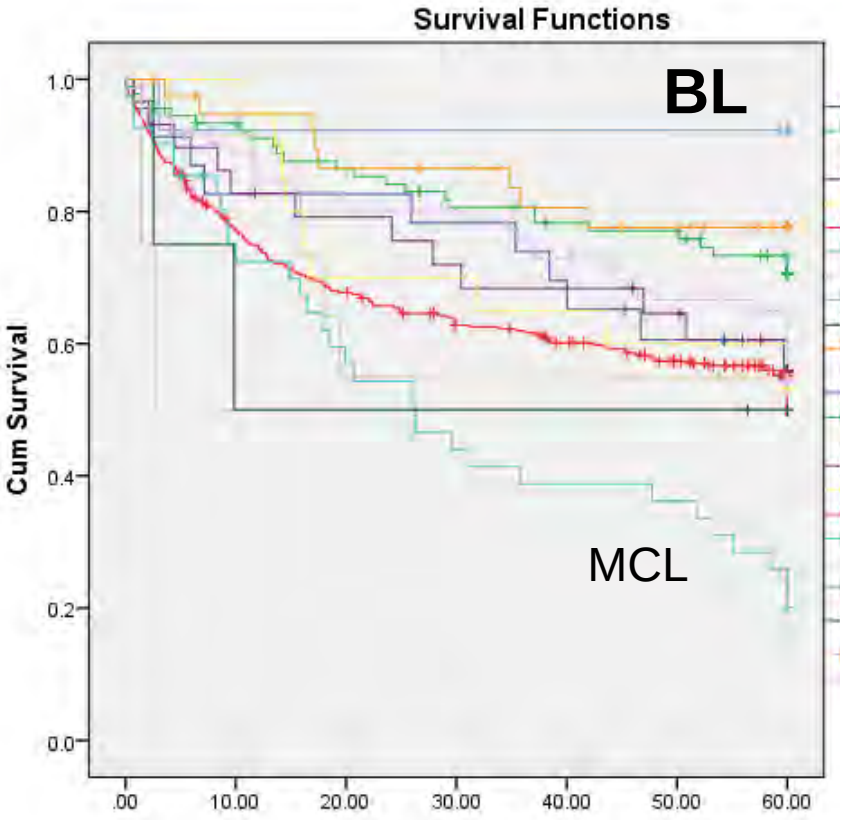
Population-based studies

- **Clinical Evaluation of the ILSG: Classification of Non-Hodgkin's Lymphoma** By The Non-Hodgkin's Lymphoma Classification Project, Blood 89:3909,1997



A not-so-bad lymphoma w/o R

- **KroHem 2015**



The best lymphoma with R

Pts. treated 1988-1990

Pts. Treated 2007-2008

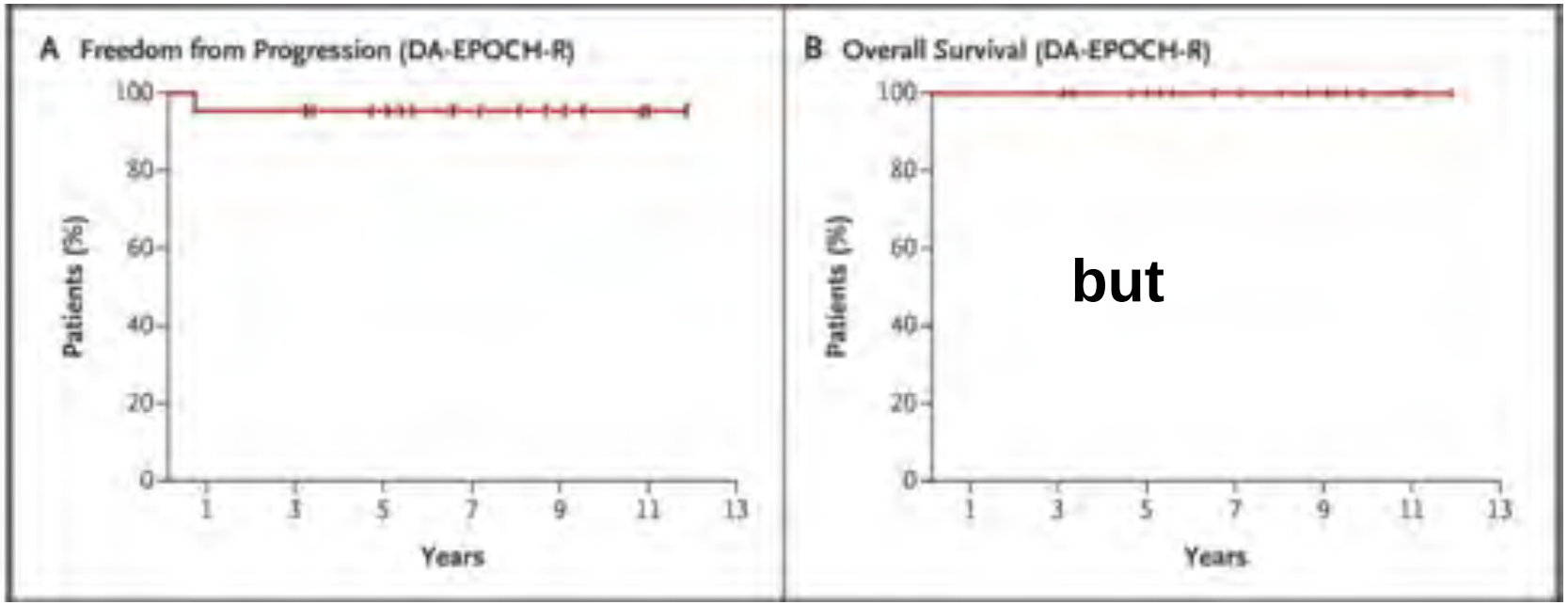
What is the issue in improving outcomes in BL?

- Toxicity of HD-MTX based therapy
  - grade III-IV universal
    - hematological, mucositis
  - TRM up to 20%
    - tumor-lysis related
      - after 1st cycle
    - hematological & infectious
      - during whole treatment
- Efficacy in high-risk populations
  - Elderly & renal failure
    - Toxicity
  - CNS involvement, stage IV, poor PS, IPI, gender
  - HIV+
    - ↑ risk & toxicity
    - HD-MTX+R based regimens feasible and effective

Possible solution

DA-R-EPOCH

- Dunleavy et al. NEJM 369:1915, 2013



- Aurer et al, Ann Hematol 93:177, 2014
- 3 pts. 2y-PFS 0%, 2y-OS 33%

How to solve the dilemma?

- Randomized trial
  - HOVON is doing it
- EHALyG based registry
- **In the meantime**
- Keep doing what you do and wait
  - Diagnose pts. rapidly, watch pts. treated with R-HD-MTX-based therapy carefully and give optimal supportive care
  - Treat elderly, comorbid and pts. with renal failure with DA-R-EPOCH

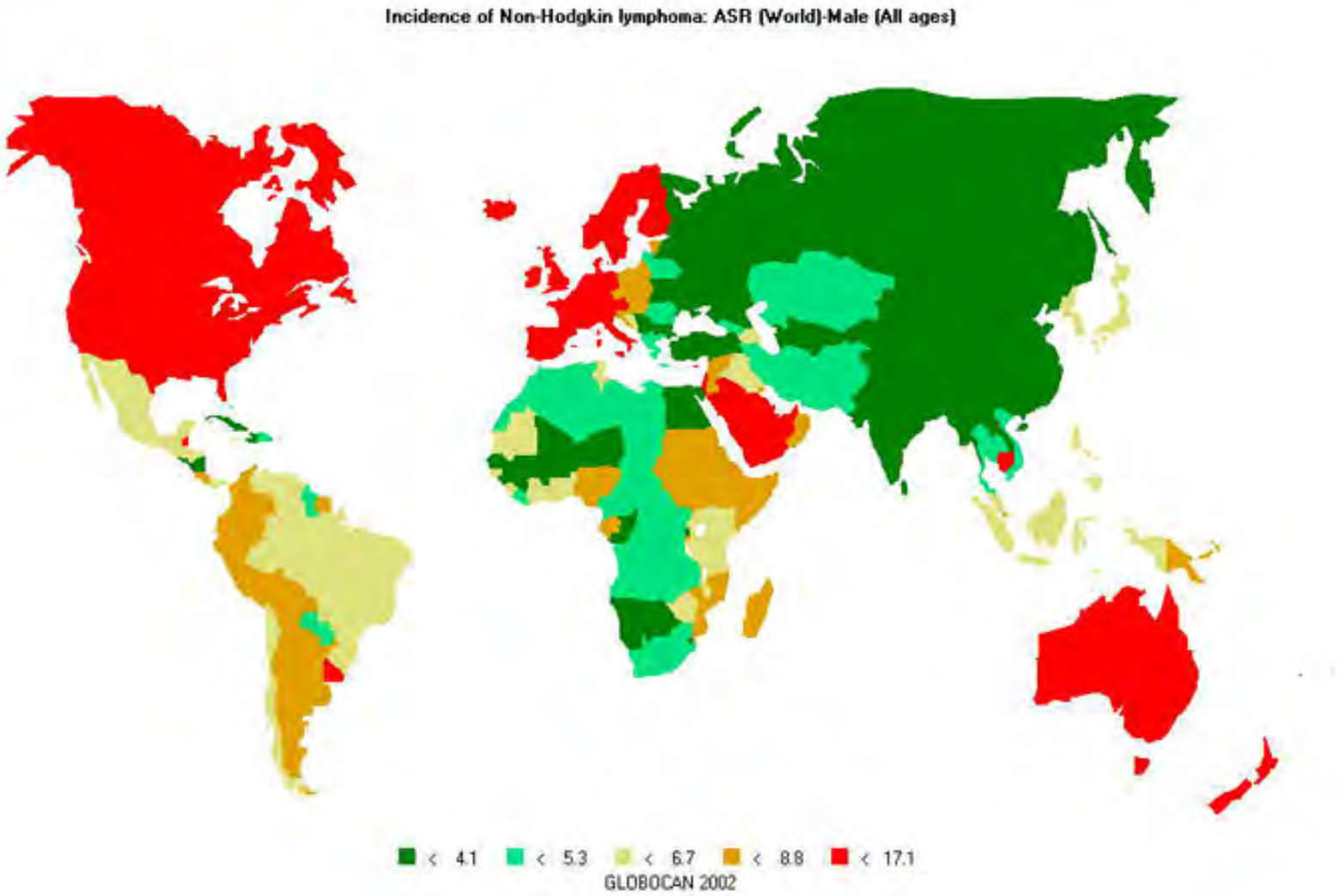
Future I

- BL cells strongly dependent on*
  - MYC and TCF3 transcription factors
    - BET bromodomain inhibitors
  - BCR tonic signalling through PI kinase pathway
    - Ibrutinib, idelalisib,...
  - CCND3 - cyclin D3
    - PD-0332991
- One of the targeted agents is going to work
- Easier to combine with DA-R-EPOCH than with R-HD-MTX-based therapies

* Schmitz et al, Nature 490:116,2012 & Cold Spring Harb Perspect Med 2014 4:a014282

Future II

- Quote:
  - These new insights into Burkitt lymphoma pathogenesis suggest new therapeutic strategies, which are sorely needed in developing regions of the world where this cancer is endemic.
- Because of pricing issues this is probably not going to happen
- Two standards: similar in efficacy, different in toxicity
  - 1. For the rich and mighty
    - DA-R-EPOCH + targeted agent
  - 2. For the less affluent
    - Anti CD20-HD-MTX-based therapy



http://www.startoncology.net/en/professional-area/non-hodgkins-lymphoma/

Acknowledgement: Thanks to all my colaborators and EHALyG board and members