

Treatment of lymphoma

Treatment modalities

- **Chemotherapy**
- **Immunotherapy – monoclonal antibodies**
 - **Cold**
 - **Radioactive**
 - **Immunotoxins**
- **Radiotherapy**
- **Autologous stem cell transplant**
- **Allogeneic stem cell transplant**
- **New treatments, small molecules**

Chemotherapy

- **First-line or salvage treatment**
- **Curative or palliative**
- **Usually combined**

Most frequent first-line for Hodgkin lymphoma:

- **ABVD: adriamycin, bleomycin, vinblastin, dacarbazin**

Most frequent first-line for non-Hodgkin's lymphoma:

- **CHOP: cyklofosamid, adriamycin, vincristin, prednison**

Režimy záchranné léčby:

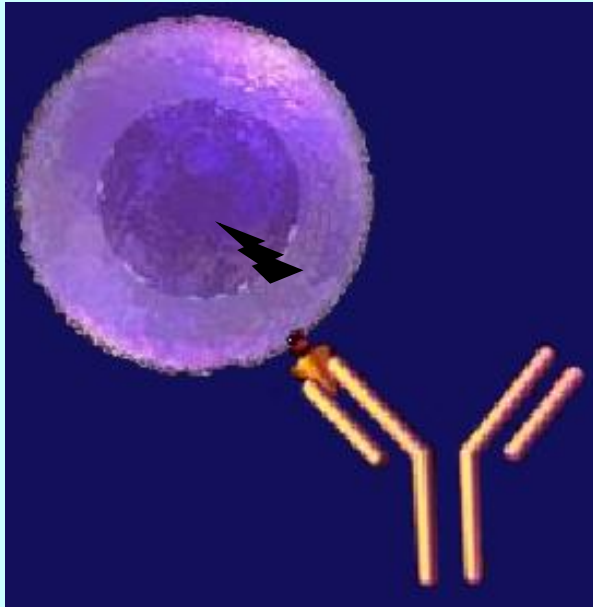
Chemotherapy - salvage and palliative treatment

- **Salvage treatment: with curative intent**
Both HL and NHL: based mostly on cisplatin, etoposid, Ara-C
- **ESHAP: etoposide, methylprednisolon, Ara-C, cisplatin**
- **Palliative treatment: may be monotherapy or mild combination treatment, usually oral (chlorambucil, cyclophosphamide, steroids)**

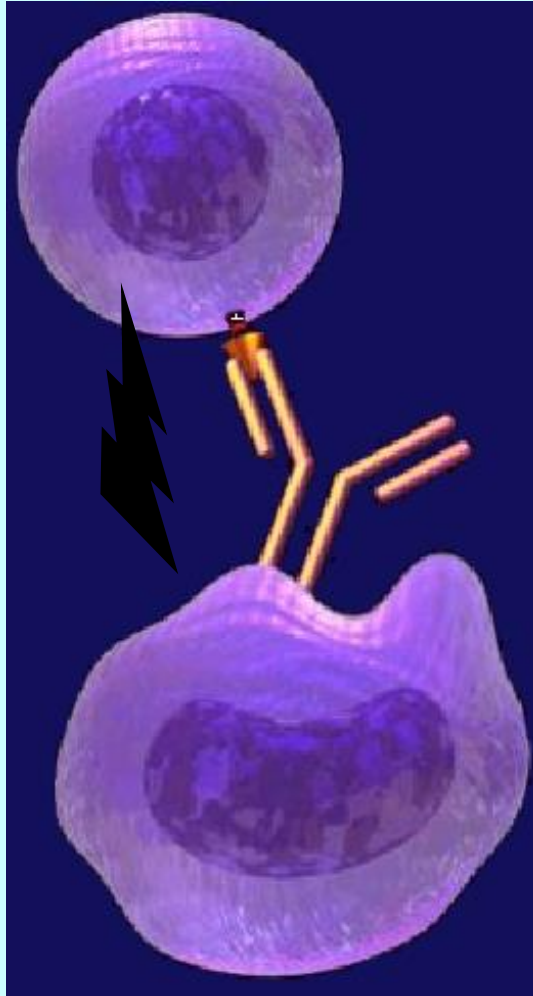
Immunotherapy

- **Passive (antibodies)**
- „Cold“ – „hot“ - immunotoxins
 - Rituximab (Rituxan, Mabthera)
 - ^{90}Y Ibritumomab tiuxetan (Zevalin)
 - Brentuximab vedotin (Adcetris)
- Alone or with chemotherapy
- **Active immunotherapy – vaccination: not very successfull so far**

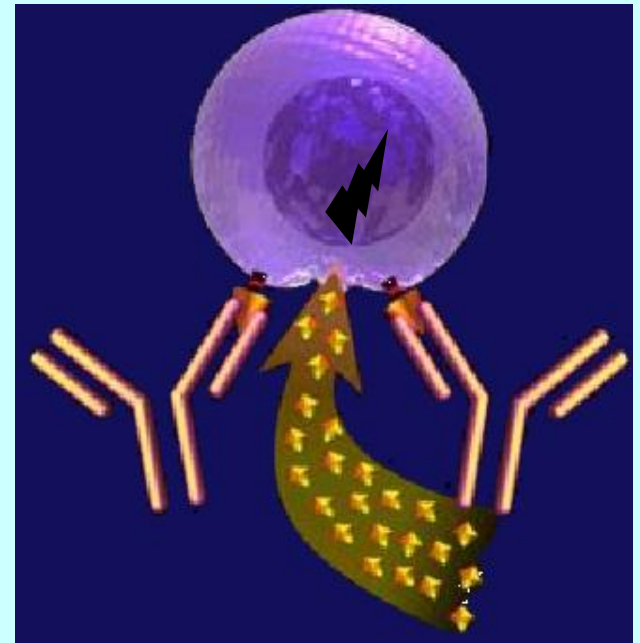
Cold antibodies - mechanisms



Direct cytotoxicity

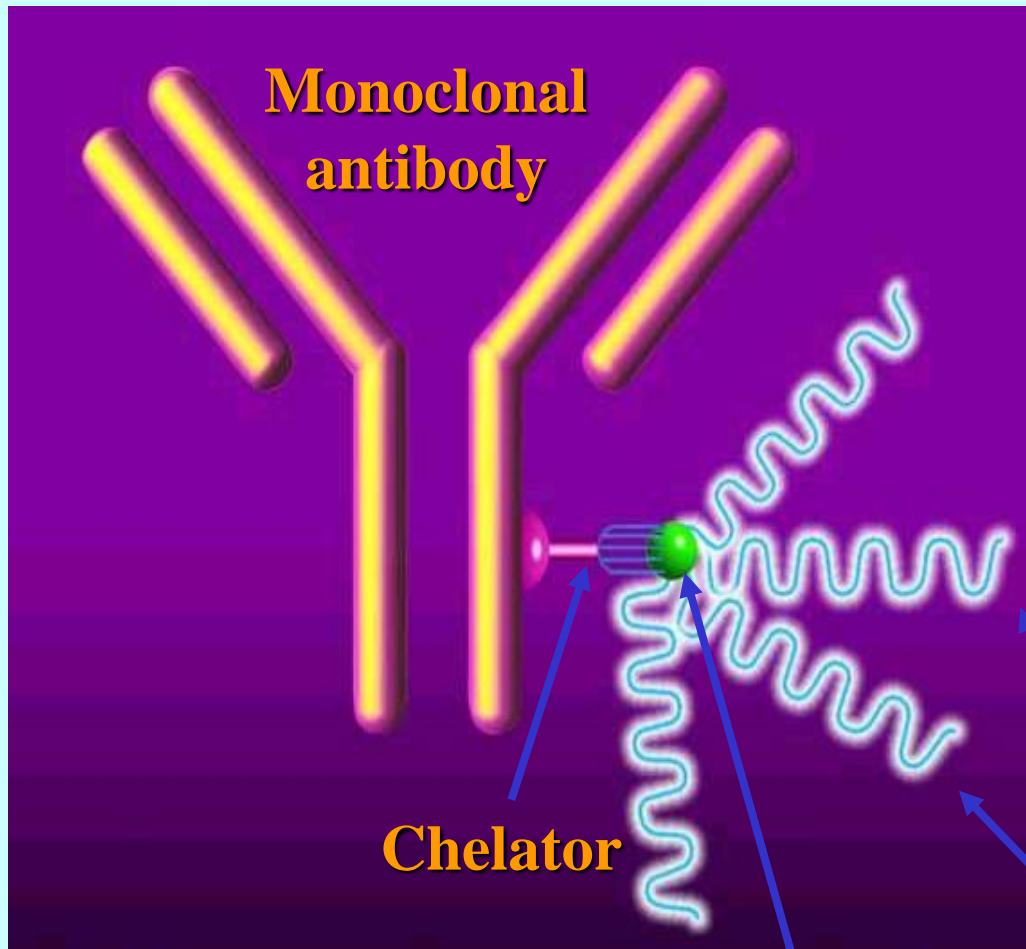


**Antibody-dependent
Cellular cytotoxicity**



**Complement dependent
Cytotoxicity**

Zevalin[®] (⁹⁰Y-Ibritumomab Tiuxetan) radioimmunoconjugate

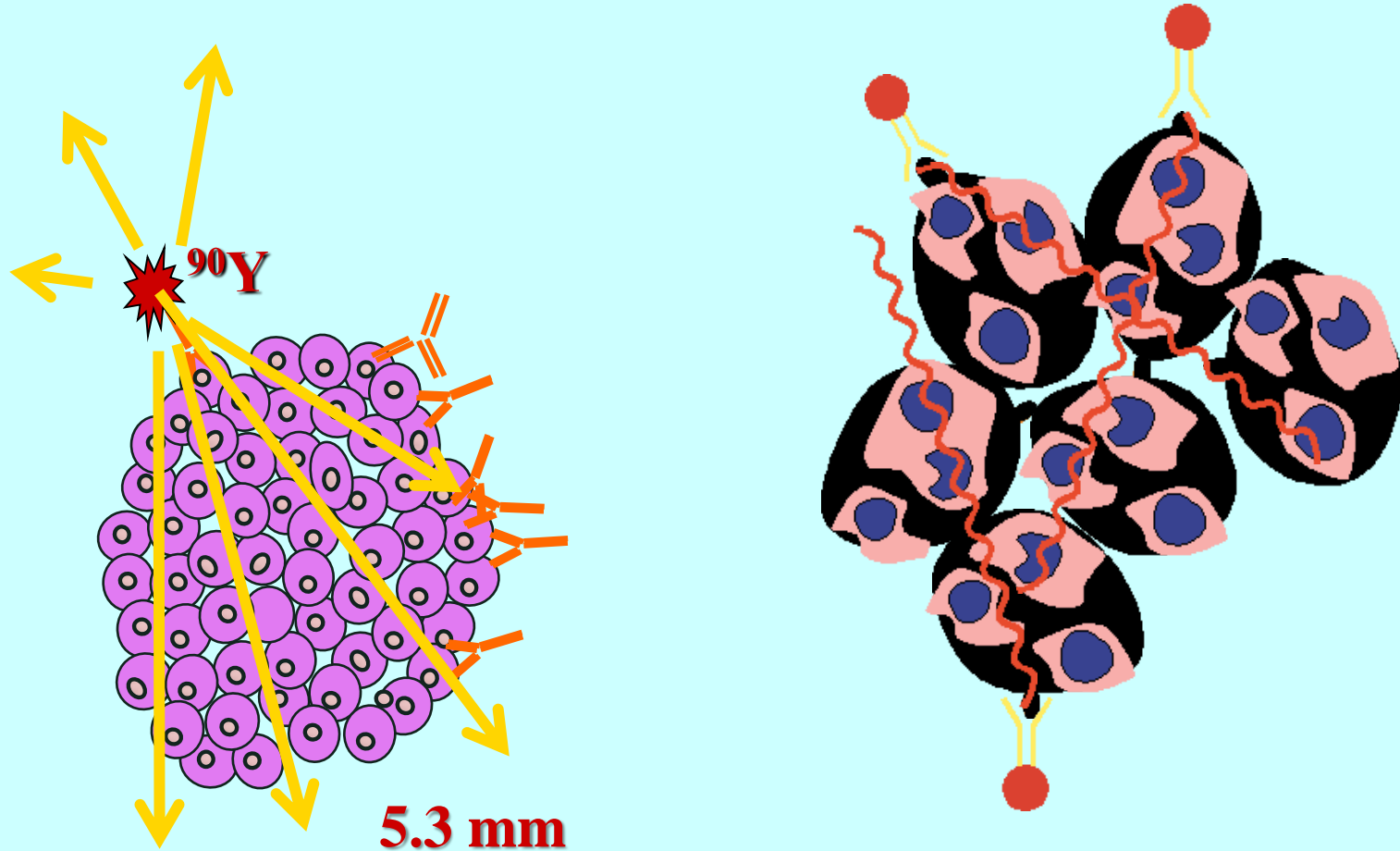


- ♦ **Ibritumomab**
 - Mouse monoclonal antibody
- ♦ **Tiuxetan (MX-DTPA)**
 - Conjugates with antibody, enables stable retention of radiolabelled ⁹⁰Yttrium

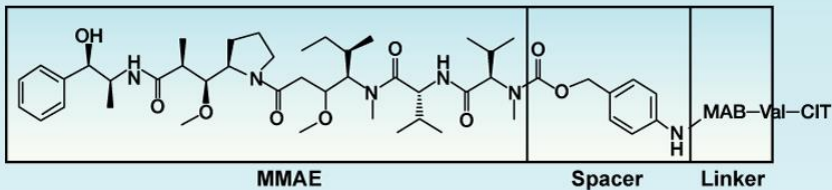
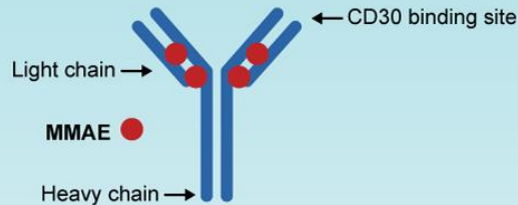
Beta radiation

⁹⁰Y radionuclide

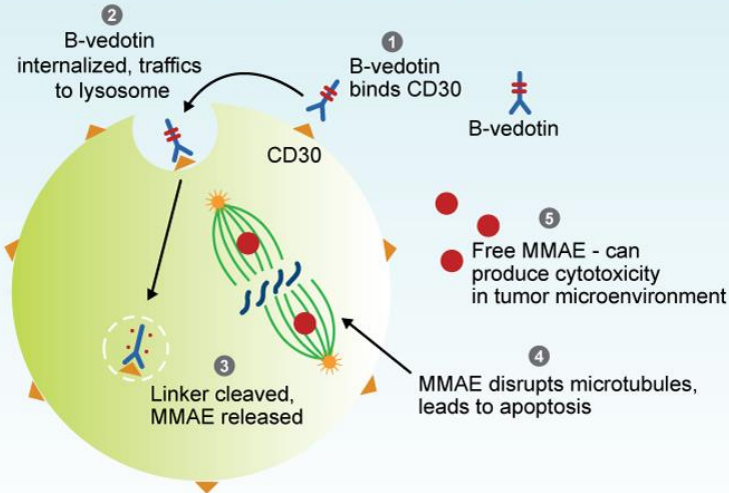
Crossfire effect of immunoconjugate



Structure of Brentuximab Vedotin (B-Vedotin)



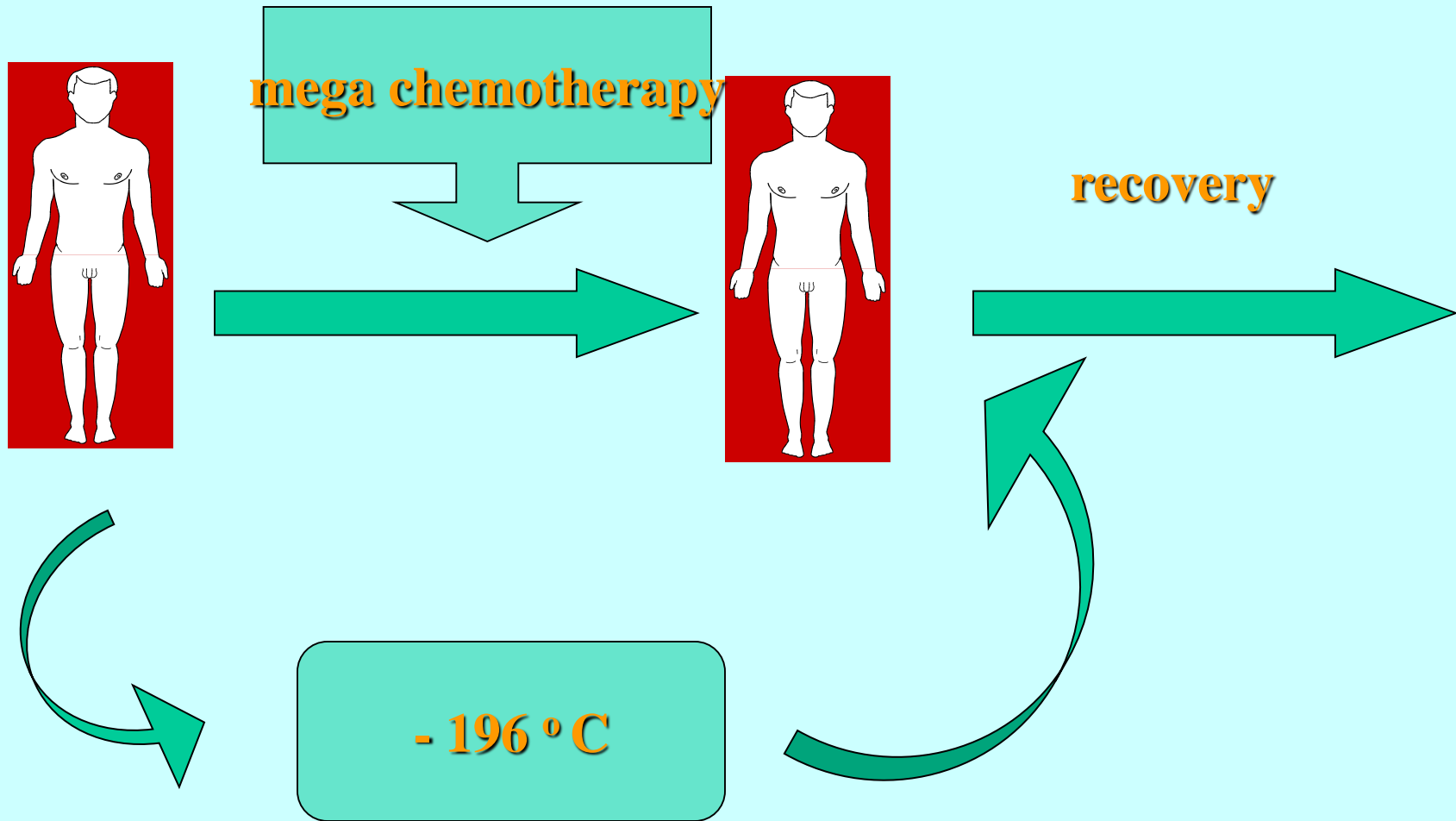
ADC Internalization Process



ADC = antibody-drug conjugate; MAB = monoclonal antibody; MMAE = monomethyl auristatin E (microtubule-disrupting agent)

**Brentuximab
vedotin (Adcetris):
anti-CD30 +
monomethyl
auristatin E
(MMAE)**

Autologous transplantation



Allogeneic transplantation

➤ **Healthy HLA-identical sibling or HLA-matched unrelated donor**



Patient



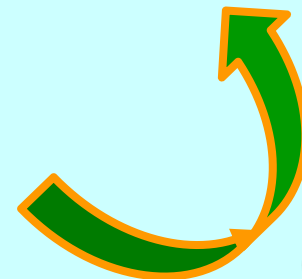
Conditioning



Healthy donor



Cell separation

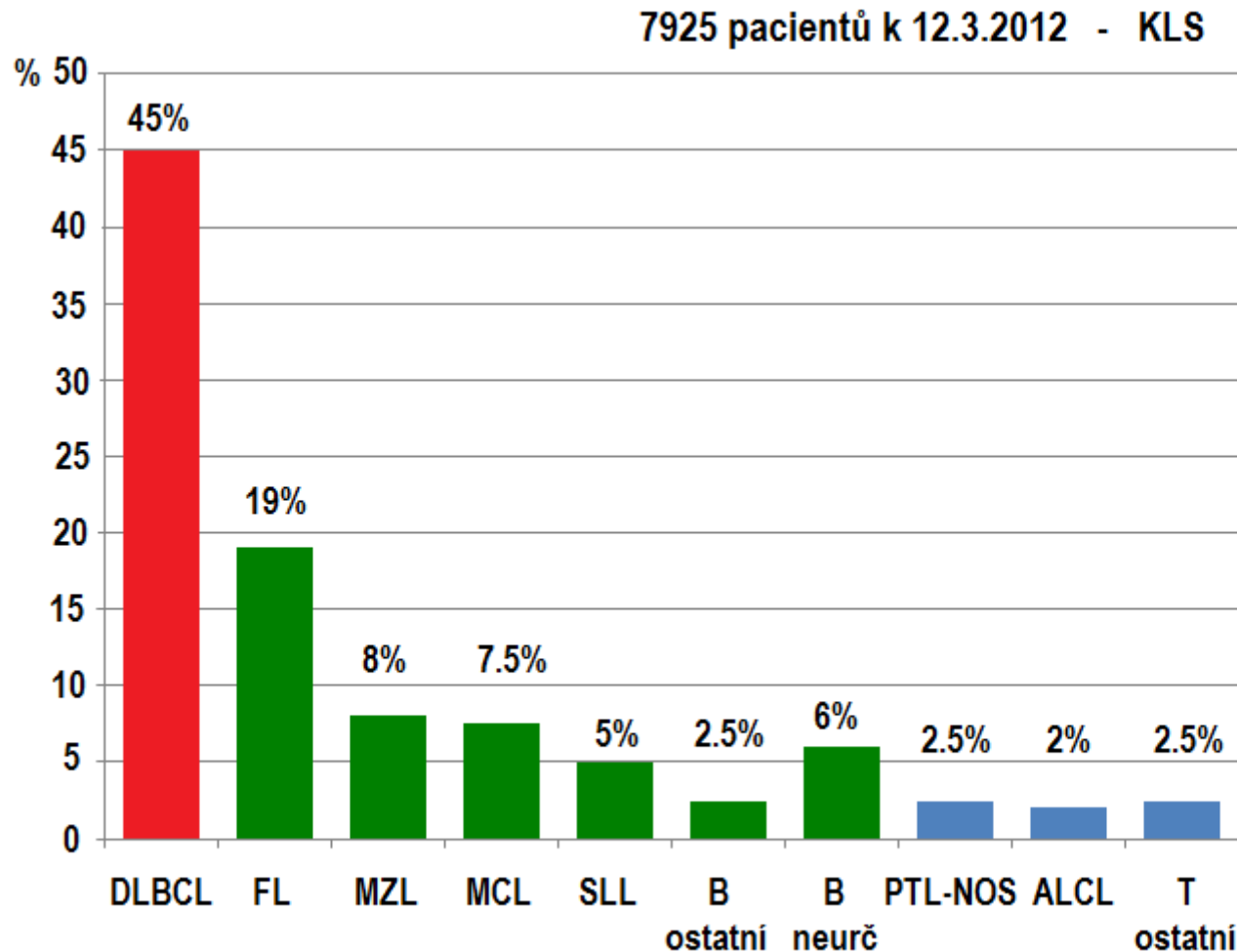


Cell Infusion

How to evaluate treatment response?

- **Complete remission** – negative CT (PET-CT), bone marrow, normal laboratory, no symptoms...
- **Partial remission** – more than 50% regression
- **Stable disease** – less than PR, but no progression
- **Progression, relapse** – new lesion or increase of existing lesion 50% or more
- **Minimal residual disease** – can be found only by very sensitive methods (FACS, molecular biology...)

Non-Hodgkin's lymphomas in Czech republic (KLS, 2012)



*Example of aggressive
lymphoma:*

**DIFFUSE LARGE B-CELL
LYMPHOMA
(DLBCL)**

Natural history:

- **Fast presentation (weeks, months...)**
- **Often B-symptoms**
- **Immediate therapy allways needed**
- **Curable, but...**
- **Treatment failure allways means poor prognosis**

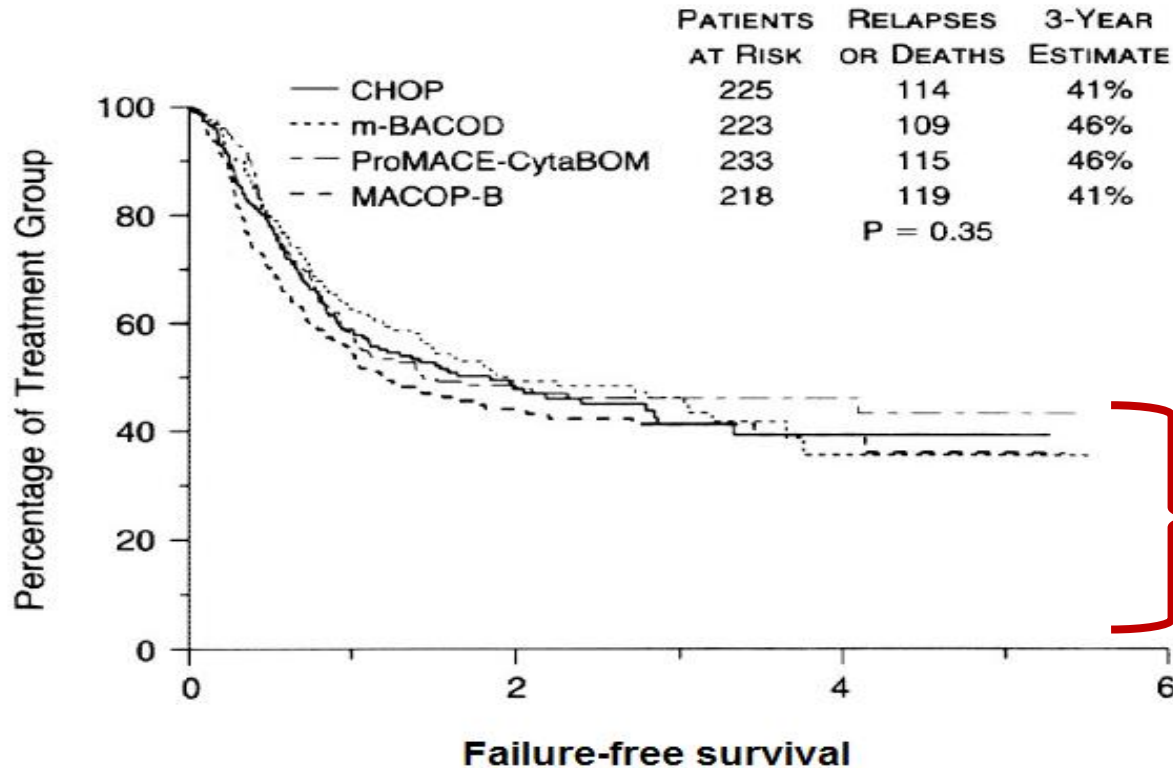
Diffuse large B-cell lymphoma (DLBCL)

- **Aggressive, CD20 positive**
- **Not homogenous disease: GC, ABC, mediastinal B-lymphoma, primary CNS lymphoma ...**
- **Oncogenes: Bcl-2 - t(14;18), Bcl-6 – t(3;14), c-myc – t(8;14)**
- **Double and triple hit lymphomas**
- **Median age >60 years**
- **15-20% have bone marrow infiltration**
- **B-symptoms frequent**

How to approach DLBCL at diagnosis

- **!! Always chemoimmunotherapy (R-CHOP) – even in stage I disease!! (DLBCL is CD20+)**
- **Radiotherapy only in bulky disease (>10 cm) or according to PET**
- **Patient who does not achieve PET-.negative complete remission after first-line treatment, continues salvage treatment immediately**

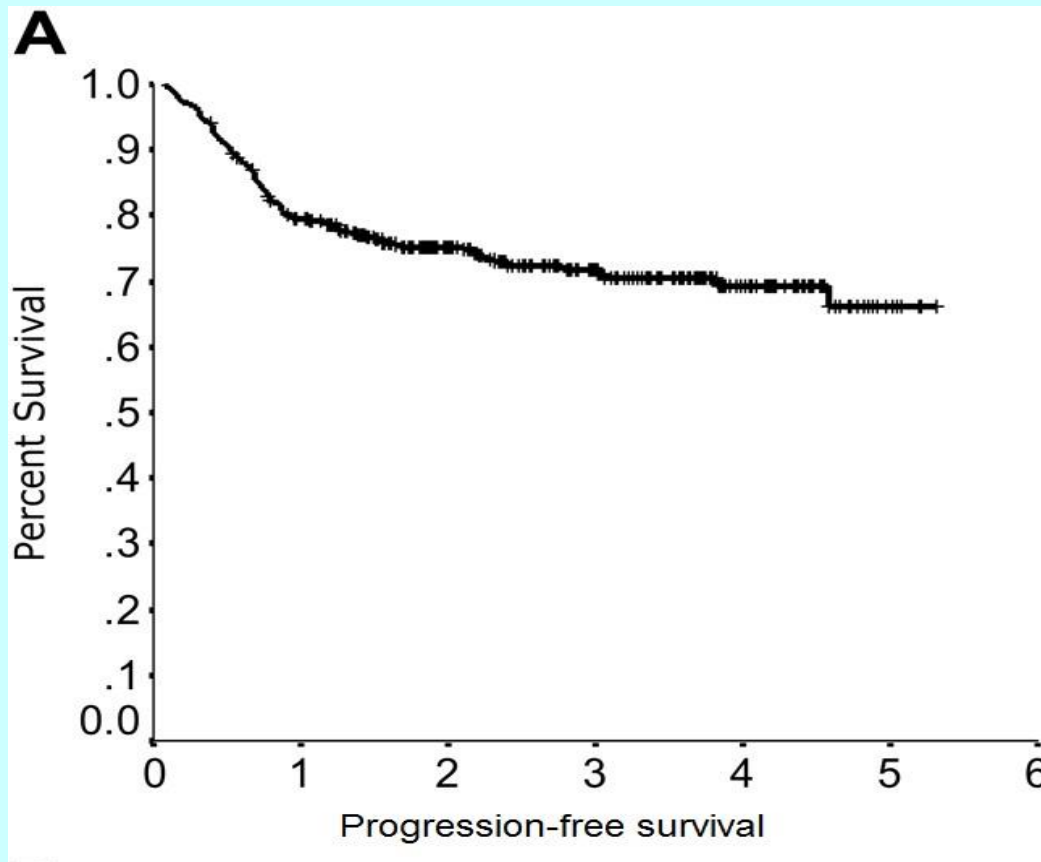
DLBCL: fate of patients before rituximab



**30-40%
cured**

Fisher RI, N Engl J Med
1993;328:1002-1006

DLBCL: fate of patients in rituximab era



**50-60%
cured**

**Sehn L, Blood,
2007;109:1857-62**



DLBCL prognosis - R-IPI:

0 risk factors

10% patients

94% PFS at 4 years

1-2 risk factors

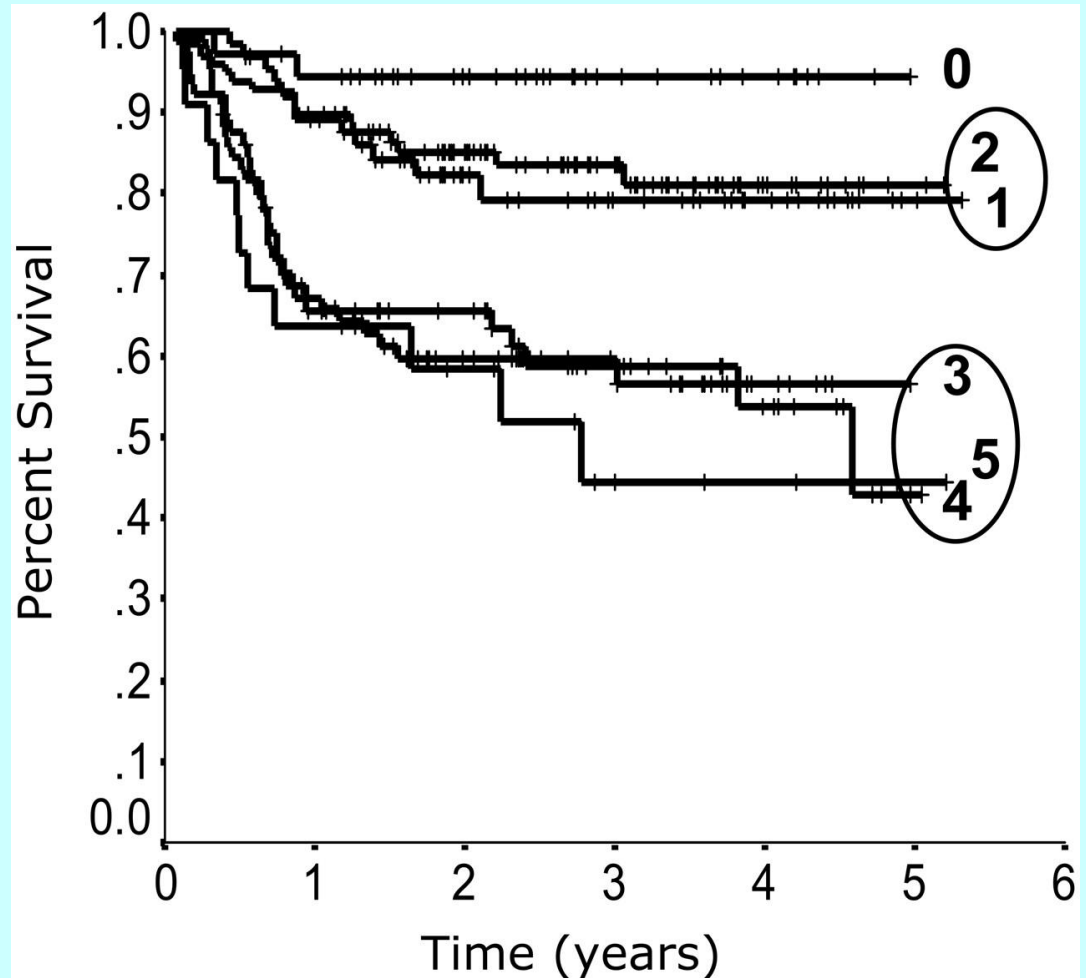
45% patients

80% PFS at 4 years

3-5 risk factors

45% patients

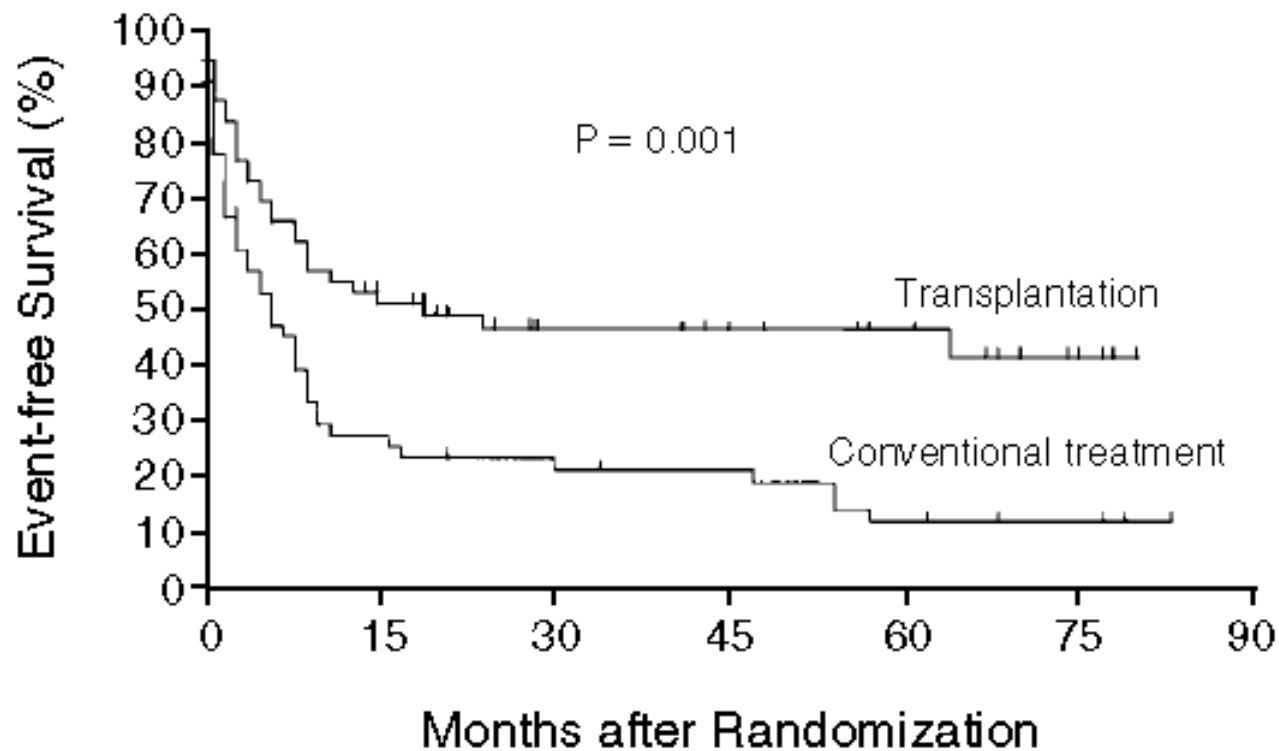
53% PFS at 4 years



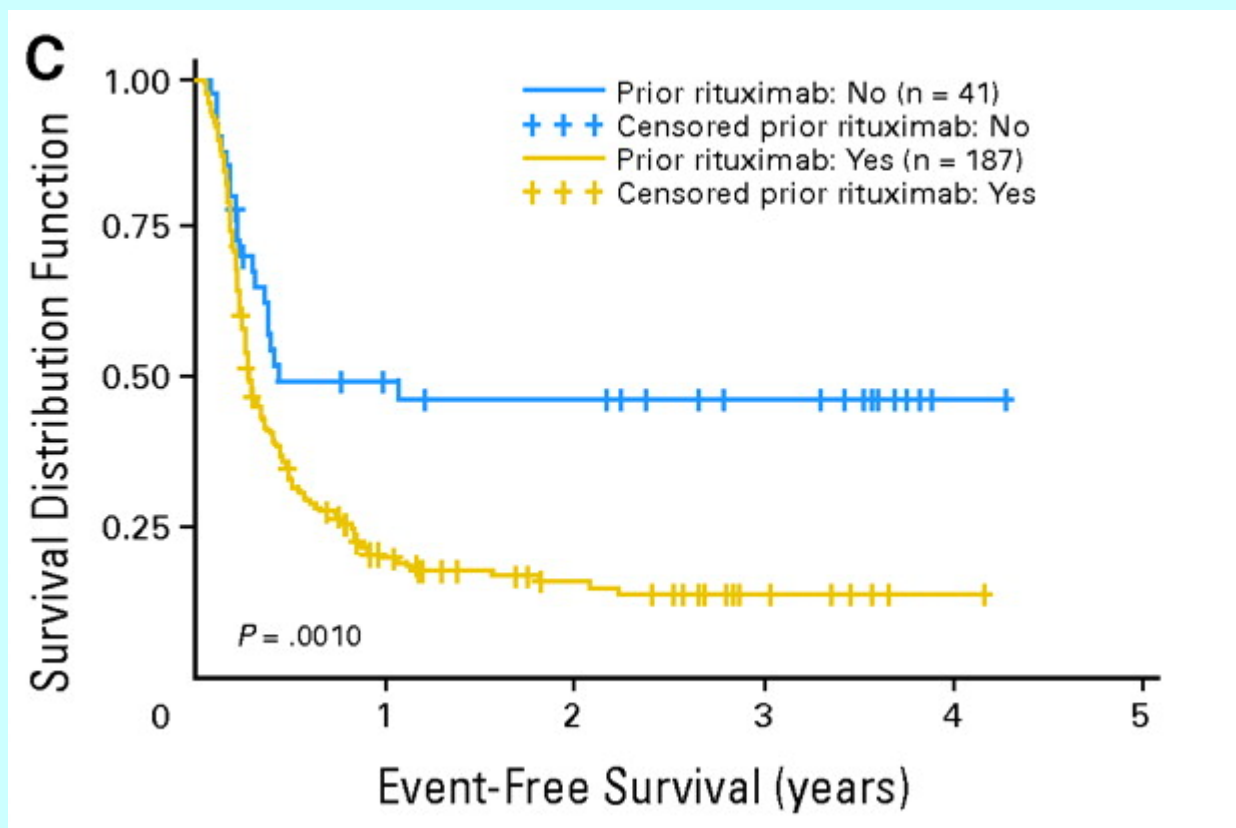
Approach to DLBCL at relapse

- **Curative v. Palliative treatment**
- **Salvage regimens: R + cisplatin, carboplatin, etoposide, steroids**
- **Autologous transplant if possible (in patients responding to salvage treatment, up to 65-70 years)**

Salvage therapy in DLBCL: platinum-based regimen + ASCT (before Rituximab)



Salvage therapy in DLBCL: platinum-based regimen + ASCT (with rituximab)



Relapse < 12 months after treatment

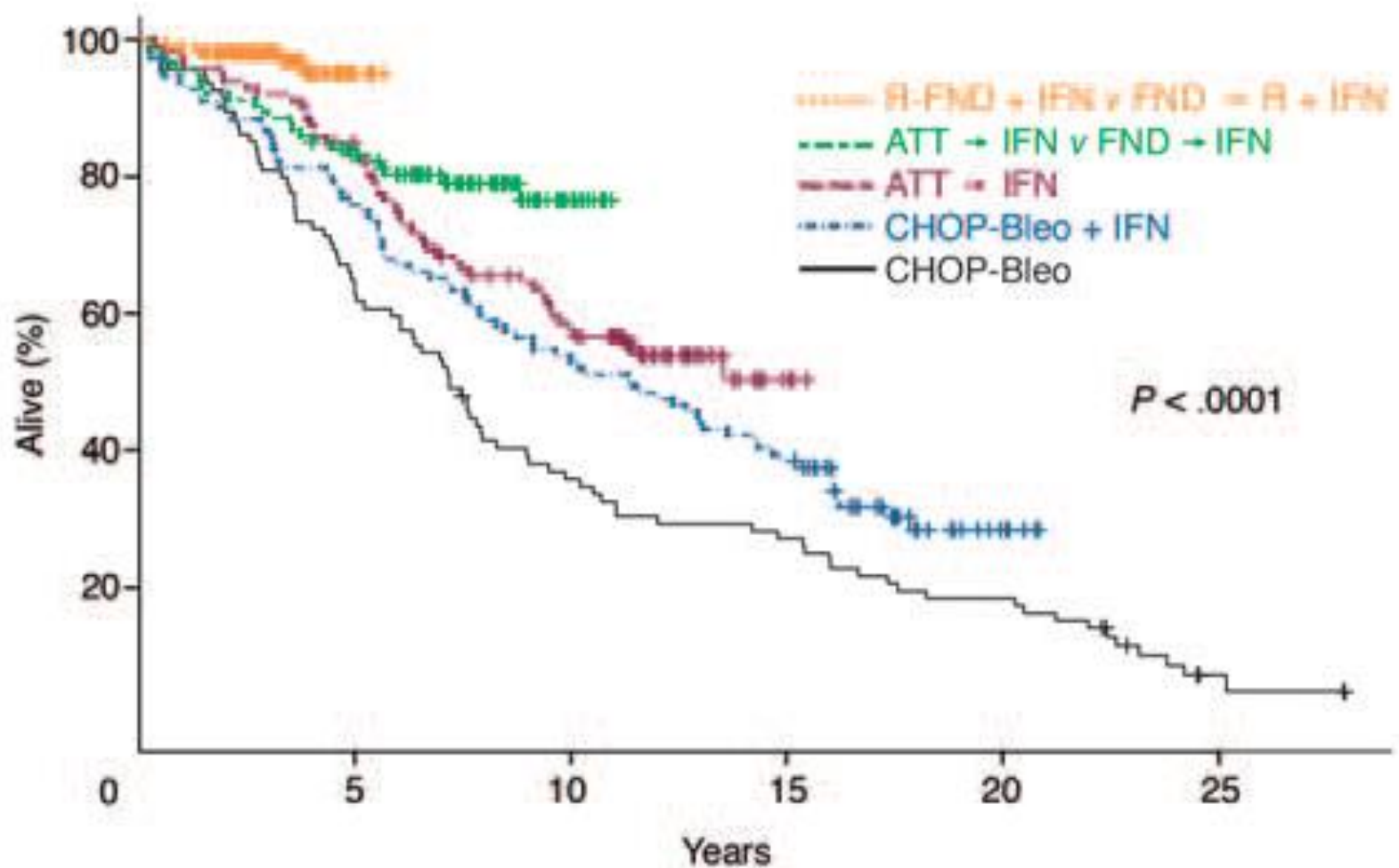
*Example of indolent
lymphoma:*

**FOLLICULAR LYMPHOMA
(FL)**

Natural history of indolent lymphoma

- Often presents months or years before diagnosis
- Treatment not needed immediately in all patients
- Good initial treatment response
- Incurable, but –
- relapsed disease still usually have good prognosis!

Follicular lymphoma - change in prognosis 1972-2002



FL - approach at diagnosis

- **Patients with localized disease:**
 localized radiotherapy
 monotherapy antiCD20 (rituximab)
- **Advanced disease, no symptoms:**
 watch and wait
 monotherapy antiCD20 (rituximab)
- **Treatment indications (GELF, BNHL criteria):**
 monotherapie antiCD20 (rituximab)
 chemoimmunotherapy R-COP, R-CHOP) + rituximab maintenance

FL - approach at relapse (1., 2., 3....)

- **Time to relapse x course (indolent, aggressive)**
- **!! New biopsy desirable (risk of transformation)**
- **Possible approaches:**

Watch and wait again

Rituximab monotherapy

Radioimmunotherapy (Zevalin)

The same or different chemotherapy (R-COP, R-CHOP, fludarabine, bendamustin...)

Salvage treatment + autologous transplantation

Allogeneic transformation, but infrequently

HODGKIN'S LYMPHOMA ***(HL)***

Natural history of Hodgkin's lymphoma

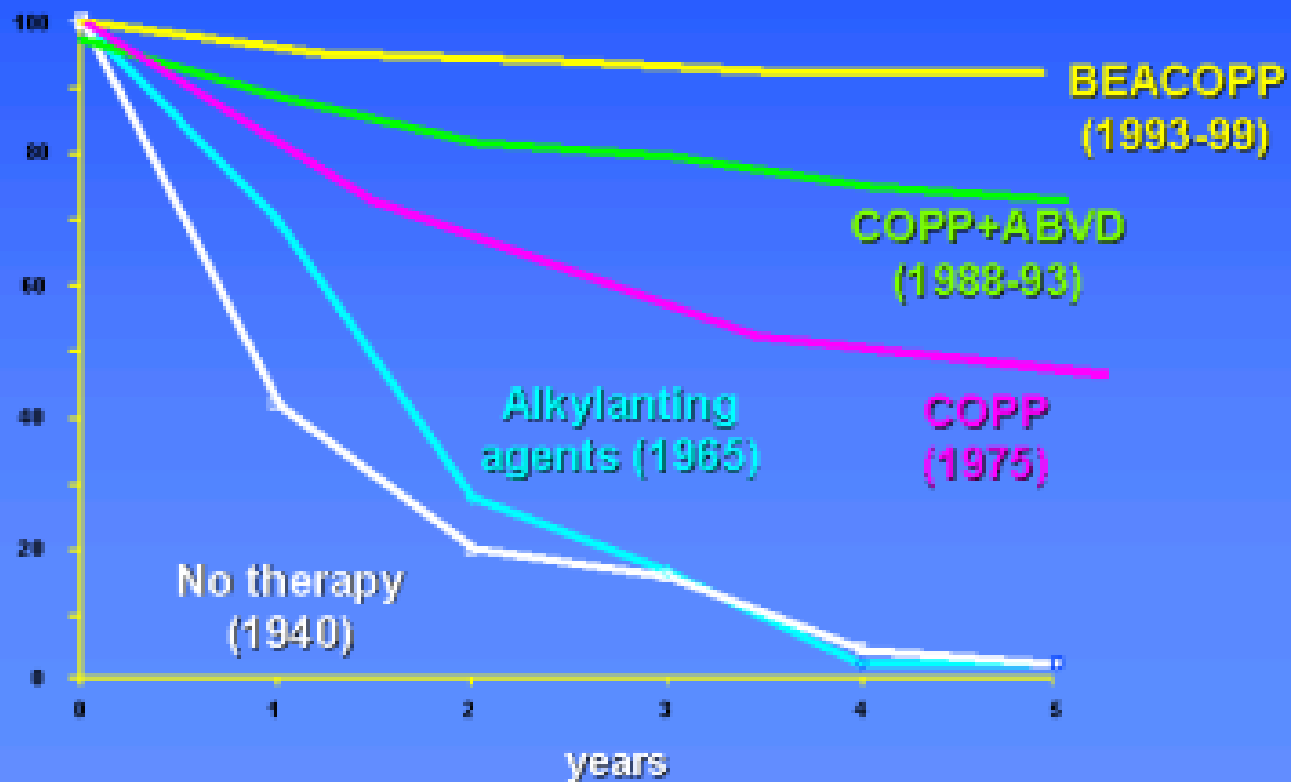
- **Very variable behaviour: indolent or aggressive**
- **90% have above diaphragm disease, most of them mediastinal involvement**
- **Most patients are cured by first-line treatment**
- **Relapsed patients have intermediate prognosis (approximately 50% cured)**

HL - approach at diagnosis

- **Patients with localized disease, good risk:**
2 cycles of chemotherapy (ABVD) + radiotherapy
- **Patients with localized disease, intermediate risk:**
4 cycles of chemotherapy (BEACOPP + ABVD) + radiotherapy
- **Patients with advanced disease:**
6 cycles of intensive chemotherapy (BEACOPP, ABVD), radiotherapy only for PET positive residual disease

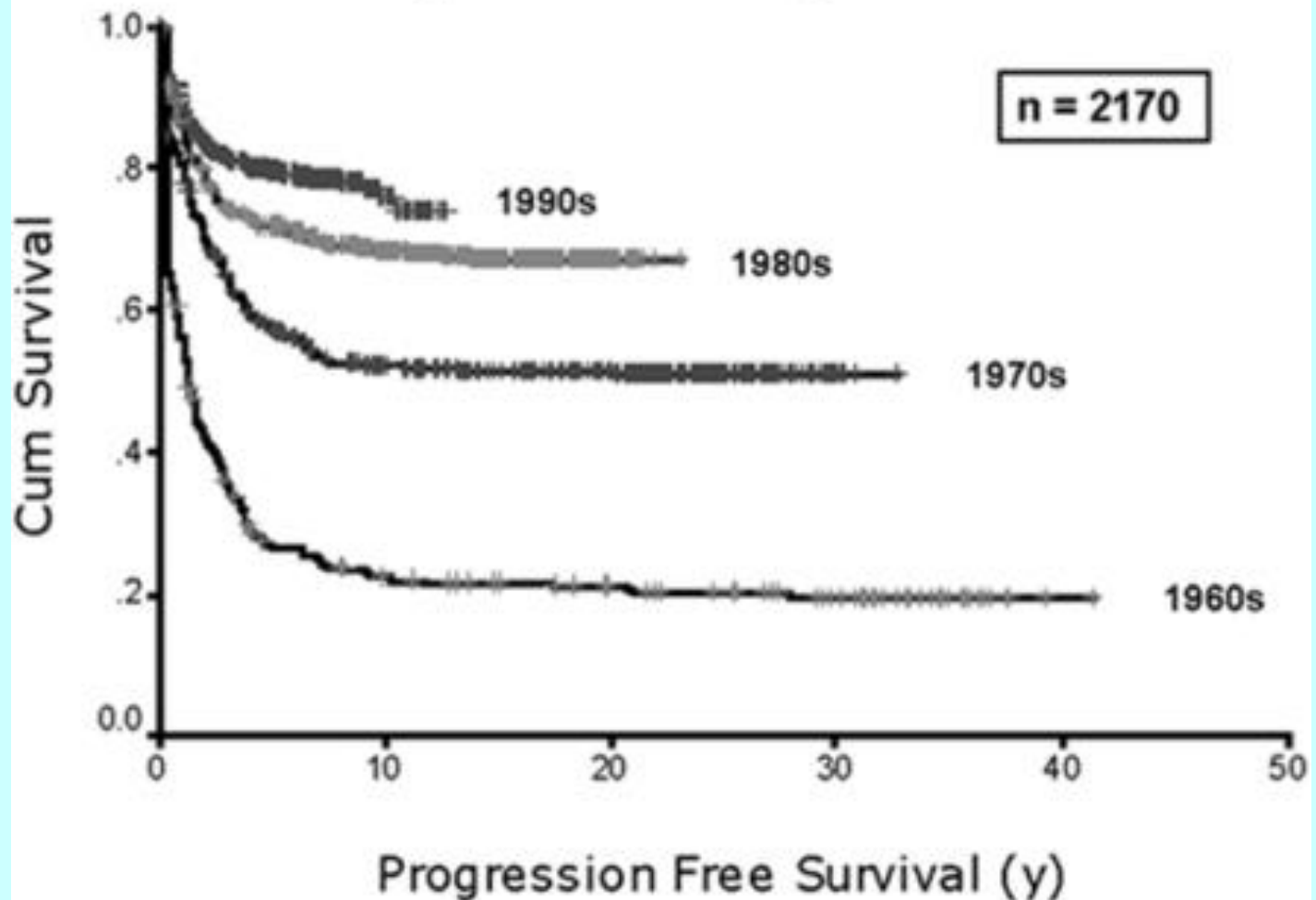
All patients have similar prognosis (85-90% cured), of course more treatment = more side effects

Fortschritte beim fortgeschrittenen Hodgkin Lymphome



Hodgkin's Lymphoma in British Columbia

Outcome by Decade of Diagnosis



HL - approach at relapse

- **Platinum-based salvage treatment + autologous transplant for most patients**
 - outcome dependent on PET before transplant
- **Relapses after autologous transplant:**
 - allogeneic transplant (quite poor outcomes)
 - brentuximab vedotin (prolongs survival, does not cure)
 - nivolumab (anti-PD1 antibody)

HL - survival after relapse

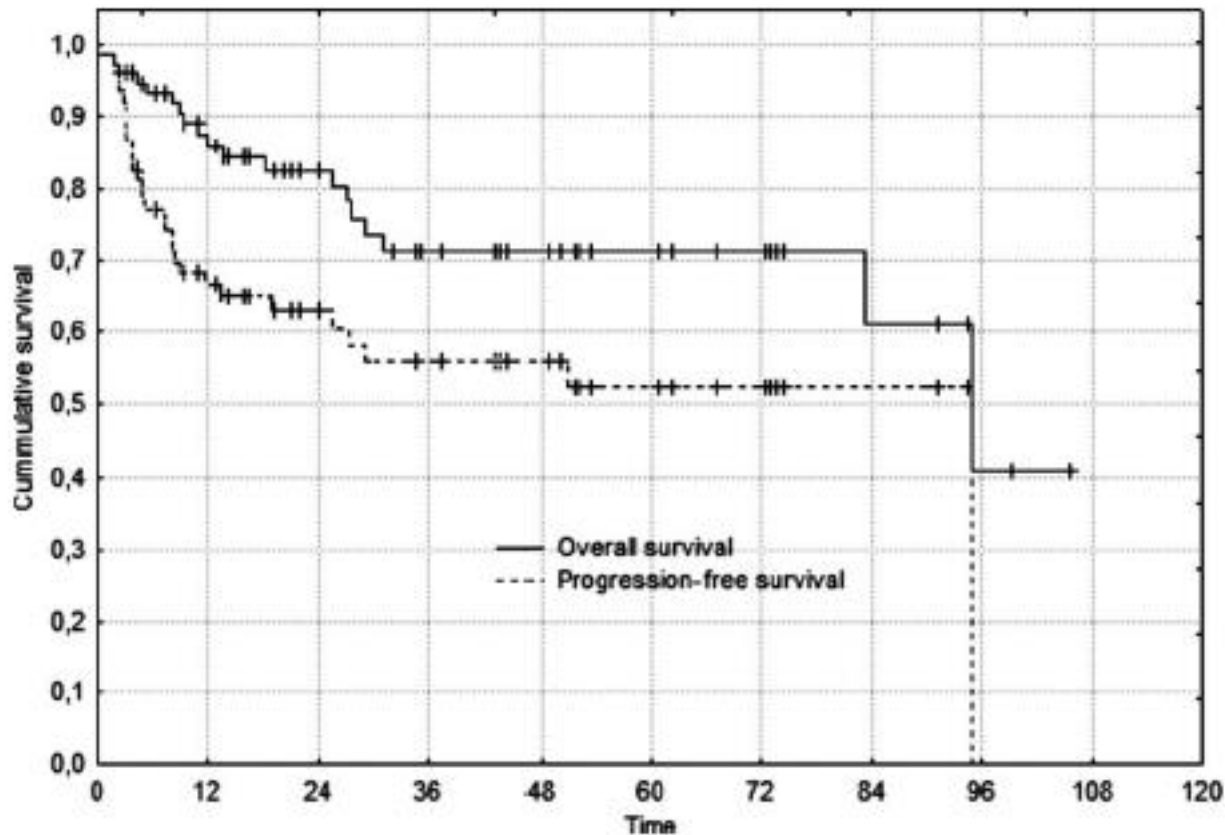


Figure 1. PFS and OS of patients with Hodgkin lymphoma ($n = 76$).

Lymphomas summary

- **Most frequent malignancies in people around 30 years**
- **One of most frequent malignancies in the elderly**
- **Beware of extremely variable presentation**
- **MAKE IT SIMPLE!! (the fastest way to tumor diagnosis is biopsy)**