Waldenstrom macroglobulinemia: new treatment options for relapsed disease: results from IWWM9!

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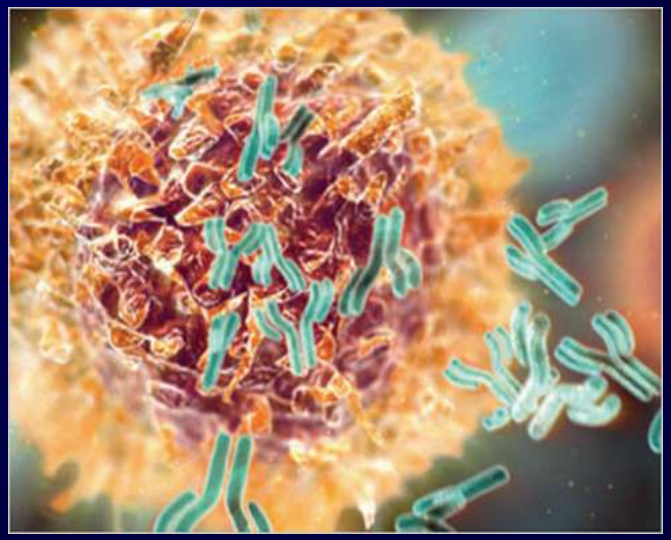
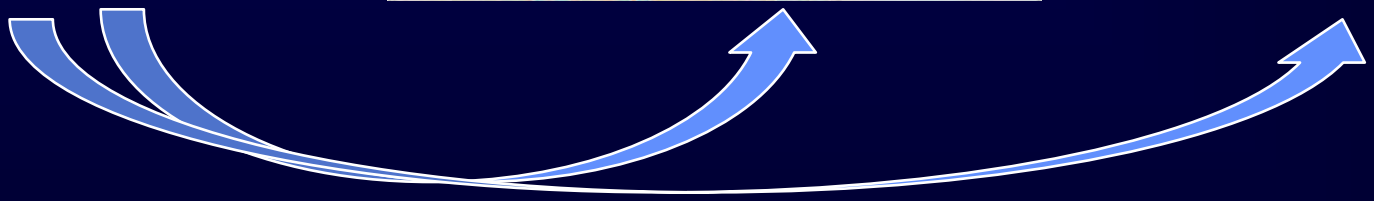
Treatment of relapsed WM



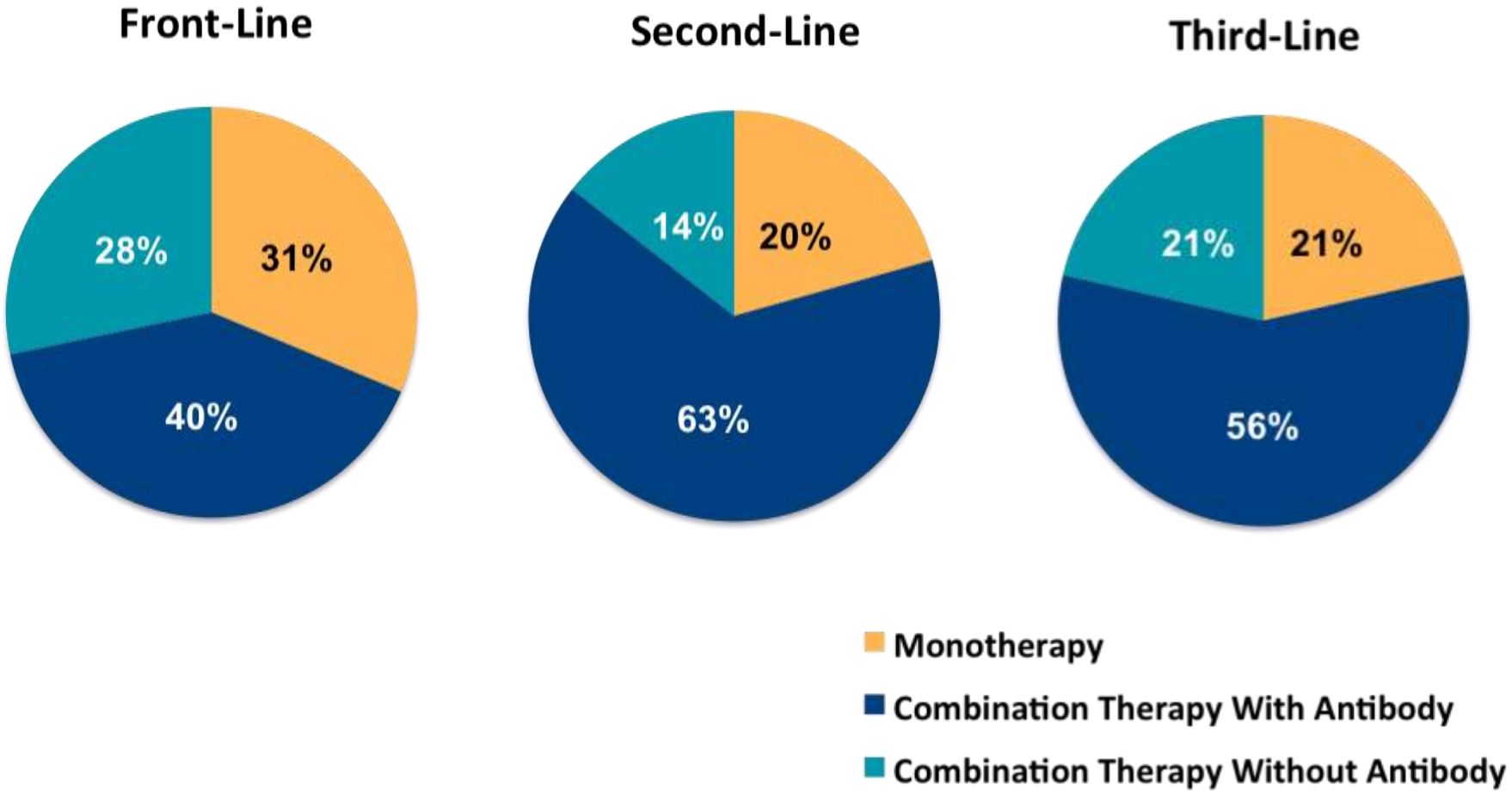


Treatment of relapsed WM in 2016

- **No signs/symptoms**: wait and see
- **If treatment is indicated: look at:**
  - Response to prior treatment (retreat)
  - Age
  - Fitness/comorbidity
  - Bone marrow reserve (cytopenia)
  - IgM level (flare)
  - Rapid control necessary?
  - Stem cell toxicity?
  - Side effects (neuropathy)

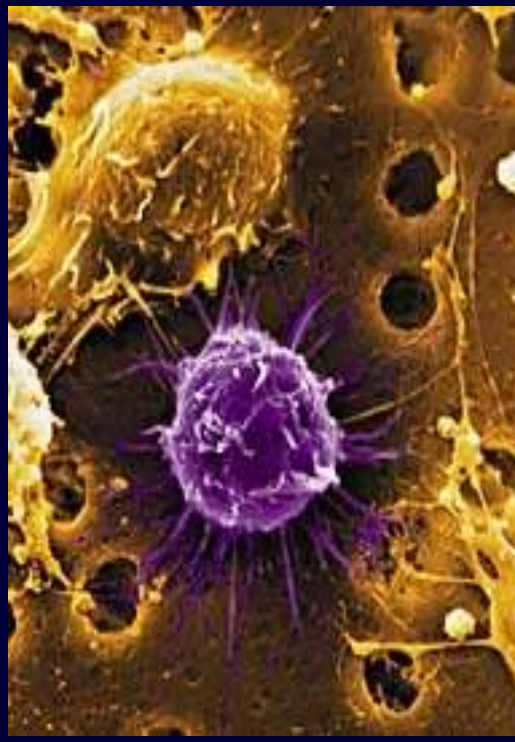
Choice of Therapy by Line of Treatment in the Overall Population

(n=368 patients European retrospective study (dr Buske)

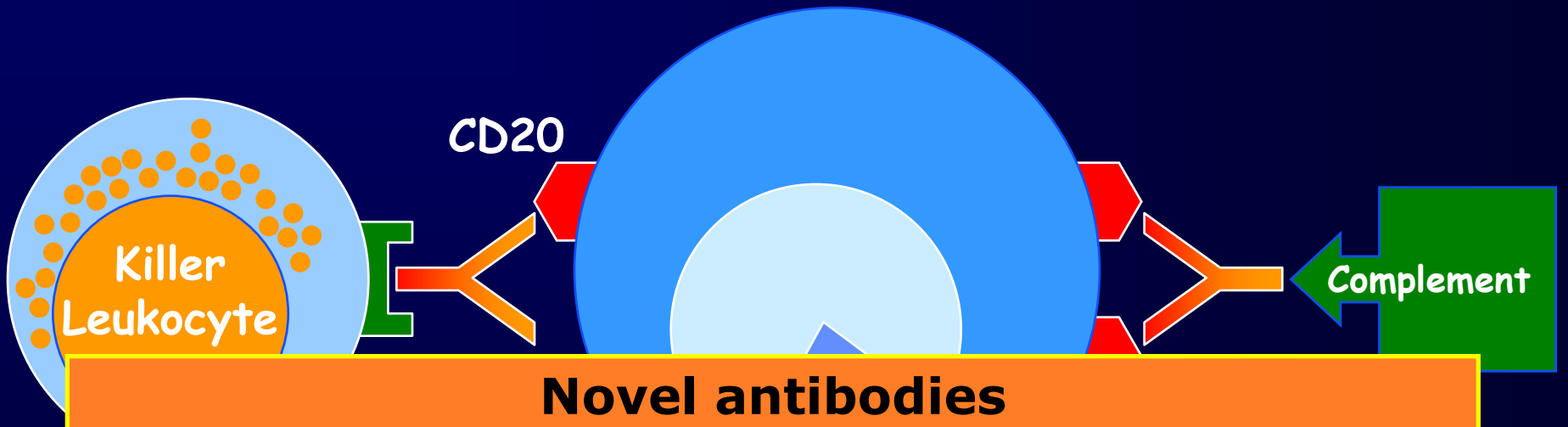


New treatment modalities (background)

- (New chemotherapy)
- New monoclonal antibodies
  - Directed at other proteins on the WM cell (eg immune checkpoint, CD38
  - Antibody drug conjugate (radioisotope or chemotherapeutic)
  - Bispecific antibodies
  - CAR-T cells
- Interaction with microenvironment
- Better understanding of what goes wrong in the tumor cell (signalling)



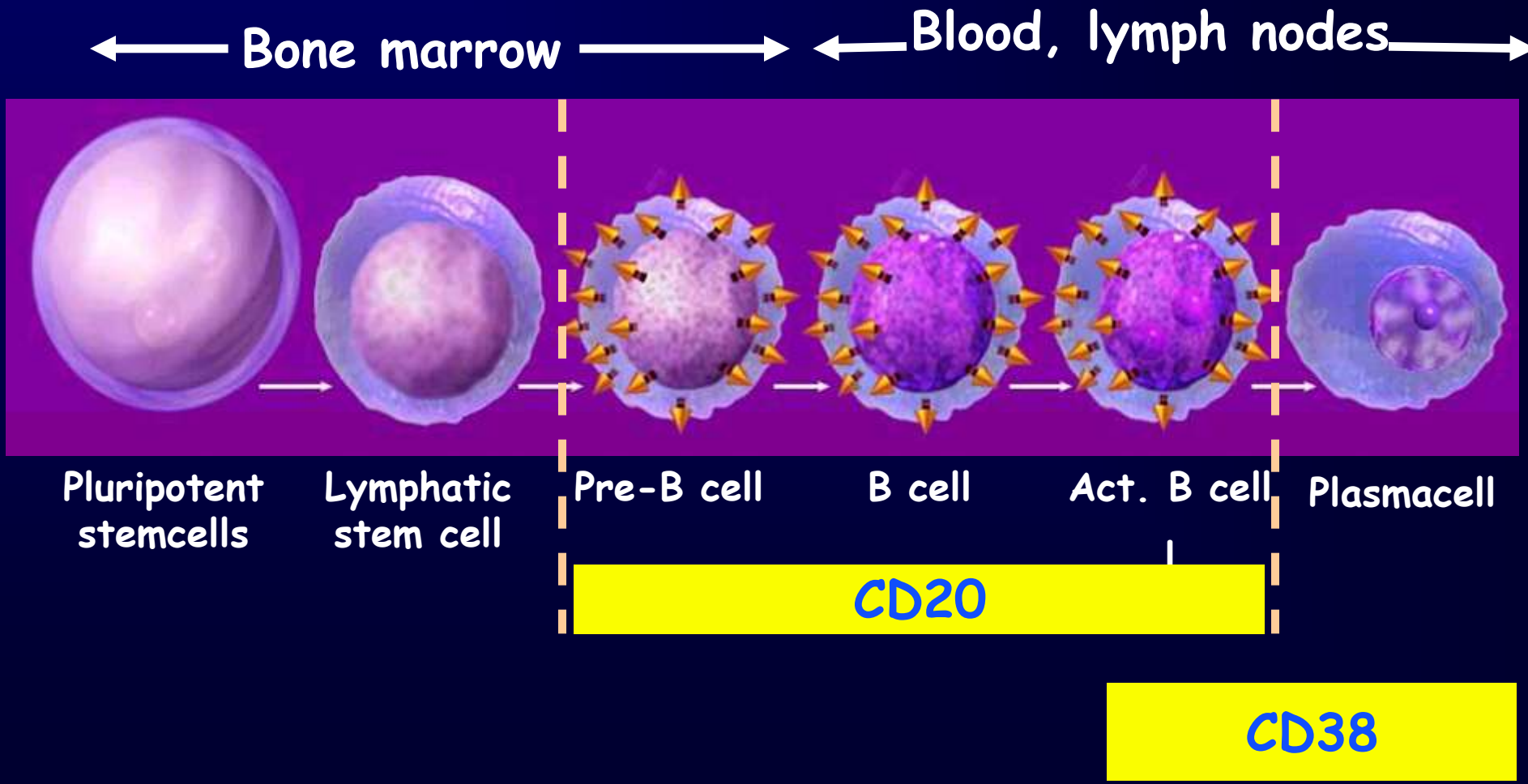
Mechanisms of action of antibodies



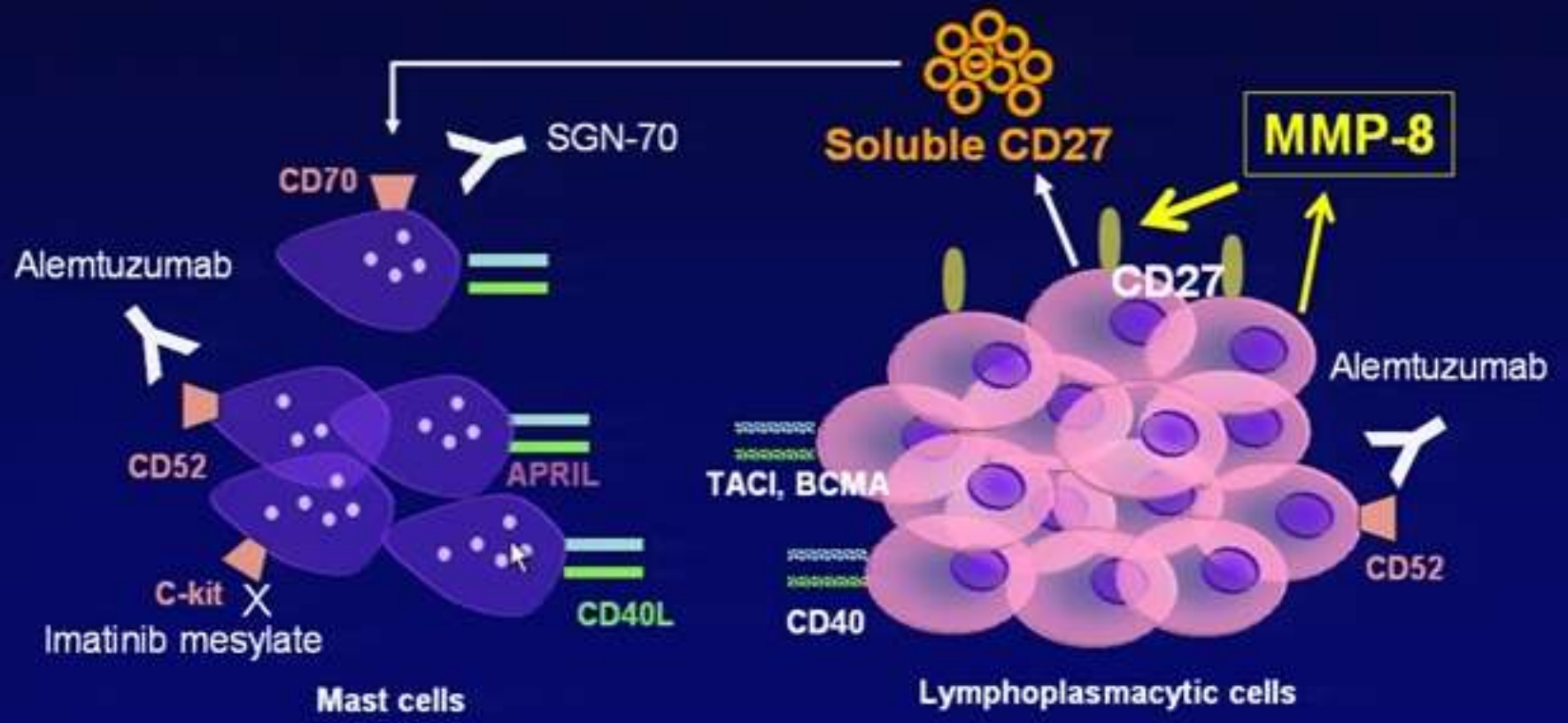
Novel antibodies
-Second generation CD20 antibodies
-Other targets, eg CD38, immune checkpoints
-Bispecific antibodies
-Radioimmunotherapy
-Antibody-drug conjugate (ADC)
-CAR-T cells

radionuclide ↑ cytostaticum

CD20 Expression during B-cell development



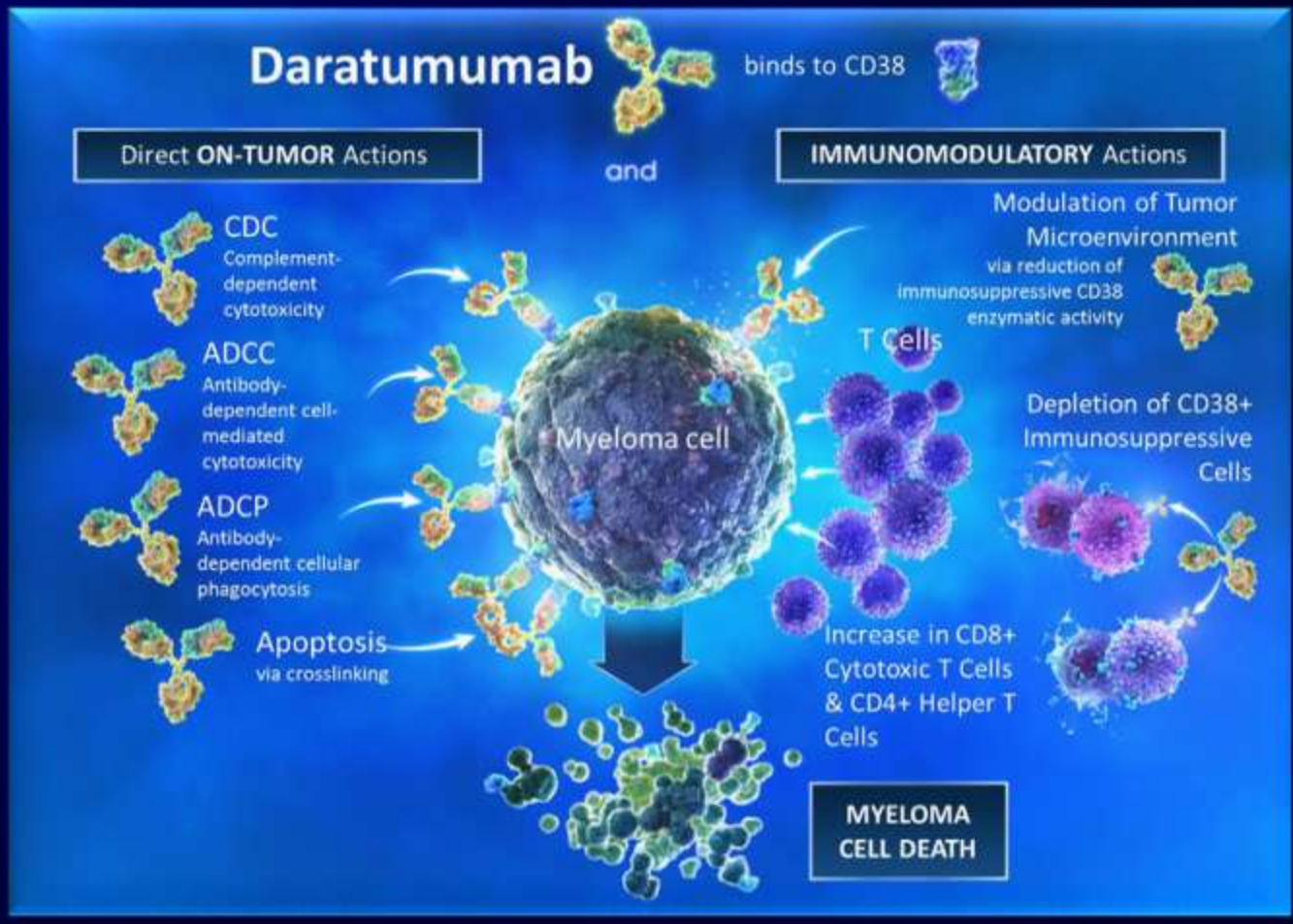
sCD27 in WM-Mast Cell Interactions



Tournilhac et al, Ann Oncol 2006; Ho et al, Blood 2008

Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]

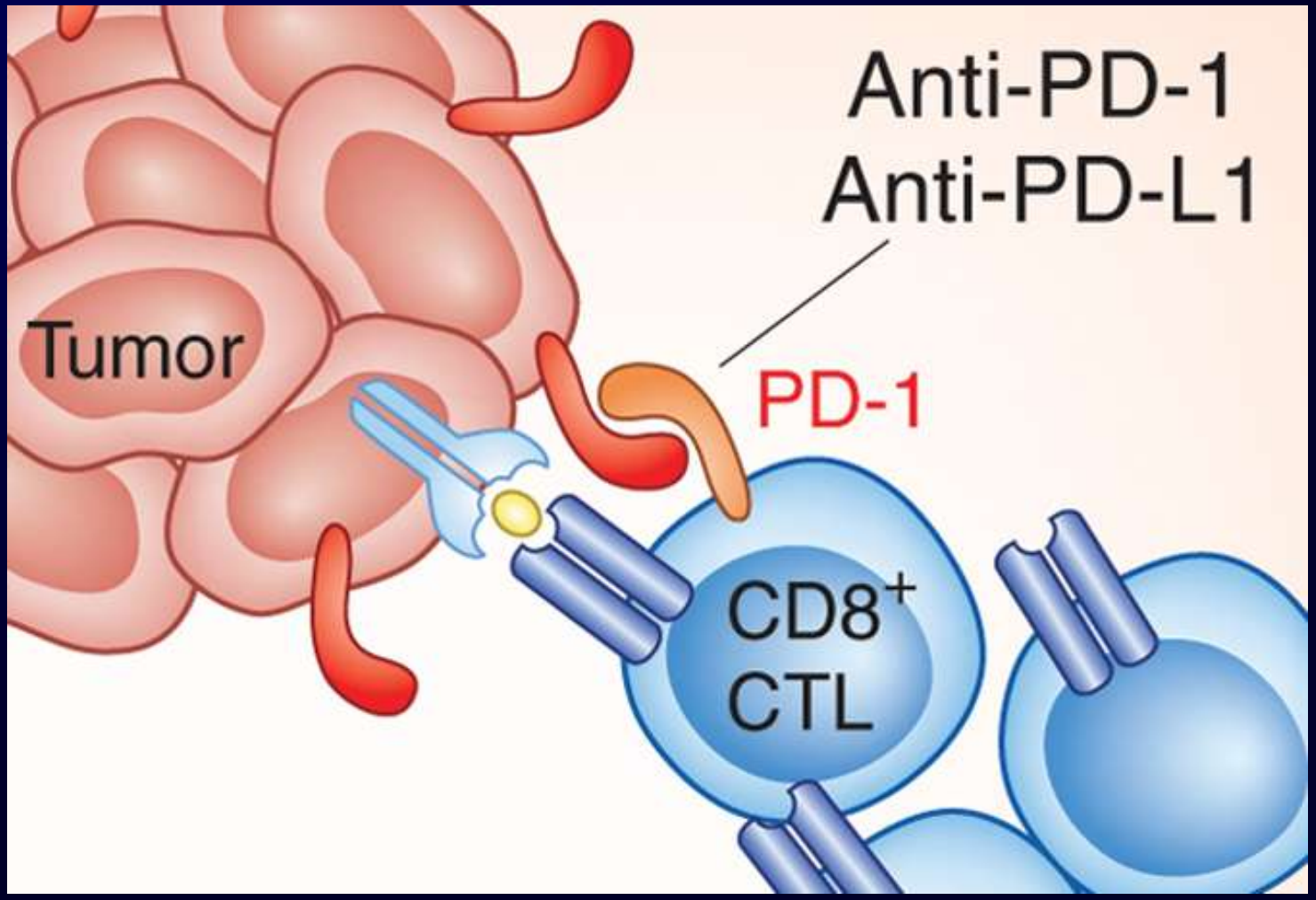


1. Lammerts van Bueren J, et al. Blood. 2014;124:Abstract 3474.
2. Jansen JHM, et al. Blood. 2012;120:Abstract 2974.
3. de Weers M, et al. J Immunol. 2011;186:1840-8.
4. Overdijk MB, et al. MAbs. 2015;7:311-21.
5. Krejcik J, et al. Blood. 2016. Epub ahead of print.

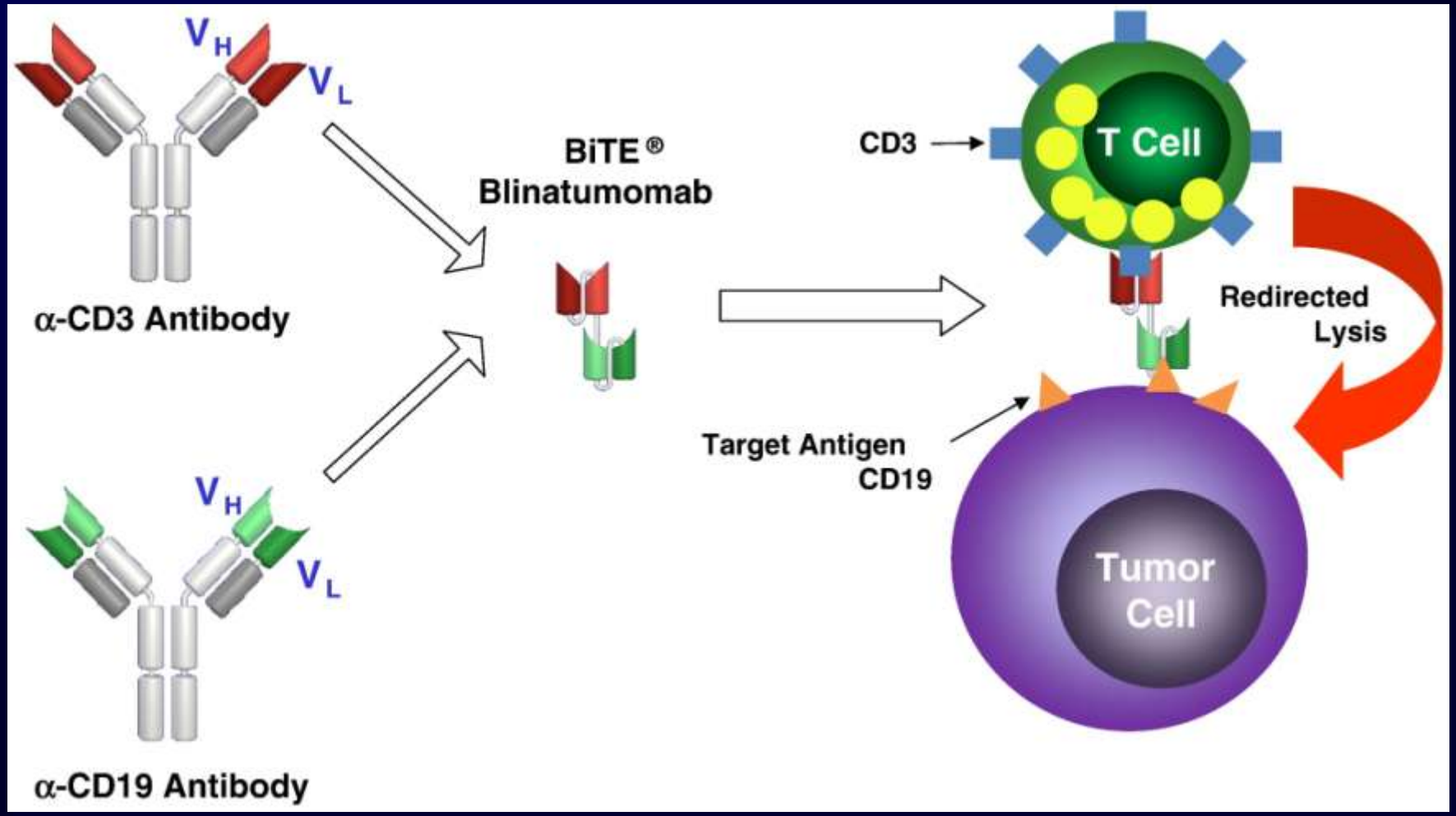
Activating your own immune system

- Patient's immune cells (T cells) can recognize tumor cells
- These T cells are on a brake

Immune system 'checkpoint' = brakes: PD-L1 tumor cells/PD-1 T cells

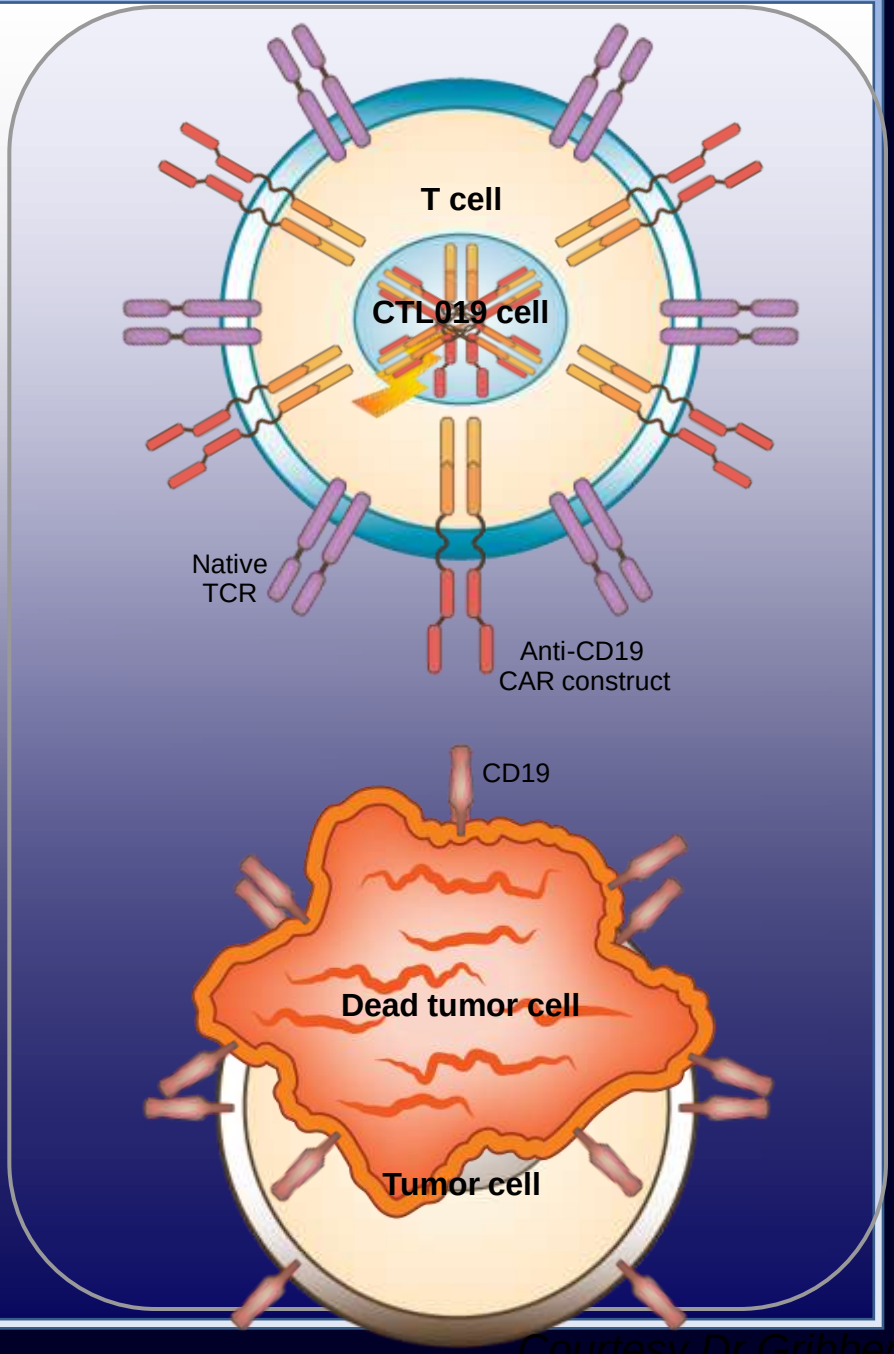


Bi-specific antibodies: Blinatumomab: they direct the T cell to the tumor cells



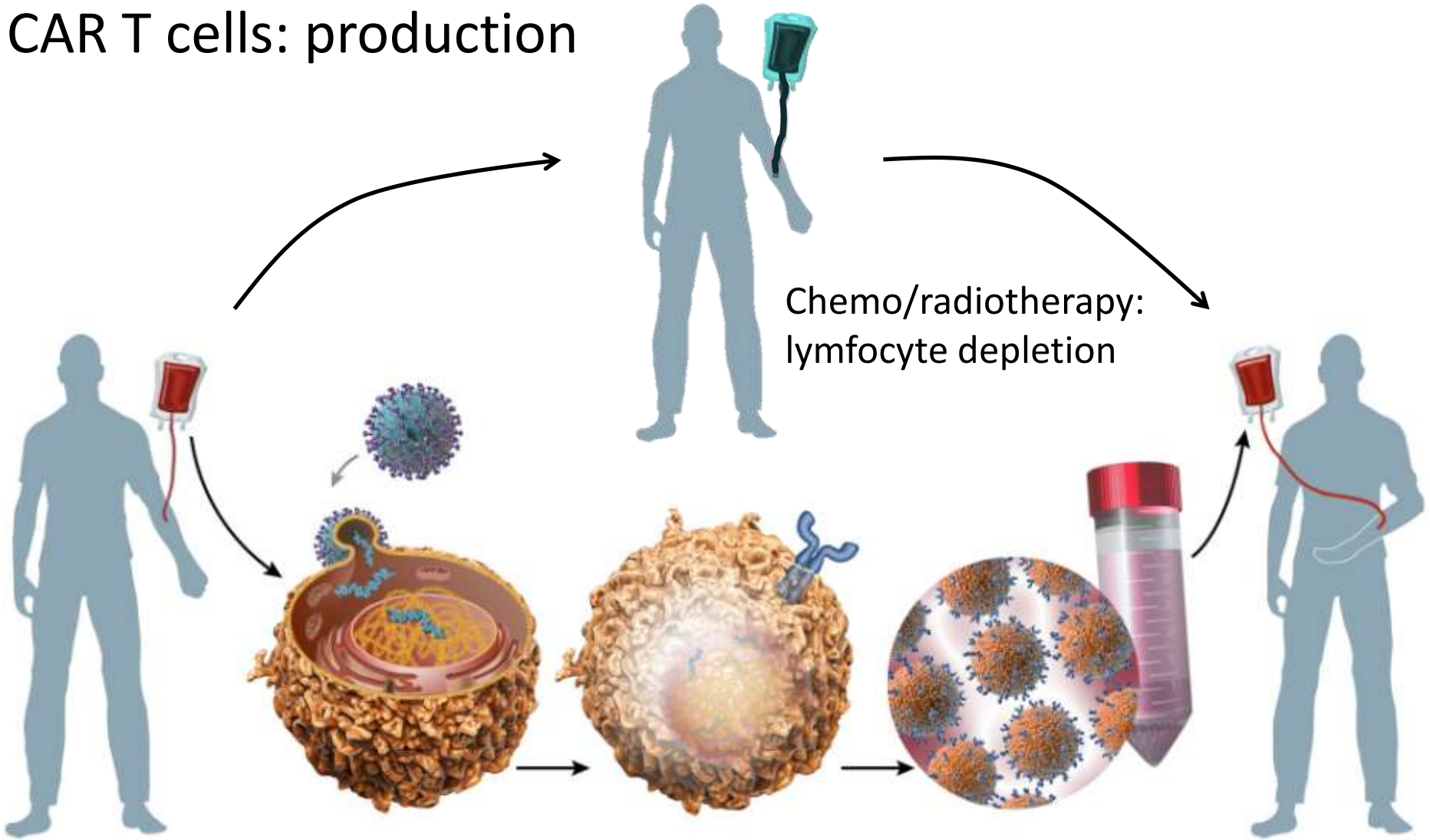
Chimeric Antigen Receptor T cellen (CAR-T cells)

- **CAR-T cells combine an antibody specific for tumorcells with properties of T cells (chimeric)**
- **With the help of a virus the chimeric receptor is transferred to the T cells**



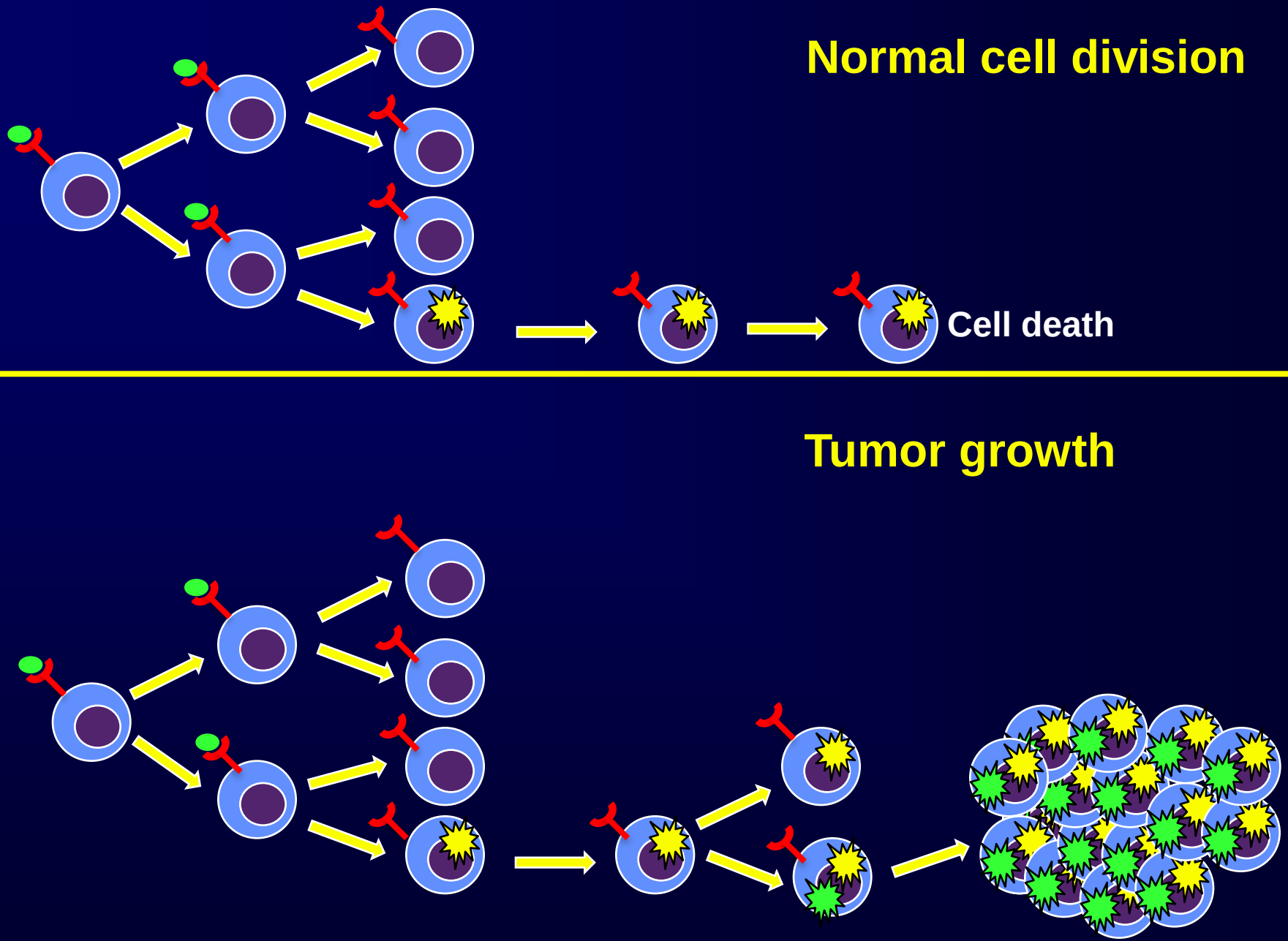
Courtesy Dr Gribben

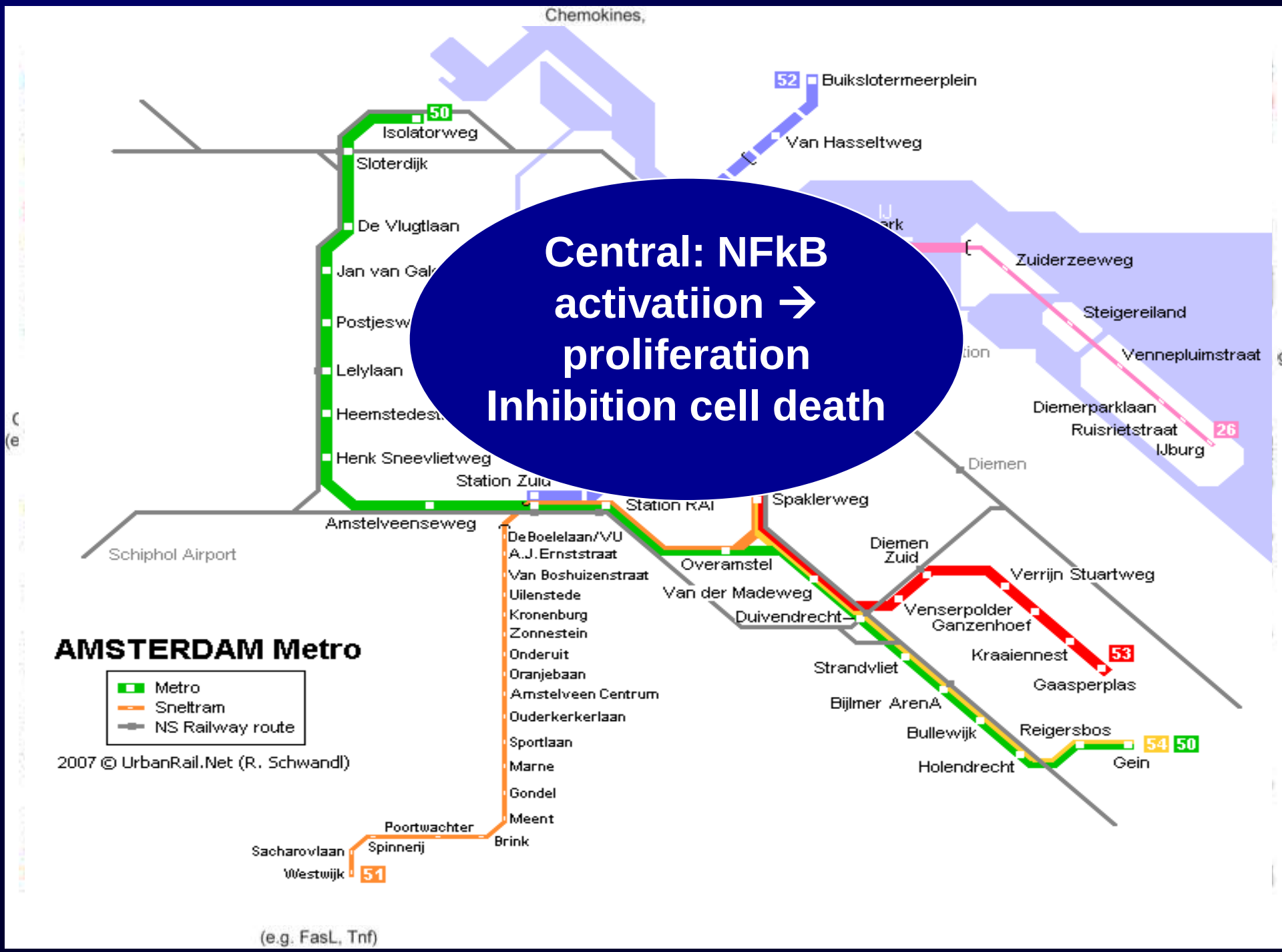
CAR T cells: production



CAR-T cells

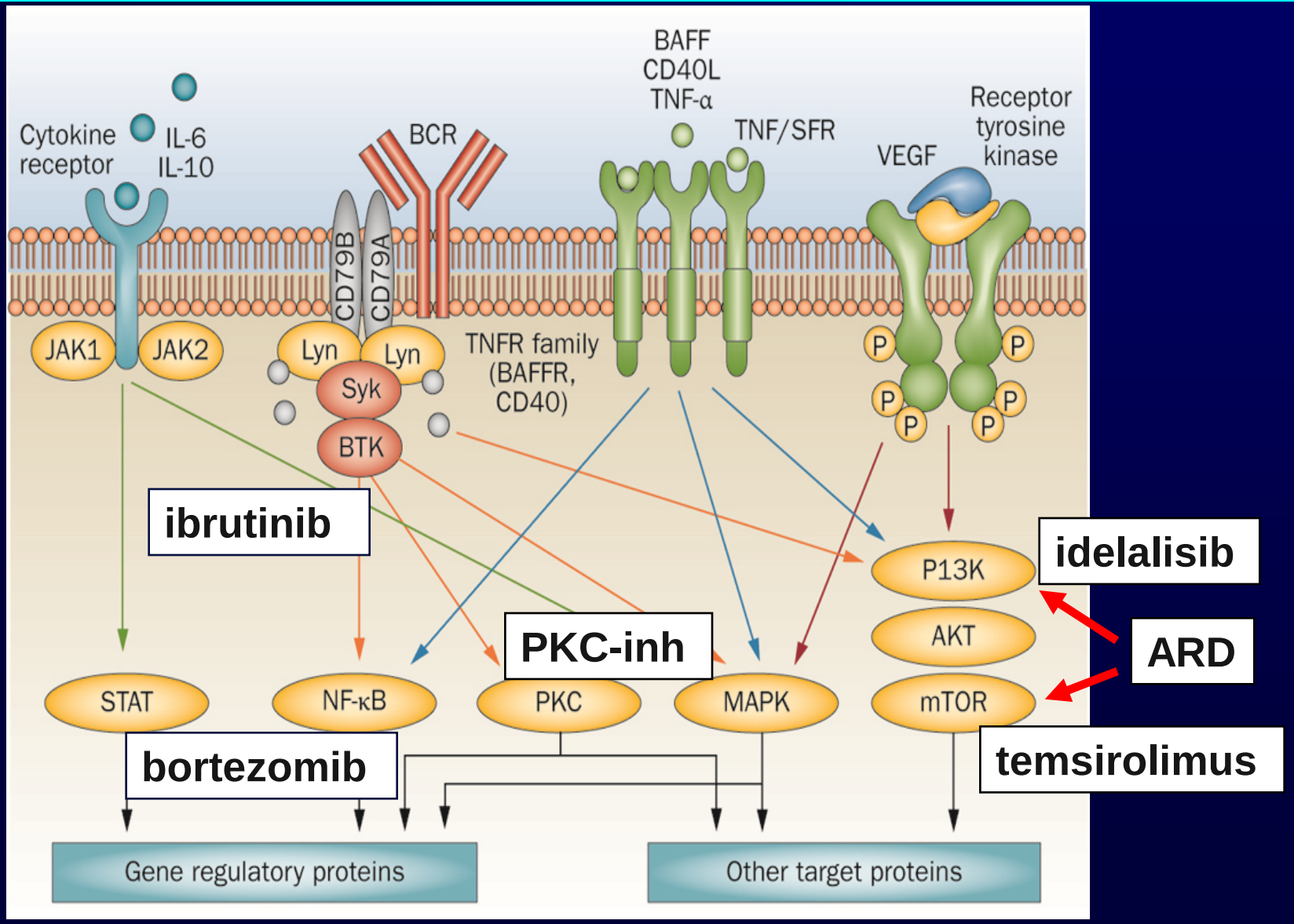
- Thus far more experience in acute leukemia, aggressive NHL
- Only a few WM patients
- Toxicity:
    - cytokine release storm (ICU)
    - Neurologic symptoms
    - B cell depletion
- Increase efficacy
- 'On-off' switch?
- Better understand/prevent toxicity


Normal cell division
Cell death
Tumor growth


Chemokines,
Central: NFkB activatiion → proliferation Inhibition cell death
AMSTERDAM Metro
Metro
Sneltram
NS Railway route
2007 © UrbanRail.Net (R. Schwandl)
52
Buiksloternmeerplein
Van Hasseltweg
50
Isolatorweg
Sloterdijk
De Vlugtlaan
Jan van Gal
Postjesw
Lelylaan
Heemstedes
Henk Sneevlietweg
Station Zuid
Station RAI
Amstelveenseweg
Schiphol Airport
Spaklerweg
De Boelelaan/VU
A.J.Ernststraat
Van Boshuizenstraat
Uilenstede
Kronenburg
Zonnestein
Onderuit
Oranjebaan
Amstelveen Centrum
Ouderkerkerlaan
Sportlaan
Marne
Gondel
Meent
Brink
Poortwachter
Spinnerij
Sacharovlaan
Westwijk
51
Overamstel
Van der Madeweg
Duivendrecht
Diemen Zuid
Diemen
Zuiderzeeweg
Steigereiland
Vennepluimstraat
Diemerparklaan
Ruisrietstraat
26
IJburg
Verrijn Stuartweg
Venserpolder
Ganzenhoef
Kraaiennest
53
Gaasperplas
Strandvliet
Bijlmer ArenA
Bullewijk
Reigersbos
54
50
Gein
Holendrecht
(e.g. FasL, Tnf)

NHL: Targeted therapy: focus on pathways

Younes Nat Rev Oncol 2012



HOVON124 study

- First HOVON study MW!
- For patients with relapsed WM
- New oral proteasome inhibitor ixazomib in combination with rituximab and dexamethason
- Followed by 2 years of rituximab maintenance
- Oral, less neurotoxic
- HOVON (NL), Belgium and Greece
- Ongoing

Ibrutinib

- Phase II study dr Treon (3 centres USA)
- 63 patients
- 420 mg ibrutinib until progression
- Response: 91% (no complete responses)
- IgM 3.2 → 1.2 g/dl
- Hematocrit 31 → 39.7%
- BM infiltration 70 to 40%

- LONG TERM FOLLOWUP (dr. Palomba)

Long-term follow-up (median f/u 37 months)

- 25/63 patients stopped, 11 because of progression
- 3 year event-free survival 68%; overall survival 90%

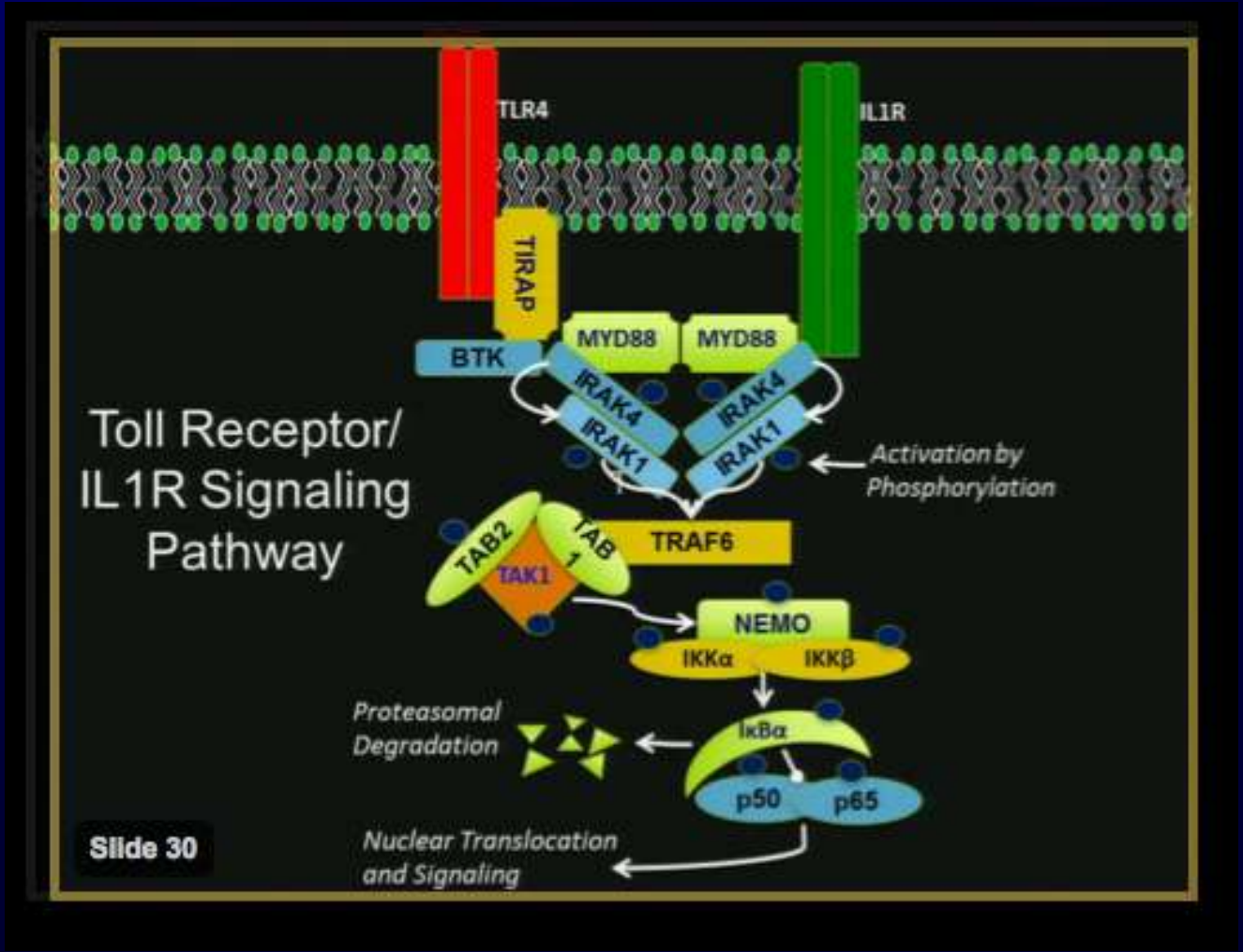
- Few new side effects with longer follow up (especially cardiac or bleeding)

- 3/6 tested progressive patients had mutations in btk or ‘downstream’

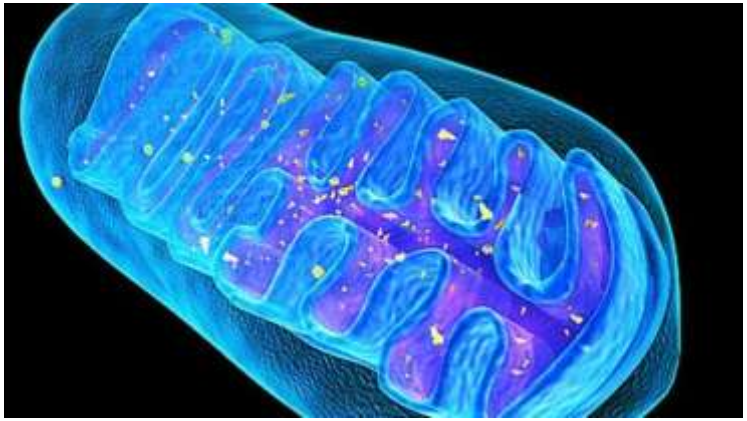
New Btk inhibitors

- New btk inhibitors
  - Acalabrutinib
  - BGB-3111
  - ONO
- Combinations with other drugs

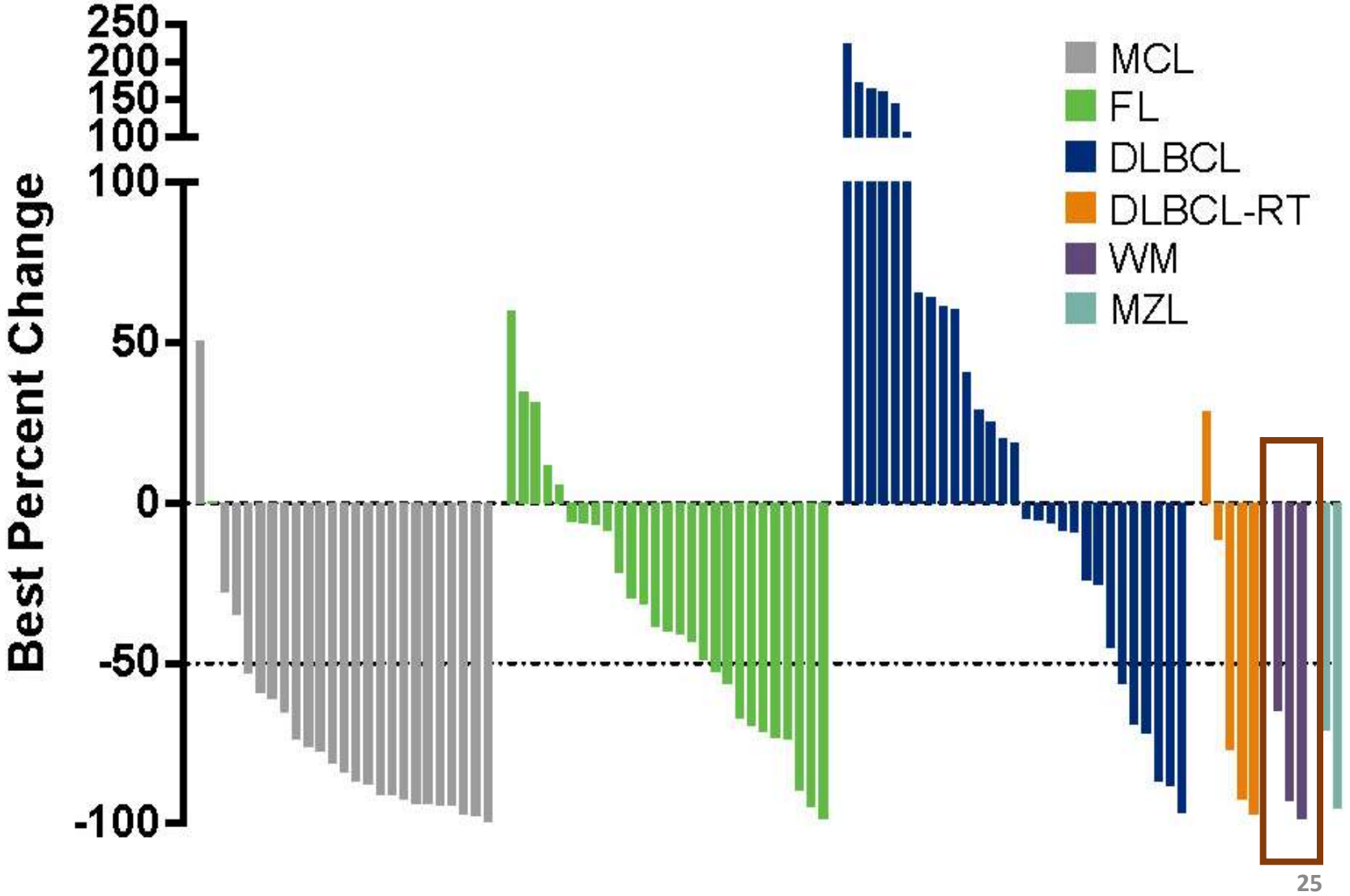
MYD88 signaling:
BTK, IRAK inhibitors, HCK



Why target Bcl-2 in WM?



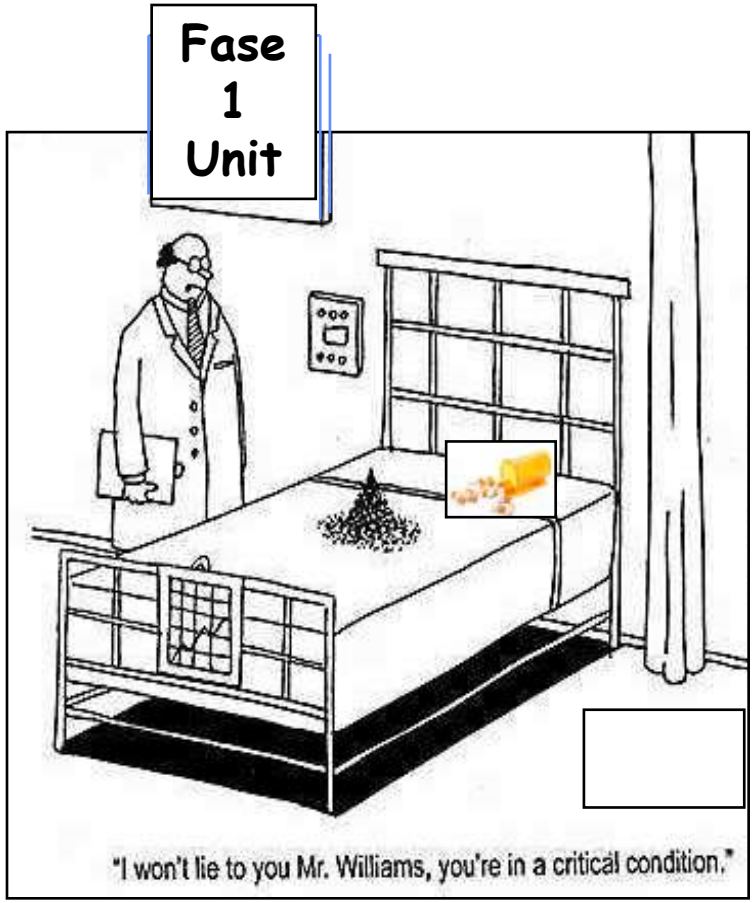
Best Percent Change From Baseline SPD Nodal Mass by CT

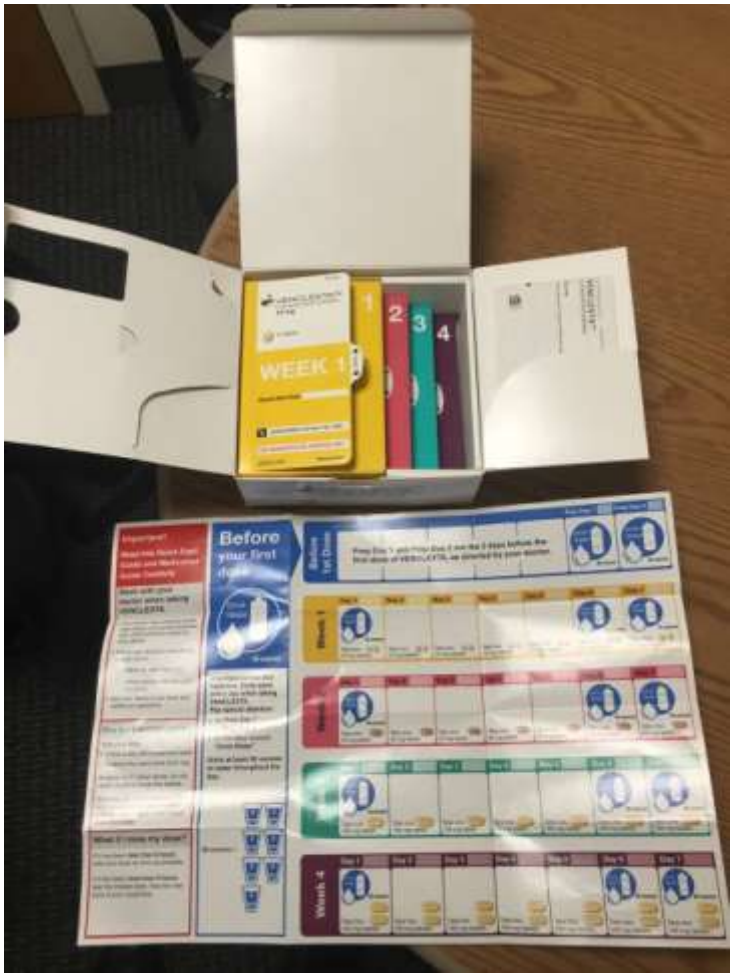


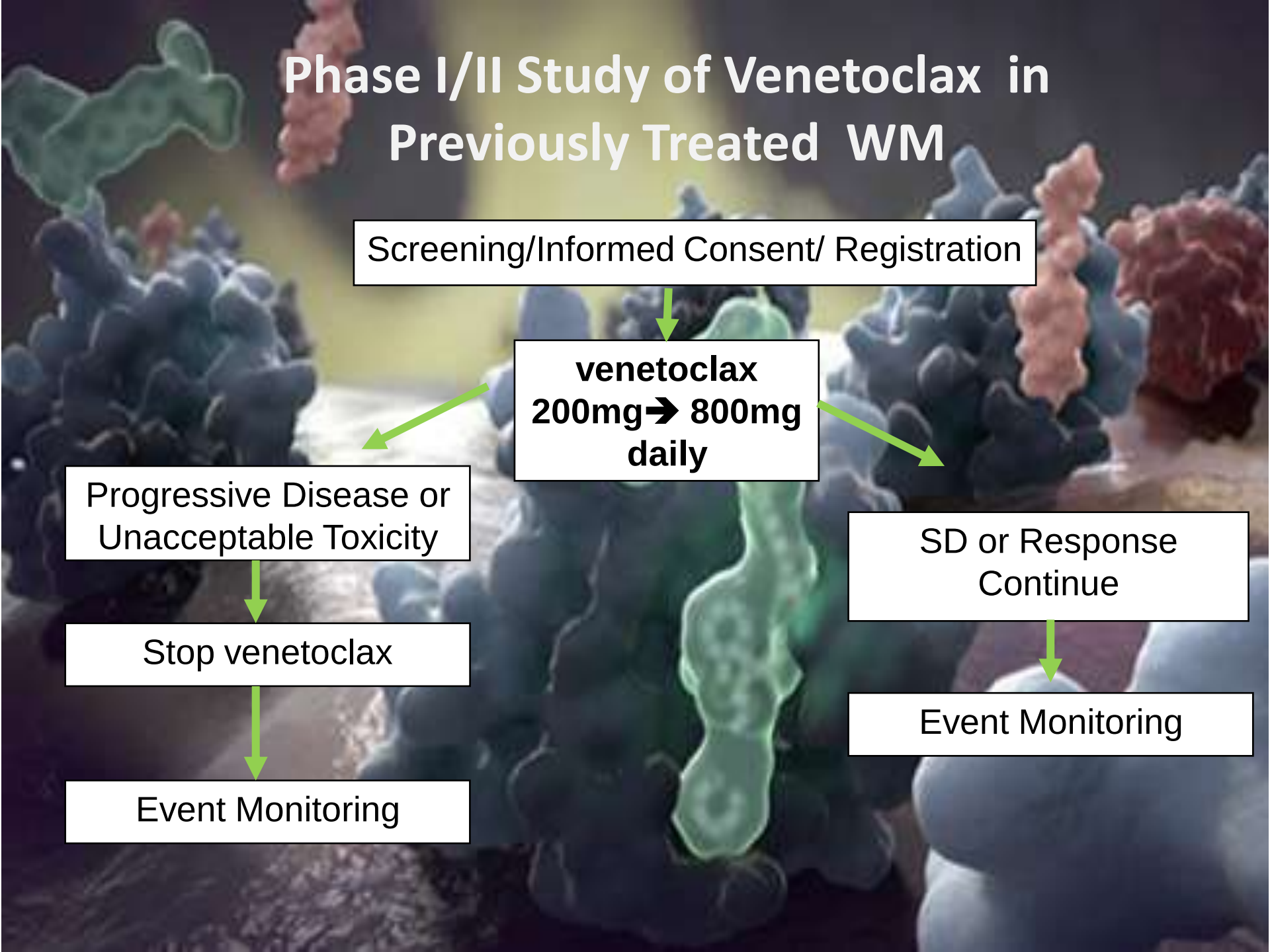
Davids et al., 2016 (in revision)

As of September 15, 2015

Is venetoclax safe and effective in patients with NHL?






Phase I/II Study of Venetoclax in Previously Treated WM
Screening/Informed Consent/ Registration
venetoclax 200mg➔ 800mg daily
Progressive Disease or Unacceptable Toxicity
Stop venetoclax
Event Monitoring
SD or Response Continue
Event Monitoring

Stem cell transplantation

Autologous: own stem cells

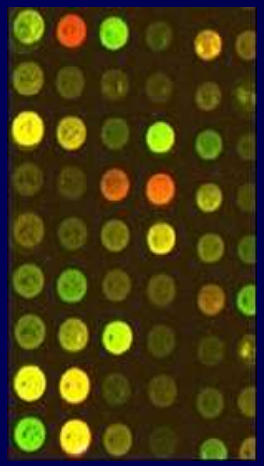
Allogeneic: donor stem cells

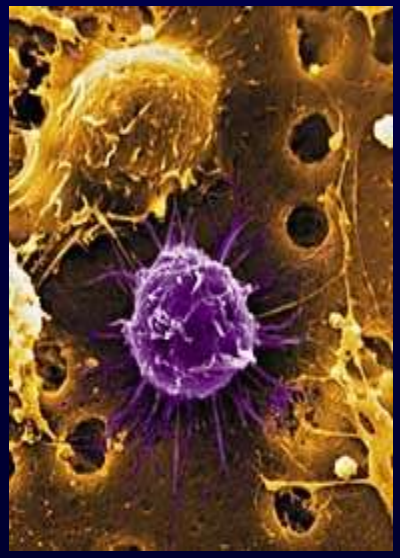
Only a small percentage of patients is eligible (very young, fit, unresponsive to other treatments)

Conclusions

- Lots of new and hopeful developments
- More knowledge of the biology of the disease is crucial →
- New targets for treatment
- More possibilities for treatment in the context of clinical trials
- In the Netherlands:
  - ↗ HOVON124 (ixazomib)
  - ↗ BGB-3111 vs ibrutinib (phase III)
- Collaboration enormously important:
  - ↗ With other countries (ECWM)
  - ↗ With patient organizations (Hematon, EWMN, IWMF

Future…





‘’Targeted therapy’’

Treatment adjusted to patietnt/disease