EHA 2018

Sekwencjonowanie następnej generacji (NGS)

- Metoda, która rewolucjonizuje diagnostykę molekularną, gdyż umożliwia uzyskanie sekwencji DNA za stosunkowo niewielką cenę i to ocenę całego genomu, a nie pojedynczych genów, a nawet genomów różnych komórek w tym samym materiale.
- Obecnie nie jest jeszcze wykorzystywana rutynowo w diagnostyce, ale już dostarczyła informacji rewolucjonizujących nasze rozumienie nowotworowych chorób krwi.

Co wykryto NGS?

- CHIP: clonal hematopoiesis of indeterminate potential: 10% zdrowych (z prawidłową morfologią krwi) 70-latków posiada komórki z mutacjami powodującymi ostre białaczki szpikowe, a 30% 100-latków. Te osoby mają 1% ryzyka rocznie rozwoju takiej białaczki.
- Nowotwory krwi okazały się być zróżnicowane nie tylko pomiędzy poszczególnymi chorymi, ale także wewnątrz jednej osoby. Inaczej mówiąc, okazało się, że u jednego chorego na ostrą białaczkę szpikową może współistnieć kilka spokrewnionych ze sobą, ale różnych ostrych białaczek szpikowych.

Sulima SO ribosomal lesions promote oncogenesis

- 2 subunits in each ribosome
- Ribosomopathies DBA, SDS – tendecy for leukemic transformtions
- Neoplastic T-ALL have higher mutational burden of ribosomal genes and CLL as well, this is related to oxygen stress\
- Cellular stress promotes mutagenesis

Vendetti-genetics of AML

- Median age of de novo AML with sAML feature increases with age – more frequent at 60-65
- Minimal residual disease free CR as new category of remission
- How to test this? Future is NGS,. For low risk core binding factor, NPM , in other flow cytometry

Haferlach T: MRD

- Cytogenetics or FISH not suitable for MRD
- Flow cytometry: two approaches: different from normal and leukemia associated phenotypes Blood 2018 january 12
- Chimerism: 17 loci sensitivity 1-5% not good for MRD
- SNP profiling: 24 SNPs for diagnostic use
- RQ-PCR
- Digital PCR sensitivity 0,05% for TP53
- NGS

Haferlach

- Hem-Panel for NGS 64 genes
- NGS-UMI (unique molecular identifiers) some errors to be eliminated by controls (polymerase errors)
- Digital Error Suppression
- Sensitivity markers Grimwade D Blood 127: 75 different molecular subgroups
- Jongen-Lacrencic M NEJM 378,1189
- Schuurhuis G, Blood 131,1275: do not use single marker, MRD shoud be tested prior and after tx

Haferlach

- Quantitation of NGS for MRD
- 38% of aloTx in Europe for AML
- Consider MRD already before Tx, MRD in all future trials

Lowenberg treatment of the de novo AML

- 7+ 3 variations in dauno 3 x 90 dose or ida
- Suggests dauno 80-90 or ida 12
- AraC 1000 with increased toxicity without benefit
- Additions: GO
- CPX-351
- Post remission: chemo 43 %, auto 9% (low risk), allo rest
- Role of previous CHIP in recurrence? No they dont predict for the relapse
- Other non DTA mutations very predictive of relapse

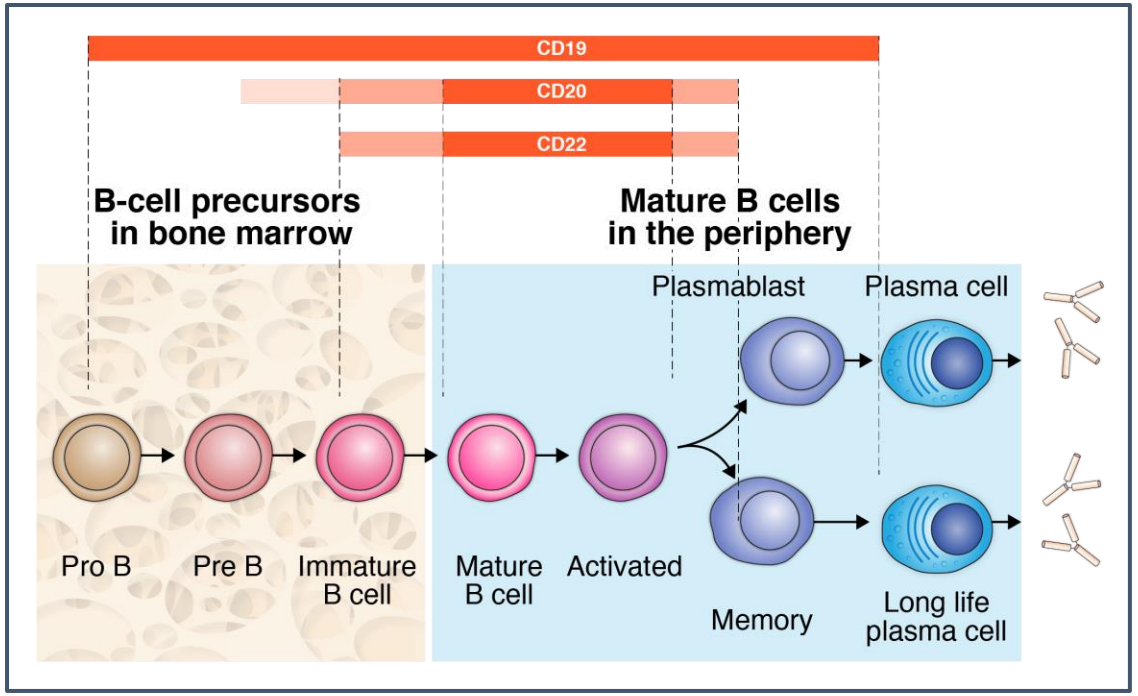
Lowenberg

- IDH as a target for therapy – 10% of patients
- AG-120 (IDH1) and AG221 (IDH2) – IDH inhibitors
- In order to perform study there is a need to screen 7000 pts within 72 hrs to find 500 IDH+ pts to perform randomized trial

Cortes J: secondary AML

- About 25% of AML pts
- Poor outcome, more frequent p53 mut than in de novo pts

Rationale for Targeting CD19 for the Treatment of B Cell Malignancies

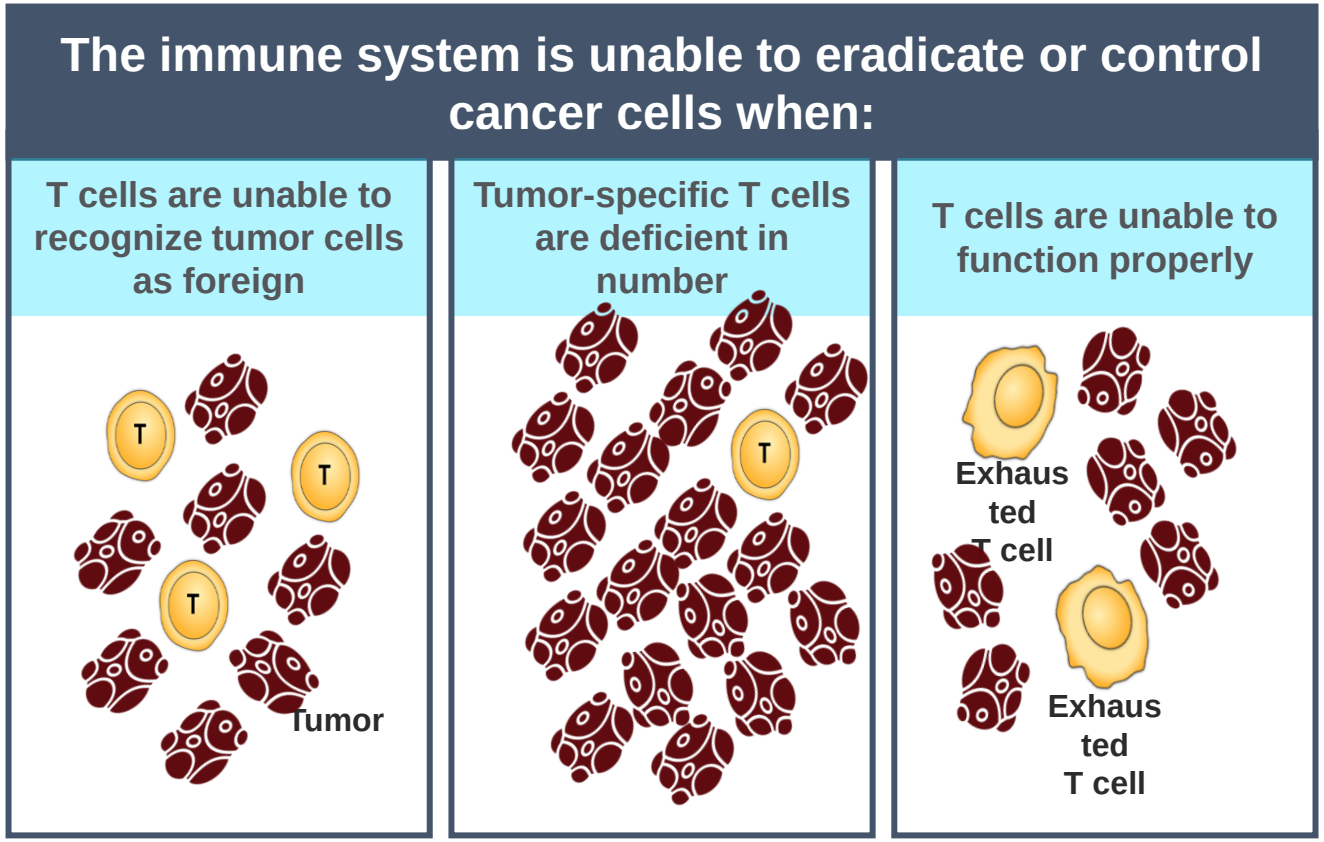


- CD19 is present almost throughout the entire B cell maturation process[1]
- CD19 is present in most B cell leukemias and lymphomas but not in any normal tissue other than the B cell lineage[2]

CAR=chimeric antigen receptor; CD=cluster of differentiation.

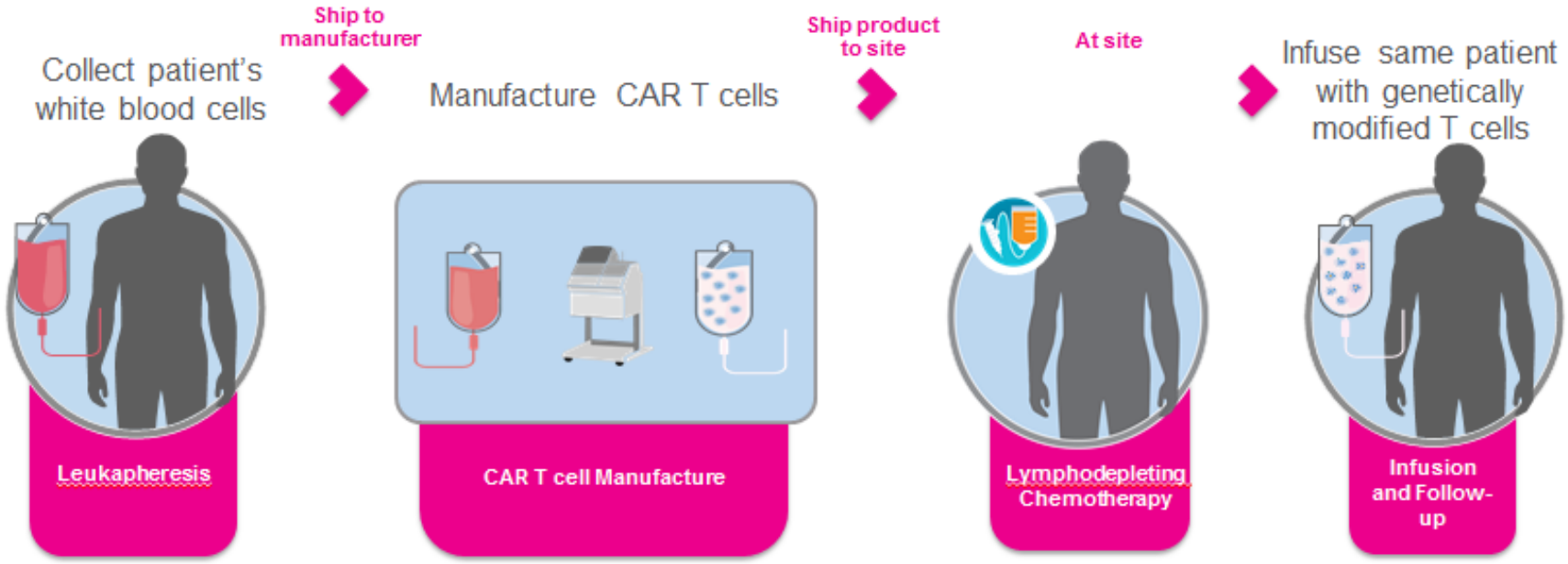
1. Giraldo WAS. Rheumatol Clin. 2012;8(4):201-207. 2. Sadelain M, et al. Cancer Discov. 2013;3:388-398.

Tumor Development Involves Evasion of Immune Surveillance



1. Sharpe M, Mount N. *Dis Model Mech*. 2015;8:337-350.

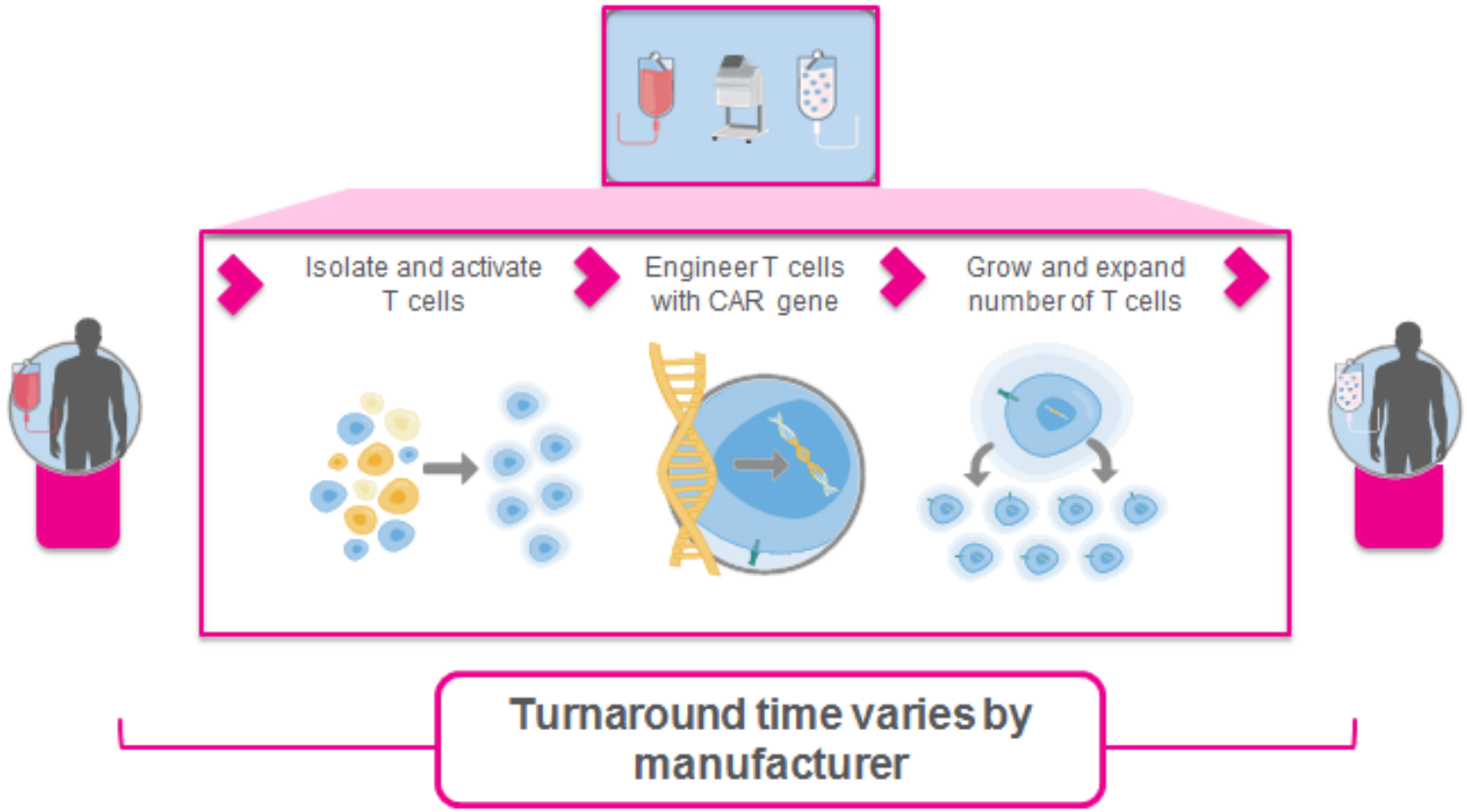
Overall Patient Flow and CAR T Cell Therapy Schedule



- CAR T cell therapy is a "*living therapy*"[1]
  - Different in development and properties than conventional drugs[2]

1. https://www.cancer.gov/about-cancer/treatment/research/car-t-cells 2. Kaiser AD, et al. *Cancer Gene Therapy*. 2015;22:72-78.

CAR T Cell Manufacturing Starts with a Patient's Own T Cells



CAR-T: Salles G

- Massive proliferation after infusion
- Cy-Flu as conditioning
- Neurological toxicity
- B cell depletion
- anaphylaxis./allergy
- CRS
- Insertional mutagenesis?

Rives Sys

- Case of 24 female 2nd relapse after alo-HCT
- Cy 2 da x 500 mg/m^2
- Flu 30 for 4 days
- HHV-6 encephalitis
- 9 months after CD19 negative relapse and death
- Another case CR, MRD 0,2%
- CR after CAR-T but lost CAR-T after 4 months than HCT now 3 months after and fine

- 3rd case did not get –manufacturing failure
- 26yr old woman
- 4thcase 13 yr old no complications surviving
- ELIANA trial 8% manufacturing failure
- IVIG replacement (B cell aplasia)
- Better tolerance than alloHCT

- DLBCL trial JULIET CTL0198 patients 2 sites Lyon and Nantes

Dombret

- Survival for RR ALL 5.8 mo if without salvage CR rate 40%, later salvage may produce CR but in decreasing frequency
- Post relapse alloHCT 35% surv, w/o allo less than 10%
- So alloHCT standard of care
- Three new options: inotuzumab ozogamicin (Besponza), blinatumomab (Blincyto), CAR-T (Eliana trial –children)
- Diffrent pts populations: best in inotuzumab, worst in CAR-T
- In ELIANA study 25% failure compared to screened pts.

Topp

- CR in blina 45% vs 25%, among CR 70% MRD-
- 3.7 months longer OS, in 1st salvage 5 mo better
- Some CRS in blina but more infections in chemo
- Better quality of life for blina
- Ino 36% CR incl 78% MRD-, but VOD in some pts
- CAR-T: 54 of enrollled 83 pts receive therapy, ORR 53%, MRD- in 75% HSCT in responders 40%, CRS in 80%, neurological in 40%
- JCAR015 trial phase 1: 55 adults, phase 2 stopped after 2 deaths

Topp

- Allo after blina OS 15.9 mo for >30, not reached for <30
- Allo after ino OS 9,2 mo, 19% VOD
- Allo after CAR surv 5 out of 17 no effect on survival in small number
- Late relapse

Dombret

- Patient with persistent MRD: 3 method, Flow and PCR and RQ PCR
- MRD strong prognostic factor
- Other high risk genetic factors KMT2A rearrangment
- Ph-like ALL may response to some TKIs
- Options for MRD+ pts : intens chemo, TKIs, all, blina, CART
- BLAST study : blina in MRD+ pts –FDA registered (1st approved for this situation)
- CAR-T cells in these patient: also in about 40% pts

Bassan

- Case of T(v;11)/KMT2A rearranged ALL (other t(4:11)+ ALL) – very high risk
- CR but high MRD level 10-4, early allo HCT MUD, day +60 still same level MRD – tapering CyA and than MRD negative day +120 but afet 1 month again 10-4 – relapse – blina relapse – DLI - neg

Boissel N small molecules

- Case B-ALL, no response to prenisone prophase, Induction FRALL-2000: Fusion NUP214-ABL1 (6% of pts in T-ALL less than 5% in B-ALL)
- Ph-like ALL and age: an AYA disease? Also in such cases Icaros deletions
- 85% MRD+ Ph-like, poor outcome, also IKZF1
- CRLF2 deregulation 50% in Down syndrome
- CRLF2 50% , ABL1 Fusion, JAK2, but more than 50 different alterations
- Case got imatinib, than blina than haplo maintenance with dasa

Cornelissen

- GvL is similar in MRD+ and MRD- patients
- Prep for allo: risk vs advantage: risk of relapse different in different cytogenetic groups but allo reduces equally in all of them.
- HLA disparity increases non-relapse mortality but overall the results are similar for all kinds of donors
- MRD: measurable residual disease
- MFC+ higher risk of death Nat Rev Clin Oncol 2017
- Versuis JCO precision Medicine
- MRD+ (<4lof red) subgroup of non-favourable who may benfit from Tx

Cornelissen

- increased HLA disparity not valid for cord blood
- Early CD4+ recovery controbutes to antileukemic activity
- Individual decision on tx based on: AML risk classification, response to therapy and MRD, non relapse mortality

Craddock C

- >80% relpases withinn 1 yr aftr Tx
- MRD critically important for relapse risk
- Intensity of conditioning critical
- Intensity of posttransplant immunosuppression determines relapse risk afeter MAC conditioning
- Pts receiving CPX did better after tx than pts receiving DA
- Three RCT comparing
- MAC vs RIC
- German study: no difference

Qazilbash M

- BuMel (140) vs Mel200 in MM randomized 104 vs 100
- Longer PFS (particularly high risk) no longer OS
- 1/3 high risk 1q gain most frequent in both gropus

Dreger P

- Haplo vs alloMSD for DLBCL 132 vs 525 pts
- Less chronić GvH for haplo
- No difference in NRM
- No difference relapse/progression
- PFS the same

Precision Medicine plenary

- Stages: driver muta. Ident. Describing and
- 10-20 drivers in average lung cancer 20 000 point mutations 100 coding mutation
- SF3B1 obvious driver mutations, and passenger mutations
- Complexity of structural variations
- Patterns of driver mutations in AML there are genes that go together

Liu F… and Yupo Ma

- CAR-T in AML (
- Target antygen expression is critical for CAR-T cell therapy
- CD33 and CD123
- CLL1 and CD33b compound CAR T cells
- Lymphodepletion with cy 3 x 500 mg/m^2/ flu 3 x30/m^2 mg prior
- Performed as a bridge to tx

Goede V obinutuzumab CLL11 trial

- Elderly (over 70 yrs)
- Obinutuzumab + chlorambucil vs R-Cl vs Cl alone
- Were same fatal cases in both arms incl second malignancies in MoAb arms
- 5yr PFS 23 mo for obi and
- OS 66 vs 57 mo, median OS for obi not reached

Vinchi F

- M1 and M2 macrophages
- RBC transfusions induce M2 antiinflammatory macrophages
- Transfusion model in mice
- Heme triggers sterile inflammation by activating M1 macrophes and promote immune tissue damage
- Dual role of iron overload by inducing either M1 or M2 macrophages

Pecquet Ch

- CALR (chaperone) activating mutations in MPN
- Do these mutants require secretory pathway
- CALR signal is required for TpoR activation
- CALR mutants are exposed on cell Surface
- Amegakaryoctic trombocytopenia: complete absence of TpoR
- Cell transformation require cell Surface localization f the tpo R

Vande Donk

- CAR T for MM
- BCMA B cell maturation antygen
- NCI trial 81% response
- Bb2121 BCMA response dose dependent 90% RR
- LCAR-BM
- BiTE Ab are of the shelf
- anti-BCMA antibody conjugated with toxin

Morschhauser F

- lymphoma

Hallek

- 8% of new CLL have TP53 mut, complex karyotype more frequent little overlap
- Stopping clonal evolution: cut the branches, cut the stem
- Idela +R
- Vene + R very impressive results
- CLL2-BAG/BIG/BIO debulking, induction, maintenance
- CLARITY: ibrutynib + venetoclax, starting from ibrutynib alone to debulk and avoid TLS

Hallek

- Still FCR for non mutant patients, BR over 65 yrs of age
- Future: combination of targeted agents

Davies FE biology of myeloma

- Double strand breaks+ risk of translocation Nand mutation
- IgH translocation chromosome 14: 11;14 CCND1
- Hyperdiploid
- Secondary Events: MYC translocations, RAS
- Pawlyn C Nature
- Myeloma genome project Walker Blood 2018: most frquent mutation NRAS and KRAS oncogenic dependencies betwee different genes
- Vene works well t11;14
- Trametinib when RAS pathwy, BRAF with vemurafenib

Davies

- Walker Leukemia 2018. Blood 2018
- TP53 and biallelic mutations define poor prognosis
- Double hit myeloma two DNA-based genomic changes + clinic
- Myeloma cells adopt to the microenvironment: adaptation and survival of the fittest
- Sites of disease evolve independently
- Different site specific clones in different sites

VandeDonk

- Profound immunsuppression
- Elotuzumab SLAMF7 targeted elo-len-dex better than len0dex
- Dara increased CD4 and CD8 T cells and increasingrenzyme in T cells
- Imids cereblon
- Combination better and also poor risk pts benefit but very high risk is better approacjed by bort
- T cells effectively kill myeloma cells

Moreau P

- 8 combinations for RR MM not available in Poland
- OPTIMISMM study (pom comb)
- Maintenance with Len after MEL200
- Different relapse early vs latte
- DaraVd in 1st relapse CASTOR study
- Pom 4 mo better than Len
- Salvage ASCT
- KRd 8 mons in OS over Rd