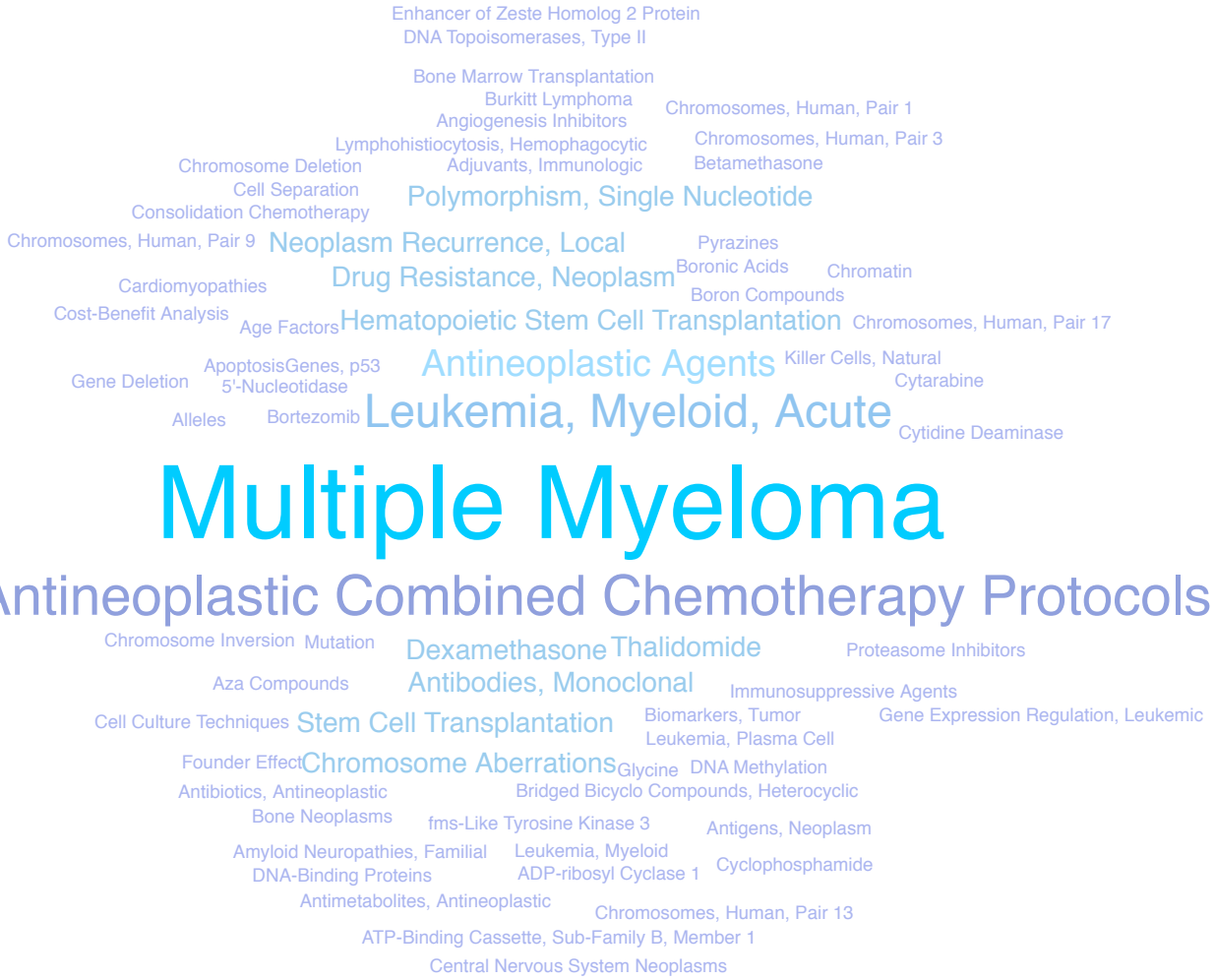
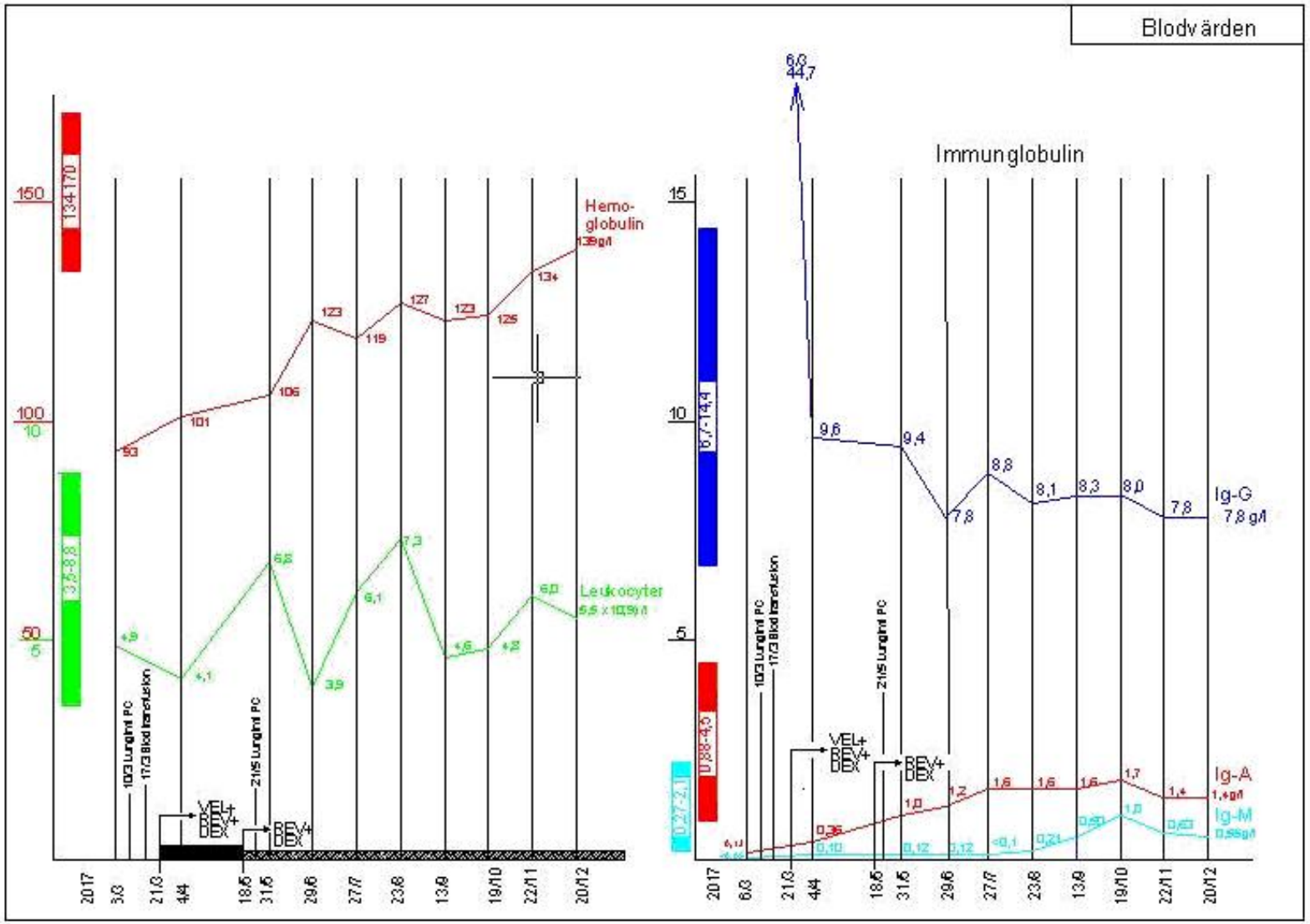

Enhancer of Zeste Homolog 2 Protein
DNA Topoisomerases, Type II
Bone Marrow Transplantation
Burkitt Lymphoma
Chromosomes, Human, Pair 1
Angiogenesis Inhibitors
Lymphohistiocytosis, Hemophagocytic
Chromosomes, Human, Pair 3
Chromosome Deletion
Adjuvants, Immunologic
Betamethasone
Cell Separation
Polymorphism, Single Nucleotide
Consolidation Chemotherapy
Chromosomes, Human, Pair 9
Neoplasm Recurrence, Local
Pyrazines
Boronic Acids
Chromatin
Cardiomyopathies
Drug Resistance, Neoplasm
Boron Compounds
Cost-Benefit Analysis
Age Factors
Hematopoietic Stem Cell Transplantation
Chromosomes, Human, Pair 17
Antineoplastic Agents
Killer Cells, Natural
ApoptosisGenes, p53
Gene Deletion
5'-Nucleotidase
Cytarabine
Alleles
Bortezomib
Leukemia, Myeloid, Acute
Cytidine Deaminase
Multiple Myeloma
Antineoplastic Combined Chemotherapy Protocols
Chromosome Inversion
Mutation
Dexamethasone
Thalidomide
Proteasome Inhibitors
Aza Compounds
Antibodies, Monoclonal
Immunosuppressive Agents
Cell Culture Techniques
Stem Cell Transplantation
Biomarkers, Tumor
Gene Expression Regulation, Leukemic
Leukemia, Plasma Cell
Founder Effect
Chromosome Aberrations
Glycine
DNA Methylation
Antibiotics, Antineoplastic
Bridged Bicyclo Compounds, Heterocyclic
Bone Neoplasms
fms-Like Tyrosine Kinase 3
Antigens, Neoplasm
Amyloid Neuropathies, Familial
Leukemia, Myeloid
Cyclophosphamide
DNA-Binding Proteins
ADP-ribosyl Cyclase 1
Antimetabolites, Antineoplastic
Chromosomes, Human, Pair 13
ATP-Binding Cassette, Sub-Family B, Member 1
Central Nervous System Neoplasms

# Acknowledgments


Blodvärden
Hemo-
globulin
Leukocyter
Immunglobulin
Ig-G
7,8 g/l
Ig-A
Ig-M
VEL+
BEV+
DEX
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21/3
4/4
18/5
31/5
29/6
27/7
23/8
13/9
19/10
22/11
20/12

# Multiple Myeloma

## Risk Factors and prognosis studies though different databases

REGIONALT CANCERCENTRUM SYD

**Outcome and survival of myeloma patients diagnosed 2008-2015. Real-world data on 4904 patients from the Swedish Myeloma Registry.**

**Incidence, characteristics, and outcome of solitary plasmacytoma and plasma cell leukemia. Population-based data from the Swedish Myeloma Register.**

International Myeloma Working Group
A RESEARCH DIVISION OF THE IMF

**Propensity score matching analysis to evaluate the comparative effectiveness of daratumumab versus real-world standard of care therapies for patients with heavily pretreated and refractory multiple myeloma.**

**Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study.**

**IMWG consensus on risk stratification in multiple myeloma.**

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

**Regional differences in the survival of patients with MM in Sweden.**

OWN

**15 different articles**

# Multiple Myeloma

## Chromosomal aberrations

**2009** **The prognostic significance of 8p21 deletion in multiple myeloma.**

**2010** **Impact of chromosome 13 deletion and plasma cell load on long-term survival of patients with multiple myeloma undergoing autologous transplantation**

**2011** **Clinical impact of chromosomal aberrations in multiple myeloma**

**2013** **In search of the molecular consequences of 8p21 deletion in multiple myeloma: commentary on Gmidéne et al.**

**2015** **Deletion of Chromosomal Region 8p21 Confers Resistance to Bortezomib and Is Associated with Upregulated Decoy TRAIL Receptor Expression in Patients with Multiple Myeloma.**

**2016** **Proteasome inhibitors and IMiDs can overcome some high-risk cytogenetics in multiple myeloma but not gain 1q21.**

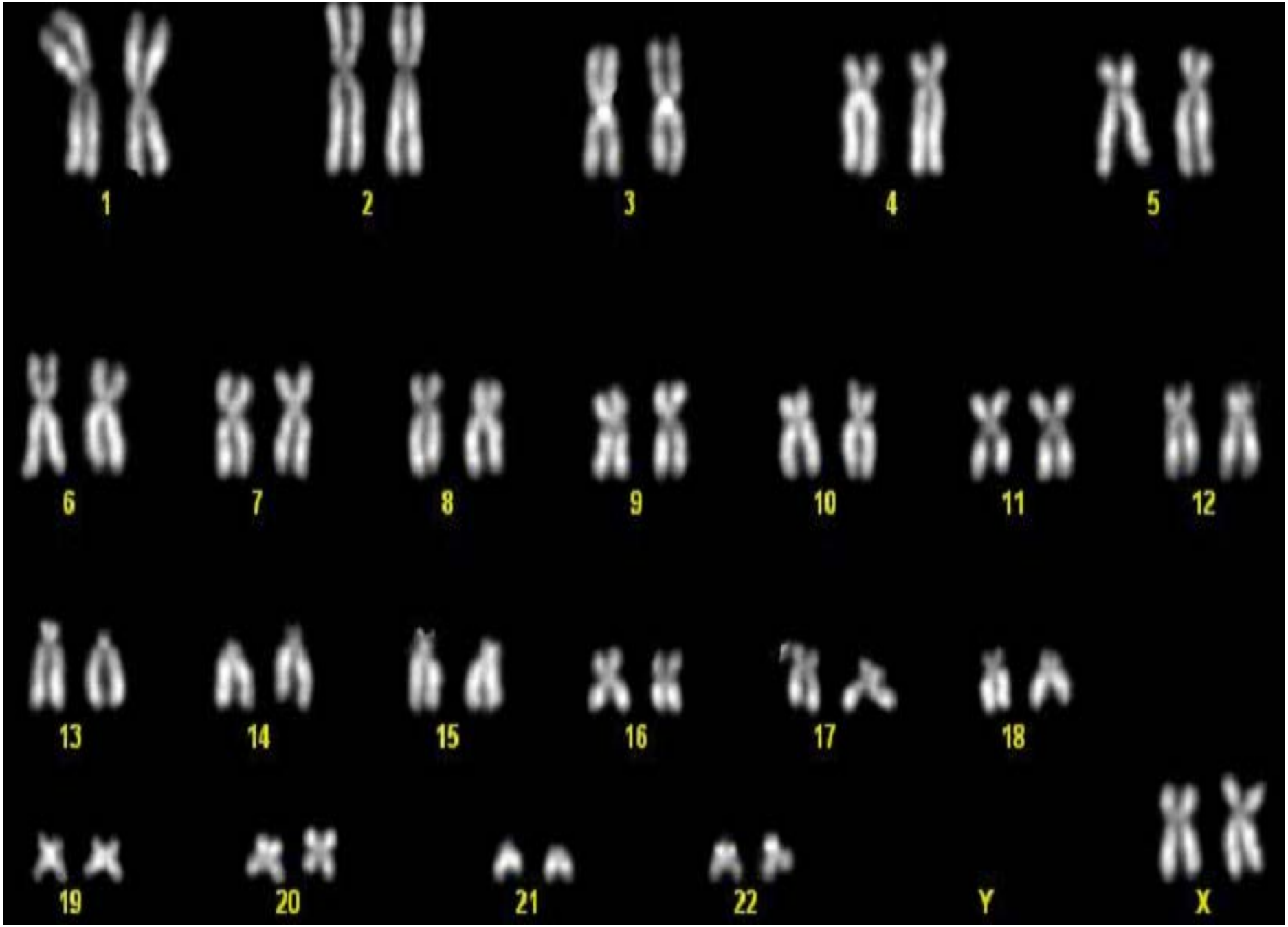

**Variants in ELL2 influencing immunoglobulin levels associate with multiple myeloma.**

**Genome-wide association study identifies multiple susceptibility loci for multiple myeloma.**

**The multiple myeloma risk allele at 5q15 lowers ELL2 expression and increases ribosomal gene expression**

# Multiple Myeloma

Gene regulation, Epigenetic and Genetics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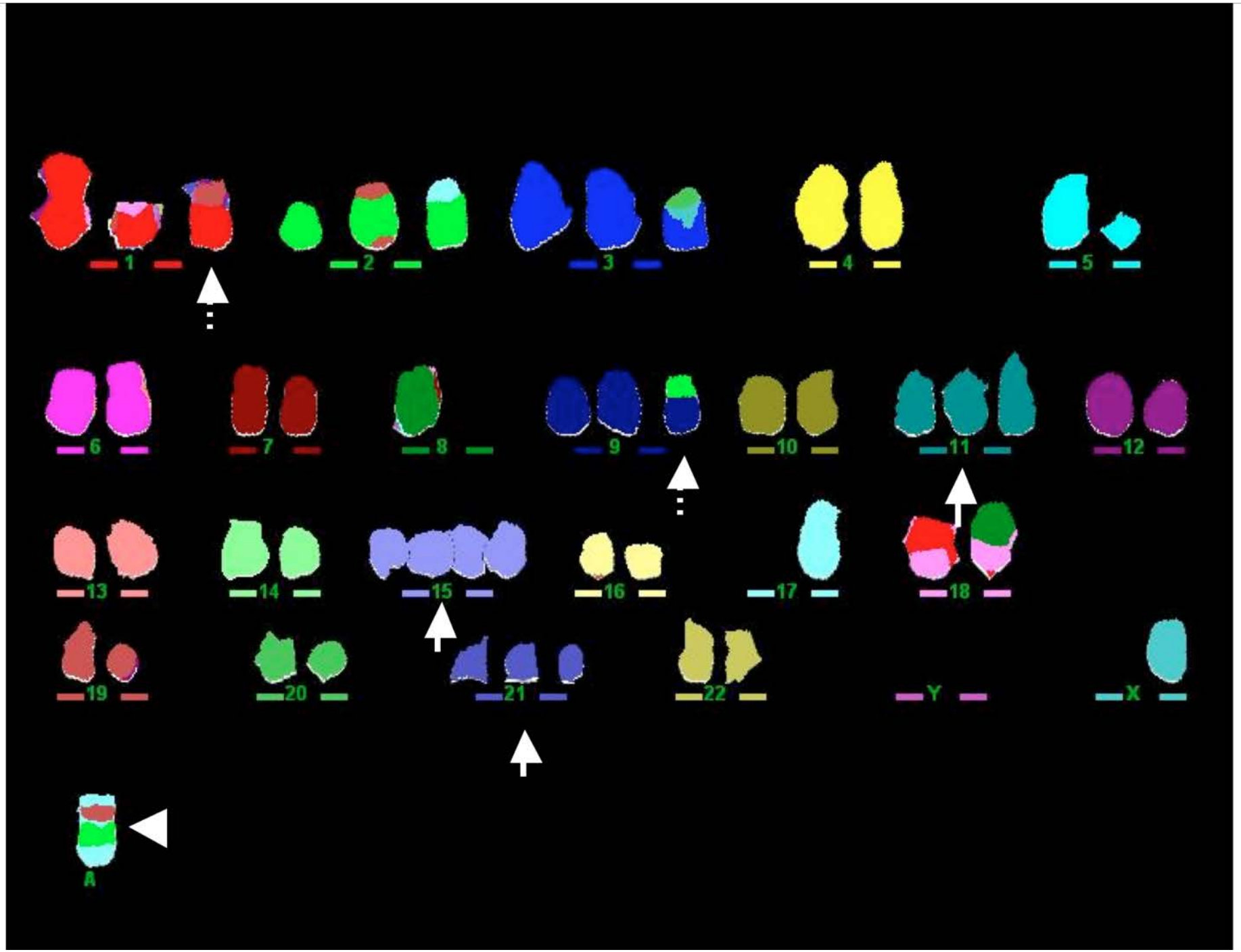
Y
X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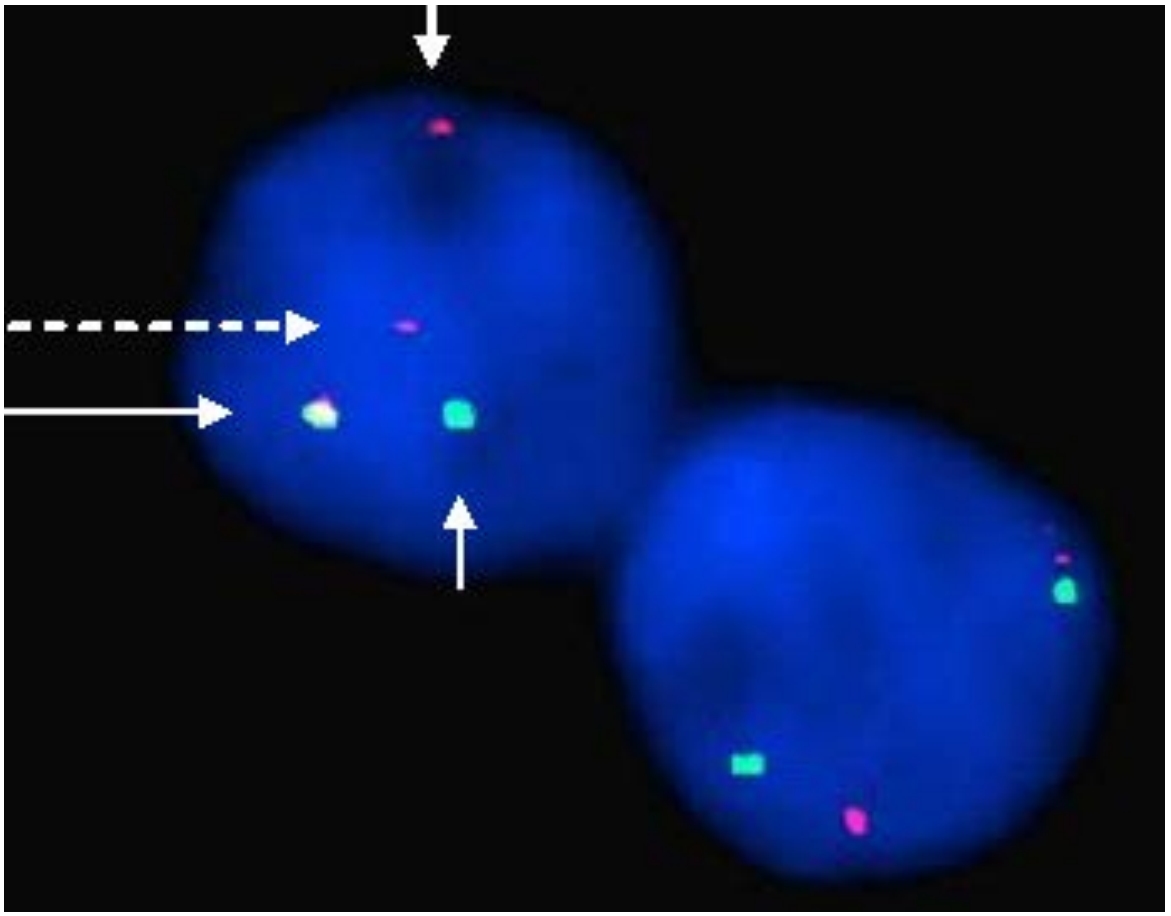
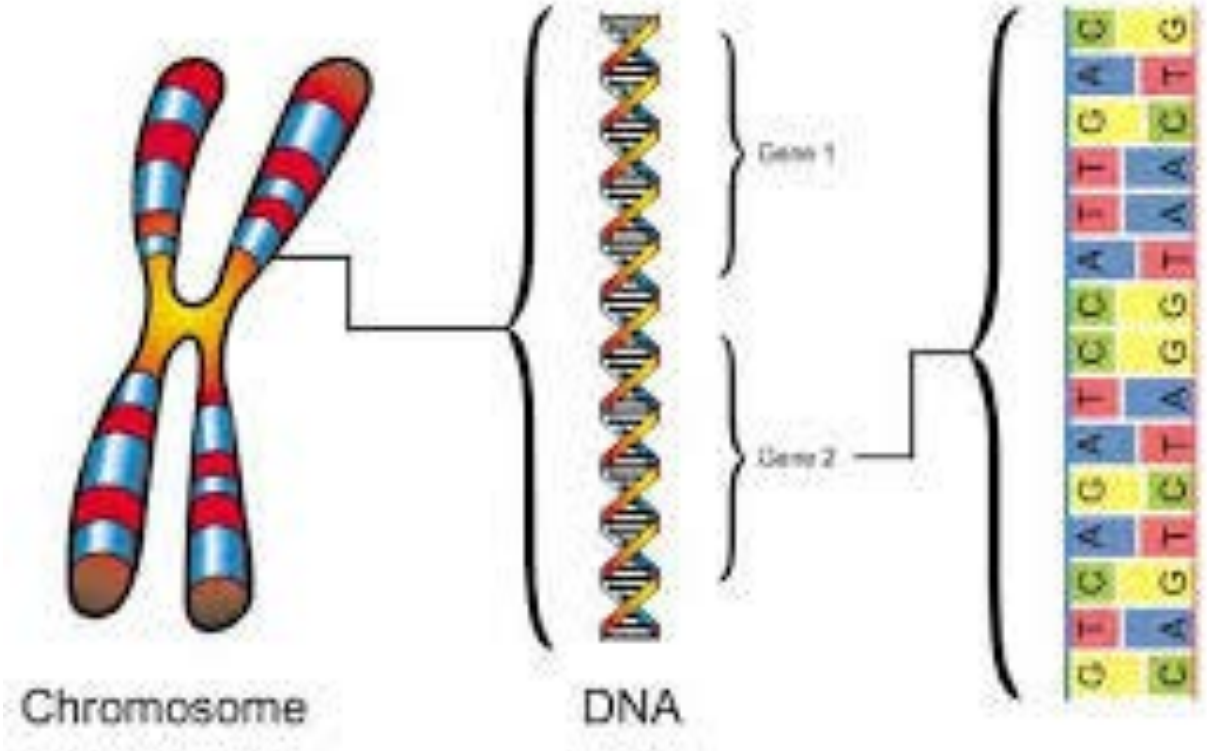
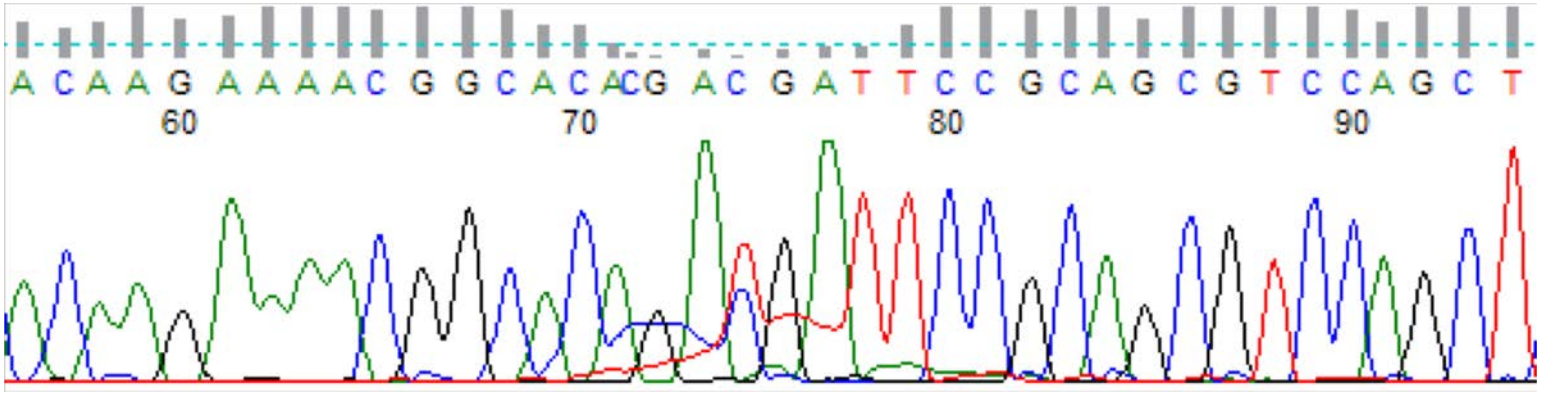


**translocation probe, t(4;14)**

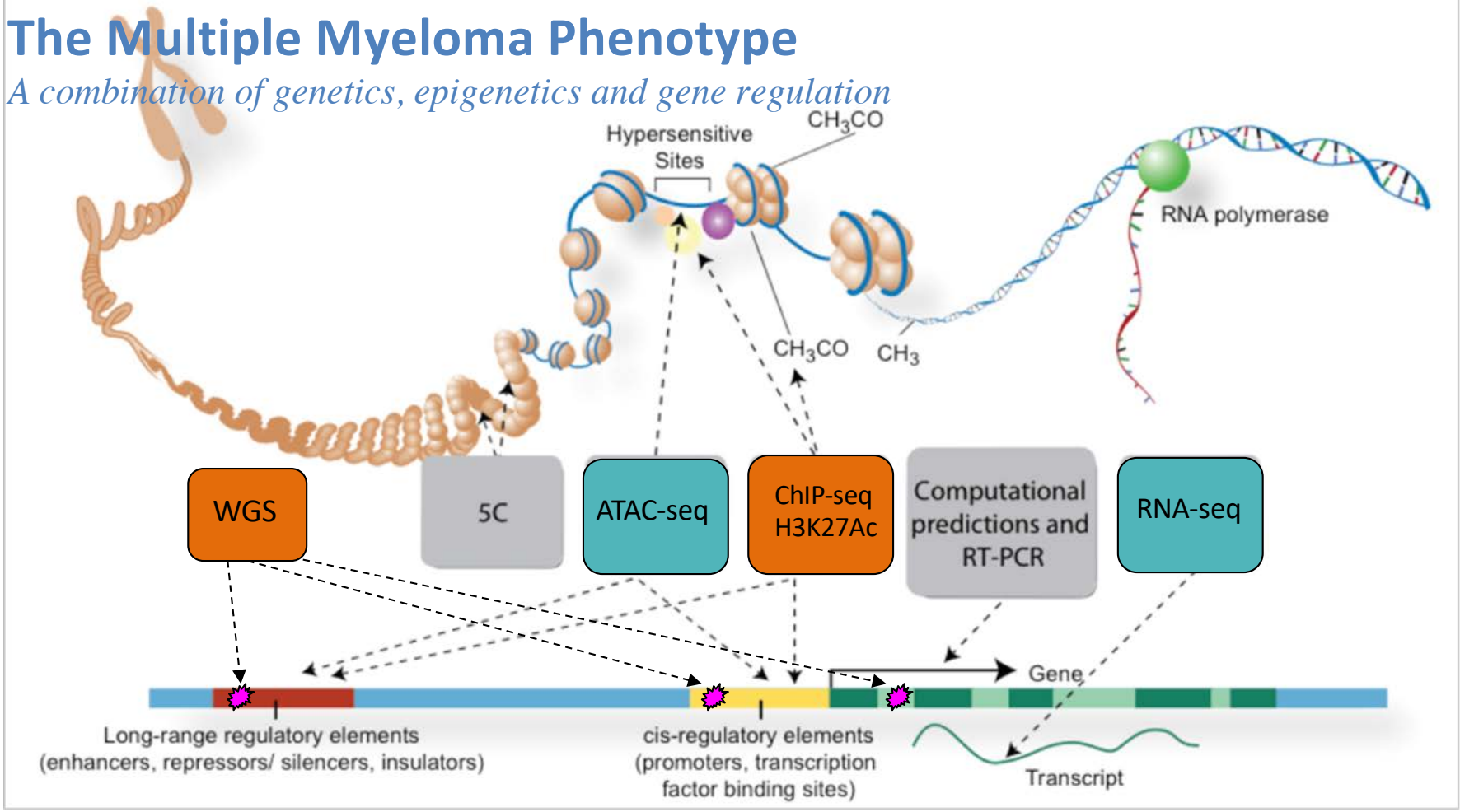



**Genes**


A C A A G A A A A C G G C A C A C G A C G A T T C C G C A G C G T C C A G C T
60
70
80
90

# The Multiple Myeloma Phenotype

*A combination of genetics, epigenetics and gene regulation*

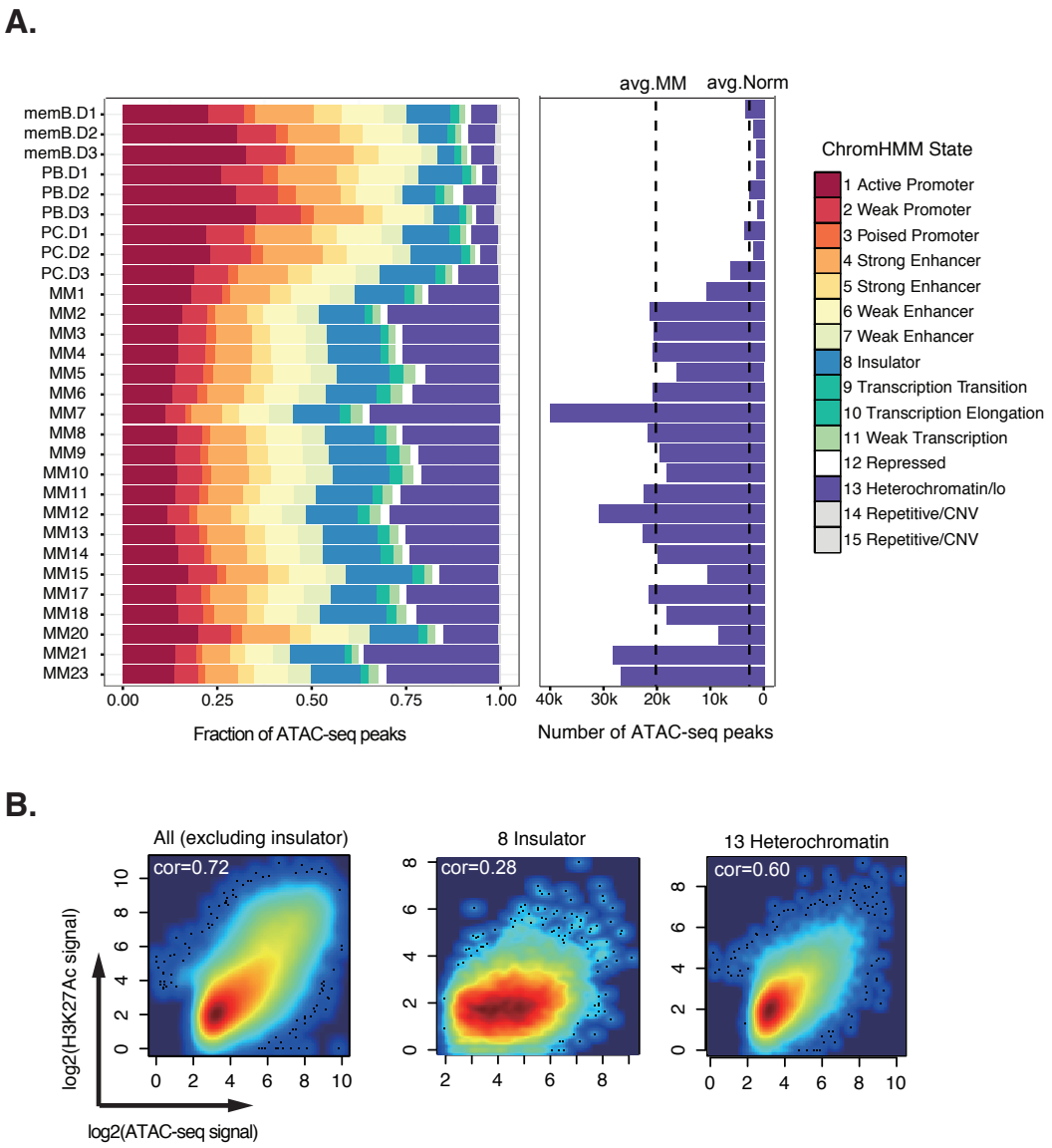



- **WGS:** Mutation identification in coding and non-coding regions
- **ATACseq:** DNA accessibility assay. Identify open chromatin regions
- **ChIP-seq:** Mapping chromatin modifications and regulatory elements genome wide. H3K27ac (active enhancers, promoters)
- **RNA-seq:** Gene expression

Modified from the ENCODE project

# Wide-spread de-compaction of chromatin

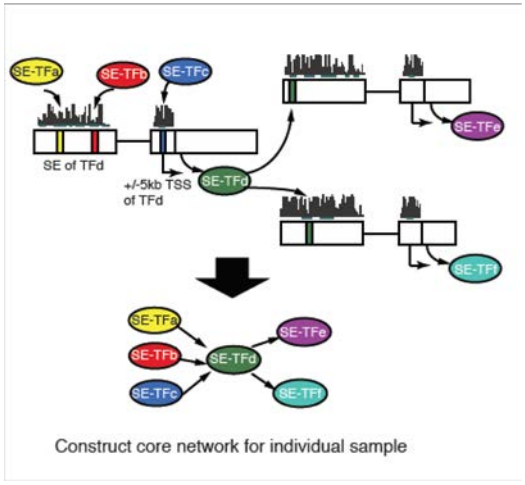
*A novel myeloma specific feature*

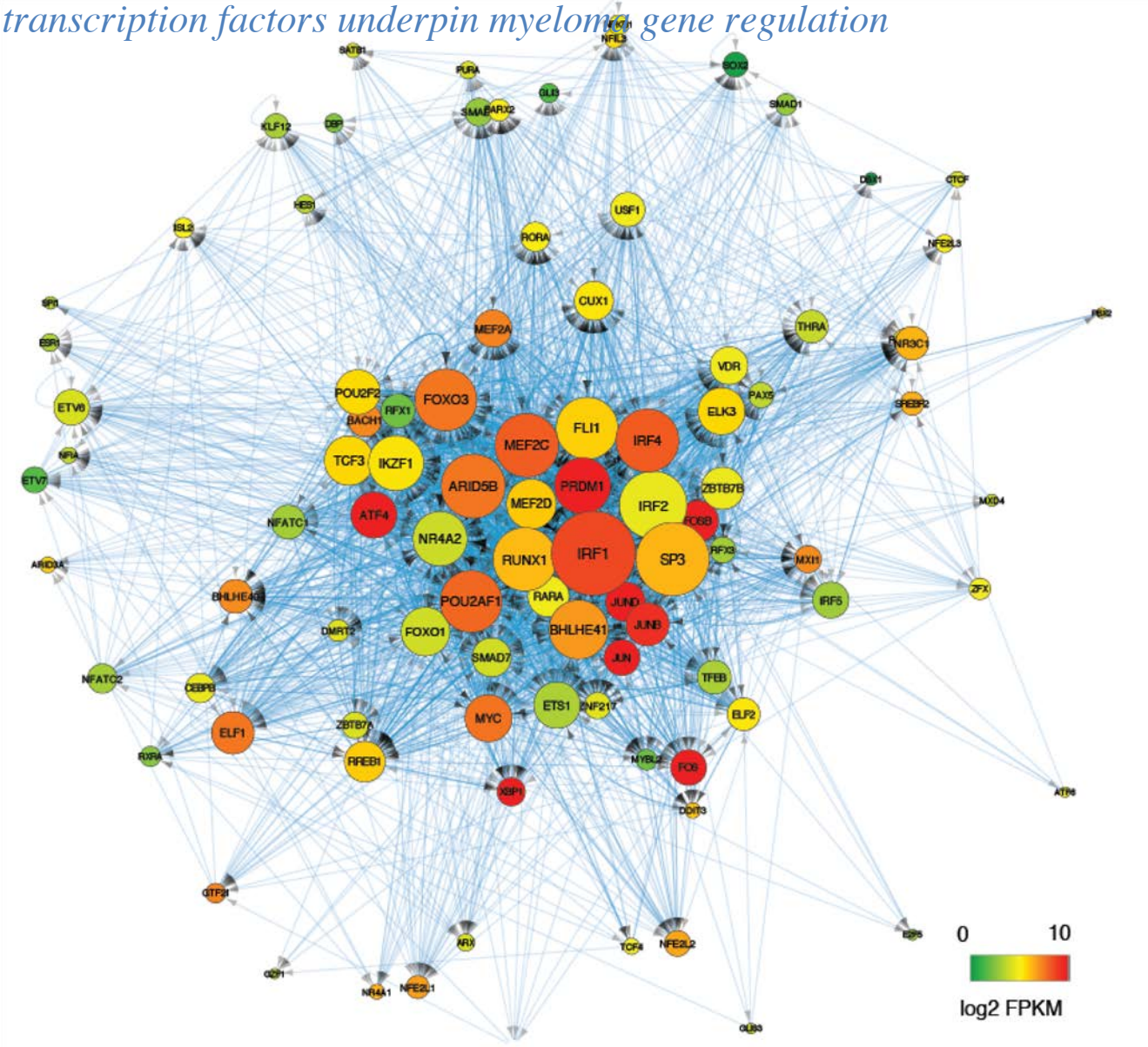



Yi et al., Blood 2018

# The Core Gene regulatory Network

*Super-enhancer regulated transcription factors underpin myeloma gene regulation*



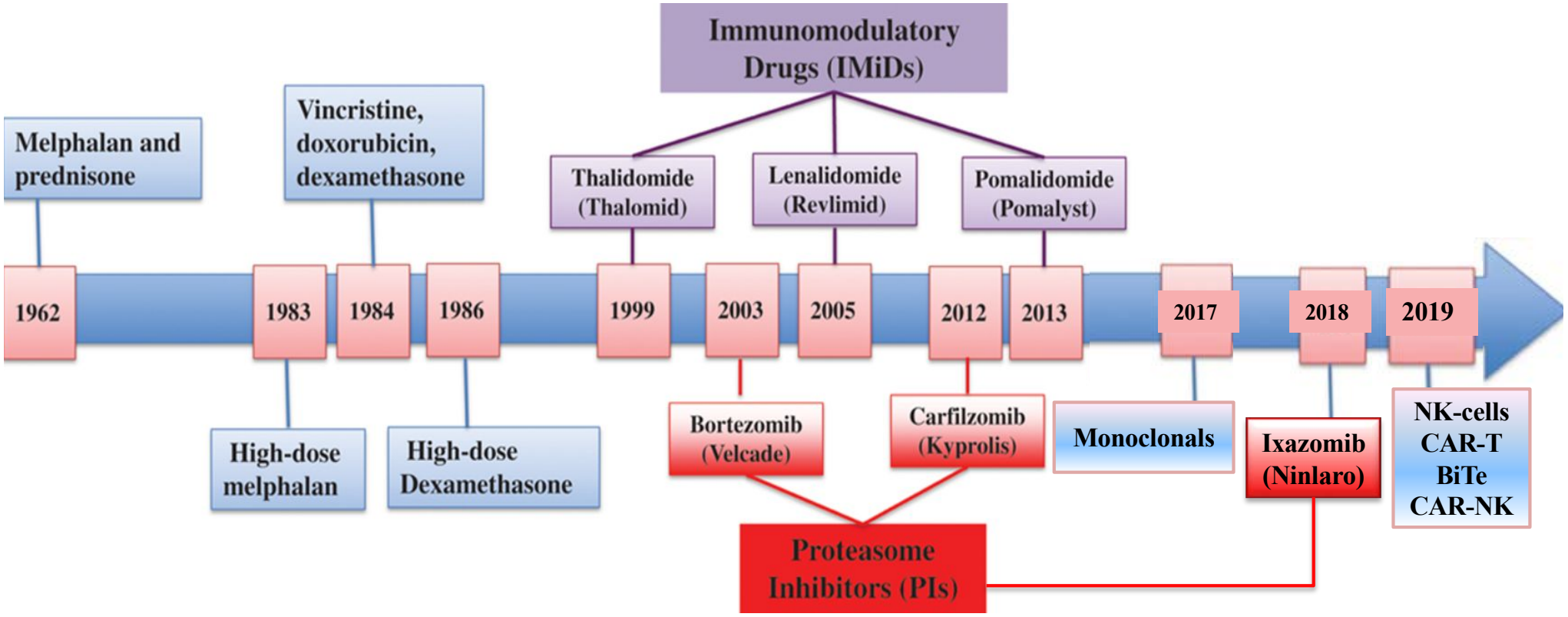



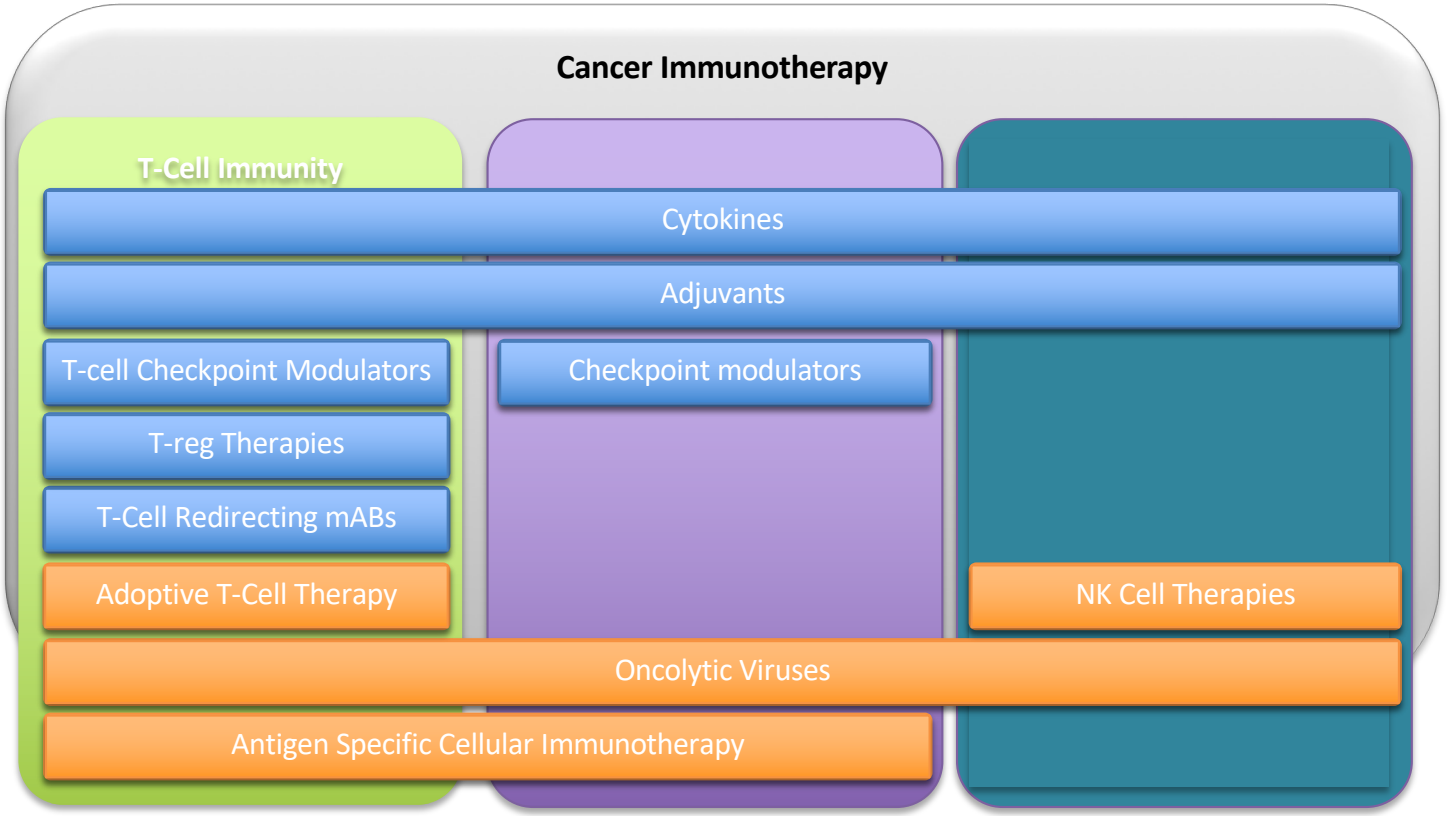

Yi et al., Blood 2018

# Future plans

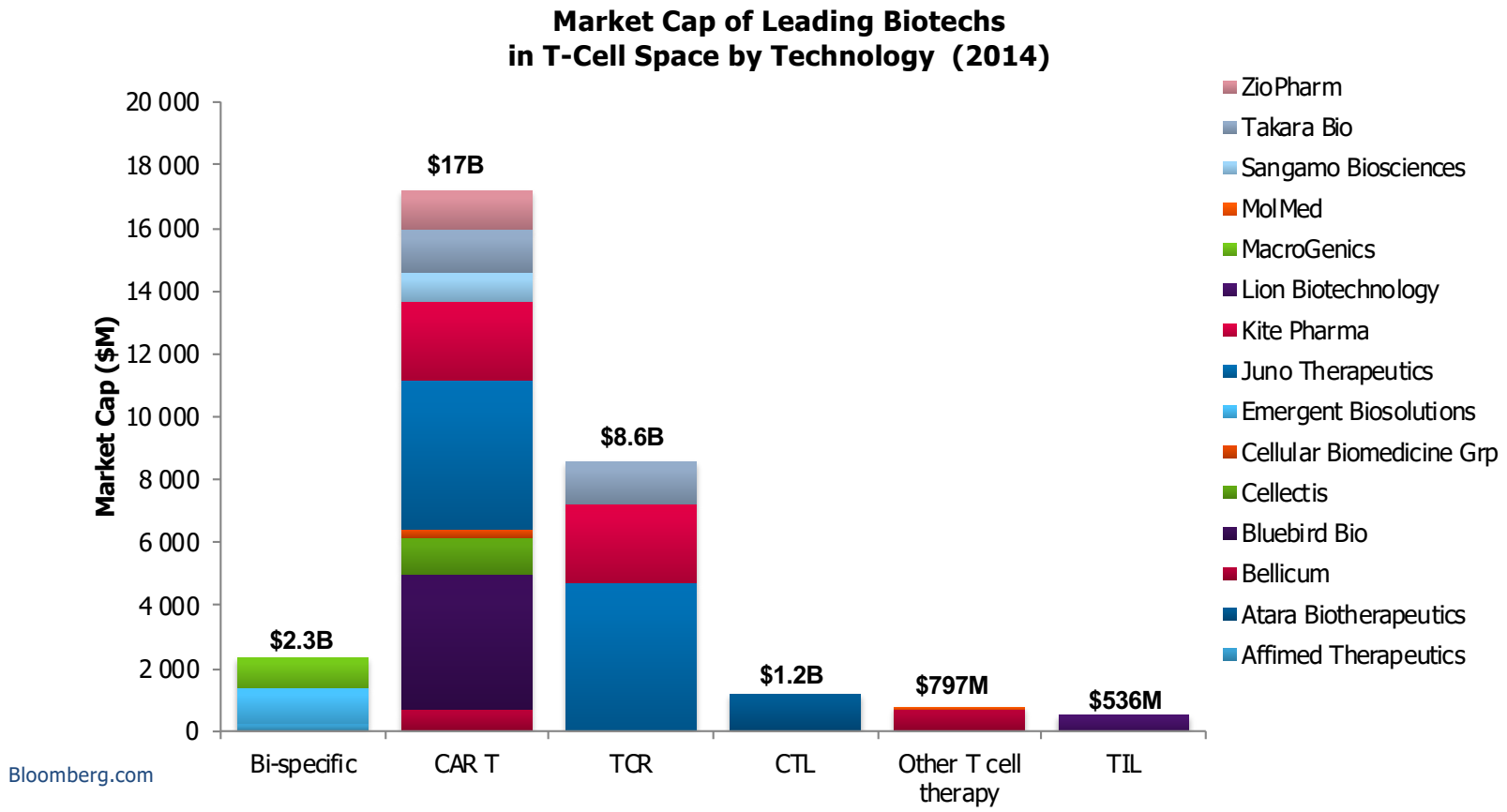
- Replace FISH analysis with phased WGS (10x Genomics Chromium).
- Investigate epigenetic subgroups of MM to identify specific gene regulatory patterns and features.
- Investigate genetic and epigenetic changes connected to relapse and disease progression.

# History + future of drugs in Multiple Myeloma




Cancer Immunotherapy
T-Cell Immunity
Cytokines
Adjuvants
T-cell Checkpoint Modulators
Checkpoint modulators
T-reg Therapies
T-Cell Redirecting mABs
Adoptive T-Cell Therapy
NK Cell Therapies
Oncolytic Viruses
Antigen Specific Cellular Immunotherapy

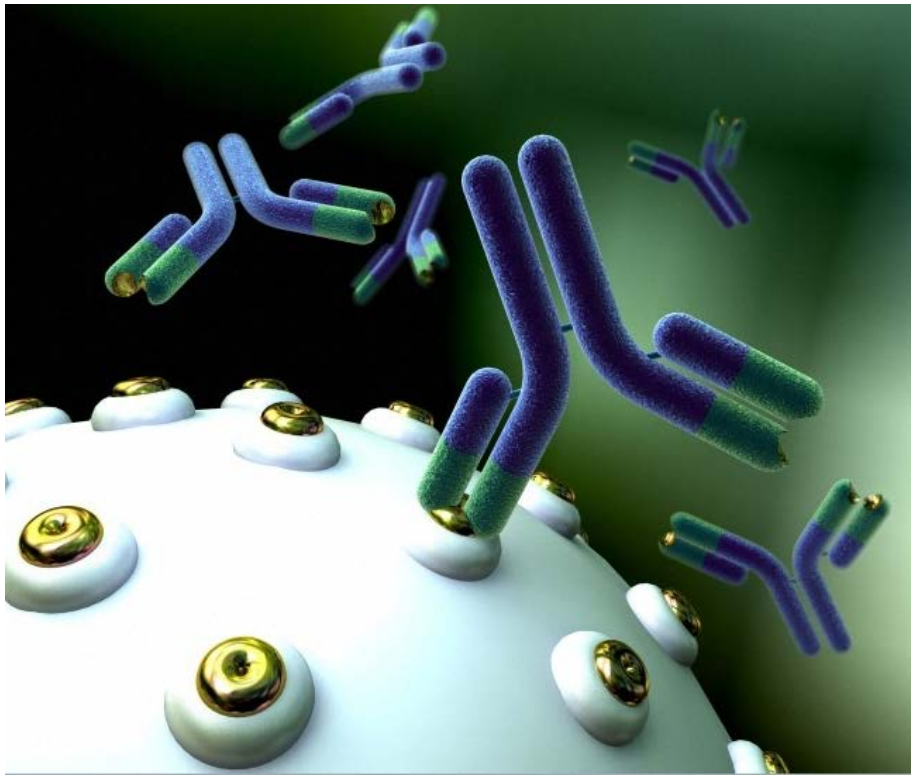
# Cell Therapy Innovators Have Access To Capital for Go To Market Strategy



# Immunotherapies – Hype or Hope?

- Immunotherapies can be a better way of treating cancer.
  - The immune system is specific. It can learn and adapt.
  - Chemotherapy can be toxic and affect the whole body.

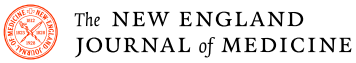
# Antibodies-Antikroppar



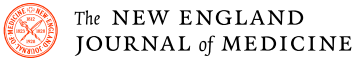
# Multiple Myeloma

## Antineoplastic Combined Chemotherapy Protocols

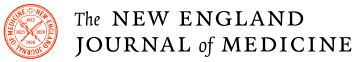
Antibodies, Monoclonal



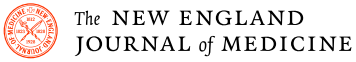
**Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma.**



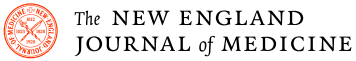
**Dratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma.**



**Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma**

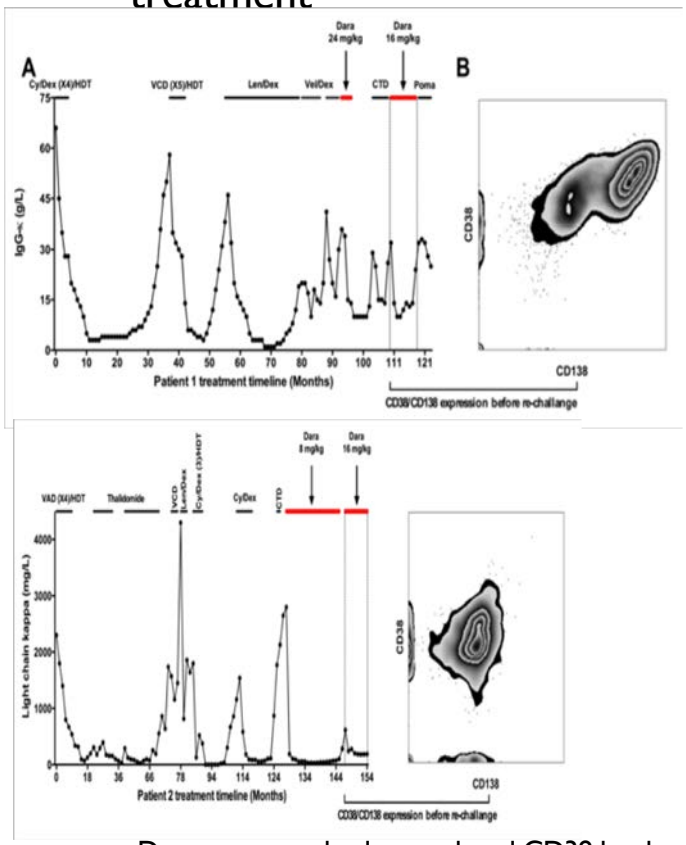


**Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma.**



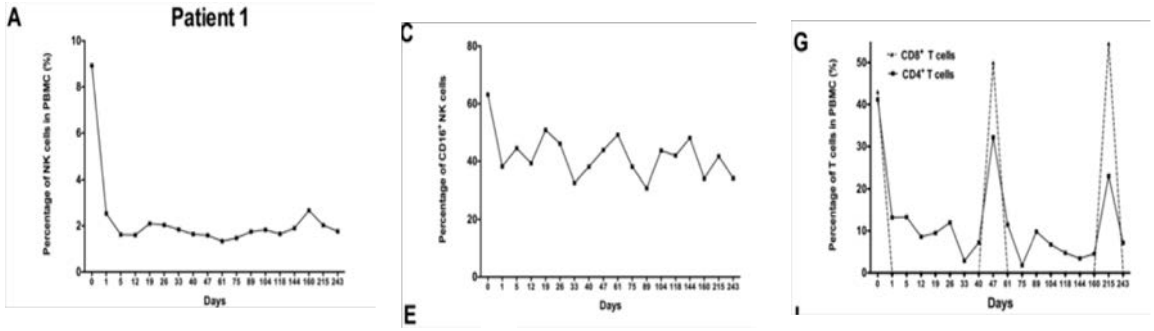
**Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.**

# CD38 expression after Dara treatment




- Dara treatment leads to reduced CD38 levels solely during treatments rechallenging is possible

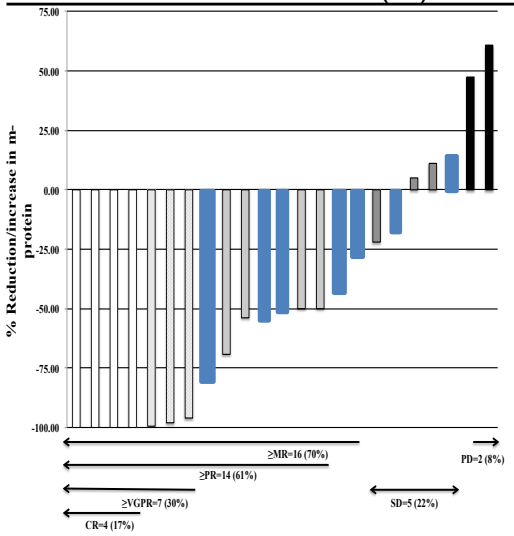
# T and NK cells decrease immediately at Dara infusion



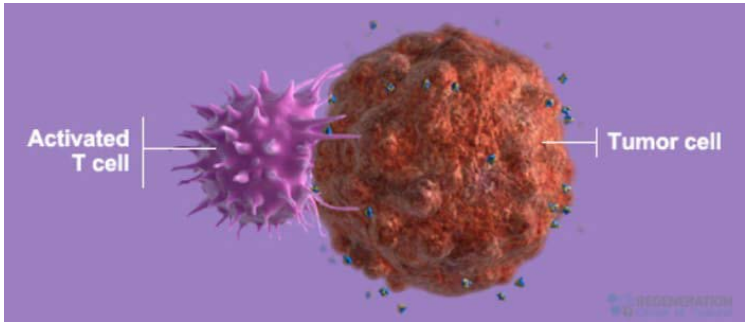

- Numbers of circulating NK cells drop after Dara treatment
- Percentage of $CD16^+$ NK cells are stable
- Decrease in $CD4^+$/$CD8^+$ T cells

# Patient parameters and outcome

| | n or mean (% or range) |
|---|---|
| Total number of patients | 23 (100) |
| Age, mean | 63 (34-82) |
| Gender, female | 6 (29) |
| Viral reactivation | 7 (30) |



# Natural Killer (NK) cells



# Natural Killer cells

NATURAL KILLER CELLS IN THE MOUSE

ADADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen
vid Karolinska institutet offentligen
försvaras i Fysiologiska institutionens
föreläsningssal, Karolinska institutet,
tisdagen den 9 mars 1976 kl. 9

Av
ROLF KIESSLING
Läk. ex.

STOCKHOLM 1976

**Selective rejection of H–2-deficient lymphoma variants suggests alternative immune defence strategy**

Klas Kärre*, Hans Gustaf Ljunggren*, Gerald Piontek* & Rolf Kiessling†

Departments of *Tumor Biology and †Immunology, Karolinska Institute, Stockholm, Sweden

**Metazoan organisms may discriminate between self and non-self not only by the presence of foreign antigens but also by the absence of normal self markers[1]. Mammalian adaptive immune responses use the first strategy, with the additional requirement that foreign antigens are recognized in the context of self-major histocompatibility complex (MHC) products at the cell surface[2]. Aberrant cells which fail to express MHC products adequately can therefore avoid detection[3–5]. A more primitive but complementary defence system, eliminating such cells on the basis of absent self-markers, is suggested by a re-interpretation[3,6] of phenomena associated with metastasis and natural resistance. We now show that murine lymphoma cells selected for loss of H-2 expression are less malignant after low-dose inoculation in syngeneic hosts than are wild-type cells, and that the rejection of such cells is non-adaptive. On the basis of our data, we suggest that natural killer cells are effector cells in a defence system geared to detect the deleted or reduced expression of self-MHC.**

More specifically, the hypothesis[3,6] stated that self-MHC genes influence the expression or recognition of inhibitor signals in interactions between potential target cells and natural effector cells. Our experimental approach was to test the prediction that selection for loss of H–2 in tumour lines should be accompanied by an increased sensitivity to natural resistance *in vitro* and *in vivo*. Three independent anti-H-2-resistant sublines from two lymphomas were selected. Such variant cells not only were able to escape adaptive alloreactivity *in vitro* and *in vivo*, but, as predicted by our hypothesis, had also become unable to grow

1986 Nature Publishing Group



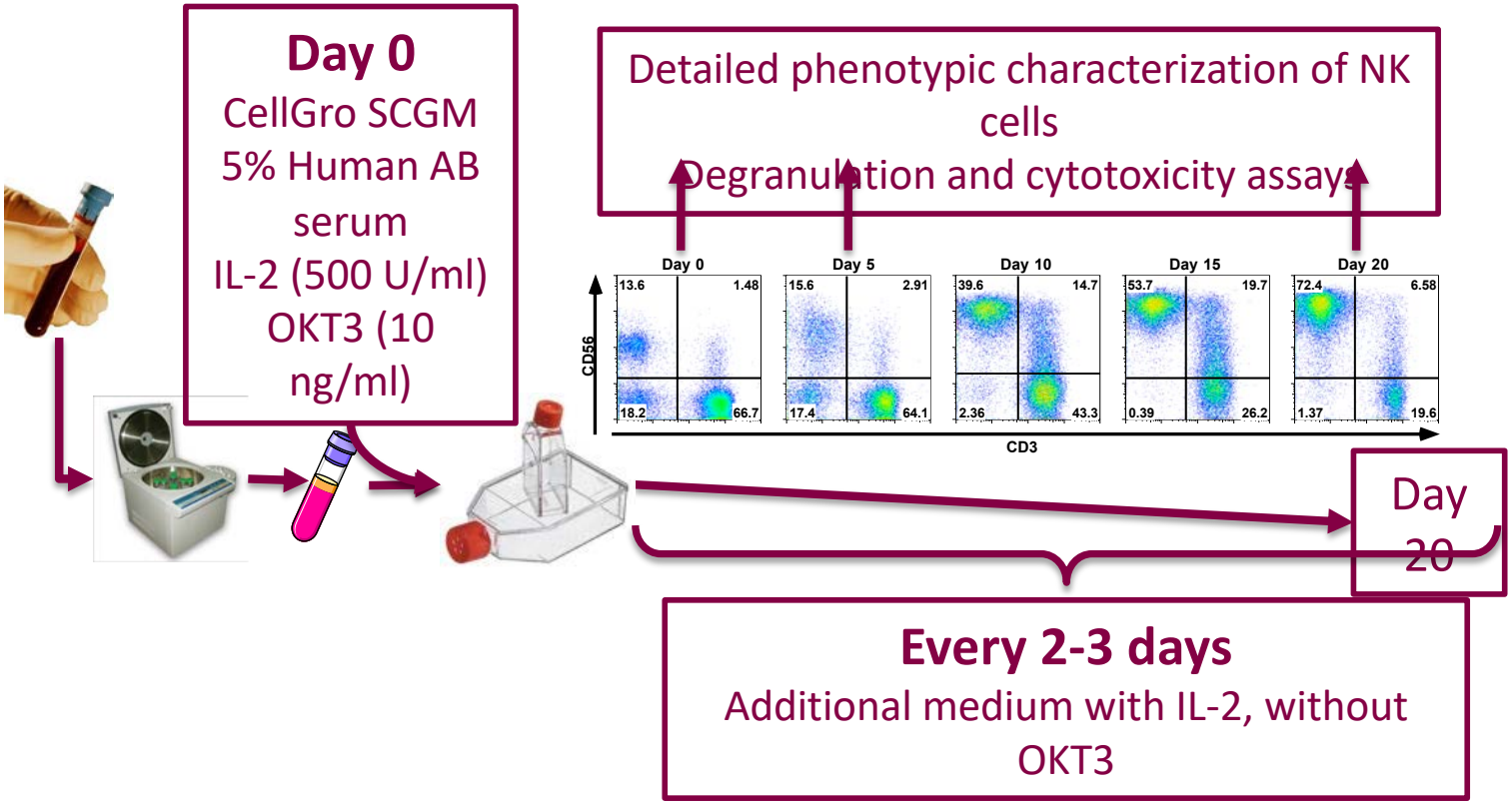
**In search of the 'missing self': MHC molecules and NK cell recognition**

Hans-Gustaf Ljunggren and Klas Kärre

# NK cell abnormalities in cancer: Born or licensed to kill?


| Abnormality | Disease | |
|---|---|---|
| Decreased cytotoxic activity | NSC lung Ca<br>**HCC**<br>**CRC**<br>H&N Ca<br>Breast Ca<br>Squam. cell Ca<br>Bronchogenic Ca | Cervical Ca<br>Ovarian Ca<br>**AML**<br>ALL<br>**B-CLL**<br>CML<br>**MM** |
| Defective expression of activating receptors | **HCC**<br>M. melanoma | **AML**<br>**MM** |
| Defective proliferation | **Renal Ca**<br>**Neuroblastoma** | Nasopharyn. Ca<br>CML |
| Increased number of $CD56^{bright}$ | H&N Ca | Breast Ca |
| Defective expression of signalling molecules | Cervical Ca<br>**CRC**<br>Ovarian Ca | Prostate Ca<br>**AML**<br>CML |
| Decreased NK cell counts | Nasopharyngeal Ca<br>**Neuroblastoma** | CML<br>ALL (Pediatric) |
| Defective cytokine production | **AML**<br>ALL | CML |

# The expansion process developed at KI



# How large?

# Different strategies for scaling up

# cGMP certified expansion process



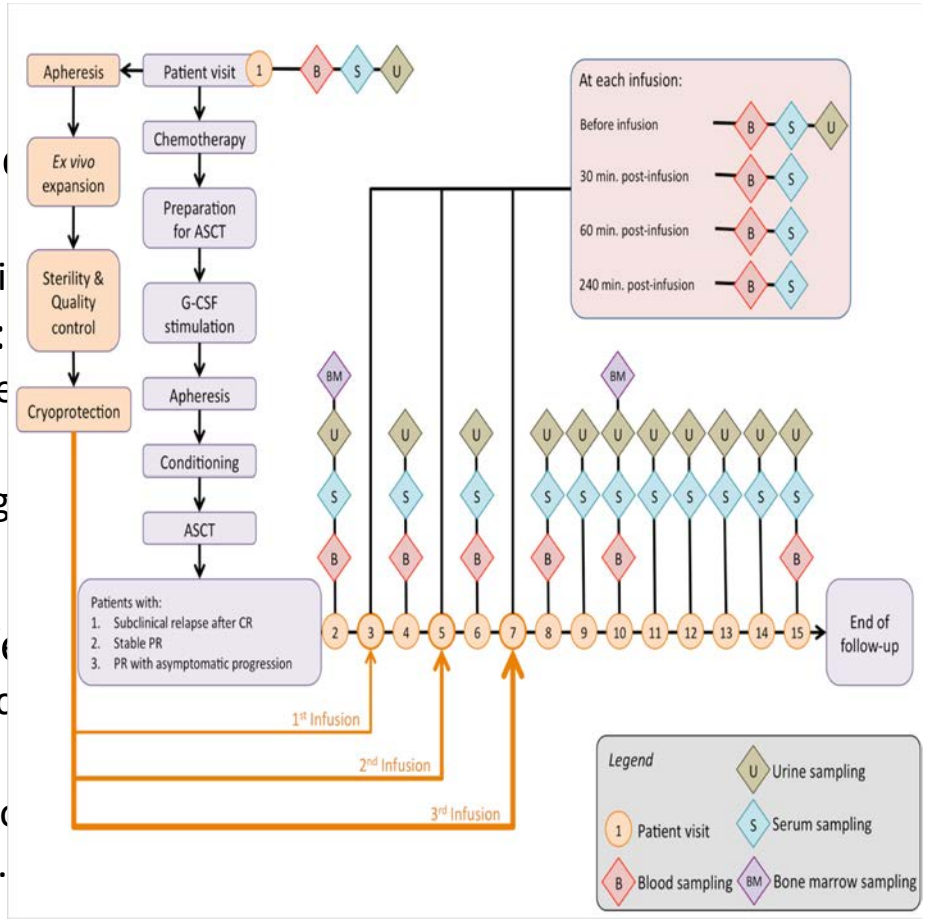




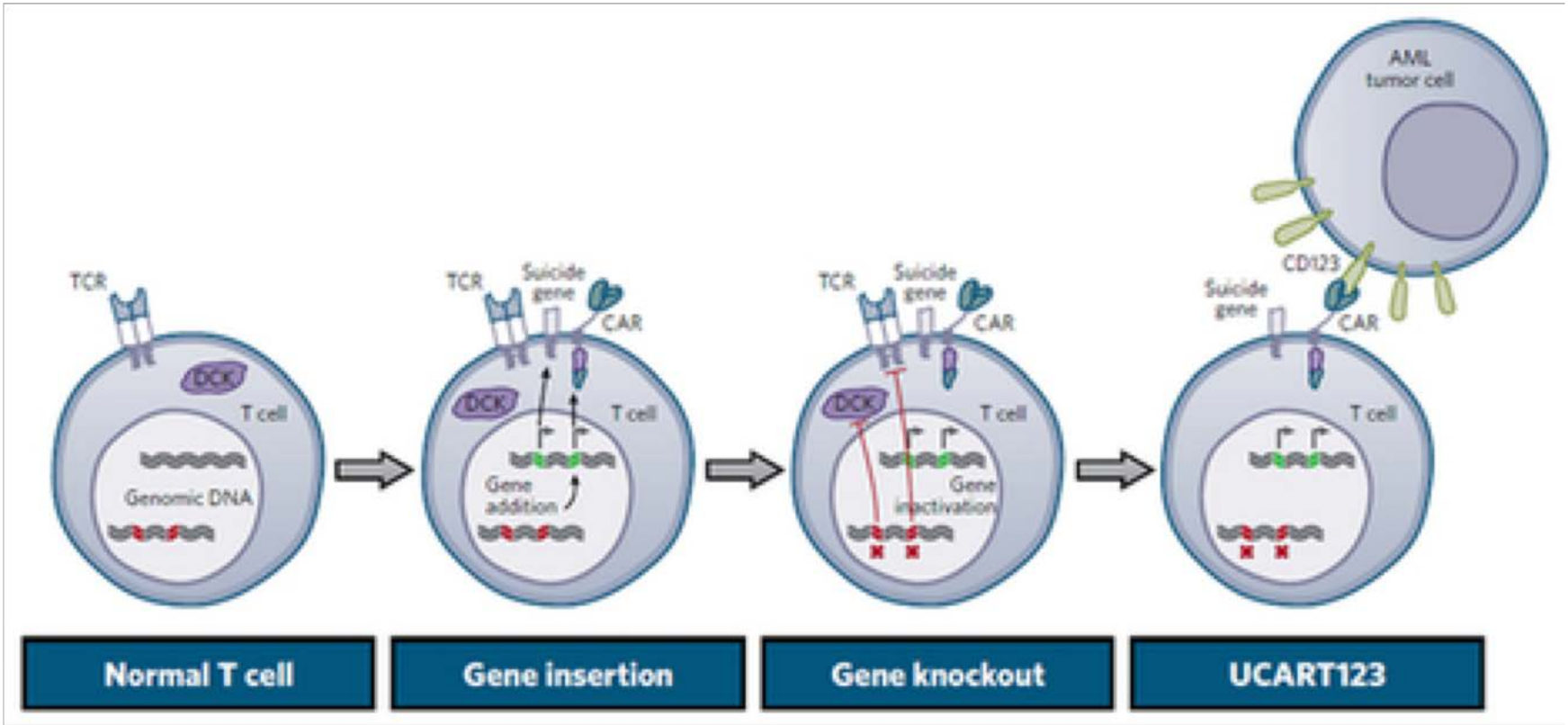

# ACP-001

CellProtect
Nordic Pharmaceuticals AB

- First-in-man, Phase I
- Open, single arm stu
- Primary objective:
  - Safety and tolerabili
- Secondary objective:
  - Effect on serum Ig le
- Inclusion:
  - 20 MM patients elig ASCT
- 3 escalating infusions/patient (W
  - $10^6$, $5X10^7$ and $10^8$ c
- Evaluation:
  - 4 weeks after infusi
  - 6 months follow up.

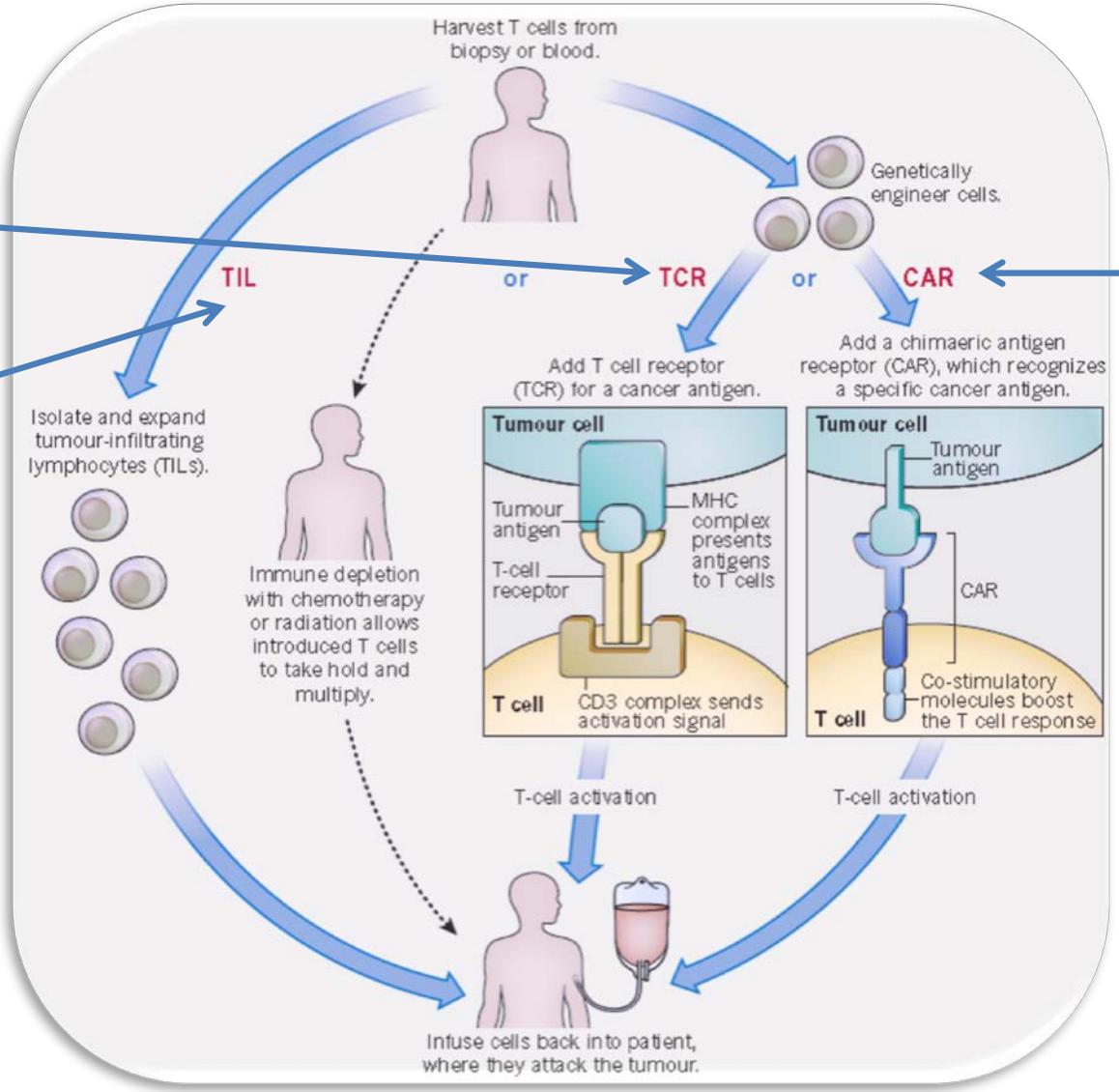


# Chimeric Antigen Receptors (CARs)

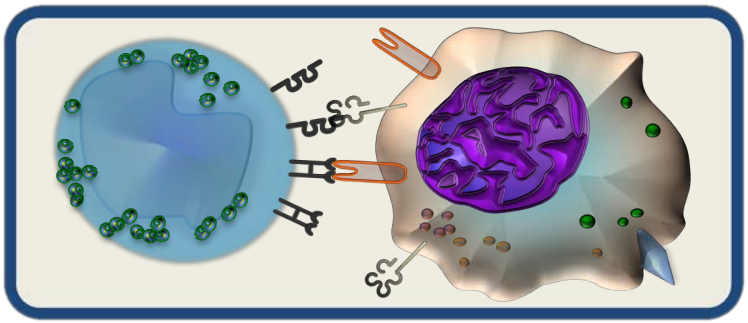


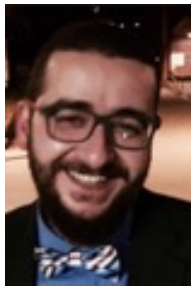
**T-Cell Receptors (TCRs)**

**Tumor Infiltrating Lymphocytes (TILs)**



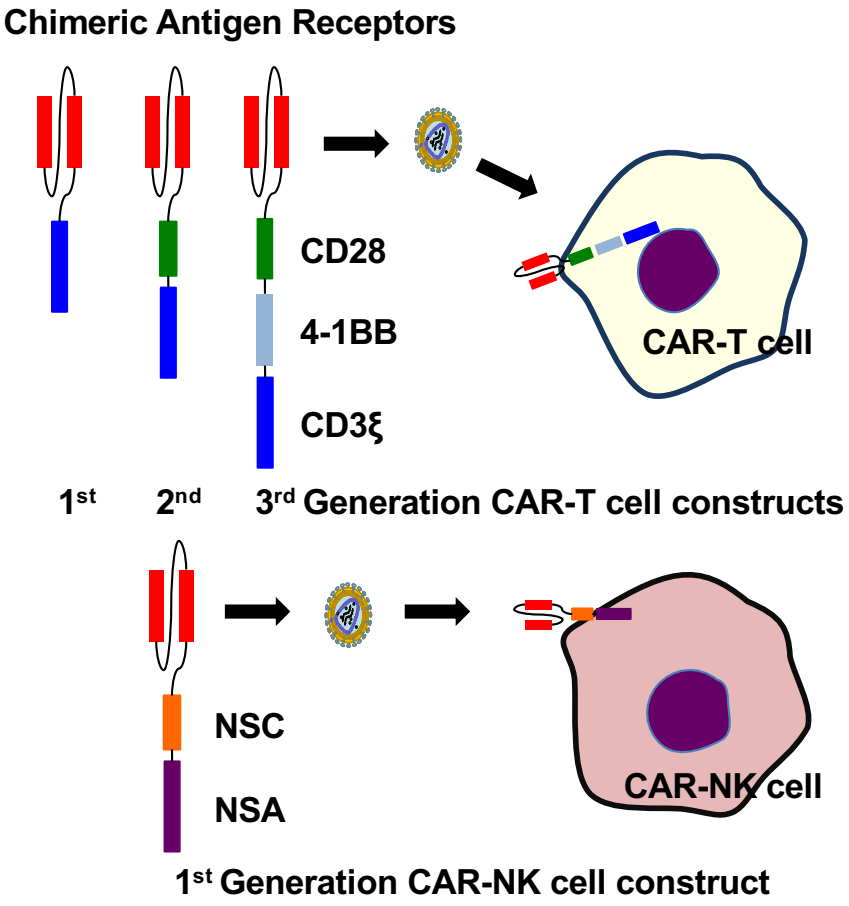

**Chimeric Antigen Receptors (CARs)**





# IMPROVING LENTIVIRAL AND RETROVIRAL GENE DELIVERY TO NK CELLS

# CAR NK cells


Chimeric Antigen Receptors
CD28
4-1BB
CD3ξ
CAR-T cell
1st
2nd
3rd Generation CAR-T cell constructs
NSC
NSA
CAR-NK cell
1st Generation CAR-NK cell construct

# NK-92 and clinical approaches

## Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: a phase I trial

S Arai, R Meagher, M Swearingen, H Myint, E Rich, J Martinson and H Klingemann

*Rush University Medical Center, Chicago, Illinois, USA*

*Cytotherapy*, 2013; 15: 1563–1570

International Society for Cellular Therapy ISCT

## Treatment of patients with advanced cancer with the natural killer cell line NK-92

TORSTEN TONN[1,2,*], DIRK SCHWABE[3,*], HANS G. KLINGEMANN[4], SVEN BECKER[1,2], RUTH ESSER[3,7], ULRIKE KOEHL[3,7], MEINOLF SUTTORP[6], ERHARD SEIFRIED[1,2], OLIVER G. OTTMANN[5] & GESINE BUG[5]

International Society for Cellular Therapy ISCT

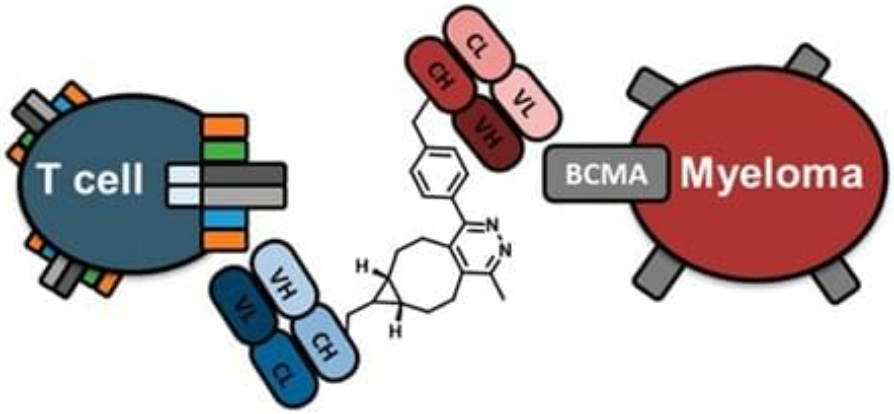
Cytotherapy (2003) Vol. 5, No. 3, 259–272

Taylor & Francis healthsciences

## *Ex vivo* expansion of the highly cytotoxic human natural killer cell line NK-92 under current good manufacturing practice conditions for clinical adoptive cellular immunotherapy

YK Tam, JA Martinson, K Doligosa and H-G Klingemann

# B-cell maturation antigen (BCMA)

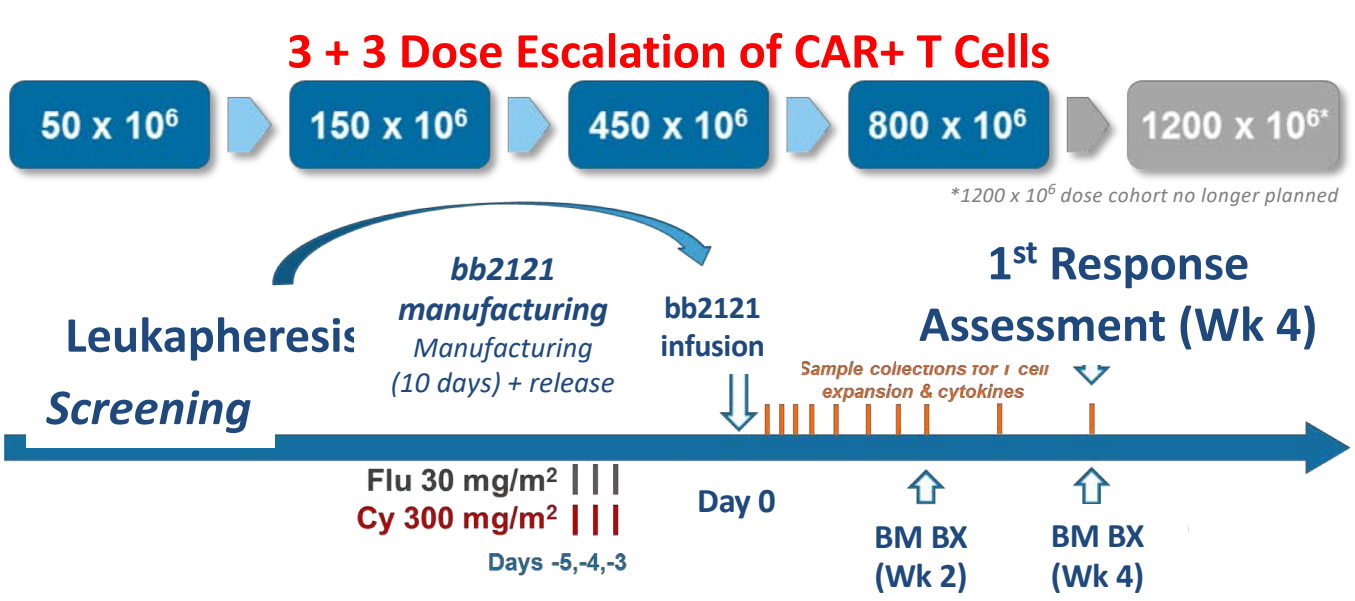


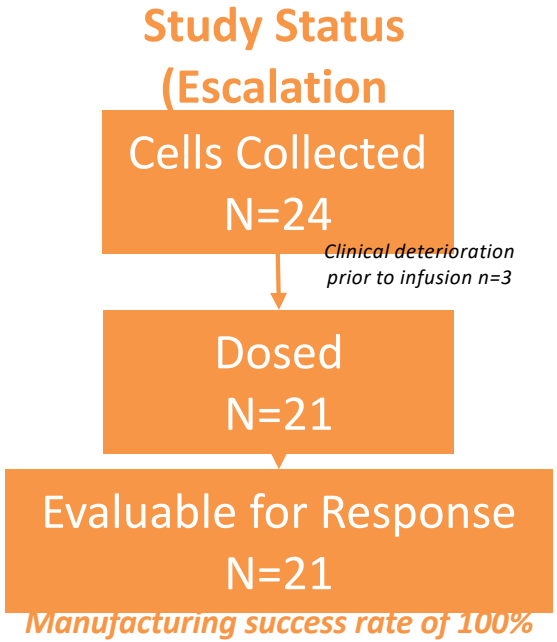
# Durable clinical responses in heavily pretreated patients with relapsed/refractory multiple myeloma: Updated results from a multicenter study of bb2121 anti-BCMA CAR T cell therapy

Jesus Berdeja MD[1], Yi Lin, MD, PhD[2], Noopur Raje, MD[3], Nikhil Munshi, MD[4], David Siegel, MD, PhD[5], Michaela Liedtke, MD[6], Sundar Jagannath, MD[7], Marcela Maus, MD, PhD[3], Ashley Turka[8],
Lyh Ping Lam, PharmD[8], Kristen Hege, MD[9], Richard A. Morgan, PhD[8], M. Travis Quigley[8],
and James N. Kochenderfer, MD[10]

*1- Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN,*
*2- Mayo Clinic, Rochester, MN, 3- Massachusetts General Hospital Cancer Center, Boston, MA, 4- Dana Farber Cancer Institute, Boston, MA, 5- Hackensack University Medical Center, Hackensack, NJ, 6- Stanford University Medical Center, Palo Alto, CA,*
*7- Mount Sinai Medical Center, New York, NY, 8- bluebird bio, Inc., Cambridge, MA, 9- Celgene Corporation, San Francisco, CA,*
*10- Experimental Transplantation and Immunology Branch, National Cancer Institute/National Institutes of Health, Bethesda, MD*

# CRB-401 Study Design and Status




**Expansion Cohort Initiated in August 2017**

- 12 additional patients have been collected and dosed in the Expansion Cohort as of 02 Nov 2017

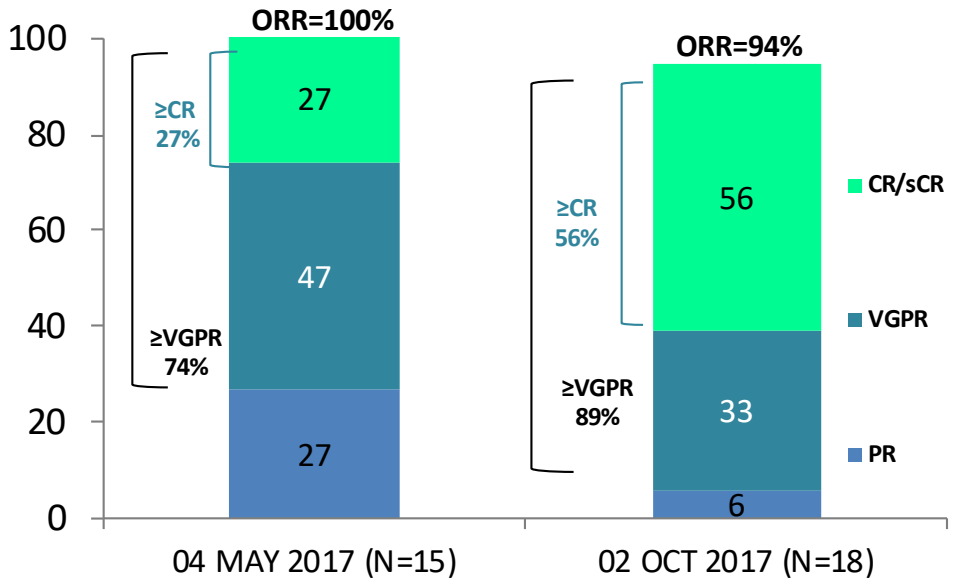
# Clinical Response: Deepening of Response over Time

## Dose Escalation: Cohorts ≥150 × $10^6$ CAR+ T Cells (N=18)

| Efficacy Parameter | Statistic | Result |
|---|---|---|
| Time (months) to First Response | Median (min, max) | 1.02 (0.5, 3.0) |
| Time (months) to Best Response | Median (min, max) | 3.74 (0.5, 13.7) |
| Time (months) to Complete Response | Median (min, max) | 3.84 (0.5, 13.7) |
| Duration of Response | Median (min, max) | NR |
| Progression free survival | Median (min, max) | NR |
| Progression free survival rate @ 6 mos | % | 81% |
| Progression free survival rate @ 9 mos | % | 71% |

**NR, not reached**

Objective Response Rate
Subjects Treated in Escalation – Cohorts ≥150 × $10^6$



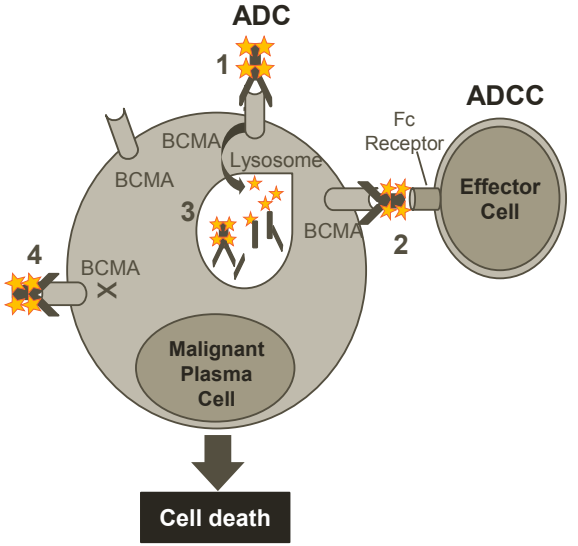

Note: Objective Response defined as attaining Stringent Complete Response, Complete Response, Very Good Partial Response, or Partial Response. Including unconfirmed responses.

# First-in-class anti-BCMA agent with multiple modes of action

| | |
|---|---|
| **The agent** | – GSK'916 is a humanised IgG1 antibody targeting BCMA (B-cell maturation antigen)<br>  – Linked to the anti-mitotic agent MMAF<br>  – Afucosylated to enhance ADCC |
| **The target** | – BCMA plays a key role in plasma cell survival<br>– It is found on the surfaces of plasma cells and is overexpressed on malignant plasma cells<br>– Not expressed in healthy tissues |
| **Key attributes** | – New modality in multiple myeloma: first ADC<br>– Easy and convenient to administer: 1h infusion q3w<br>– No pre-medication for infusion reactions<br>  – Pre-medication with steroid eye drops<br>– New MoA enabling diverse combinations |

**Four mechanisms of action:**

1. ADC mechanism
2. ADCC mechanism
3. BCMA receptor signaling inhibition
4. Immunogenic cell death




ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; MMAF, monomethyl auristatin-F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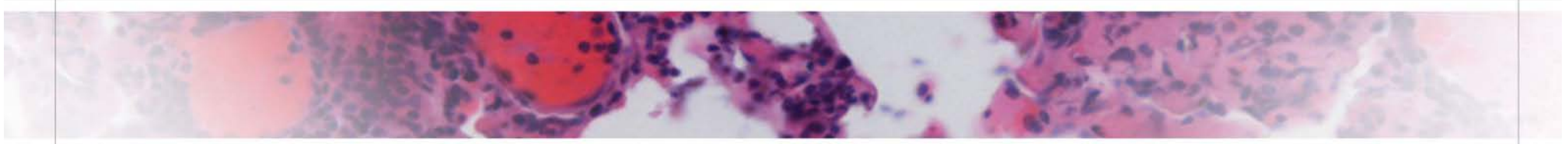
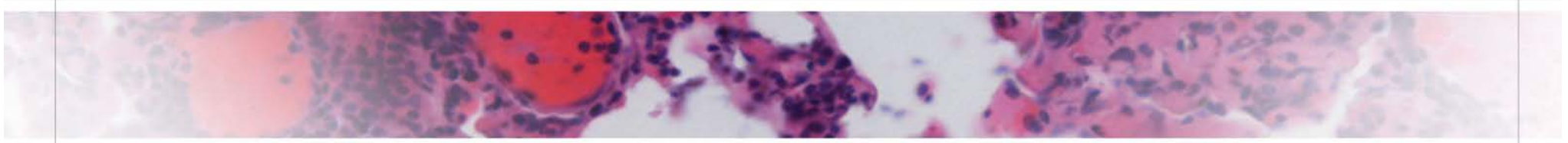
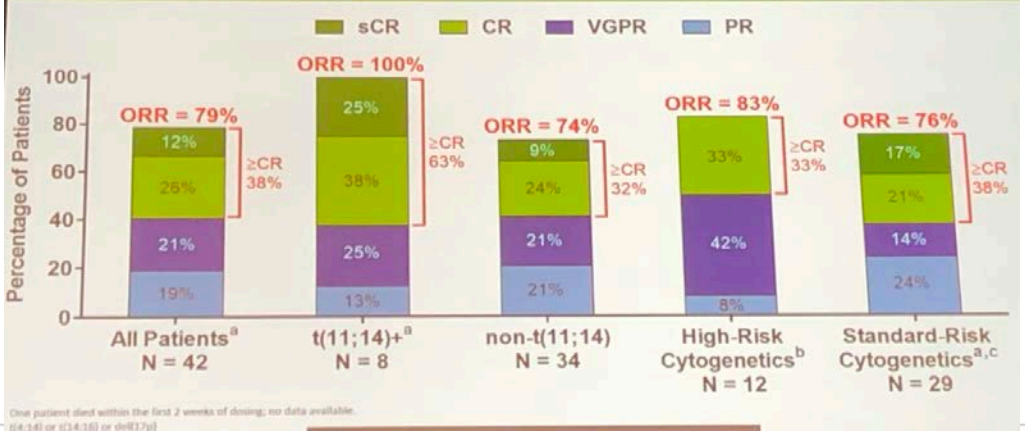


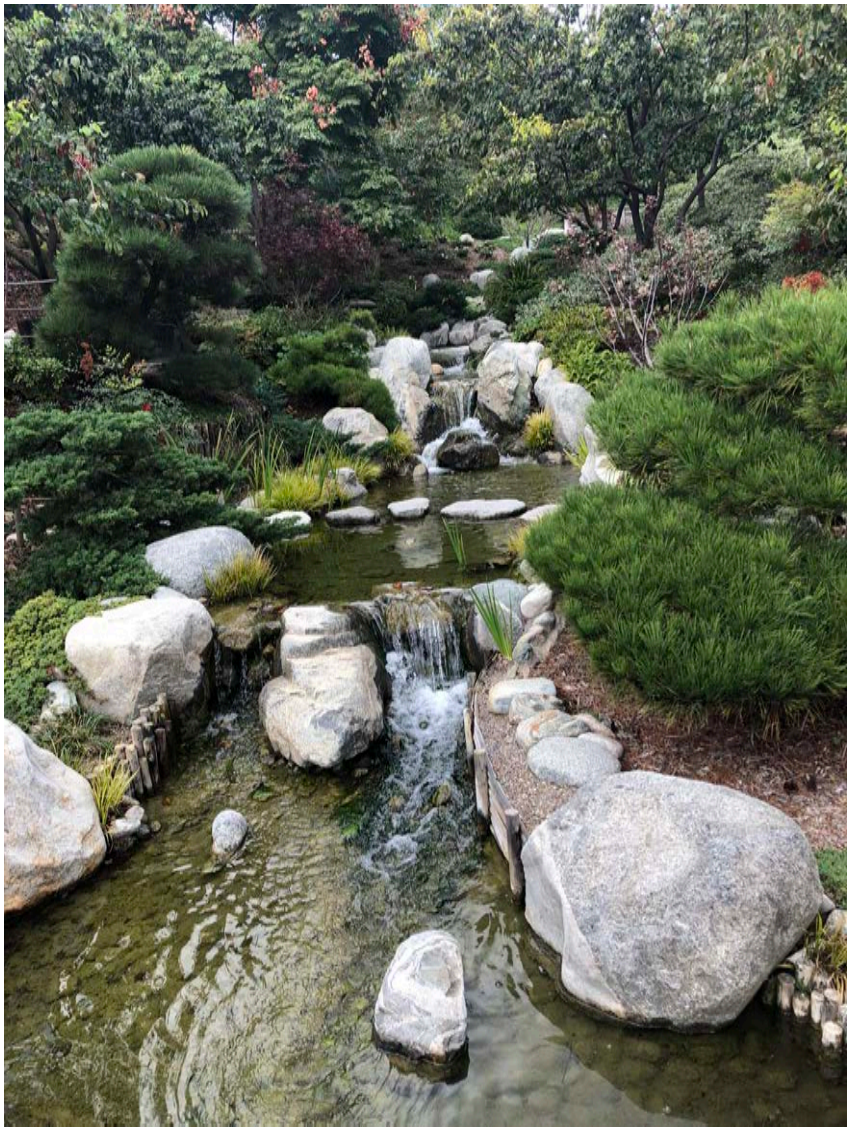
# Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma

Luciano J. Costa,[1] Edward A. Stadtmauer,[2] Faith Davies,[3] Gregory Monohan,[4] Tibor Kovacsovics,[5] Nicholas Burwick,[6] Andrzej Jakubowiak,[7] Jonathan L. Kaufman,[8] Mehrdad Mobasher,[9] Kevin J. Freise,[10] Jeremy A. Ross,[10] John Pesko,[10] Wiji Munasinghe,[10] Saketh Gudipati,[10] Sarah Mudd,[10] Orlando F. Bueno,[10] Shaji K. Kumar[11]



## Objective Responses in Patients Based on Cytogenetic Status





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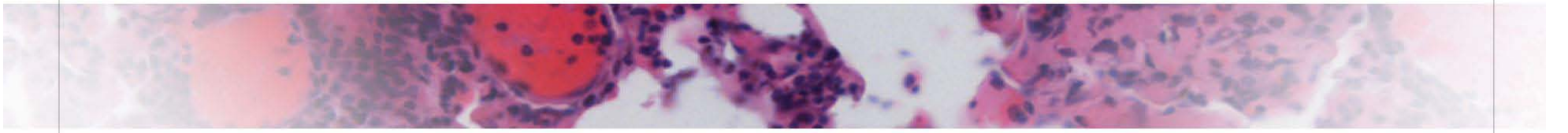
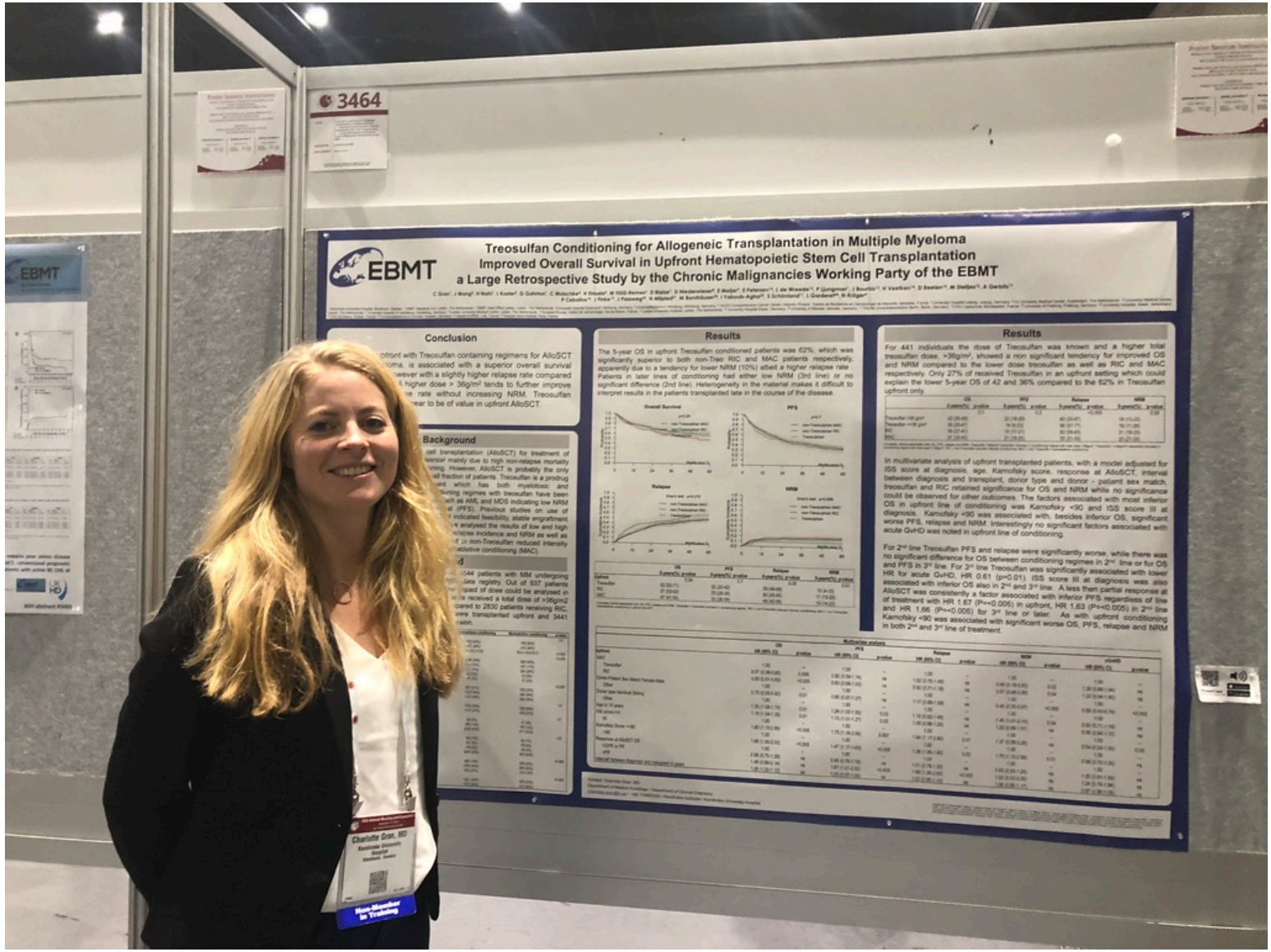


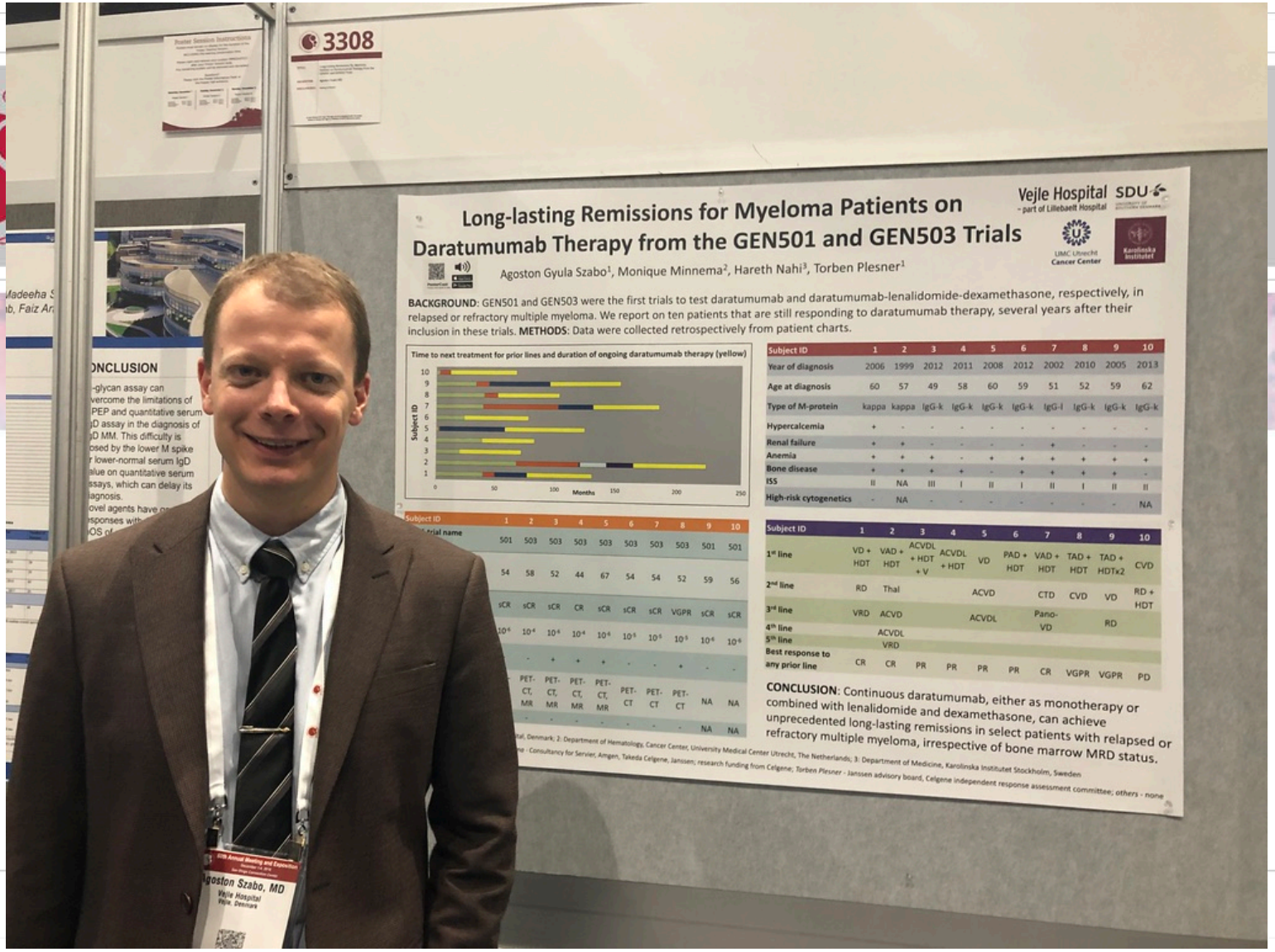
# Phase 3 Randomized Study of Daratumumab Plus Lenalidomide and Dexamethasone (D-Rd) Versus Lenalidomide and Dexamethasone (Rd) in Patients With Newly Diagnosed Multiple Myeloma (NDMM) Ineligible for Transplant (MAIA)*

**Thierry Facon**,[1] Shaji Kumar,[2] Torben Plesner,[3] Robert Z. Orlowski,[4] Philippe Moreau,[5] Nizar Bahlis,[6] Supratik Basu,[7] Hareth Nahi,[8] Cyrille Hulin,[9] Hang Quach,[10] Hartmut Goldschmidt,[11] Michael O'Dwyer,[12] Aurore Perrot,[13] Christopher P. Venner,[14] Katja Weisel,[15] Joseph R. Mace,[16] Tahamtan Ahmadi,[17] Christopher Chiu,[18] Jianping Wang,[19] Rian Van Rampelbergh,[20] Clarissa M. Uhlar,[18] Rachel Kobos,[19] Ming Qi,[18] Saad Z. Usmani[21]

[1]Service des Maladies du Sang, Hôpital Claude Huriez, Lille, France; [2]Department of Hematology, Mayo Clinic Rochester, Rochester, MN, USA; [3]Vejle Hospital and University of Southern Denmark, Vejle, Denmark; [4]Department of Lymphoma-Myeloma, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [5]Hematology, University Hospital Hôtel-Dieu, Nantes, France; [6]University of Calgary, Arnie Charbonneau Cancer Institute, Calgary, AB, Canada; [7]Royal Wolverhampton Hospitals NHS Trust, Wolverhampton, United Kingdom; [8]Karolinska Institute, Department of Medicine, Division of Hematology, Karolinska University Hospital at Huddinge, Stockholm, Sweden; [9]Department of Hematology, Hospital Haut Leveque, University Hospital, Pessac, France; [10]St. Vincent's Hospital, University of Melbourne, Melbourne, Australia; [11]University Hospital Heidelberg and National Center of Tumor Diseases (NCT), Heidelberg, Germany; [12]Dept. of Medicine/Haematology, NUI, Galway, Republic of Ireland; [13]Hematology Department, University Hospital, Vandoeuvre Les Nancy, France; [14]Division of Medical Oncology University of Alberta, Edmonton, AB, Canada; [15]Universitaetsklinikum Tuebingen der Eberhard-Karls-Universitaet, Abteilung fuer Innere Medizin II, Tuebingen, Germany; [16]Florida Cancer Specialists & Research Institute, St. Petersburg, FL, USA; [17]Genmab US, Inc., Princeton, NJ, USA; [18]Janssen Research & Development, Spring House, PA, USA; [19]Janssen Research & Development, Raritan, NJ, USA; [20]Janssen Research & Development, Beerse, Belgium; [21]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA.

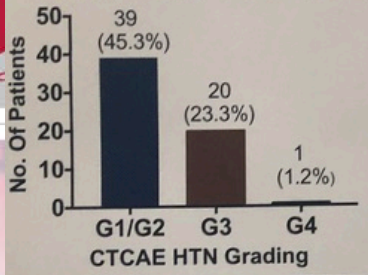
*ClinicalTrials.gov Identifier: NCT02252172


3464
EBMT
Treosulfan Conditioning for Allogeneic Transplantation in Multiple Myeloma
Improved Overall Survival in Upfront Hematopoietic Stem Cell Transplantation
a Large Retrospective Study by the Chronic Malignancies Working Party of the EBMT
Conclusion
Background
Results
Results
Charlotte Gran, MD
Non-Member in Training

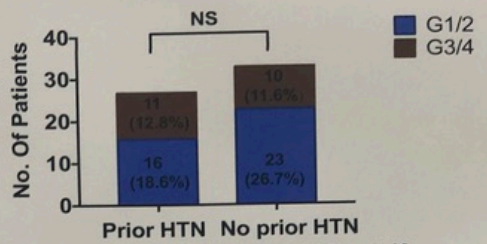

3308
Long-lasting Remissions for Myeloma Patients on Daratumumab Therapy from the GEN501 and GEN503 Trials
Vejle Hospital – part of Lillebaelt Hospital
SDU
UMC Utrecht Cancer Center
Karolinska Institutet
Agoston Gyula Szabo[1], Monique Minnema[2], Hareth Nahi[3], Torben Plesner[1]
BACKGROUND: GEN501 and GEN503 were the first trials to test daratumumab and daratumumab-lenalidomide-dexamethasone, respectively, in relapsed or refractory multiple myeloma. We report on ten patients that are still responding to daratumumab therapy, several years after their inclusion in these trials. METHODS: Data were collected retrospectively from patient charts.
Time to next treatment for prior lines and duration of ongoing daratumumab therapy (yellow)
Subject ID
Months
Subject ID 1 2 3 4 5 6 7 8 9 10
Year of diagnosis 2006 1999 2012 2011 2008 2012 2002 2010 2005 2013
Age at diagnosis 60 57 49 58 60 59 51 52 59 62
Type of M-protein kappa kappa IgG-k IgG-k IgG-k IgG-k IgG-l IgG-k IgG-k IgG-k
Hypercalcemia + - - - - - - - - -
Renal failure + + - - - - + - - -
Anemia + + + - + + + + + +
Bone disease + + + + - + + + + -
ISS II NA III I II I II I II II
High-risk cytogenetics - NA - - - - - - - NA
Subject ID 1 2 3 4 5 6 7 8 9 10
1st line VD + HDT VAD + HDT ACVDL + HDT + V ACVDL + HDT VD PAD + HDT VAD + HDT TAD + HDT TAD + HDTx2 CVD
2nd line RD Thal ACVD CTD CVD VD RD + HDT
3rd line VRD ACVD ACVDL Pano-VD RD
4th line ACVDL
5th line VRD
Best response to any prior line CR CR PR PR PR PR CR VGPR VGPR PD
CONCLUSION: Continuous daratumumab, either as monotherapy or combined with lenalidomide and dexamethasone, can achieve unprecedented long-lasting remissions in select patients with relapsed or refractory multiple myeloma, irrespective of bone marrow MRD status.
Agoston Szabo, MD
Vejle Hospital
Vejle, Denmark

## ults

**Higher incidence of G1/2 HTN (45.4%) v G3/4 (24.5)**

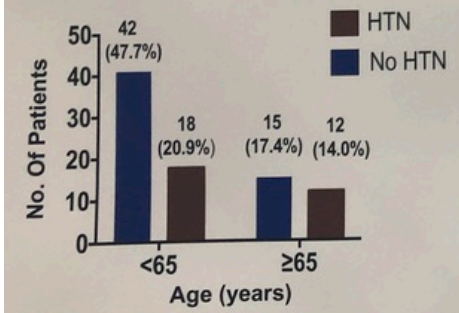



**No significant difference for the development of HTN seen in patients with a history of HTN**




OR 1.58, 95% CI: 0.56-4.65 p=0.43

**Age did not affect the development of HTN**




OR 1.82, 95% CI: 0.71-4.60 p=0.21

Chi squared test p=0.1

- 11(13%) patients required intervention with anti-HTN medications for ≥G2 HTN which then returned the BP to baseline.
- Ethnicity did not affect the development of HTN on CFZ

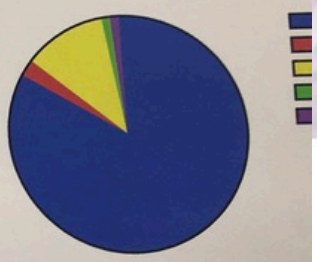
**Higher incidence of HTN with CFZ**

## Results

Development of cardiac comp

Cardiac complications occurred dosing levels and were not rela

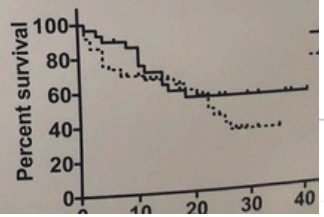
**Most pt. did not experience complications on CFZ**



Total=86

Effects of HTN and Cardia

**PFS and OS were unaffe HTN or cardiac toxicitv**



Americ
Helping hemato

the jaw was 2.8 per 100 patient-years in the denosumab arm and 1.9 per 100 patient-years in the zoledronic acid arm[7]

- Hypocalcemia AEs were reported in 16.9% vs 12.4% of patients in the denosumab and zoledronic acid groups, respectively

## CONCLUSIONS

- Denosumab has been shown to be noninferior to zoledronic acid in the prevention of SREs in patients with NDMM
- When added to antimyeloma therapy, denosumab provided improved PFS vs zoledronic acid in patients with NDMM by almost 11 months
  - The observed benefit of denosumab was independent of the first-line novel therapy used
- The observed benefit of denosumab vs zoledronic acid on PFS was also observed in patients with the intent to receive an autologous stem cell transplan
- Taken together, these positive PFS results suggest that denosumab should be considered as an alternative to zoledronic acid in the standard treatment of patients with NDMM to protect from debilitating bone complications, adding clinical meaningful benefit on top of anti-myeloma therapy
- Further translational research might contribute to understanding of PFS benefit, such as assessments of risk based on cytogenetics and effects of depth of response on PFS
- In this analysis, no factors or imbalances were identified between the treatment arms that appeared to influence PFS, indicating the mechanism of action for denosumab may indirectly benefit patient outcomes by influencing the bone/tumor environment

## REFERENCES

1. Terpos E, et al. *Blood*. 2003;102:1064-1069.
2. Terpos E, et al. *Blood*. 2013;121:3325-3328.
3. Dimopolous MF, et al. *J Clin Oncol*. 2010;28:4976-4984.

# BiSpecific Antibodies (BiTe)