

Maintenance Therapy after a Transplant for Multiple Myeloma

Celebrating a Second Chance at Life
Survivorship Symposium



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Maintenance: (French, Old English)

- the process of maintaining or preserving someone or something, or the state of being maintained

Oxford English Dictionary

Maintenance Therapy is an Old Concept in Multiple Myeloma Treatment

- 1975: Randomized maintenance therapy clinical trial
 - Melphalan + Prednisone versus
 - Carmustine + Prednisone versus
 - No Maintenance Therapy
 - 137 patients
- No significant difference in survival between the three groups

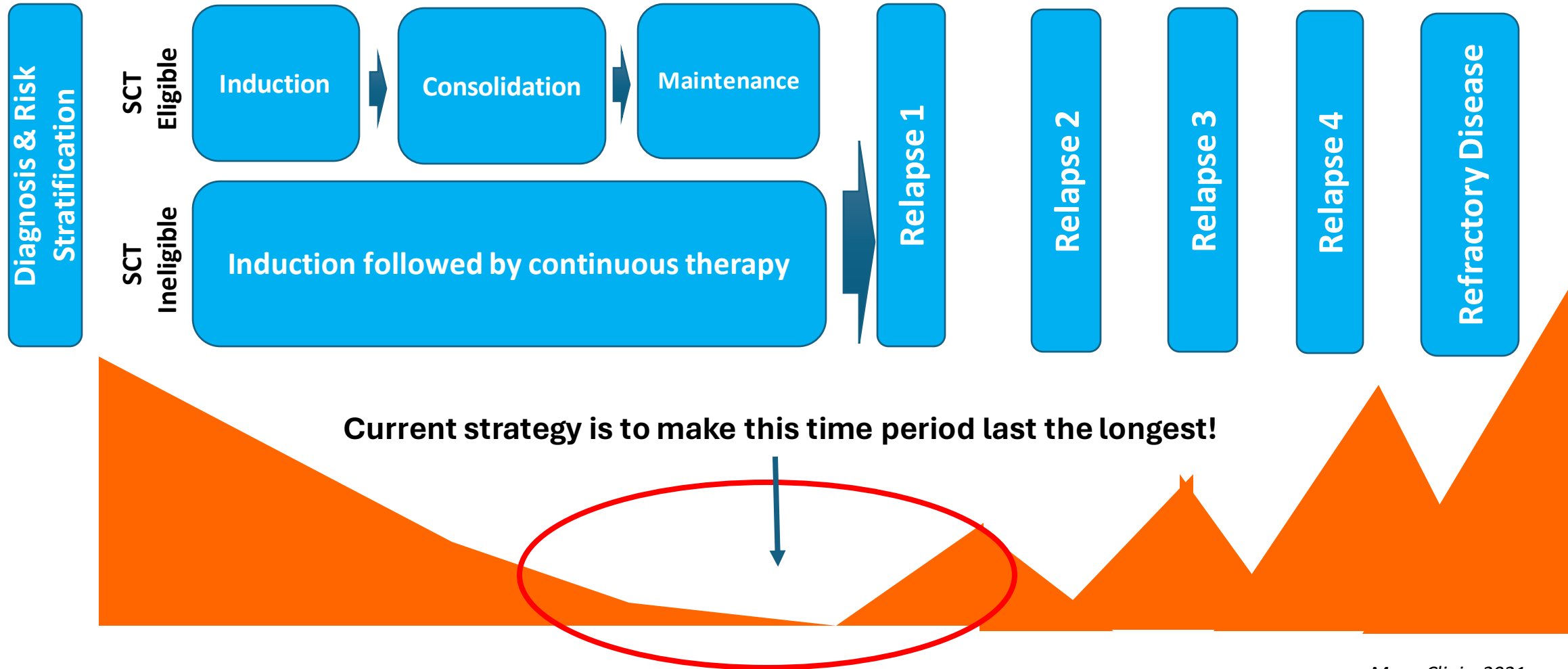
Alexanian R Arch Int Med 1975 135:147

Other Drugs Have Been Studied

- **Prednisone**, 50 mg every other day, improved progression-free survival
- **Interferon** did not improve progression-free survival
- **Thalidomide** had some positive effect but also issues with
 - Peripheral neuropathy
 - Constipation
 - Sedation
 - Potential for birth defects

Berenson, 2002

Modern Myeloma Treatment Paradigm

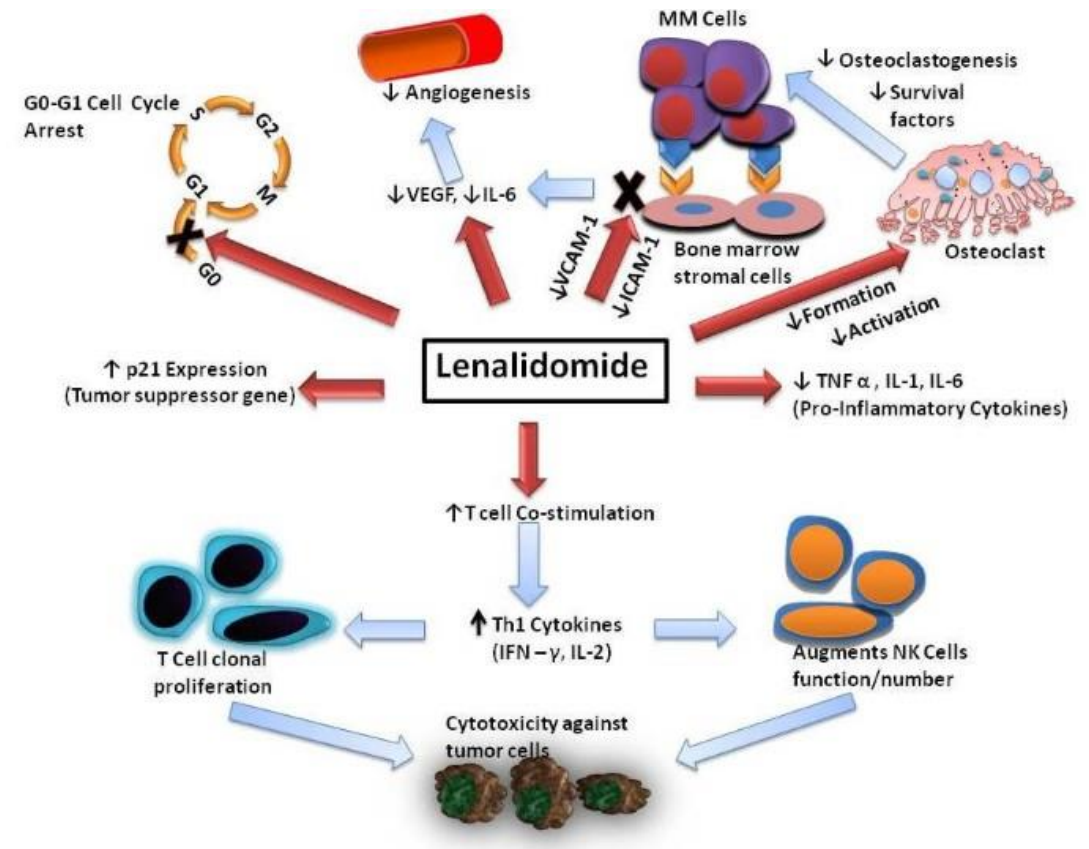


What are the Goals of Maintenance Therapy?

- Prolong control of myeloma
- Reduce risk of early death
- Enhance quality of life by helping to delay/avoid additional (and possibly toxic) chemotherapy
- Ideally maintenance should:
 - not cause harm
 - be reasonable return for investment, i.e. benefit > risk of side effects, harm

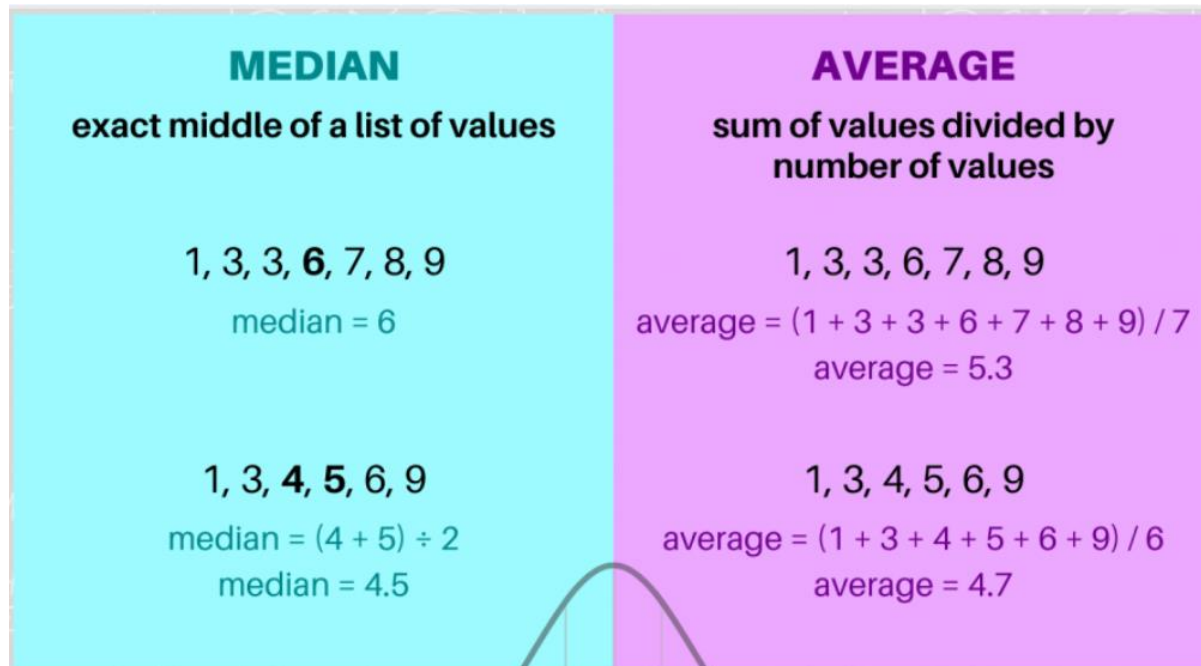
Lenalidomide Studied for Maintenance Therapy

- Chemically very close to thalidomide
- Initially thought to be less likely to cause birth defects
- Not a targeted therapy
- Useful in myeloma, in part, because of its many mechanisms of action



Hematology & Oncology 2009, 2:36

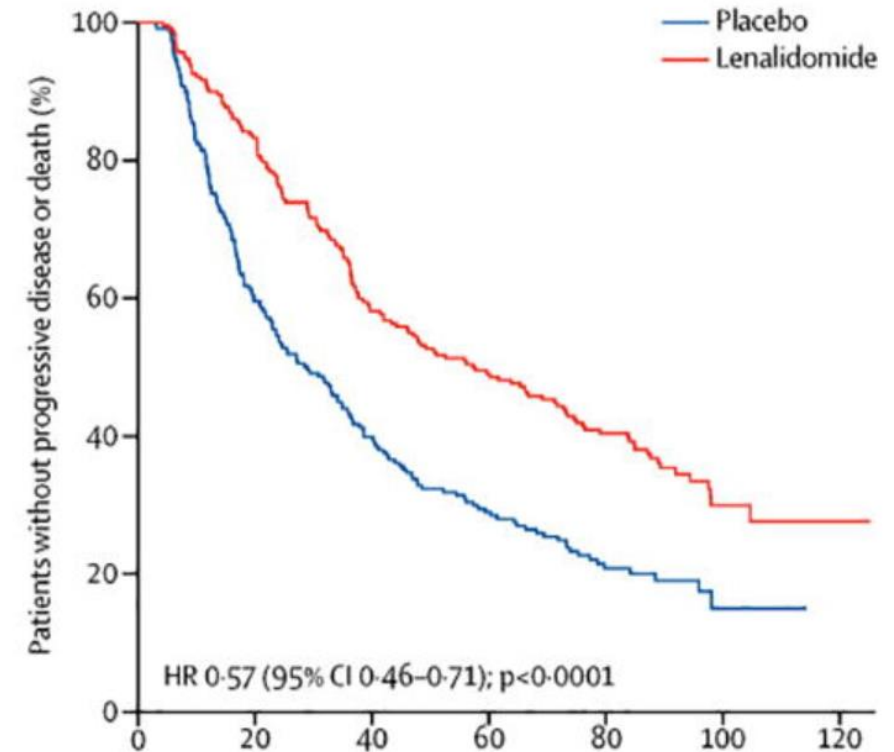
Definition of Terms



- Progression free:
 - no evidence of relapse of MM
- Median Progression Free Survival:
when the middle pt in a group develops MM
- Overall survival:
 - how long a person lives (whether or not in remission)
- Response:
 - at least 50% reduction in monoclonal protein and/or light chains

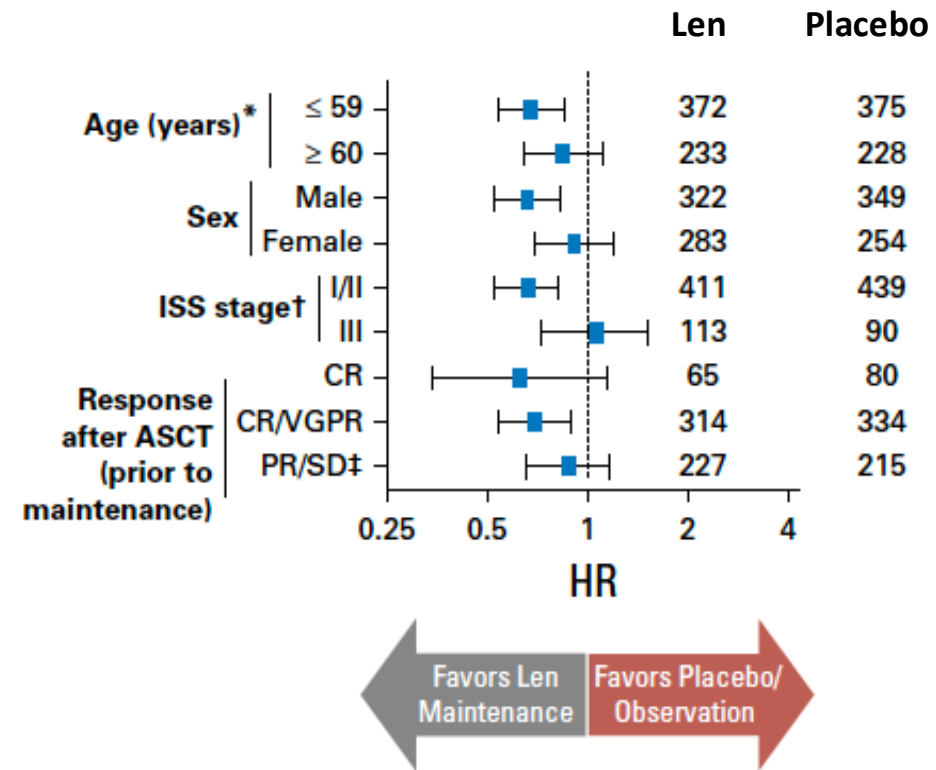
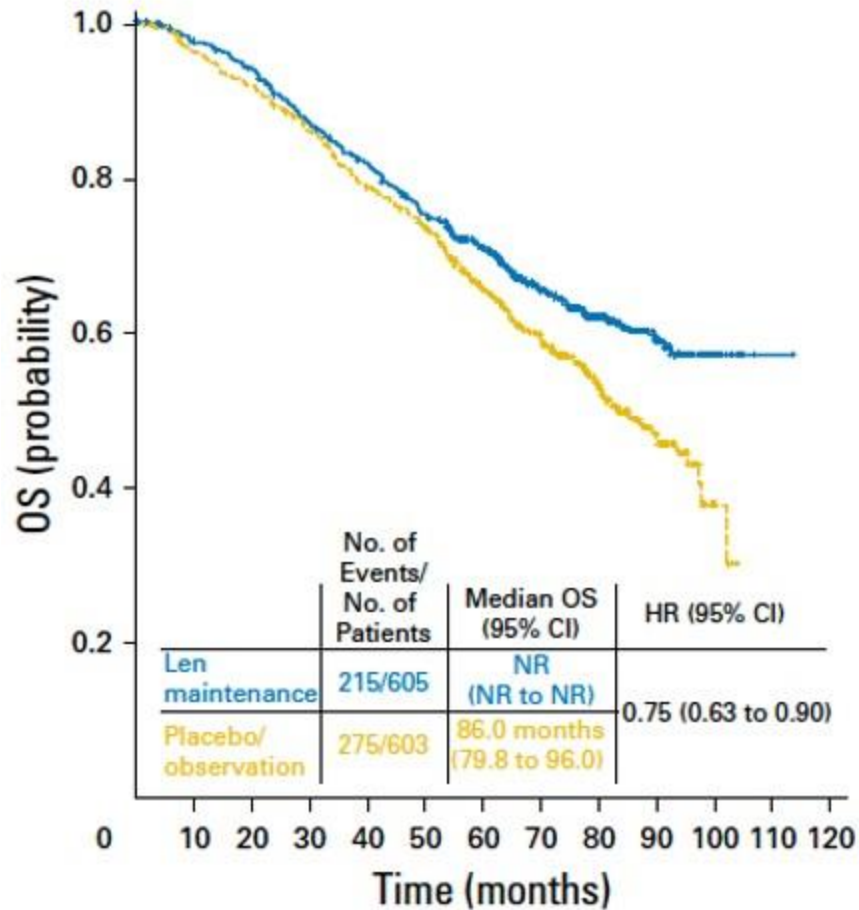
2009 Clinical Trial: Lenalidomide vs Placebo

- 410 patients (2005-2009)
- 2-12 months prior therapy, < 2 regimens
- **Median time to progression:**
 - Lenalidomide - 57.3 months
 - Placebo - 28.9 months
- **Median overall survival:**
 - Lenalidomide -113.8 months
 - Placebo - 84.1 months
- There is a lenalidomide maintenance benefit if started within 6 months of transplant
- BUT initial analysis showed NO survival advantage



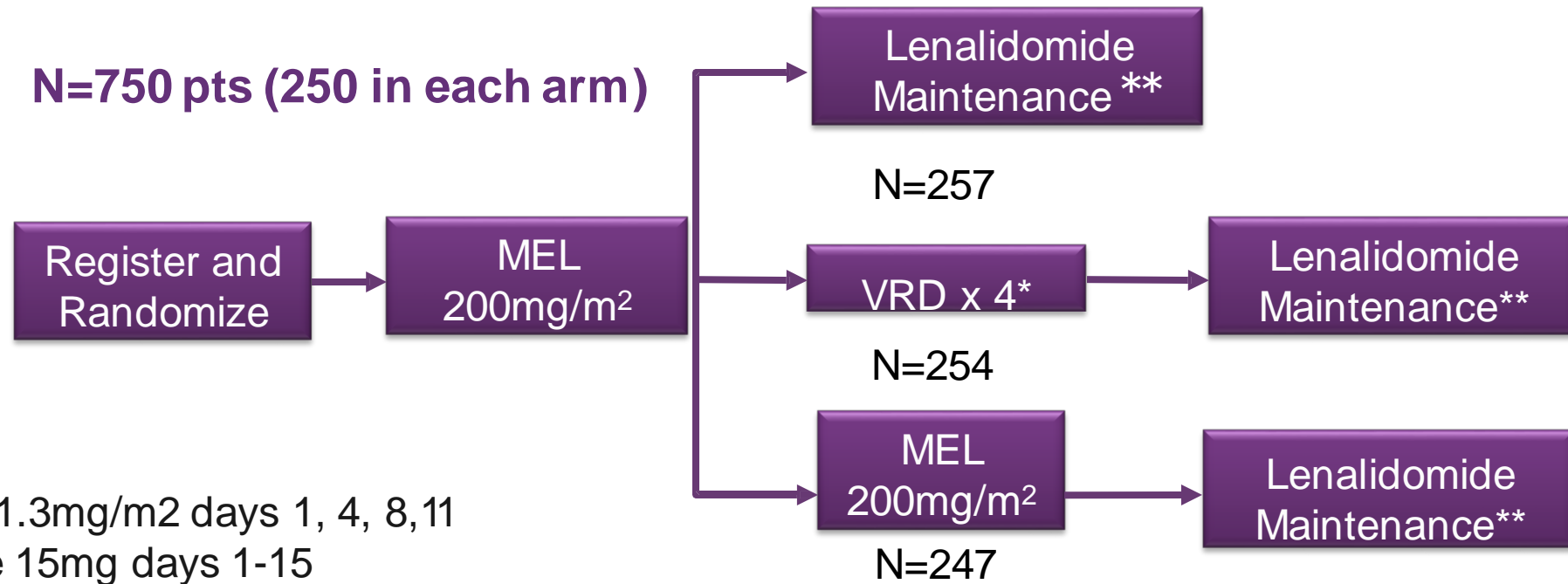
Holstein S Lan Oncol 2017 4:e431

Lenalidomide Maintenance: improved SURVIVAL in most groups



McCarthy et al, JCO 2017

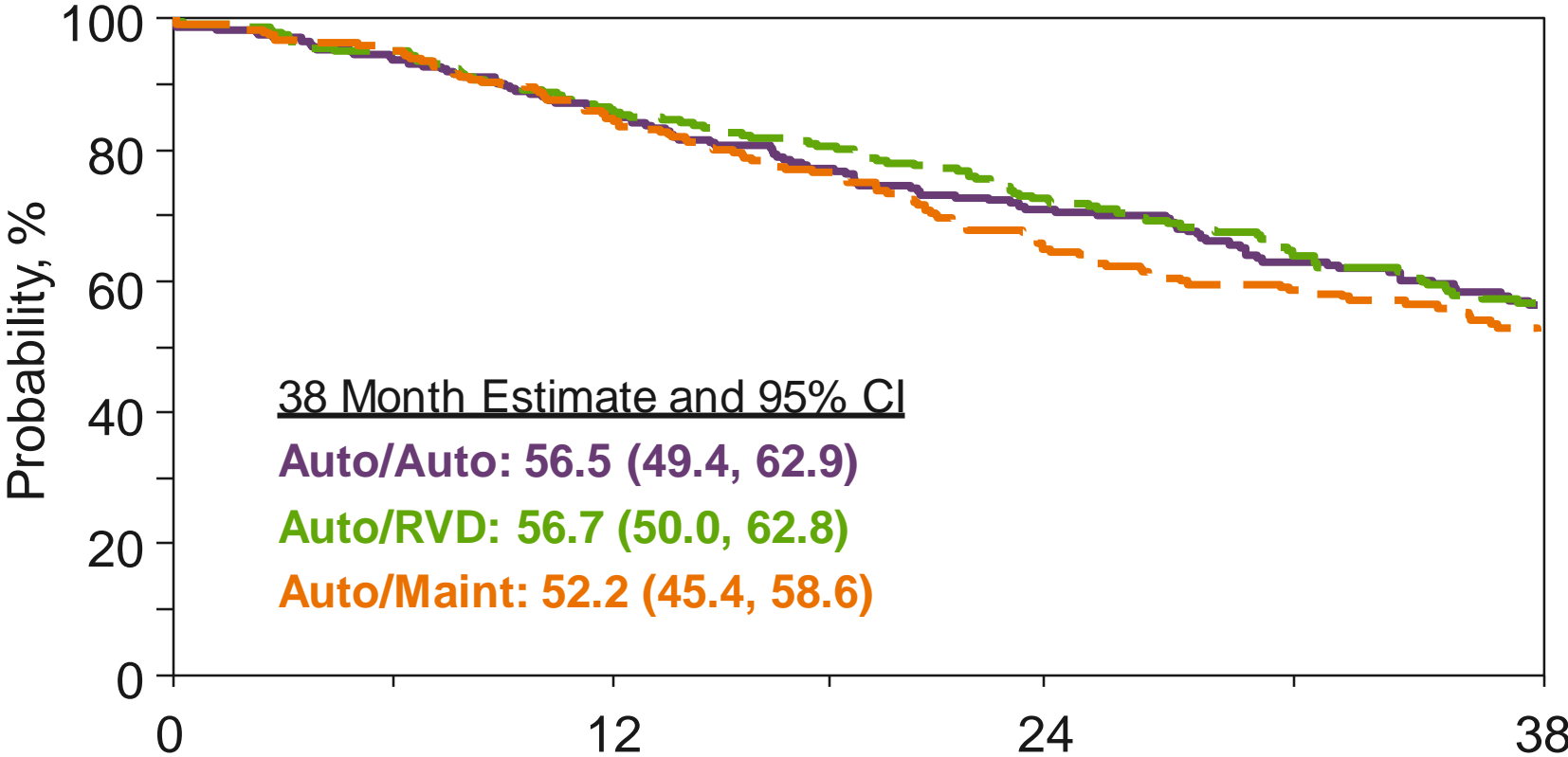
Extra Treatment (called Consolidation) Did Not Seem to Keep People in Remission Longer



*Bortezomib 1.3mg/m² days 1, 4, 8,11
Lenalidomide 15mg days 1-15
Dexamethasone 40mg days 1, 8, 15,
Every 21 days

**Lenalidomide x 3years :
10mg/d for 3 cycles , then 15 mg/d
Amendment in 2014 changed Lenalidomide maintenance until disease progression after report of CALGB 100104.

BMT-CTN Found No Advantage with Consolidation Following an Autologous Transplant



Not All Patients appear to get the Same Benefit from Lenalidomide Maintenance

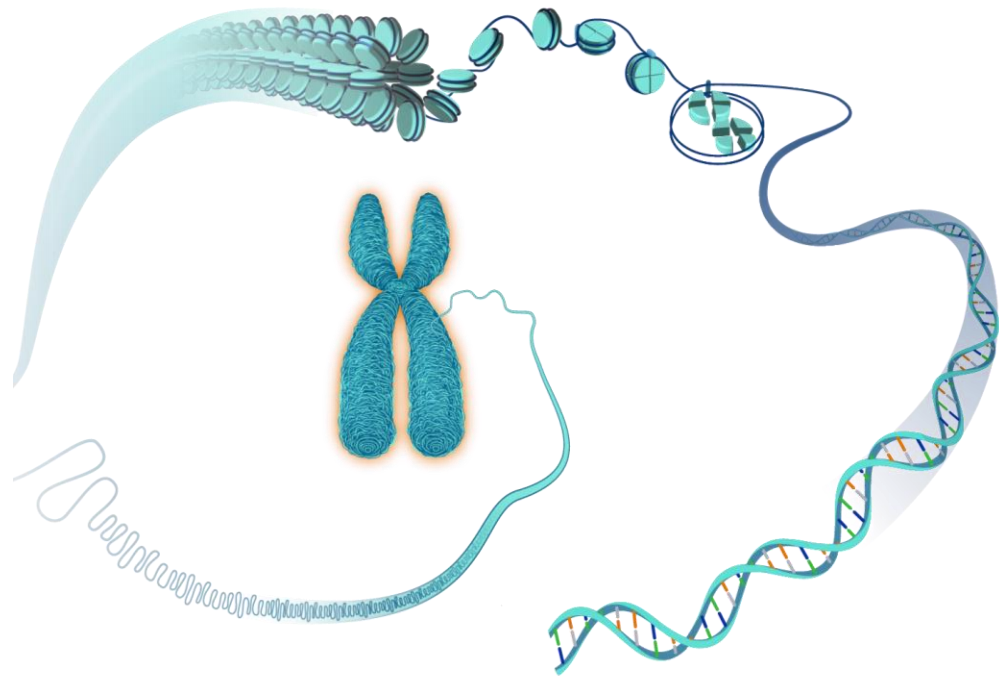
- “No hit” (lower risk) myeloma
 - **Good** lenalidomide maintenance benefit
- “Single hit” (intermediate risk) myeloma
 - **Exceptional** lenalidomide maintenance benefit
- “Double hit” (higher risk) myeloma
 - **High unmet need**, despite lenalidomide maintenance
- No overall survival benefit for continuation of lenalidomide after 38 months
- Dose of lenalidomide probably does not matter



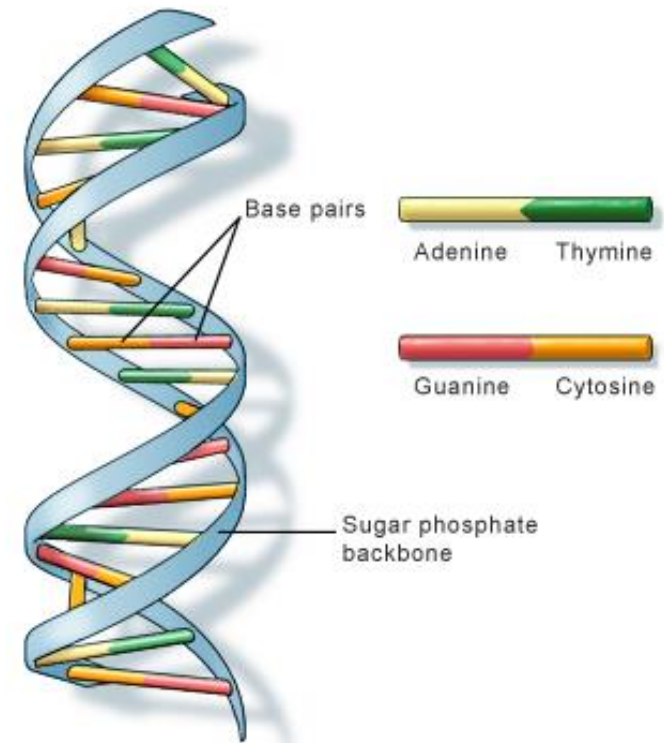
Panopoulou A Blood 2023 141:1666

Hari. ASCO 2020. Abstr 8506.

What do we mean by chromosome and FISH (fluorescent in situ hybridization) risk in myeloma?

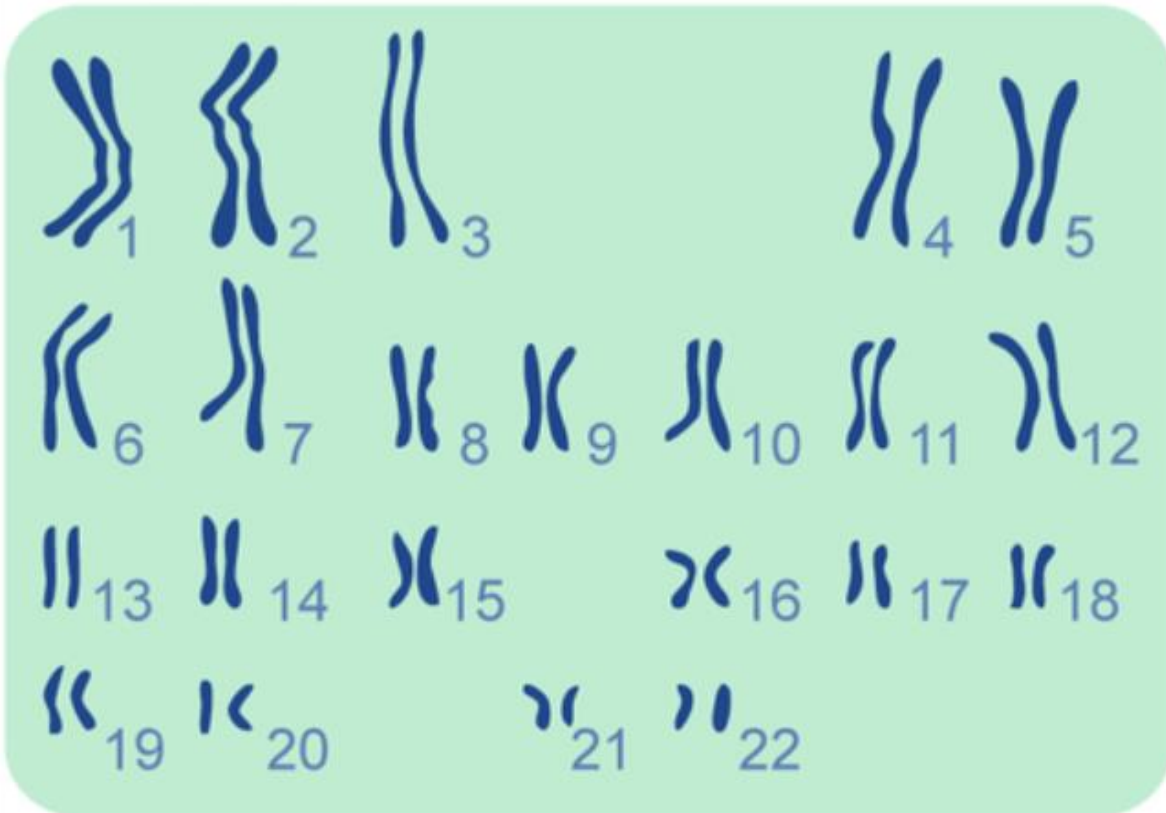


Each chromosome contains between 50 and 250 million base pairs

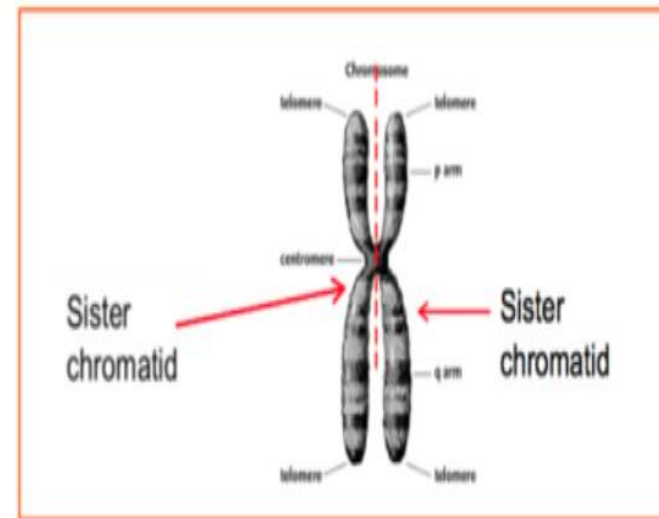


U.S. National Library of Medicine

Autosomes



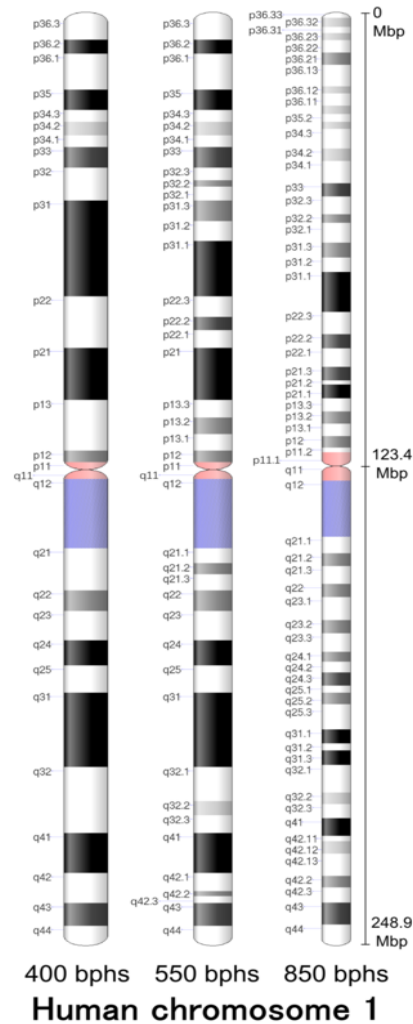
Sex chromosomes



- Somatic (body) cells usually contain **46** chromosomes
 - **Autosomes** (non-sex chromosomes): 22 pairs
 - **Sex chromosomes:**
 - XX → female
 - XY → male

Multiple myelom cells often show changes in chromosome numbers, or parts (loss or switches)

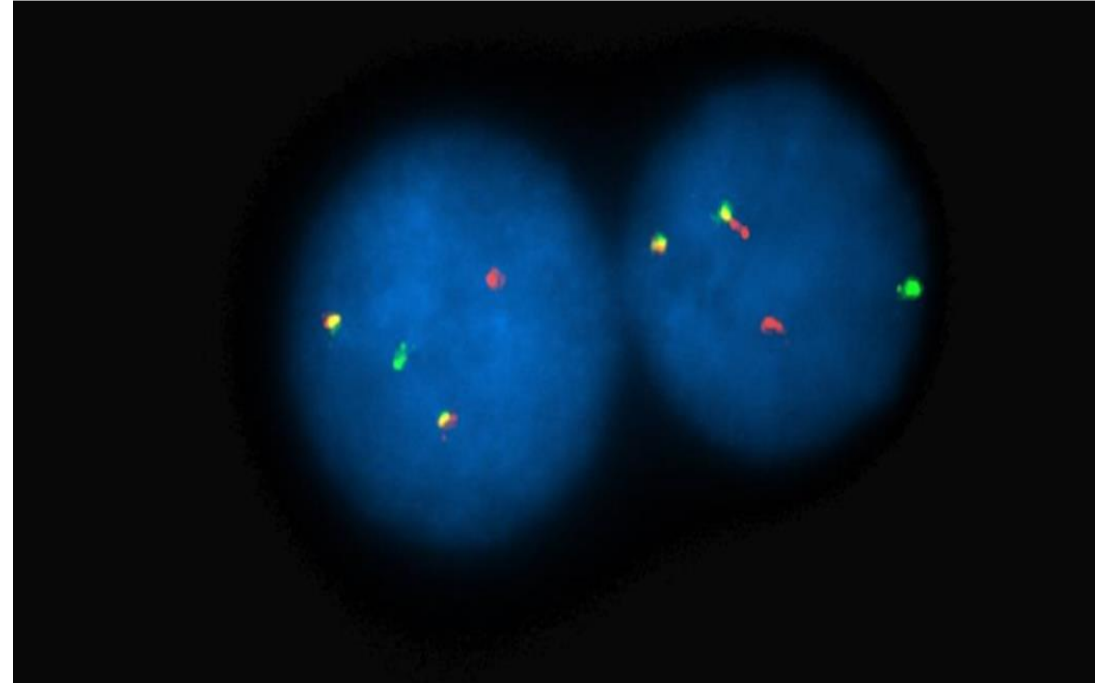
Many Myeloma Patients Have Abnormalities Involving Chromosome 1.



- How do extra copies (gain) or loss affect risk?
- Chromosome 1 has 250 million base pairs
- Approximately 2000 genes encoded
- One of the most common abnormalities among MM patients
- MM relevant genes include
 - CSK1B (1q21 amp/gain): confers growth advantage
 - FAM46C at 1p12
 - CDKN2C (tumor suppressor) at **1p32.3**, so LOSS contributes to tumor progression

FISH and Cytogenetic Changes Associated with Higher Risk Myeloma (Higher Risk is in Relapse, Not in Response to Initial Therapy)

- t(4;14),
- t(14;16),
- t(14;20),
- p53
- 1q amp or gain
- Del1p32¹
- ≥ 2 HR CA²



1 Blood 2023 141:1308. 2. J Clin Oncol. 2022 Sep 1;40(25):2901-2912;

Lenalidomide Approved by FDA for Maintenance 2/2/17

- Pooled analysis of four trials showed improved progression-free survival and overall survival with lenalidomide.
- Longer follow-up of participants in the 2009 lenalidomide versus placebo trial demonstrated progression-free survival and overall survival advantage with lenalidomide.
- UK trial with 1,917 patients demonstrated progression-free survival advantage with lenalidomide vs placebo in all risk groups.
- These results established lenalidomide as the standard of care.
- Only FDA-approved drug for myeloma maintenance



*Holstein S Lan Oncol 2017 4:e43
Jackson G Lan Oncol 2018*

Downside of Lenalidomide Maintenance Therapy

- **Cost:**
 - \$18,000 - \$25,000/month (~\$250,000/year)
 - Same price for every size capsule
 - Despite intro of “generic” no price decreases yet
- **Side Effects:**
 - 25% higher risk of infection (most not serious)
 - Gastrointestinal side effects
- Risk of secondary malignancies-hematologic cancer, but others as well



Lenalidomide – Gastrointestinal Side Effects

- Diarrhea
- Bloating
- Flatulence
- Gas
- Lower fat diet helps some individuals
- Bile salt binders, e.g. colestipol 1-2 grams daily, are quite helpful and may resolve symptoms completely



Pawlyn C Blood 2014 124: 2467

Secondary Cancers

- Secondary cancers are new cancers linked to previous cancer treatment
- Many examples across all types of cancers:
 - Leukemia and other blood disorders linked to previous breast cancer treatments
 - Young persons receiving radiation therapy for disorders such as Hodgkin lymphoma have increased risk of breast cancer, lung cancer
 - Children treated for cancers also have increased risks of new cancers later in life
- Risk of secondary cancer after auto transplant for myeloma = 4%
 - Death due to relapse is bigger risk

Other Agents Studied for Maintenance in Myeloma

- Ixazomib (Ninlaro®)
 - Currently not recommended as a single agent—two large randomized trials showed inferior survival to placebo
- Bortezomib (Velcade®)
 - Has been less promising than lenalidomide when used alone; no prolongation of survival
- Carfilzomib (Kyprolis®) *combined with* lenalidomide (Revlimid®)
 - Prolongs time over lenalidomide alone before myeloma becomes active again

Sonnevel P et al. Proc Ash; Abstract 404
Gay F Lancet Oncol 2021; 22: 1705–20

Anti CD 38 Antibodies as Maintenance Therapy

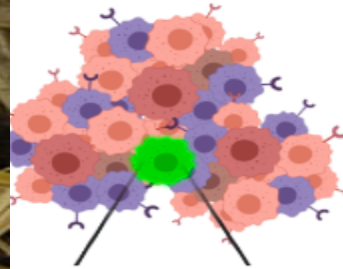
Daratumumab (Darzalex[®]) improved progression-free survival compared to no maintenance therapy in relapsed or refractory myeloma patients



Daratumumab (Darzalex[®]) – Pros and Cons

- Advantages:
 - Monthly or bi-monthly subcutaneous injection
 - Has been tested as single agent; initial analysis shows this is reasonable, but may be superfluous if person received daratumumab as part of initial therapy
 - Covered by Medicare part B (in clinic) so drug coverage not an issue
 - No significant GI side effects, like lenalidomide
- Disadvantages:
 - Increased risk of infection (mostly respiratory)
 - Decreased response to vaccines (e.g. COVID)

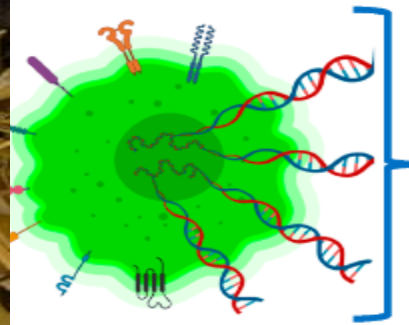
Is It Ever Possible to Stop Maintenance?



Need a baseline
Bone marrow sample

Minimal Residual Disease (MRD)

of rare neoplastic cells (<1%)
post-treatment follow-up,
complementary approaches:



**Molecular
diagnostics
(PCR, RT-qPCR)**

Genetic analysis to detect
specific DNA signatures

- sensitivity $10^{-3} - 10^{-6}$
- applicability >90%

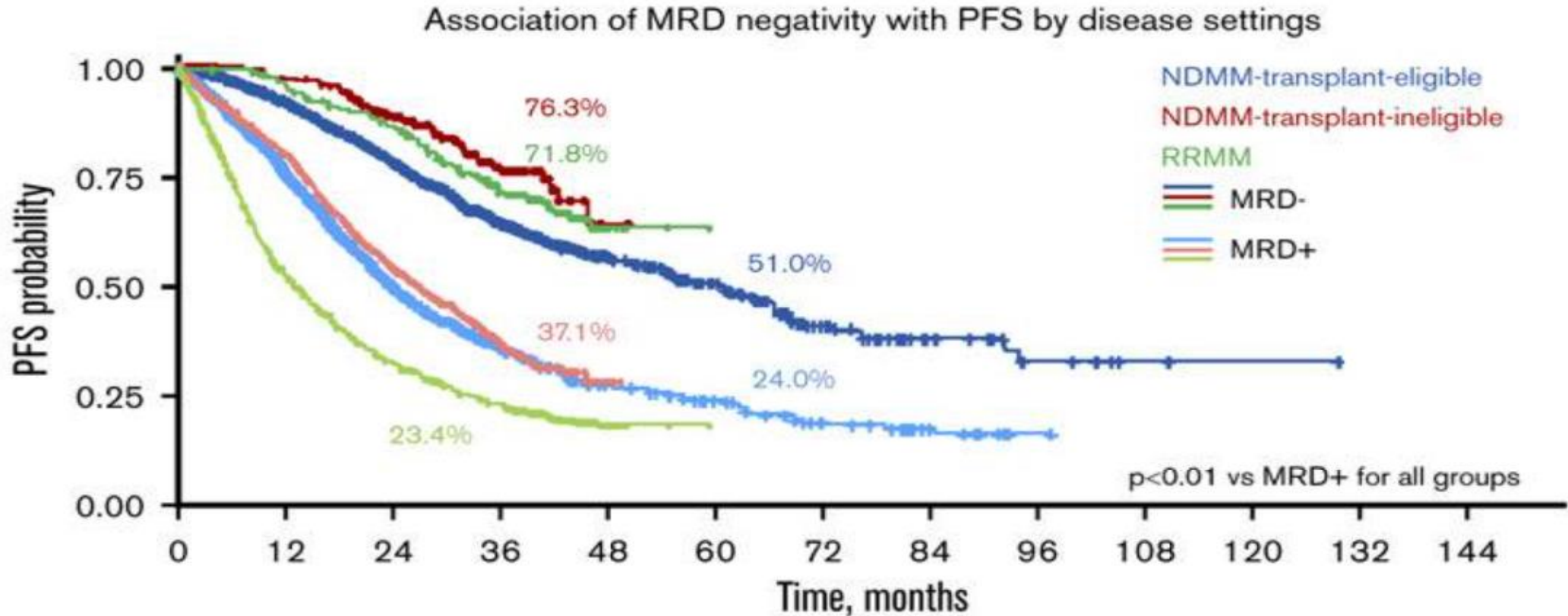


**Next Generation
Sequencing (NGS),
Digital PCR (ddPCR)**

**Next Generation
Flow (NGF)**

- sensitivity $< 10^{-5} - 10^{-6}$
- applicability >99%

Obtaining and Maintaining “Minimal Residual Disease” Status after Initial Treatment seems very important



Munshi N Blood Advances 2020

Daratumumab + Lenalidomide/Bortezomib/Dexamethasone versus Revlimid followed by auto transplant and either Daratumumab/Lenalidomide or Lenalidomide maintenance

- Improved complete remission rate
- 58% reduction in risk of disease progression or death compared to RVD alone
- 66% of patients became MRD negative and were able to stop daratumumab after two years

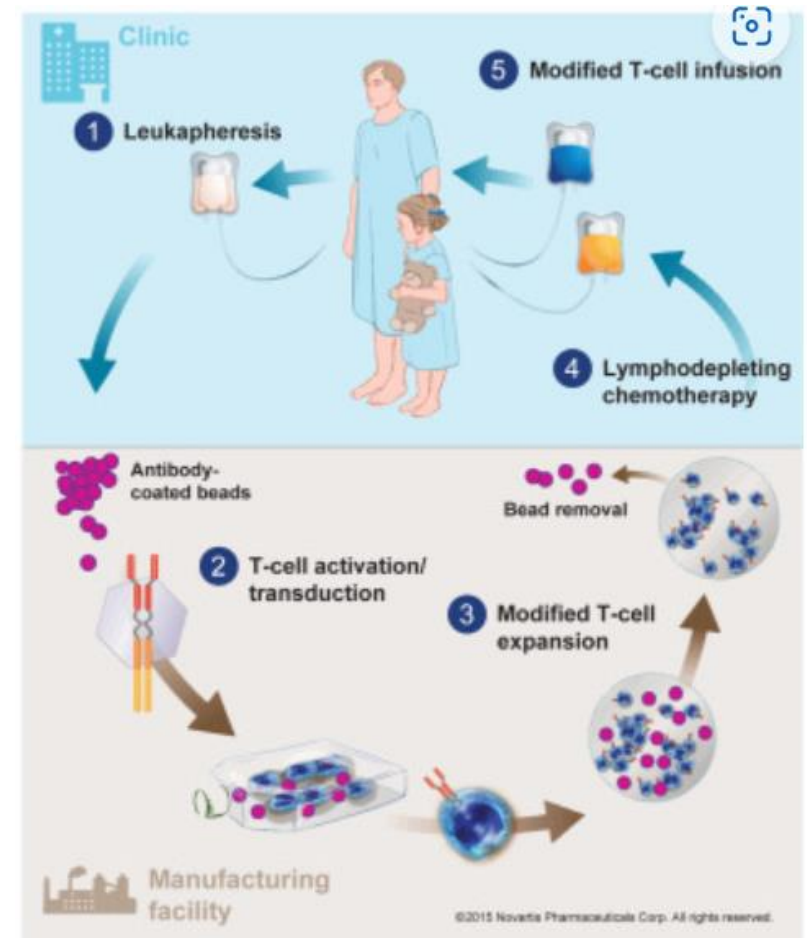
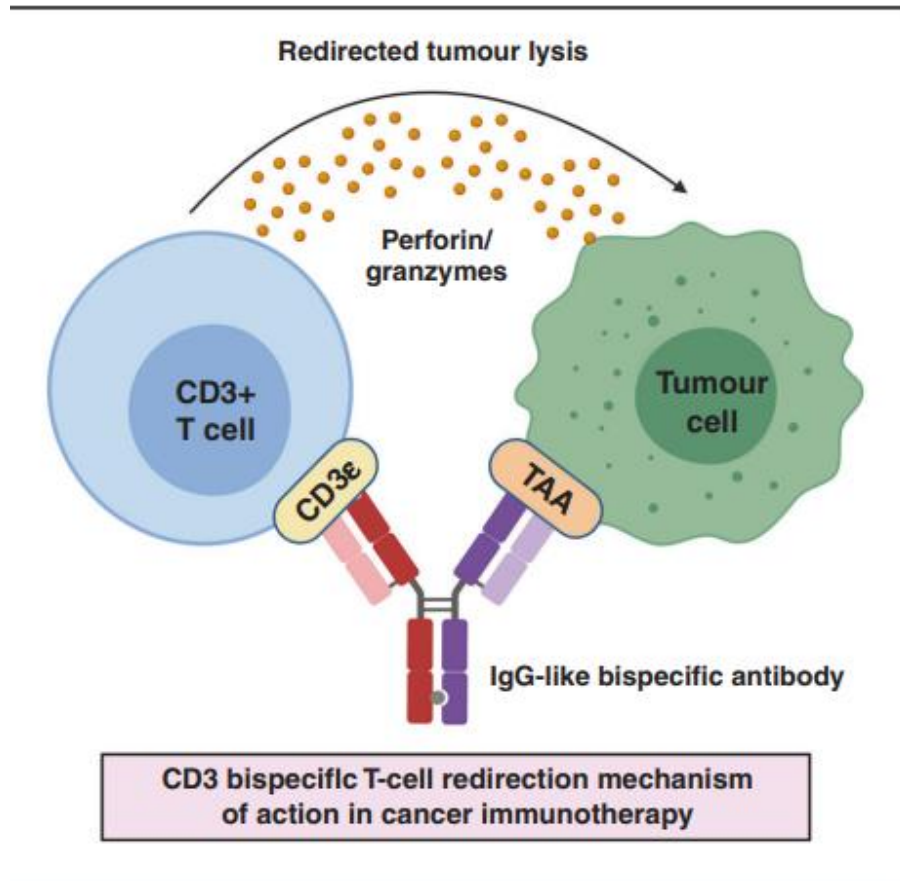
Sonnevold P NEJM 2024 390:301

Recent and Ongoing Maintenance Clinical Trials

- **DRAMMATIC trial (SWOG 1803):**
 - Compares lenalidomide versus lenalidomide +daratumumab
 - When completed, this will be the largest study conducted to date that examines the possibility of stopping maintenance treatment in patients with very “deep” remissions
- **MUK five protocol for relapsed myeloma-**
 - multi-center trial of carfilzomib, cyclophosphamide and dexamethasone (KCD) vs. cyclophosphamide, bortezomib (Velcade) and dexamethasone (VCD); then randomized to K maintenance or not
 - Carfilzomib maintenance associated with longer median progression-free survival

Up Next for Maintenance – T-cell Redirecting Therapy

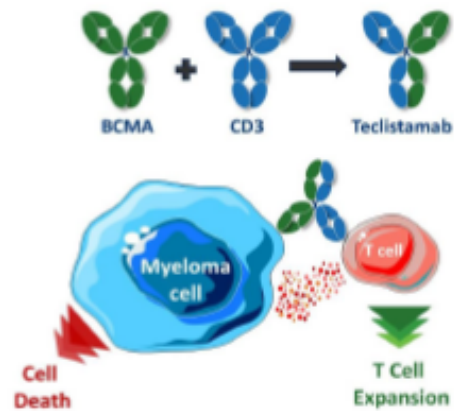
Bispecific Engager vs CAR T-cell Therapy



Three Bispecific Drugs Approved for Treatment of Relapsed Myeloma Being Tested in Maintenance

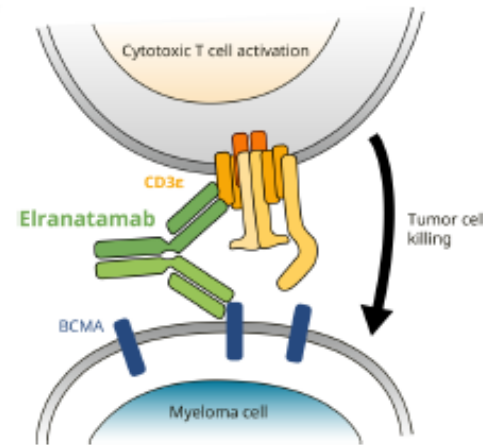
Teclistamab

Oct 2022



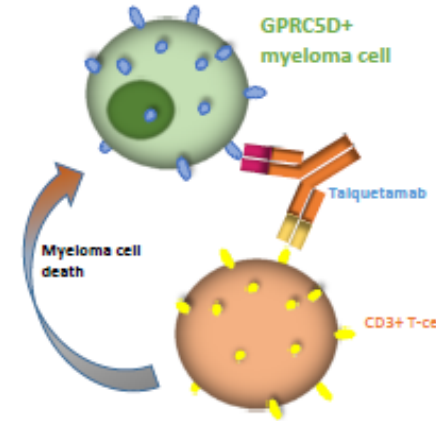
Elranatamab

Aug 2023



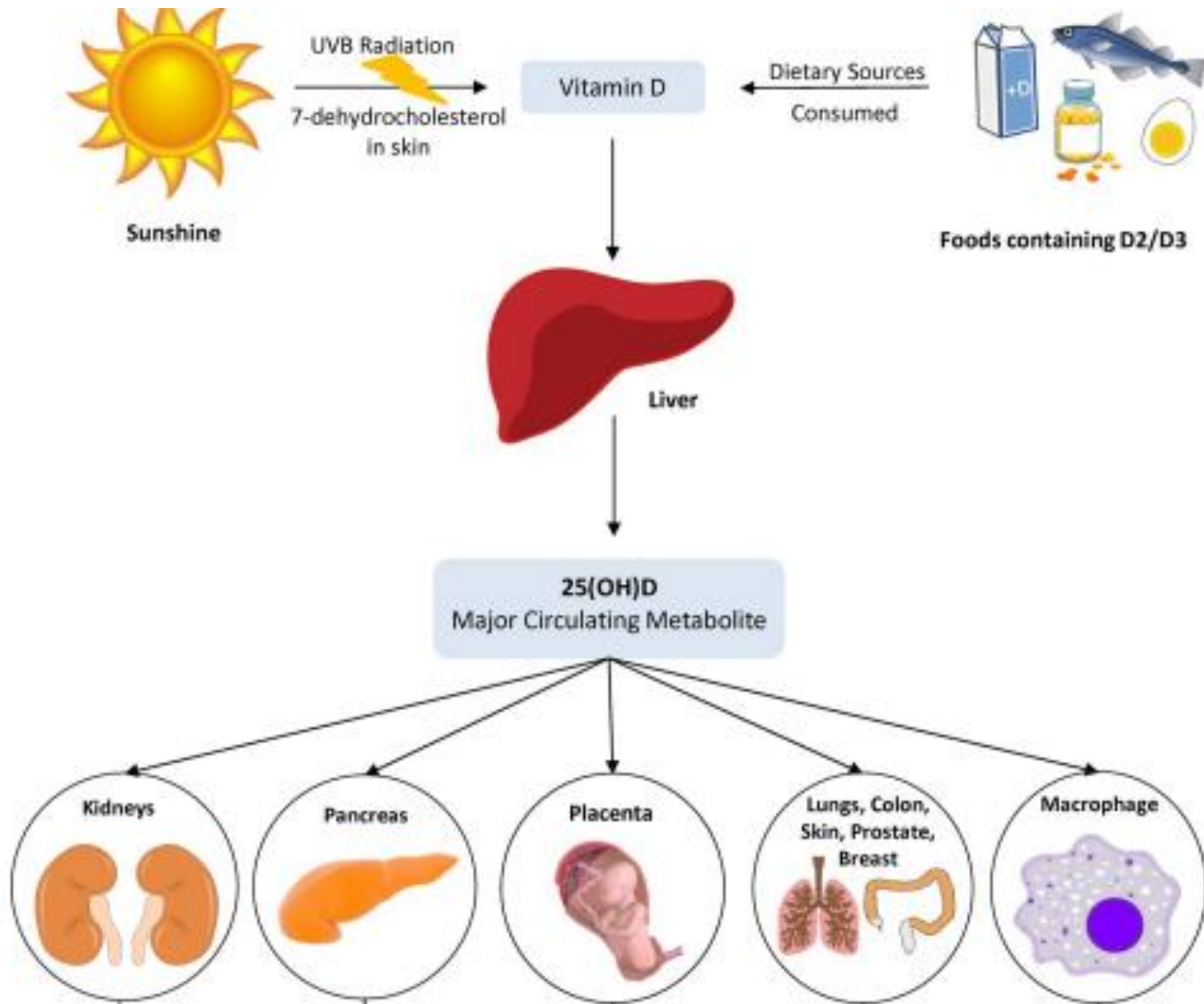
Talquetamab

Aug 2023



**FDA Label:

- Four Prior Lines of Therapy
- Previously treated with IMiD, PI and anti-CD38 monoclonal antibody



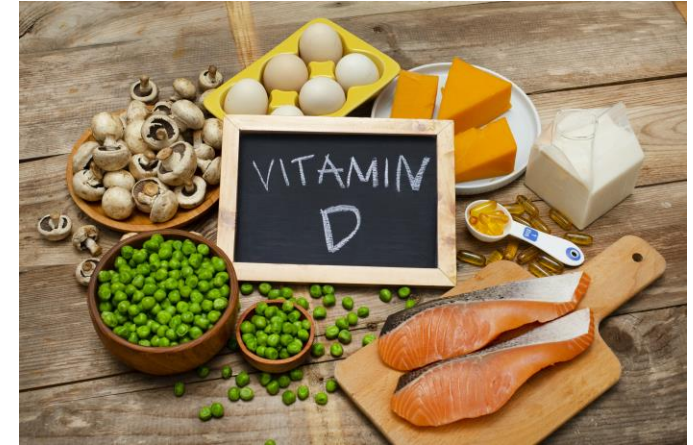
Vitamin D is important for calcium, cell production, immune function

Deficiency Linked to Short Time in Remission and Worse Overall Survival

Yellapragada Blood Adv (2020) 4(8):1643–6.

What about Non-Pharmaceutical Interventions?

- Diet
 - lower intake of red meat, more plant-based diet has been correlated with lower likelihood of developing myeloma
- Alcohol
 - Most studies show increased risk of cancer with increased alcohol intake
 - Several epidemiological studies have shown correlation between consumption and **lower risk** of developing MM



Jeon KH *Cancer Epidemiol Biomarkers Prev* (2022) 31 (3): 670–678;
Rota M *Euro J Canc Prev* 2014 23:113

CHAMPIONSHIPS
Tampa, FL



Conclusions

- Maintenance therapy for myeloma clearly extends the time from initial treatment to next treatment and probably increases survival
- Agents with strong evidence for this effect include lenalidomide, daratumumab
- Multi-agent maintenance may be appropriate for some high-risk multiple myeloma patients
- Unfortunately, routine maintenance brings cost and side effects
- Strategies to shorten time on maintenance are coming





Questions?



Natalie Callander MD

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