

EBMT European Society for Blood and Marrow Transplantation

Clinical benefit after galinpepimut-S (GPS), a Wilms' tumor 1 (WT1) immunotherapeutic, correlates with antigen-specific immune responses in high-risk multiple myeloma:

Complete analysis of the Phase 2 GPS maintenance study

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Disclosures

- G. Koehne is a consultant to Sellas Life Sciences Group, Inc.

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WT1 gene product in MM

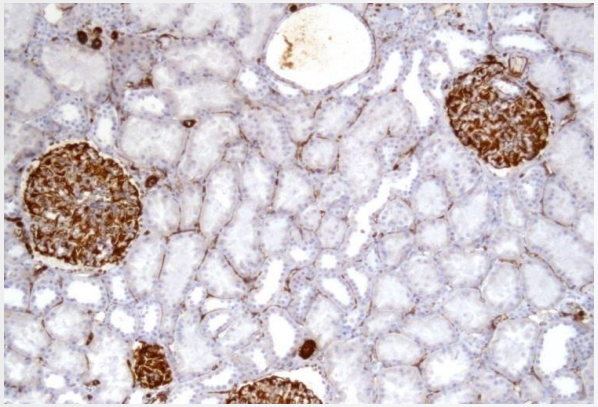
- The WT1 protein is a zinc finger transcription factor
  - A true oncogene, with roles in cell proliferation, differentiation, apoptosis, and organ development
  - National Cancer Institute top-ranked antigen for anticancer immunotherapy[1]
- WT1 overexpression in MM cells by IHC, and formation of peptide fragment (RMFPNAPYL)/ HLA-A*0201 complex on the MM–T-cell engagement interface in HLA-A*0201+ patients[2]
- WT1-specific IRs following donor lymphocyte infusion post–CD34(+)-selected allografts in MM patients[3]
- Encouraging clinical and preliminary IR results in patients with MM immunized with GPS, a first-in-class WT1-targeting heteroclitic peptide vaccine, following ASCT, previously reported in a Phase 2 study, along with absence of high-grade systemic adverse events[4–7]

ASCT, autologous stem cell transplantation; CD, cluster of differentiation; GPS, galinpepimut-S; HLA, human leukocyte antigen; IHC, immunohistochemistry; IR, immune response; MM, multiple myeloma; WT1, Wilms' tumor 1.

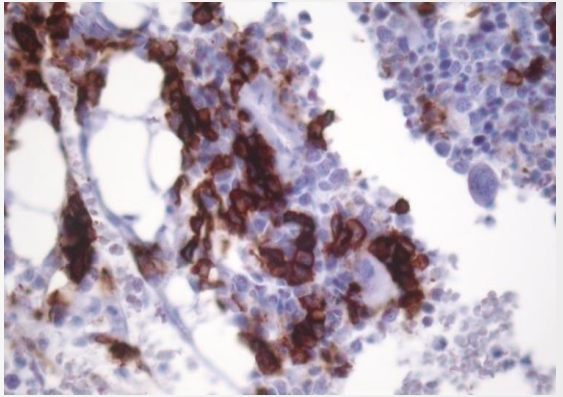
1. Cheever MA, et al. *Clin Cancer Res*. 2009;15:5323–37. 2. Koehne G, et al. *ASH 2015*. Abstr. 98. 3. Tyler EM, et al. *Blood*. 2013;121:308–17. 4. Koehne G, et al. *EBMT 2017*. Abstr. O094. 5. Koehne G, et al. *ASCO 2017*. Abstr. 8016. 6. Koehne G, et al. *EHA 2017*. Abstr. E1252. 7. Koehne G, et al. *SOHO 2017*. Abstr. MM–252.

IHC with WT1 monoclonal antibody 6F-H2 in MM

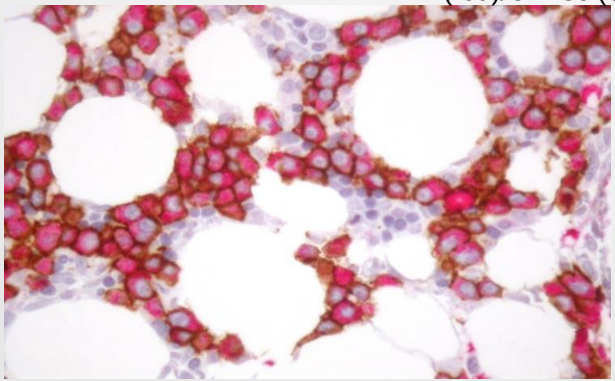
WT1 (red) staining of kidney biopsy

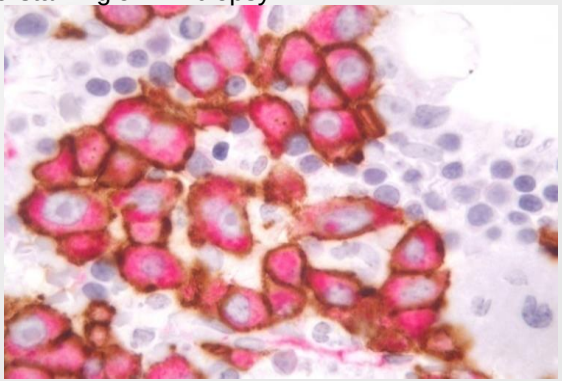


CD138 (brown) staining of BM biopsy



WT1 (red)/CD138 (brown) co-staining of BM biopsy



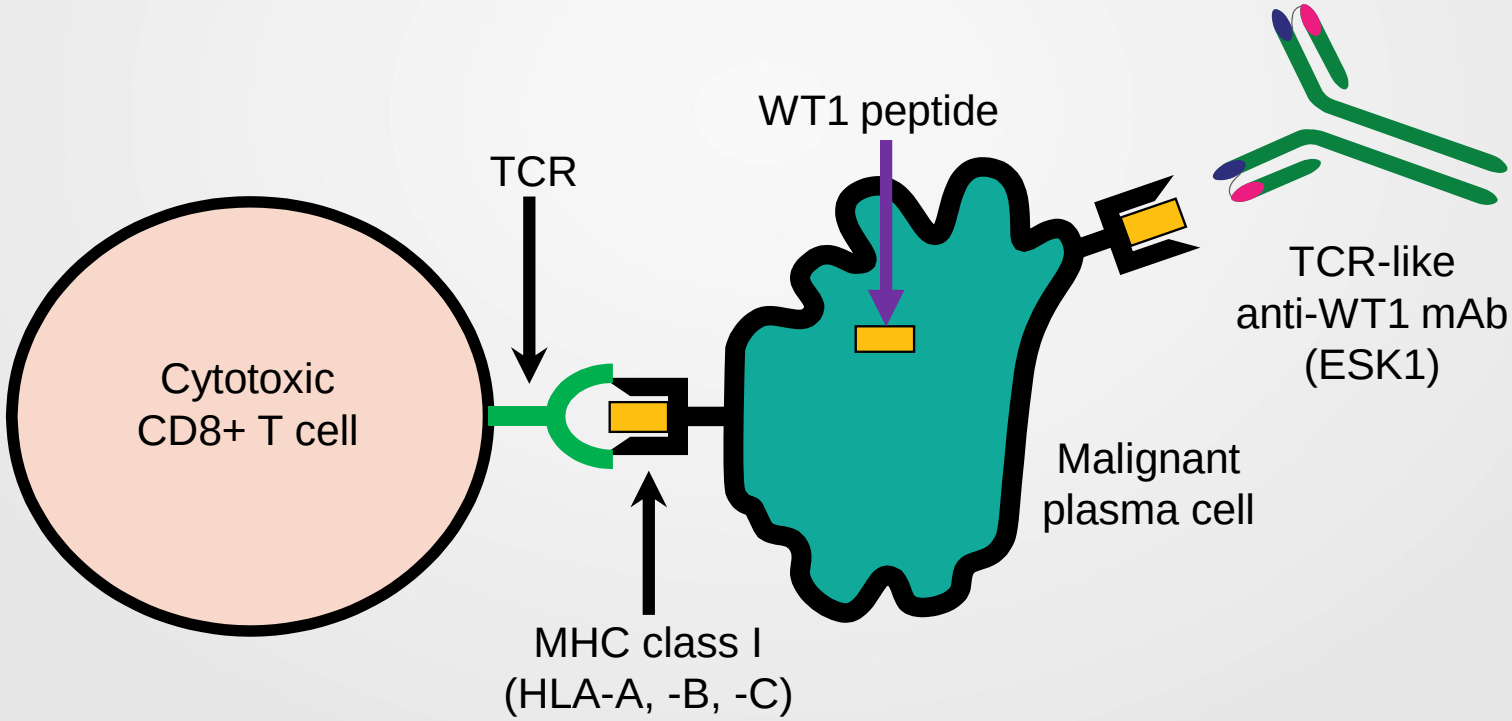


BM, bone marrow; CD, cluster of differentiation; IHC, immunohistochemistry; MM, multiple myeloma; WT1, Wilms' tumor 1.

Tyler EM, et al. *Blood.* 2013;121:308–17.

WT1 peptides are presented efficiently via an MHC/antigen complex to the TCR

Demonstrated by successful targeting of WT1 by TCR-like mAbs (ESK1)

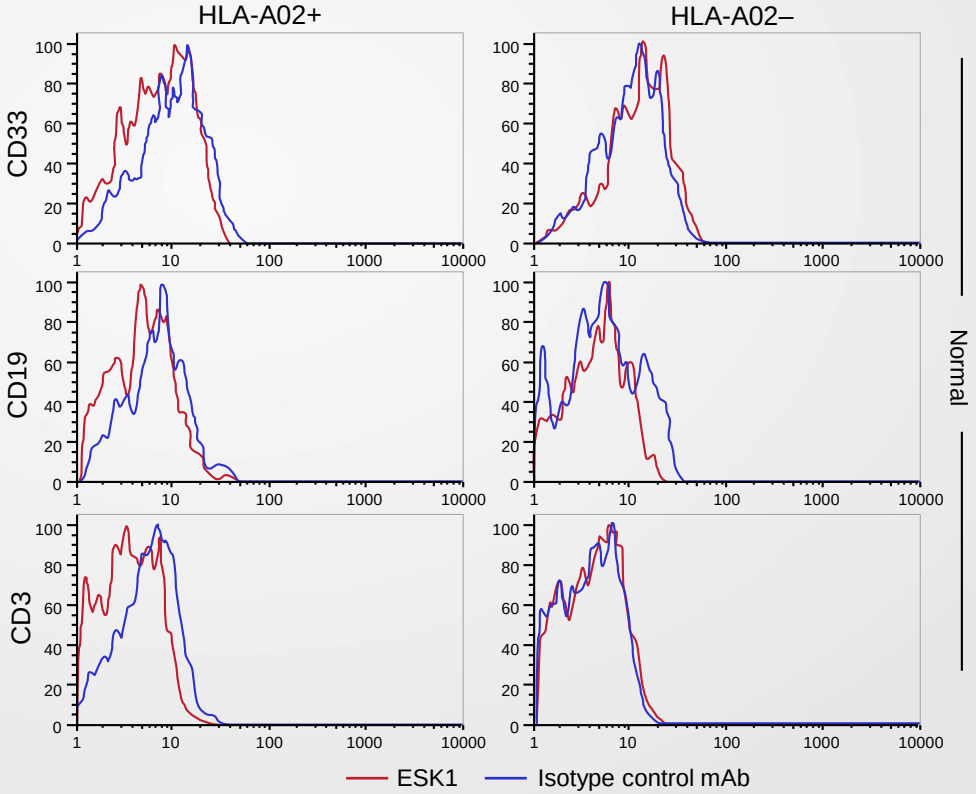


CD, cluster of differentiation; HLA, human leukocyte antigen; mAb, monoclonal antibody; MHC, major histocompatibility complex; TCR, T-cell receptor; WT1, Wilms' tumor 1.

Rafiq S, et al. *Leukemia.* 2017;31:1788–97.

Binding of anti-WT1 monoclonal antibody ESK1 to PBMCs from healthy donors

- Gated cells are listed on the y-axis (single representative of 16 samples)

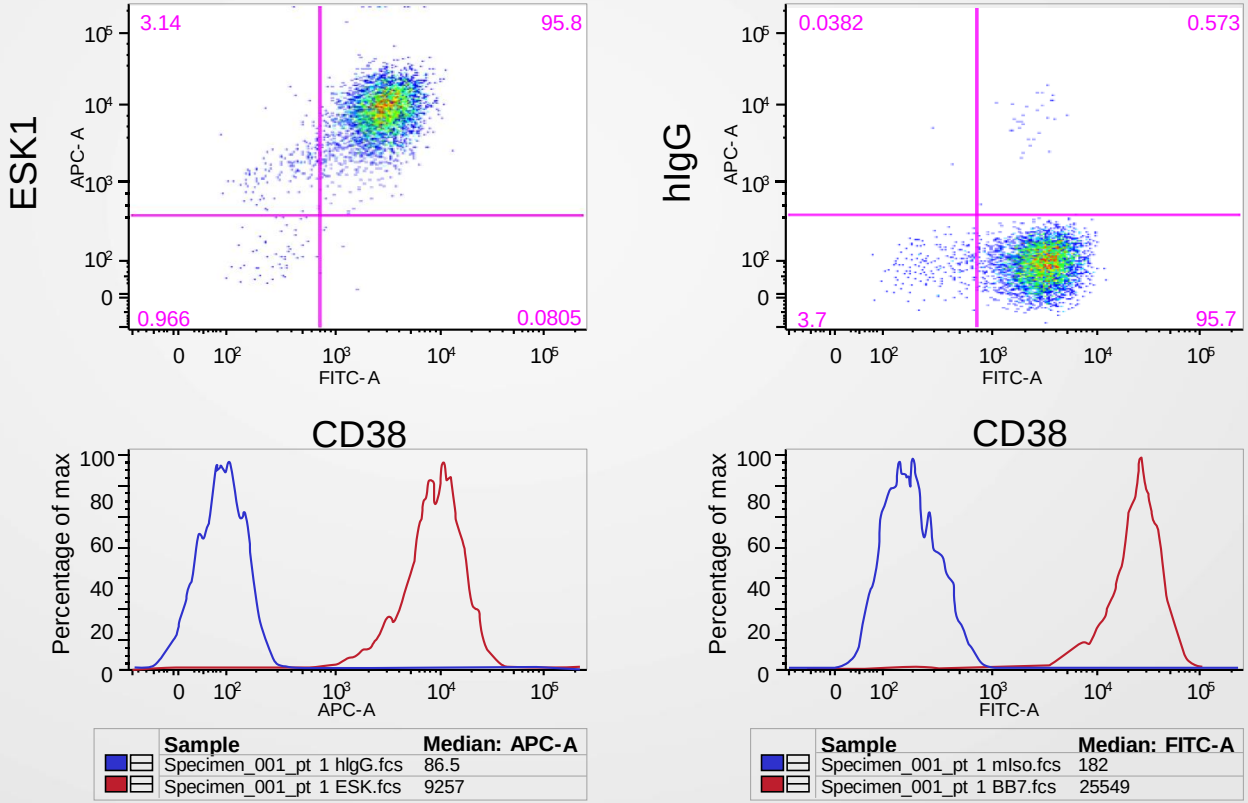


CD, cluster of differentiation; HLA, human leukocyte antigen; PBMCs, peripheral blood mononuclear cells; WT1, Wilms' tumor 1.

Dao & Scheinberg, MSKCC; data on file.

ESK1 staining of MM BMMCs of a patient with plasma cell leukemia

- BB7: mouse Ab against HLA-A02



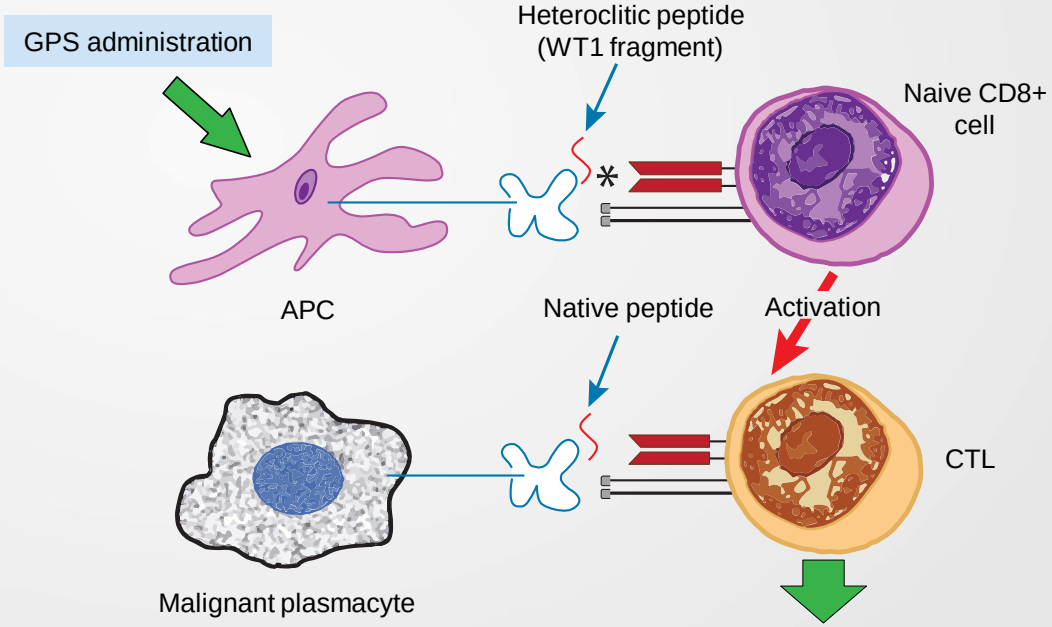
Ab, antibody; APC, allophycocyanin; BMMC, bone marrow mononuclear cell; CD, cluster of differentiation; FITC, fluorescein isothiocyanate; HLA, human leukocyte antigen; hIgG, human immunoglobulin G; MM, multiple myeloma.

Koehne & Scheinberg, MSKCC; data on file.

Heteroclitic technology-based cancer immunogens/ vaccines

- GPS is a mixture of 2 native and 2 synthetic WT1 peptide sequences: the heteroclitic peptides – bearing point mutations (*) – were created to stimulate both CD4+ and CD8+ T-cell responses

- Heteroclitic peptides
  - Have higher affinity for HLA,
  - Are prone to break tolerance, and
  - Generate a response to the native peptide sequence (of the cognate target antigen) expressed by cancer cells



APC, antigen-presenting cell; CD, cluster of differentiation; CTL, cytotoxic T lymphocyte; GPS, galinpepimut-S; HLA, human leukocyte antigen; TCR: T-cell receptor; WT1, Wilms' tumor 1.

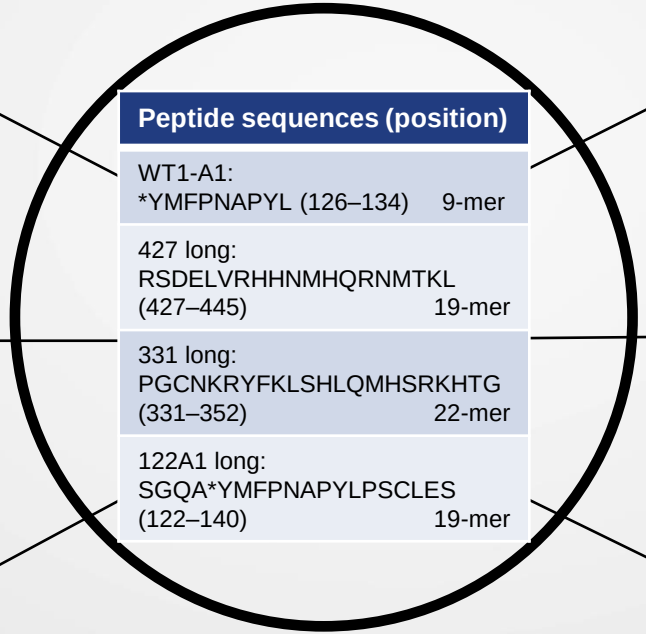
Krug LM, et al. *Cancer Immunol Immunother*. 2010;59:1467–79. May RJ, et al. *Clin Cancer Res*. 2007;13:4547–55. Pinilla-Ibarz J, et al. *Leukemia*. 2006;20:2025–33.

GPS: Differentiated WT1 vaccine immunotherapeutic[1–6]

Multivalent immunogen – 4 peptide chains:
Two of the 4 peptides are heteroclitic – bearing point mutations (*)

Elicits **multi-epitope, broad cross-reactivity** along the full length of the WT1 protein

Broad specificity across **multiple HLA types** and potential application to **~20 types of malignancies**



Heteroclitic peptide increases immune response and mitigates tolerance, while maintaining antigenicity profile

- Also strengthens MHC class I and II binding for optimal recognition of the corresponding native peptide sequence

Production of both **CD4+ and CD8+** WT1-specific activated cells

Activity predicated upon **overcoming barriers of adverse/ immunosuppressive TME**

- Monotherapy studies are in the setting of complete remission/MRD

*Mutated (heteroclitic) peptides – whereby Tyr (Y) replaces Arg (R), R being in the native sequence.

CD, cluster of differentiation; GPS, galinpepimut-S; HLA, human leukocyte antigen; MHC, major histocompatibility complex; MRD, minimal residual disease; TME, tumor microenvironment; WT1, Wilms' tumor 1.

1. Maslak PG, et al. *Blood Adv*. 2018;2:224–34. 2. Maslak PG, et al. *Blood*. 2010;116:171–9. 3. Krug LM, et al. *Cancer Immunol Immunother*. 2010;59:1467–79. 4. Pinilla-Ibarz J, et al. *Leukemia*. 2006;20:2025–33. 5. Gomez-Nunez M, et al. *Leuk Res*. 2006;30:1293–8. 6. May RJ, et al. *Clin Cancer Res*. 2007;13:4547–55.

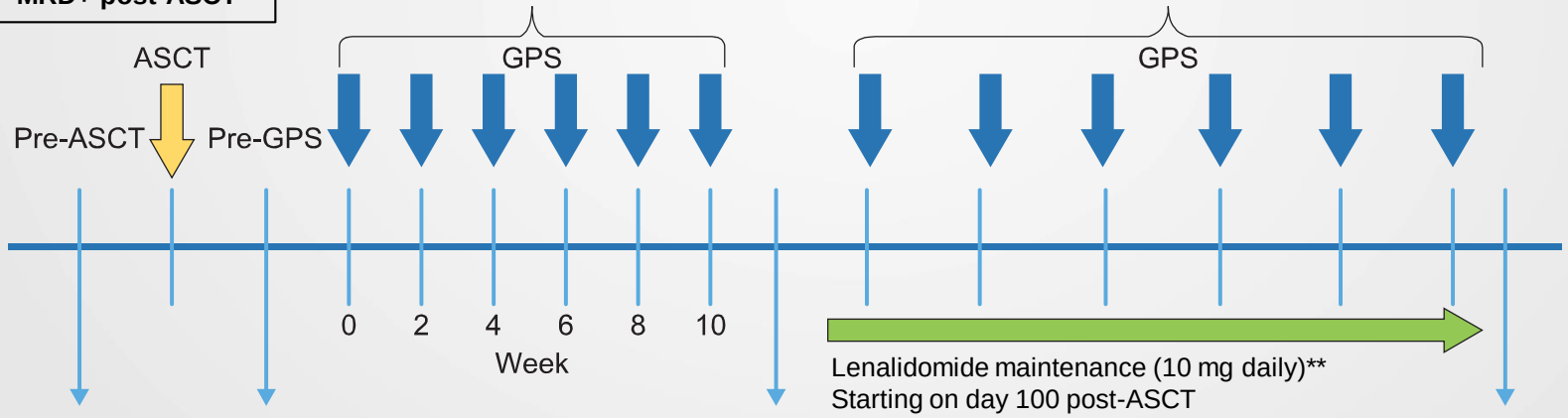
Phase 2 study of GPS in MM: Key features and GPS administration schedule

N = 19 (evaluable)
- **15/19 pts HR CG*,[1] at baseline**
- **18/19 pts at least MRD+ post-ASCT**

- GPS biweekly s.c. administration (dose of 200 µg for each of the 4 peptides)
- First GPS administration within 22 days of ASCT
- 6 doses over 10 weeks

- GPS monthly s.c. administration (dose of 200 µg for each of the 4 peptides)
- 6 additional doses

Study number:
NCT01827137
MSK 12-288



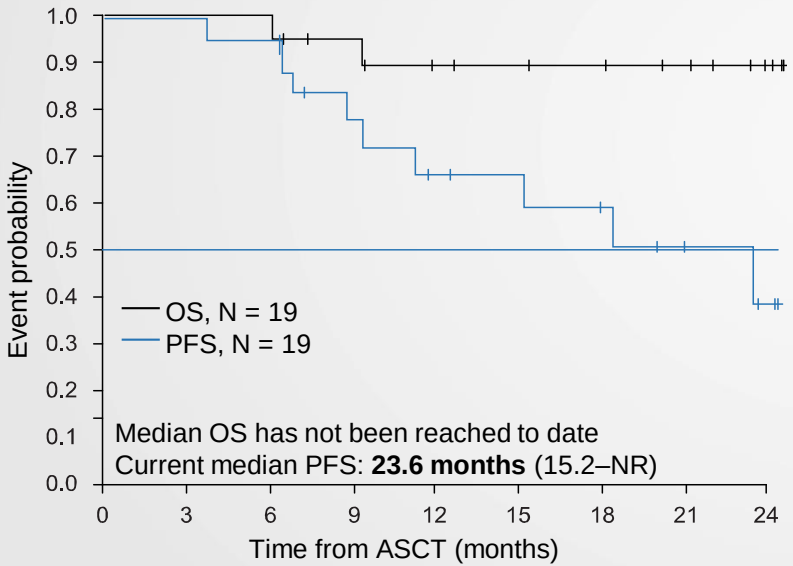
*HR CG included the following aberrations: -13/del[13q], -17/del[17p], t[4;14], t[14;16], t[14;20], hypodiploidy [<45 chromosomes, excluding -Y], and Chr 1 aberrations [+1, -1, t(1;x)], per IMWG risk classification.[1]
**One patient was maintained with bortezomib instead.

ASCT, autologous stem cell transplantation; Chr, chromosome; correl., correlative translational studies (serially assessed results, incl. IR, CG, MRD, WT1 expression by RT-PCR, and select molecular markers); GPS, galinpepimut-S; HR CG, high-risk cytogenetics; ICS, intracellular cytokine staining; IFNγ, interferon gamma; IMWG, International Myeloma Working Group; IR, immune response (WT1-specific T-cell responses, assessed by ICS for IFNγ); MM, multiple myeloma; MRD, minimal residual disease; pts, patients; RT-PCR, reverse transcription polymerase chain reaction; s.c., subcutaneous; WT1, Wilms' tumor 1.

1. Sonneveld P, et al. *Blood*. 2016;127:2955–62.

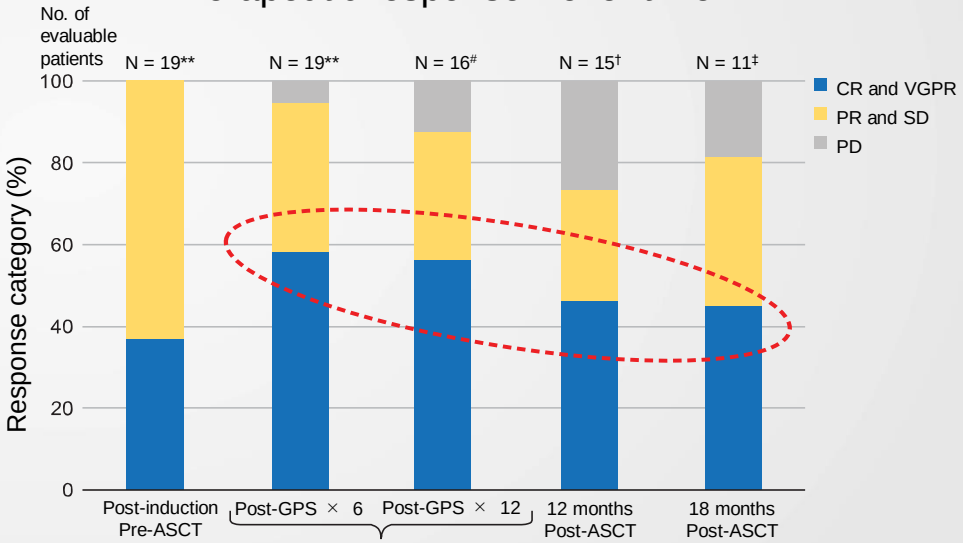
Efficacy endpoints: Updated results

OS and PFS



Median follow-up among survivors: 20 months
(range: 7–34 months)

Therapeutic response*,[1] over time



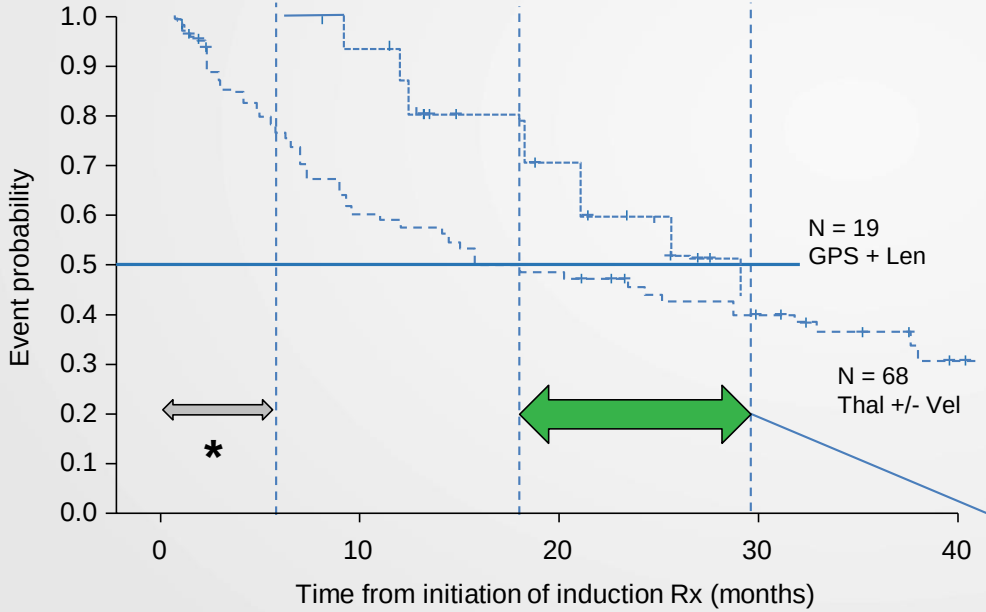
*CR/VGPR, PR/SD, and PD, per IMWG criteria.[1]
**Eighteen of 19 patients had MRD or worse at post-induction and pre-ASCT.
#Progressed at previous assessment (n = 1) and had not received full course of GPS by the time of analyses (n = 2).
†Progressed or died at previous assessment (n = 2) and had not received full course of GPS by the time of analyses (n = 2).
‡Progressed or died at previous assessment (n = 2), had not received full course of GPS by the time of analyses (n = 2), withdrew consent (n = 1), and had not yet undergone response assessment by the time of analyses (n = 3).

ASCT, autologous stem cell transplantation; CR, complete response; GPS, galinpepimut-S; IMWG, International Myeloma Working Group; MRD, minimal residual disease; NR, not reached; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VGPR, very good partial response.

1. Kumar S, et al. *Lancet Oncol*. 2016;17:e328–46.

PFS of MM patients with high-risk cytogenetics

GPS + Len vs. Thal +/- Vel maintenance



PETHEMA 2005–001110–41
Thal +/- Vel maintenance

PFS = 12.6 months
(estimated from time of ASCT)
PFS = 18.1 months
(from initiation of induction Rx)

GPS MSK study
GPS + Len maintenance

PFS = 23.6 months
(from time of ASCT)
PFS = 29.1 months
(from initiation of induction Rx)

Difference in PFS = 11 months
(1.87–fold higher with GPS + Len)

Notes: High-risk cytogenetics are defined per IMWG risk classification[1]. Thal +/- Vel maintenance: After induction therapy followed by melphalan conditioning and successful ASCT. *Median time period from induction therapy initiation to ASCT = 5.5 months in the first-line setting. Historical control Kaplan-Meyer curve from Rosinol L, et al[2]. Juxtaposition of results is shown for illustrative purposes only.

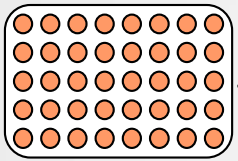
ASCT: autologous stem cell transplant; GPS, galinpepimut-S; IMWG, International Myeloma Working Group; Len: lenalidomide; MM: multiple myeloma; PFS: progression-free survival; Rx, radiotherapy; Thal, thalidomide; Vel: (Velcade®, bortezomib);.

1. Sonneveld P, et al. *Blood.* 2016;127:2955–62. 2. Rosinol L, et al. *Blood.* 2012;120:1589–1596.

WT1-specific T-cell IRs over time: Methodology



PBMC sample

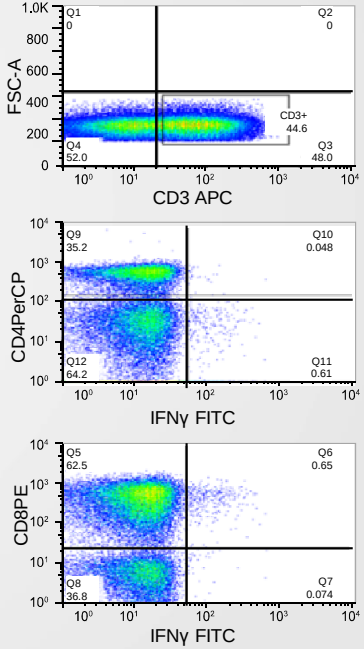


WT1 peptides + brefeldin A

- Fix cells
- Permeabilize
- Stain



FACS with gating to CD8+ and CD4+ T cells
Plotting against post-incubation production of IFNγ



Host IR tested against

6 WT1 individual peptides

- 2 natives (of GPS mixture)
- 2 heteroclitics (of GPS mixture) and their native counterparts (set of 4)

"All-pool" WT1 peptides

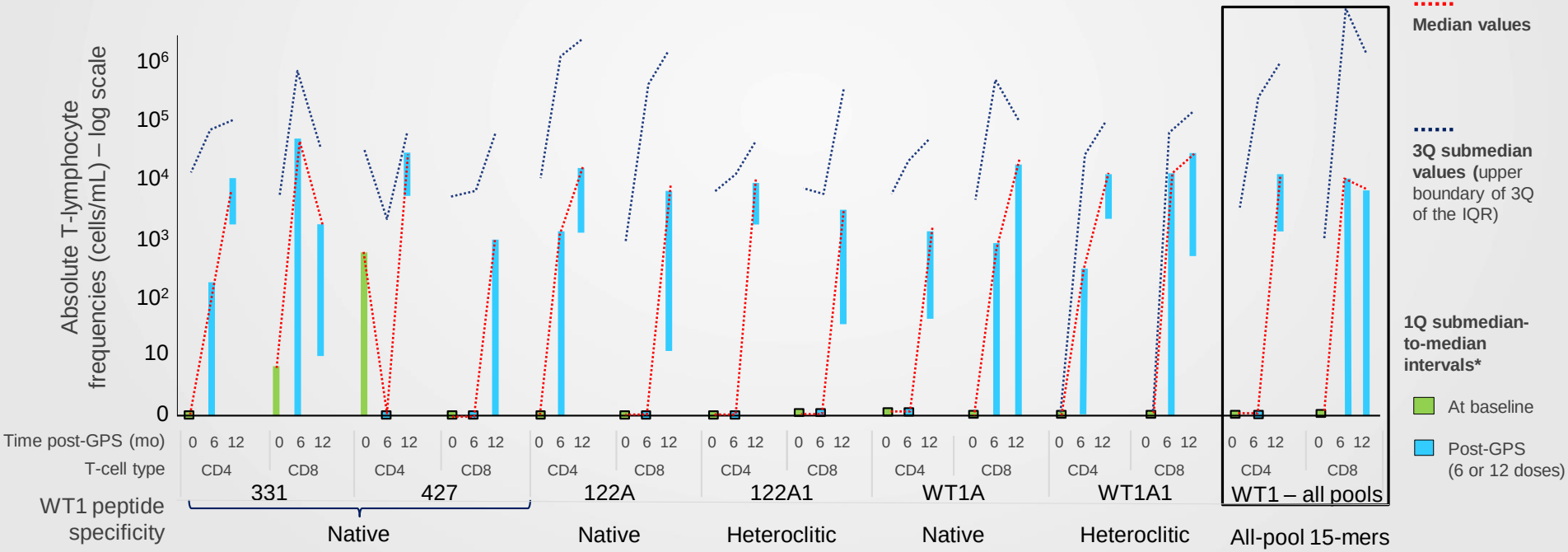
- 113 partially overlapping 15-mers along the entire WT1 protein

Surrogate marker of cross-epitope reactivity (akin to "epitope spreading")

Readout:
Absolute frequency of T cells of interest

APC, allophycocyanin; CD, cluster of differentiation; FACS, fluorescence-activated cell sorting; FITC, fluorescein isothiocyanate; FSC-A, forward side scatter area; GPS, galinpepimut-S; IFNγ, interferon gamma; IR, immune response; PBMC, peripheral blood mononuclear cell; PE, phycoerythrin; PerCP, peridinin-chlorophyll-protein; WT1, Wilms' tumor 1.

Induction of antigen-specific IRs (CD8/CD4) by GPS: T-cell frequencies over time (complete study database)



*Interval between the median value and the upper boundary of the 1Q of the IQR; shown as thin vertical colored bars.

1Q, 1st quartile; 3Q, 3rd quartile; CD, cluster of differentiation; GPS, galinpepimut-S; IQR, interquartile range; IR , immune response; mo, months; WT1, Wilms' tumor 1.

Absolute number and percentage of patients with IR positivity (CD8/CD4) over time

	Against any of the WT1 antigenic variants of GPS			Against "all-pool" WT1 fragments (cross-epitope reactivity)	
Timepoint	Baseline (pre-ASCT; N = 15)	Post-GPS × 6 (N = 15)	Post-GPS × 12 (N = 12)	Baseline (pre-ASCT; N = 15)	Post-GPS × 12 (N = 12)
Patients, N (%)	6 (40)*	9 (**60**)	12 (**100**)	4 (27)**	9 (**75**)[#]

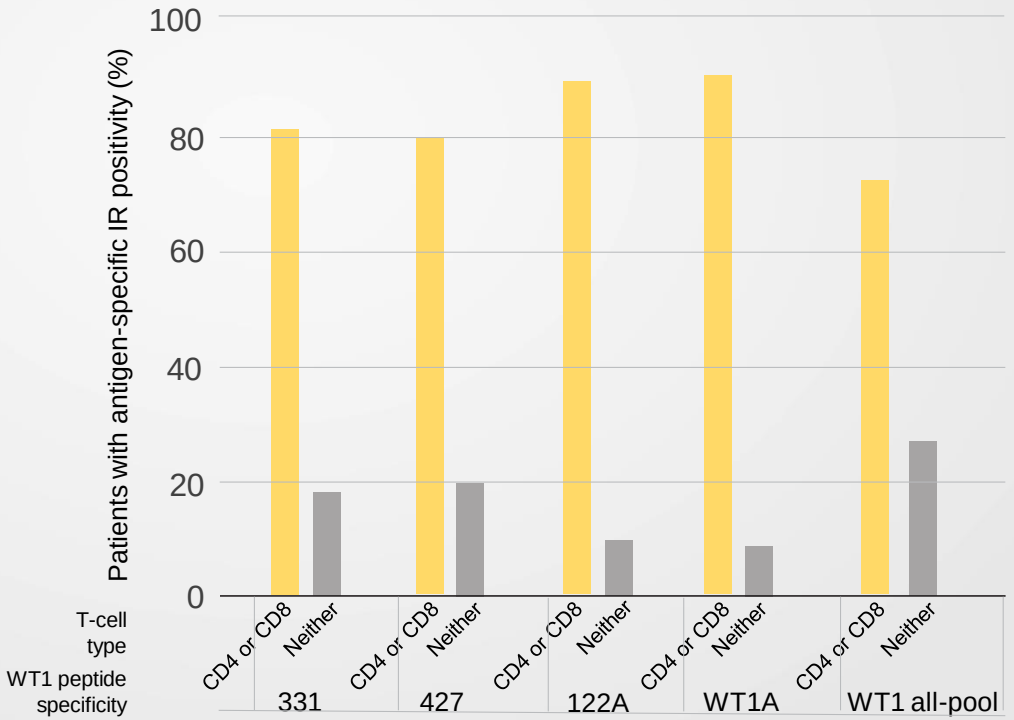
*Out of the 6 pts who were IR+ at baseline, only 2 had presence of reactive CD8+ cells (at a low level, <200 cells/mL), while all 6 pts had detectable presence of reactive CD4+ cells (2 at a low level,<200 cells/mL).
**All 4 pts who were IR+ to "all-pool" antigens had only detectable CD4+ cells; no CD8+ baseline reactivity was seen.
[#]Approximately equal frequency of CD4 and CD8 IR positivity.

ASCT, autologous stem cell transplantation; CD, cluster of differentiation; GPS, galinpepimut-S; IR, immune response; pts, patients; WT1, Wilms' tumor 1.

Rates of antigen-specific IR positivity (CD8/CD4) at the time of completion of GPS therapy

- **IR+ rates for:**
  - The **4 peptides in GPS**
    - CD4 OR CD8: **72%–91%**
  - The **"all-pool" peptides**
    - CD4 OR CD8: **75%**

- Up to 64% of patients demonstrated IR positivity (CD4/CD8) against >1 WT1 peptide (multivalent IRs)



Note: Completion of GPS therapy was achieved after 12 GPS doses.

CD, cluster of differentiation; GPS, galinpepimut-S; IR, immune response; WT1, Wilms' tumor 1.

Exploratory correlations between IR positivity and clinical response (achievement of CR/VGPR) at the time of completion of GPS therapy

- **Rate of IR positivity in patients who achieved CR/VGPR**
  - **81.8%** demonstrated prior **CD8 IR+** (N = 9)
  - **100%** demonstrated prior **CD4 IR+** (N = 11)

- **Rate of achievement of CR/VGPR in patients who maintained IR positivity***
  - **54.6%** – if **CD4 IR+ was maintained** to any of the *4 native GPS* peptides (N = 11)
  - 44.0% – if CD8 IR+ was maintained to any of the *4 native GPS* peptides (N = 9)
  - **62.5%** – if **CD4 IR+ was maintained to *"all-pool"*** peptides (N = 8)
  - **57.1%** – if **CD8 IR+ was maintained to *"all-pool"*** peptides (N = 7)

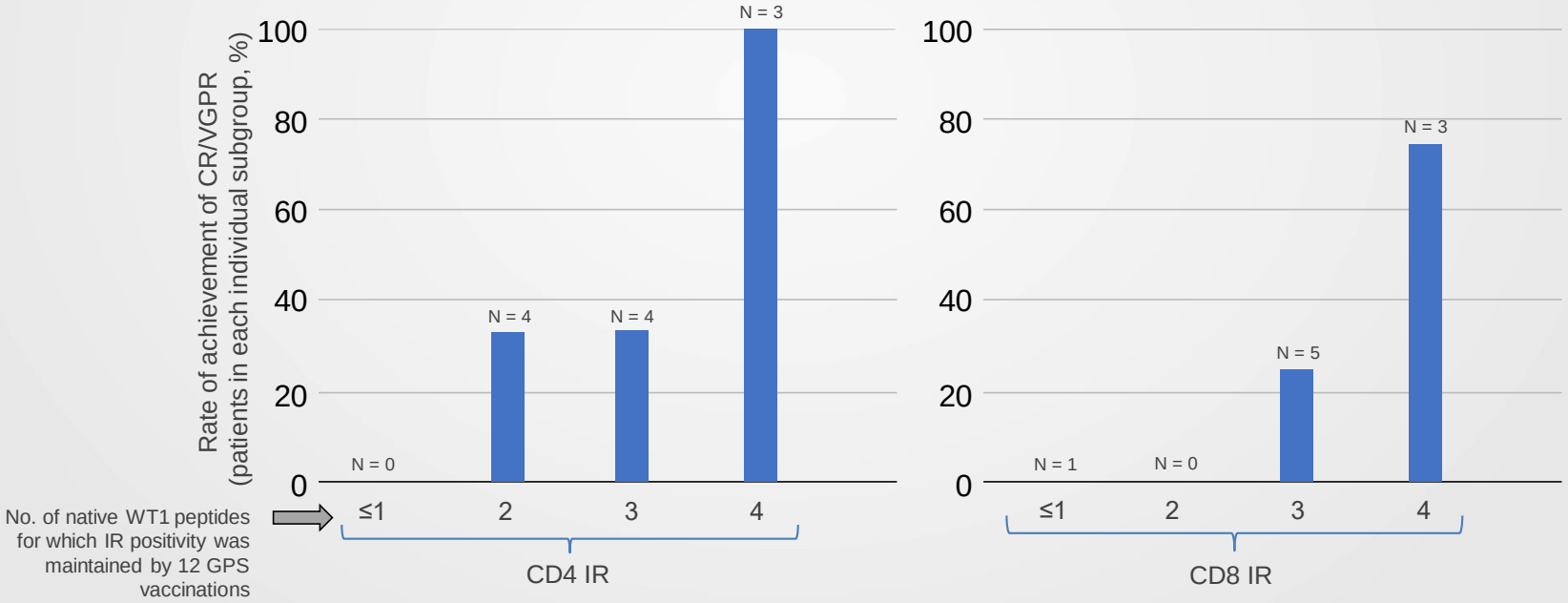
* Rates of >50% denote strong association

Note: CR/VGPR was assessed per IMWG criteria[1] at the time of completion of GPS therapy (after 12 doses of GPS). Varying number of patients were evaluable for each pair of these exploratory correlative analyses.

CD, cluster of differentiation; CR, complete response; GPS, galinpepimut-S; IMWG, International Myeloma Working Group; IR, immune response; VGPR, very good partial response.

1. Kumar S, et al. *Lancet Oncol.* 2016;17:e328–46.

MM patients maintaining multivalent IRs (CD8/CD4) were more prone to achieve clinical response (CR/VGPR) at the time of completion of GPS therapy



Note: CR/VGPR was assessed per IMWG criteria[1] after 12 doses of GPS (completion of GPS therapy). Varying number of patients were evaluable for each pair of these exploratory analyses; hence, the rates shown cannot be added across subgroups.

CD, cluster of differentiation; CR, complete response; GPS, galinpepimut-S; IMWG, International Myeloma Working Group; IR, immune response; MM, multiple myeloma; VGPR, very good partial response; WT1, Wilms' tumor 1.

1. Kumar S, et al. *Lancet Oncol.* 2016;17:e328–46.

Conclusions (1)

- Administration of the WT1 heteroclitic peptide mixture immunizer GPS in a Phase 2 study of 19 high-risk patients with MM has shown an excellent safety profile and a promising median PFS of 23.6 months (post-ASCT in first line) in a particularly challenging setting

- Impressive, time-dependent, and robust CD8 or CD4 IRs specific for the 4 WT1 peptides within GPS, as well as the 2 native counterpart peptides, were confirmed in up to 91% of patients across HLA allele types
  - Multivalent IRs emerged in up to 64% of patients

ASCT, autologous stem cell transplantation; CD, cluster of differentiation; GPS, galinpepimut-S; HLA, human leukocyte antigen; IR, immune response; MM, multiple myeloma; PFS, progression-free survival; WT1, Wilms' tumor 1.

Conclusions (2)

- Multifunctional cross-epitope T-cell reactivity was observed in 75% of patients to antigenic epitopes against which hosts were not specifically immunized, in a pattern akin to antigen cross-reactivity
- A strong and bidirectional association was observed between achievement of CR/VGPR clinical status (per IMWG criteria) and frequency as well as potency of IRs at the time of completion of all planned vaccination boosters; this effect was more notable for CD4+ T-cell responses or IR multivalency
- These data suggest a distinctive link between clinical and immune responses, which has not been previously described for a peptide vaccine in MM. The results offer mechanistic underpinnings for immune activation against WT1 in patients with aggressive MM, and point to the urgent need for further testing of the putative antimyeloma activity of GPS in more extensive clinical studies

CD, cluster of differentiation; CR, complete response; GPS, galinpepimut-S; IMWG, International Myeloma Working Group; IR, immune response; MM, multiple myeloma; VGPR, very good partial response; WT1, Wilms' tumor 1.

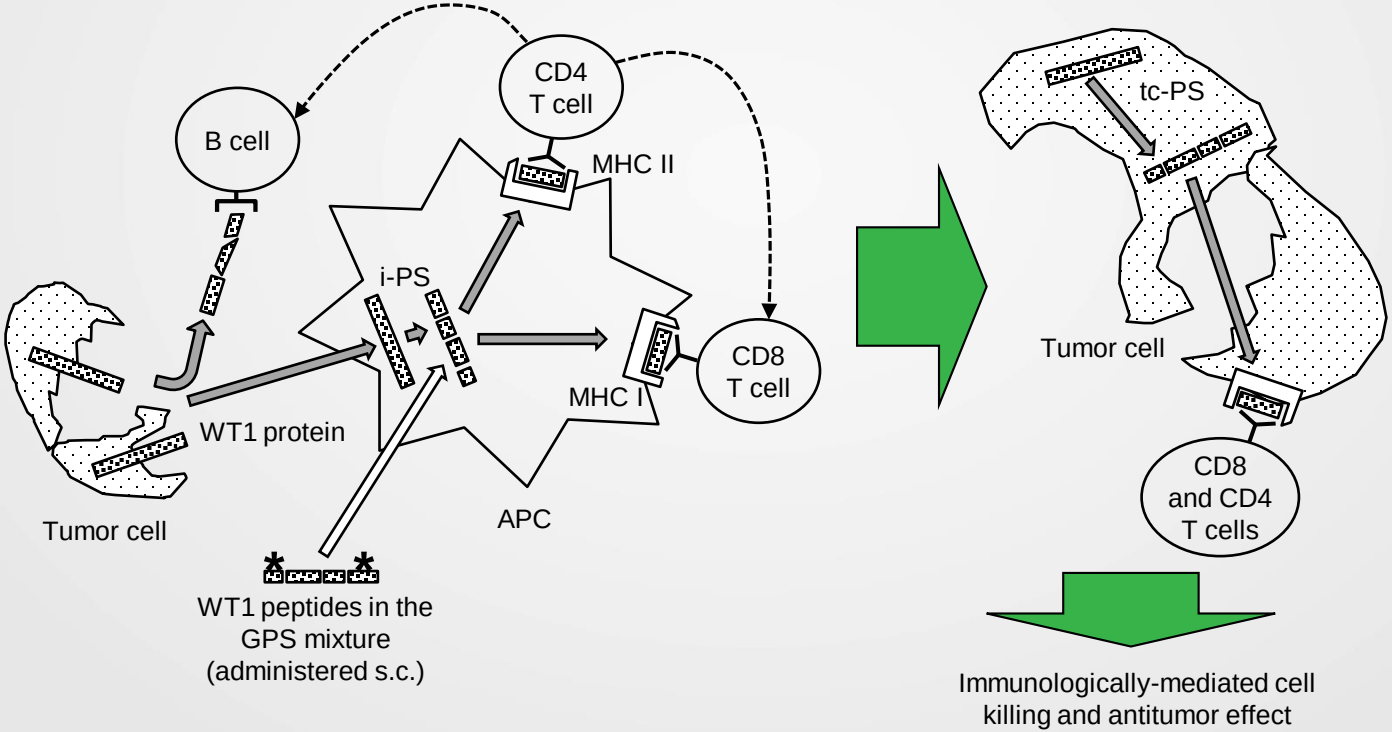


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Questions?

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GPS: Mechanism of action

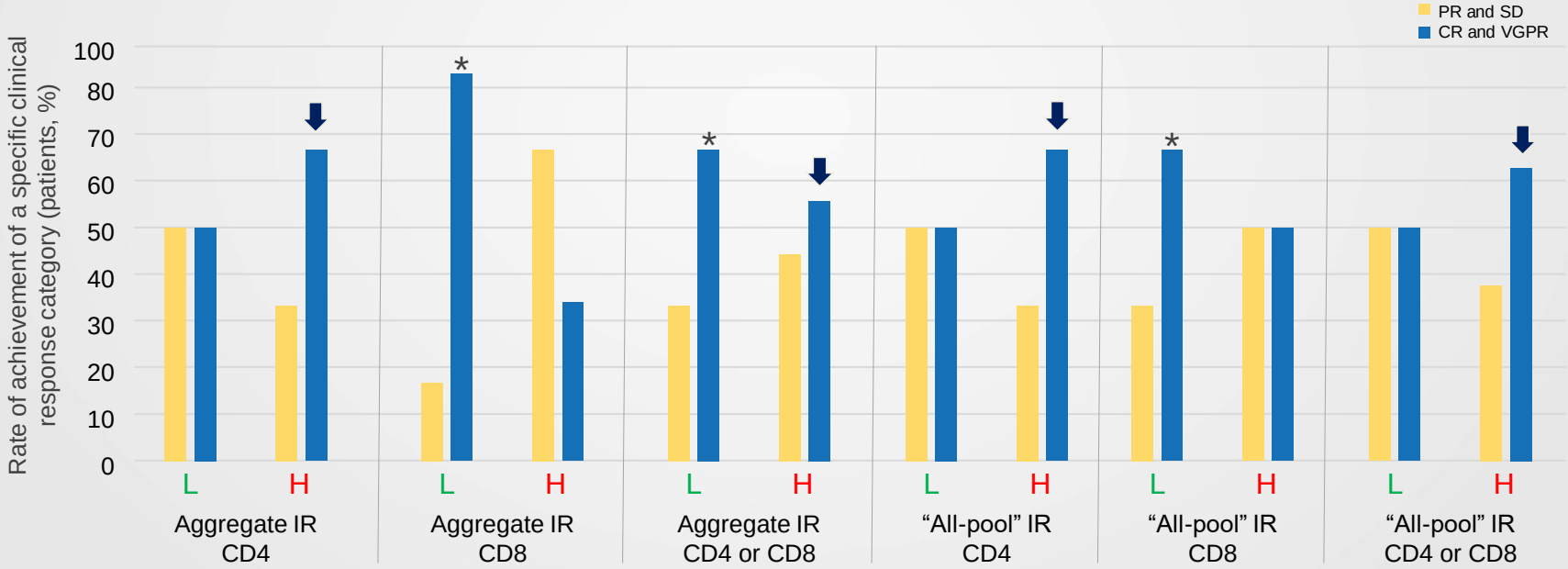


*Mutated (heteroclitic) peptides.

APC, antigen-presenting cell; CD, cluster of differentiation; GPS, galinpepimut-S; i-PS: immuno-proteasome; MHC, major histocompatibility complex; s.c., subcutaneous; tc-PS: tumor cell proteasome; WT1, Wilms' tumor 1.

Based on information in: 1. Oka Y, et al. *Sci World J.* 2007;7:649–65. 2. Oka Y, et al. *Oncol Res Treat.* 2017;40:682–90.

Clinical response category (CR/VGPR vs. less) at the time of completion of GPS therapy is associated with CD4 IR potency (high vs. low)



Notes: a. A total N = 12 patients were evaluable for each pair of these exploratory correlative analyses.
b. Aggregate potency of IR against WT1 peptides was arbitrarily derived as follows: the "per patient average" of absolute T-cell frequencies against any of the 4 antigens was first calculated, and then the median value of those averages was derived and used to divide IRs into high vs low potency subgroups of equal patient numbers.
c. CR/VGPR and PR/SD were assessed per IMWG criteria[1] at the time of completion of GPS therapy (after 12 doses of GPS).

1. Kumar S, et al. *Lancet Oncol.* 2016;17:e328–46.

CD, cluster of differentiation; CR, complete response; GPS, galinpepimut-S; H, high; IMWG, International Myeloma Working Group; IR, immune response; L, low; PR, partial response; SD, stable disease; VGPR, very good partial response; WT1, Wilms' tumor 1.