SELLAS LIFE SCIENCES GROUP

R&D Day 2019
Welcome and Introductions

Angelos M. Stergiou, MD, ScD h.c.

New York City, NY

15 November 2019

NASDAQ: SLS

FORWARD LOOKING STATEMENTS

Today's presentations contain forward-looking statements. You can identify such forward-looking statements by the use of the words "expect," "believe," "will," "anticipate," "estimate," "plan," "project" and other words of similar import. The forward-looking statements in these presentations include, but are not limited to, statements related to the potential of our clinical candidates as therapeutic options for various cancers, the general development of the Company's product candidate pipeline and anticipated milestone dates, and the effects of the Company's approach to cancer treatment. These forward-looking statements are based on current plans, objectives, estimates, expectations and intentions, and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, without limitation, risks and uncertainties associated with immune-oncology product development and clinical success thereof, the uncertainty of regulatory approval, and other risks and uncertainties affecting SELLAS and its development programs. These risks and uncertainties are described more fully under the caption "Risk Factors" in the in SELLAS' Annual Report on Form 10-K filed on March 22, 2019 and in its other filings with the Securities and Exchange Commission. Other risks and uncertainties of which SELLAS is not currently aware may also affect SELLAS' forward-looking statements. The forward-looking statements herein are made only as of the date hereof. SELLAS undertakes no obligation to update or supplement any forward-looking statements to reflect actual results, new information, future events, changes in its expectations or other circumstances that exist after the date as of which the forward-looking statements were made.

AGENDA

Sellas Life Sciences KOL Breakfast Symposium

Galinpepimut-S (GPS): The Next Generation of Cancer Immunotherapy

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8:15 - 8:25 **Welcome and Introduction**

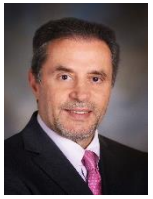
Dr. Angelos Stergiou, President & CEO of SELLAS Life Sciences



8:25 - 8:45 **Acute Myeloid Leukemia (AML) Landscape**

Dr. Hagop M. Kantarjian, University of Texas MD Anderson Cancer Center

- Current treatment landscape and future direction
- Potential role of GPS in AML



8:45 - 9:10 **Cancer Vaccines**

Dr. Javier Pinilla-Ibarz, H. Lee Moffitt Cancer Center

- Overview of competitive landscape
- GPS as a differentiated approach



9:10 - 9:35 **Multiple Opportunities for GPS**

Dr. Nicholas J. Sarlis, Chief Medical Officer of SELLAS Life Sciences

- Clinical overview of Phase 3 trial of GPS in AML patients in CR2



Dr. Jeffrey S. Weber, Perlmutter Cancer Center & NYU Langone Cancer Center

- Overview of GPS in combination with PD1 inhibitors



9:35 - 10:00 **Q&A and Concluding Remarks**

Dr. David A. Scheinberg, Memorial Sloan Kettering Cancer Center & SELLAS Board of Directors

Dr. Angelos Stergiou, President & CEO of SELLAS Life Sciences





COMPANY OVERVIEW

ΣELLAS
LIFE SCIENCES GROUP

LATE-STAGE CANCER IMMUNOTHERAPY COMPANY

Pivotal Phase 3 Development Program	• **Galinpepimut-S (GPS) WT1 peptide immunotherapy**
	  • Acute myeloid leukemia (AML) in second complete remission (CR2)
	  • Orphan drug designation (ODD) and fast track status
	  • Trial to be initiated by end of 2019

Innovative Technology: GPS	• **Invented at and in-licensed from Memorial Sloan Kettering Cancer Center (MSKCC)**
	• **Incorporates heteroclitic technology to preserve and increase WT1 antigenicity**
	  • Multivalent to address 25 WT1 optimally selected epitopes
	  • Induces CD4 and CD8 activation across multiple tumor types without HLA type restrictions
	• **Phase 1/2 basket study in five additional indications in combination with PD1 inhibitor (pembrolizumab) ongoing: Merck collaboration**

NPS: Partnerable Asset	• **Nelipepimut-S (NeuVax, NPS) HER-2 peptide vaccine from MD Anderson Cancer Center**
	  • Combination NPS + trastuzumab in triple negative breast cancer (TNBC) with fast track status
	  • Clinically and statistically significant Phase 2b study efficacy results in TNBC
	  • Seeking most optimal clinical and regulatory development path forward: additional information provided to FDA in September 2019

Strong Intellectual Property	• **GPS:** Composition of matter (and method of use) protection to at least 2033 • **NPS:** Method of use protection to at least 2028 (additional applications pending)
Experienced Leadership Team	• Leadership with significant experience in vaccine and immunotherapy development, as well as deep operational and business development expertise

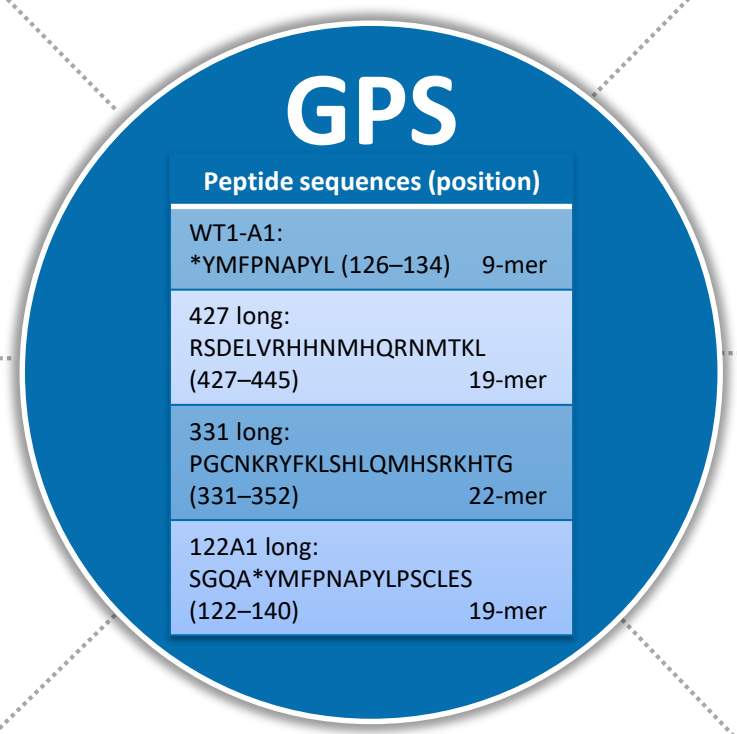
EXPERIENCED MANAGEMENT TEAM

	NAME	POSITION	PRIOR EXPERIENCE / AFFILIATIONS
	**Angelos Stergiou, M.D., ScD h.c.**	President, Chief Executive Officer	PAION, Biovest International, ACCENTIA BIOPHARMACEUTICALS, Analytica INTERNATIONAL, anavex LIFE SCIENCES Corp.
	**Nicholas J. Sarlis, M.D., Ph.D., FACP**	Chief Medical Officer	NIH, MD Anderson Cancer Center, SANOFI, Incyte
	**Barbara Wood, J.D.**	EVP, General Counsel & Corporate Secretary	OPHTHOTECH, (osi) pharmaceuticals
	**John T. Burns, CPA**	VP, Finance & Corporate Controller	GALENA BIOPHARMA, MOSSADAMS

GPS: ENGINEERED & DIFFERENTIATED IMMUNOTHERAPY

WT1: #1 ranked immunotherapy target by the NCI; oncogene, which is highly tumor selective, found in cancer cells and cancer stem cells

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



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

Multivalent 4 peptide chains targeting 25 carefully selected WT1 epitopes: designed to target CD4 and CD8 WT1-specific immune responses

Specificity across **multiple HLA types** and potentially applicable to **20+ cancer types**

Activity predicated upon **overcoming barriers of adverse/ immunosuppressive tumor micro-environment** (TME)

*Mutated peptide (native sequence has R instead of Y)

Clinical Data Overview

Galinpepimut-S (GPS): WT1 peptide vaccine

In settings of Minimal Residual Disease/ low disease burden → used as maintenance monotherapy

- **Acute myeloid leukemia (AML):** In CR1 setting, Phase 2 study with older patients (≥60 years; historical controls: ~12 months) median overall survival (OS) reached **35.3** months and **67.6** months across all ages; strong CD4 and/or CD8 reactivity;

  In CR2 setting, OS with GPS considerably longer vs. the compared group, **16.3** months **vs. 5.4** months (p = 0.0175)

- **Malignant pleural mesothelioma (MPM):** Randomized, blinded Phase 2 demonstrated **22.8** months median overall survival compared with **18.3** months with controls; GPS induced CD4 and/or CD8 T-cell activation

- **Multiple myeloma (MM):** In an open-label Phase 2 study median progression-free survival reached **23.6** months (historical controls: **14.0** months); median overall survival not yet reached; high frequency of WT1-specific immune responses by CD4 and/or CD8 and evidence of epitope spreading

- **Ovarian cancer (with nivolumab):** In an open-label Phase 1 study in combination with PD-1 inhibitor (nivolumab) progression-free survival rate at one year was 70% in patients treated with at least two doses of GPS, with updated data at a median follow-up of 33 months showing 30% of patients being progression free at 2-years (historical controls: 3-10%); WT1-specific IgG observed in 86% of patients (wks 6 – 27) and also CD4 and CD8 T cell responses

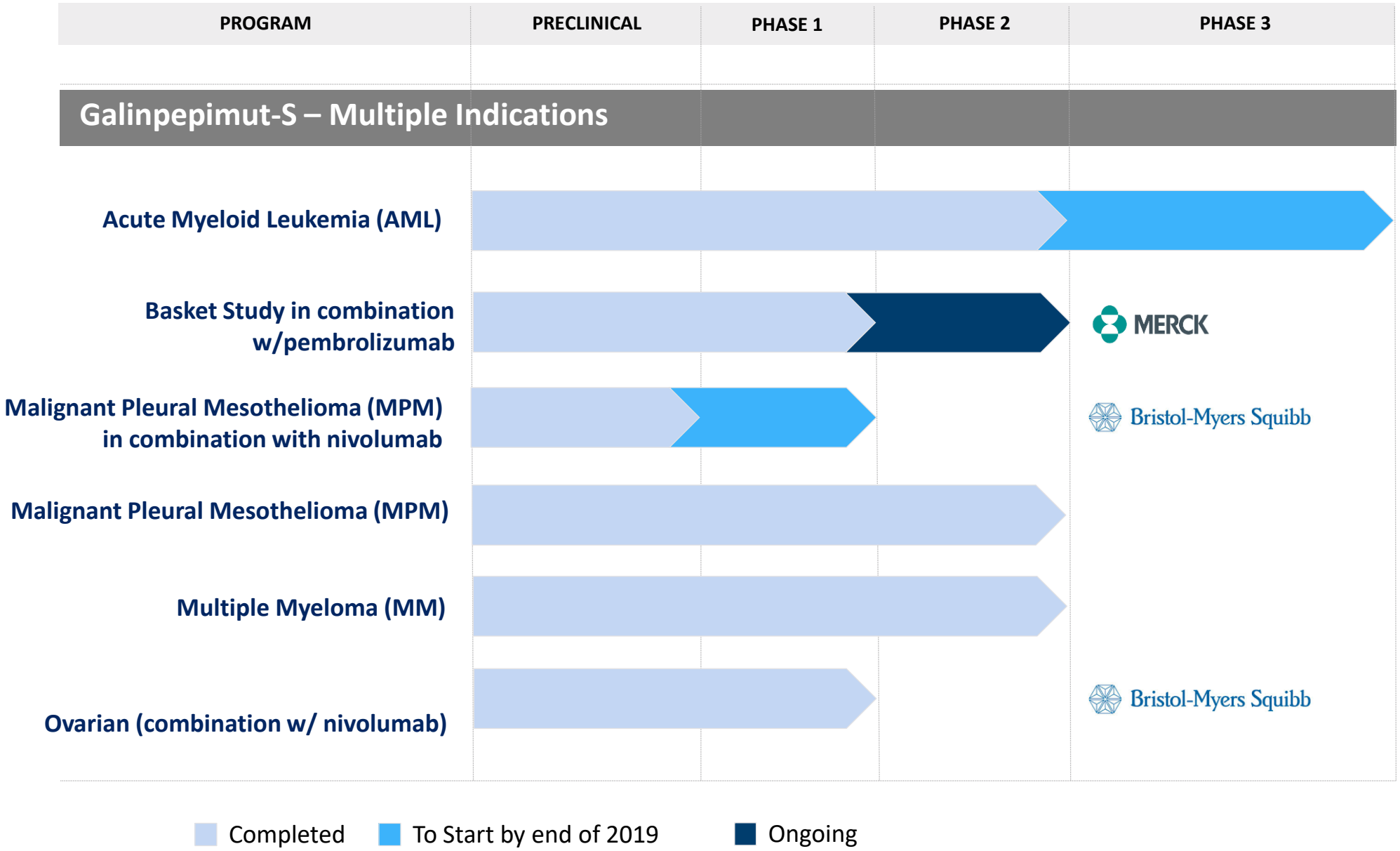
In settings of measurable disease burden → administered in combination with PD-1 inhibitor (pembrolizumab)

- **Five tumor types (with pembrolizumab):** Phase 1/2 study with immune and clinical response endpoints in advanced metastatic disease (CRC, SCLC, TNBC, ovarian, AML on hypomethylating agents); initial focus on ovarian and CRC patients - study is enrolling

Nelipepimut-S (NPS): HER2 peptide vaccine

- **Triple Negative Breast Cancer (TNBC) (in combination with trastuzumab) in the adjuvant setting after frontline standard therapy for early-stage disease:** Randomized, blinded Phase 2b resulted in a **75.2%** reduction in relative risk of tumor recurrence in the active arm vs. control with a **HR=0.26 (p=0.013)**

DEVELOPMENT PIPELINE: GPS



ANTICIPATED GPS NEAR-TERM MILESTONES

Program	Milestone	Projected Date
AML PH3	Start AML Phase 3 randomized trial	Q4 2019
MPM Combo	Start MPM Phase 1 trial in combination with nivolumab	Q4 2019
Basket Study	First set of clinical data from Phase 1/2 combination trial with PD-1 inhibitor (pembrolizumab)	2H 2020
AML PH3	Interim analysis of AML Phase 3 randomized trial	Q4 2021

BOARD OF DIRECTORS

NAME	POSITION	PRIOR EXPERIENCE / AFFILIATIONS
 **Jane Wasman**	Board Chair, Nominating and Governance Committee Chair	ACORDA THERAPEUTICS; Schering-Plough
 **Angelos Stergiou, MD, ScD h.c.**	Chief Executive Officer	PAION; Biovest International; ACCENTIA BIOPHARMACEUTICALS; Analytica INTERNATIONAL; anavex LIFE SCIENCES Corp
 **John Varian**	Audit Committee Chair	XOMA; ARYx THERAPEUTICS; VERSARTIS
 **Robert Van Nostrand**	Compensation Committee Chair	(OSI) pharmaceuticals; ACHILLION; Yield10 BIOSCIENCE; Intra-Cellular Therapies
 **Dr. David Scheinberg**	Science Committee Chair	Memorial Sloan Kettering Cancer Center

SCIENTIFIC ADVISORY BOARD – WORLD RENOWNED EXPERTS IN IMMUNOTHERAPY AND ONCOLOGY

NAME	POSITION
 **Jeffrey Weber, M.D., Ph.D. - Chair**	Deputy Director of the Perlmutter Cancer Center, Co-director of the Melanoma Research Program at the New York University (NYU)-Langone Cancer Center
 **Jedd D. Wolchok, M.D., Ph.D.**	Chief, Melanoma & Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center (MSKCC)
 **Alexander M.M. Eggermont, M.D., Ph.D.**	(Former) Director General of Institut Gustave Roussy, Grand Paris, Villejuif, France & Chief Scientific Officer of Prinses Máxima Centrum, Utrecht, Netherlands
 **Larry W. Kwak, M.D., Ph.D.**	Associate Director Cancer Center, Translational Research & Developmental Therapeutics for the City of Hope National Medical Center
 **Javier Pinilla-Ibarz, M.D., Ph.D.**	Director of Immunotherapy for Malignant Hematology at the H. Lee Moffitt Cancer Center
 **Sattva Neelapu, M.D., Ph.D.**	Associate Professor, Department of Lymphoma/Myeloma, Division of Cancer Medicine, The University of Texas - MD Anderson Cancer Center
 **Guenther Koehne, M.D., Ph.D.**	Chief, Bone Marrow Transplantation and Hematologic Oncology, Miami Cancer Institute

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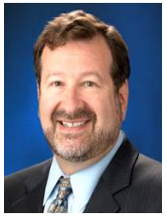


Acute Myeloid Leukemia (AML) Therapeutic Landscape

Hagop M. Kantarjian, MD

Professor and Chair of the Department of Leukemia

Samsung Distinguished Leukemia Chair in Cancer Medicine

The Univ. of Texas – M D Anderson Cancer Center

Houston, Texas

THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Overview of AML Therapeutic Landscape: 1973 - 2017

Cytosine Arabinoside (NSC-63878) and Daunorubicin (NSC-83142) Therapy in Acute Nonlymphocytic Leukemia [1,2,3]

Jerome W. Yates, H. James Wallace, Jr., Rose Ruth Ellison, and James F. Holland [4]

Brief Reports and Preliminary Communications

Early destruction of leukemic infiltration in the induction phase of treatment may reduce the duration of time most hazardous for infection as well as the total period of necessary hospitalization. Daunorubicin produces rapid bone marrow depression, and when administered intensify the effects of cytosine arabinoside and daunorubicin thereby producing rapid destruction of leukemic cells. Such an effect might attain more remissions and earlier discharges from the hospital.

Yates, Cancer Chemother Rep. 1973

First Line: Intensive Remission Induction ChemoRx followed by Allogeneic SCT

Relapse

Second Line: Salvage ChemoRx

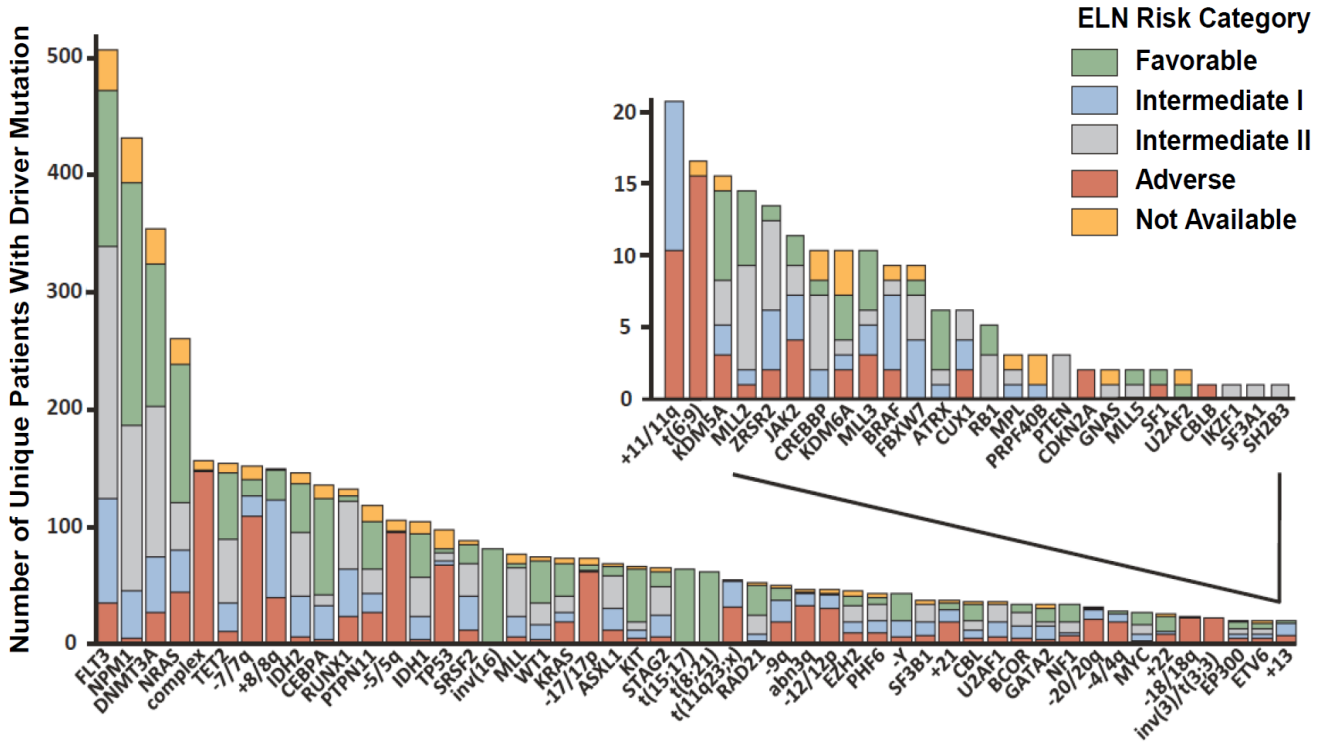
For Patients Unable to Undergo or Declining Intensive Remission Induction: Low-intensity Chemotherapy; Palliative Rx

Overview of AML Therapeutic Landscape:

2017 to Today

Major Changes Due to Introduction of Novel, More Effective and Generally Better Tolerated **Molecularly Targeted Therapies**

Recognition of the Complexity of the Genomic Landscape (Molecular Heterogeneity) of AML



Papaemmanuil, N Engl J Med. 2016

AML Therapeutic Landscape (any line of Rx) - 2019

Approved Agents & Corresponding Molecular Targets (excluding standard cytotoxic ChemoRx)

Target	**Agent (Marketed products** and Agents in Clinical Studies**)**
Bcl2	**Venetoclax**
CD123	Tagraxofusp-erzs^ (approval for BPCDN)
CD33	**Gemtuzumab ozogamicin**; Actimab-A; AMG 330; AMG 673; IMGN779
DNA Methyltransferase	**Azacitidine; Decitabine**; Guadecitabine
DNA replication	**Liposomal Ara-C + Dauno (VYXEOS®)**; SJG-136; DFP 10917; Lurbinectedin
FLT3	**Midostaurin; Gilterinib**; Quizartinib; XL999; AMG 427; Crenolanib
IDH1 or 2	**Enasidenib; Ivosidenib**
NOX2	Histamine dihydrochloride (Ceplene®) plus interleukin-2 (IL2)*
Sonic hedgehog (Hh)	**Glasdegib**; Sonidegib^
XPO1/CRM1	Selinexor (approval for multiple myeloma)^

^ Approved in indications/tumor types other than AML
* EMA (EU) only approved agent
BPCDN: blastic plasmacytoid dendritic cell neoplasm

FDA-approved drugs for AML are noted in bolded text; all other agents in non-bolded text are in various stages of clinical development in AML (any line of therapy)

Focus on Relapsed/Refractory (R/R) AML Standard Definitions (ELN)

- Primary refractory disease
  - No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause
- Relapse
  - Hematologic (morphological) relapse: bone marrow blasts ≥5%; or reappearance of blasts in the blood, or development of extramedullary disease
  - Molecular relapse: if studied pretreatment, recurrence of MRD as assessed by RT-qPCR or by MFC

ELN: European LeukemiaNet; MRD: minimal residual disease; MFC: multicolor flow cytometry; RT-qPCR: reverse transcriptase-quantitative polymerase chain reaction;

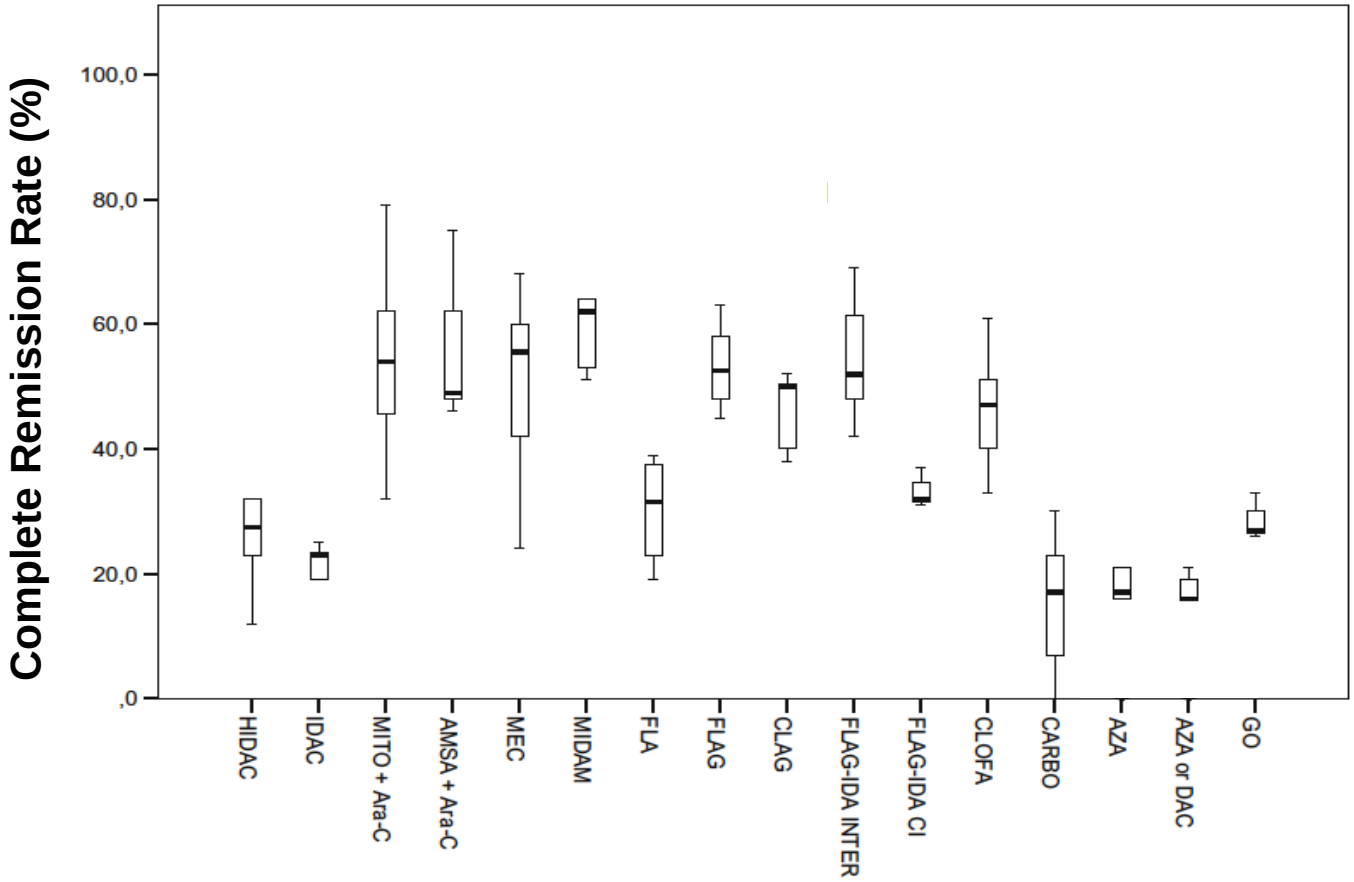
Döhner, Blood. 2017

Common salvage regimens in patients not responding to a 1st induction cycle or with relapsed disease who are candidates for intensive therapy

IDAC†† (with or without anthracycline)	IDAC (1000-1500 mg/m^2 IV over 3 h q12 h, d1-3 [500-1000 mg/m^2 in patients >60 y]; or 1000-1500 mg/m^2 IV over 3 h d1-5 or 6 [500-1000 mg/m^2 in patients >60 y]); with or without daunorubicin 45-60 mg/m^2, IV, d1-3; idarubicin 8-10 mg/m^2, IV, d3-5, or mitoxantrone 8-10 mg/m^2, IV, d1-3
FLAG-IDA‡‡	Fludarabine 30 mg/m^2 IV, d2-6; cytarabine 1500-2000 mg/m^2 IV over 3 h, starting 4 h after fludarabine infusion, d2-6; idarubicin 10 mg/m^2 IV, d2-4; G-CSF 5 μg/kg, SC, d1-5; additional G-CSF may be administered starting 7 d after end of chemotherapy until WBC count >500/uL Consider dose reduction in patients >60 y: fludarabine 20 mg/m^2; cytarabine 500-1000 mg/m^2; idarubicin 8 mg/m^2
MEC	Mitoxantrone 8 mg/m^2, d1-5; etoposide 100 mg/m^2, d1-5; cytarabine 1000 mg/m^2, d1-5
Allogeneic HCT	Consider transplantation for patients with primary refractory disease, for patients in second CR or with major cytoreduction but still active disease following salvage therapy Consider second transplantation under certain conditions (see “Salvage treatment”) Perform early HLA typing

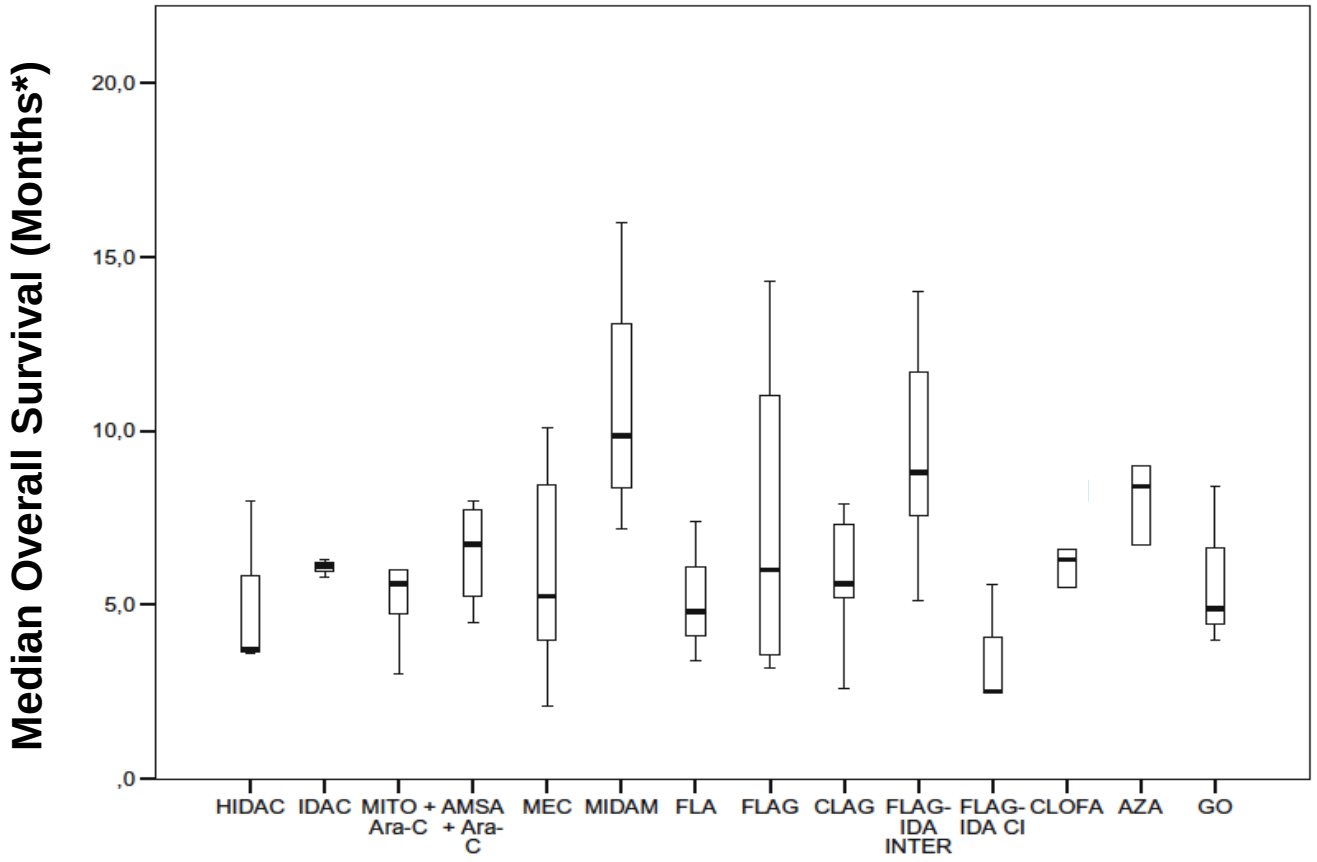
Döhner, Blood. 2017

CR Rates with Various Salvage (2nd Line) Regimens using Conventional Chemotherapy in R/R AML Patients



Megias-Vericat, Ann Hematol. 2018

Median Overall Survival (OS) with Various Salvage Regimens using Conventional Chemotherapy in R/R AML Patients

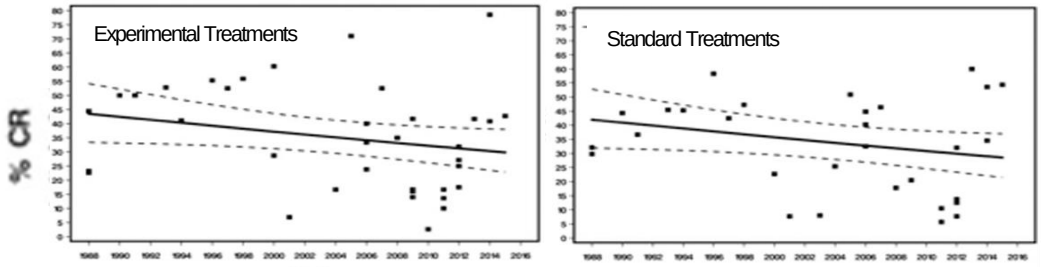


*From the time of relapse (not time of achievement of CR2)

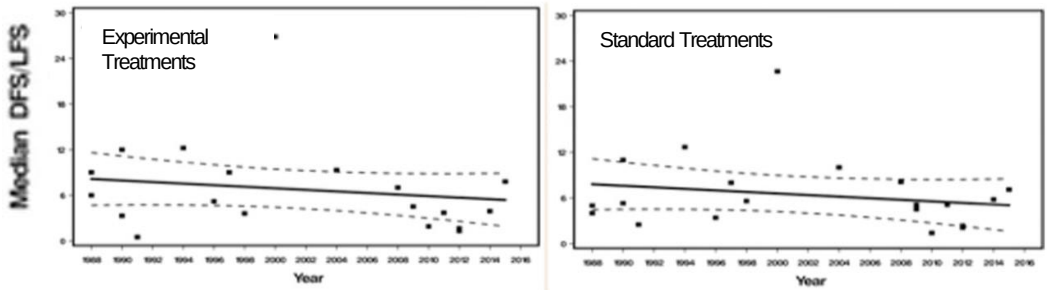
Megias-Vericat, Ann Hematol. 2018

Outcomes in R/R AML Patients Treated in Rand. Clinical Trials: Persistence of Large Unmet Medical Need

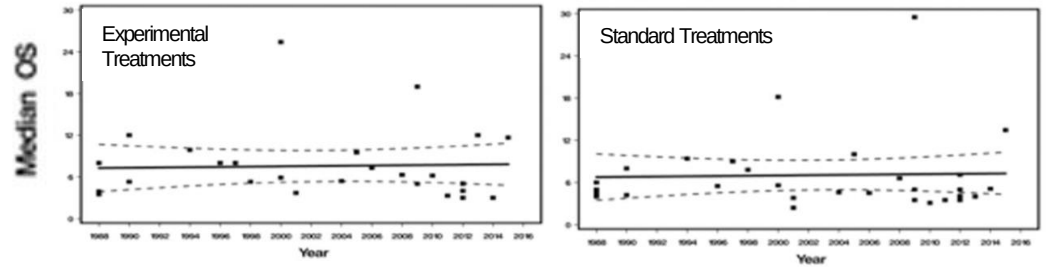
Trends in **CR rates (%)** over time



Trends in **median DFS/LFS (mo)** over time



Trends in **median OS (mo)** over time



"No … improvement in disease outcomes, including OS, in RR AML patients treated within randomized clinical trials over the past 3 decades"

- N = 5,500 pts
  - 40.5% treated on 21 two-arm, phase II trials
  - 51% on 10 phase III trials
  - 6.6% on 4 large retrospective studies

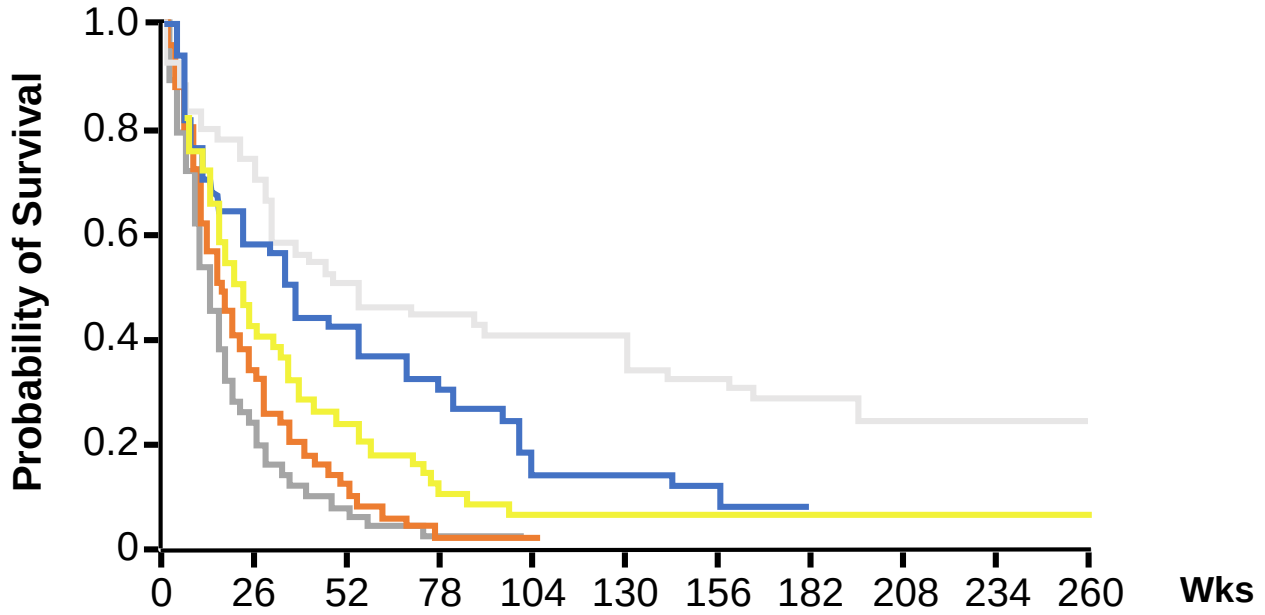
Tchekmedyian. ASH Abst. 4000, Blood. 2016

AML Outcomes by Age: ECOG Data

Pts	N	CR1, %	**Relapse rates, %**	5-Yr OS Rates **From Relapse**, %
Age ≤ 55 yrs	1,699	68	**35**	**11**
Age > 55 yrs	742	49	**65**	**6**

Rowe, ASH Abst. 546, Blood. 2005; Ganzel, Am J Hematol. 2018

Survival for Pts With Relapsed AML
Effect of Duration of Historical CR1



	Wks of CR1	Pts	Deaths	Pts Censored at > 1, 2 Yrs
CR1 <12 mo (78% of pts)	0-26	436	413	0, 0
	27-52	175	162	2, 0
	53-78	98	86	6, 3
	79-104	37	34	1, 1
	≥ 104	56	38	8, 7

mOS ~ 5-6 mo

Estey, Leukemia. 1996

Slide credit: clinicaloptions.com

Most AML Patients Die Within 1 Year After R/R Disease Diagnosis

Therapy	Data Source	No. Pts	ORR, % (CR + CRi)	mOS* (mo)
IDAC	VALOR (phase III study)[1]	355	**19**	**6.1**
Intensive salvage^	Phase II study[2]	44	**41**	**6.3**
Investigator's choice†	CLAVELA (phase III study)[3]	190	**21**	**3.3**
Hypomethylating agents (HMA)	Multicenter retrospective (2006-2016)[4]	514	**18**	**6.9**

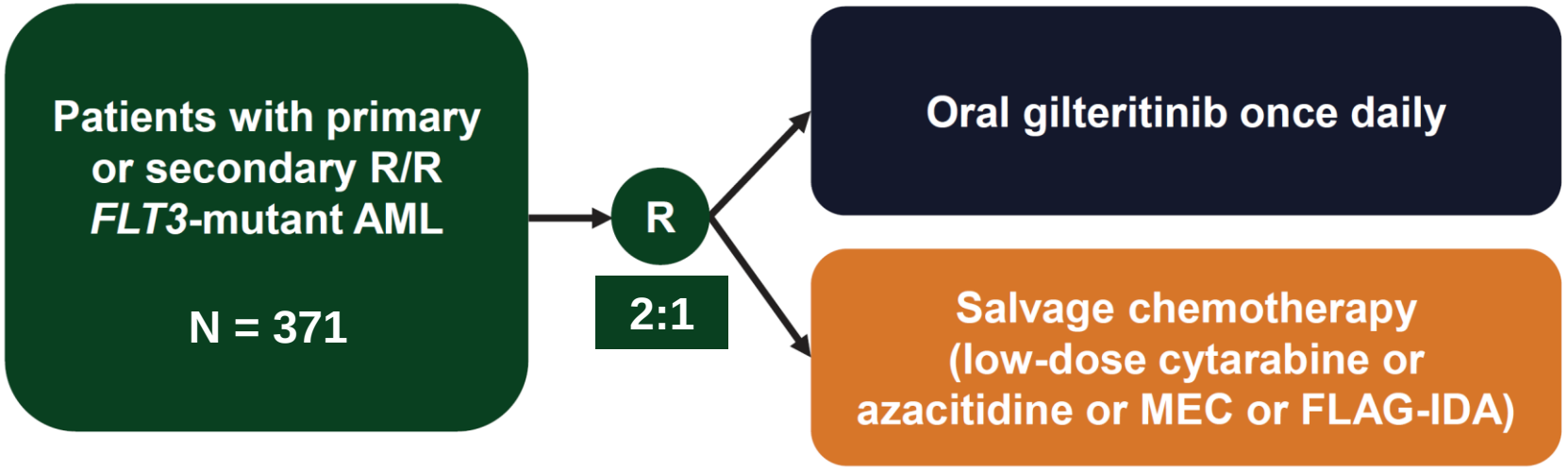
^Intensive salvage regimens included: MEC (n = 23); idarubicin/cytarabine (n = 8); cytarabine-based induction + fludarabine ± gemtuzumab ozogamicin (n = 5); cytarabine-based induction + amsacrine (n = 2); cytarabine-based induction + mitoxantrone ± gemtuzumab ozogamicin (n = 2); cytarabine-based induction + gemtuzumab ozogamicin (n = 1); cytarabine-based induction + cladribine (n = 1); cytarabine alone (n = 1); mitoxantrone + etoposide (n = 1).
†Investigator's choice included: high-dose cytarabine (n = 22); MEC (n = 44); fludarabine, cytarabine, granulocyte colony-stimulating factor with or without idarubicin (n = 65); low-dose cytarabine (n = 12); hypomethylating agents (n = 34); hydroxyurea plus supportive care (n = 13).

* From the time of relapse (not time of achievement of CR2)

1. Ravandi, Lancet Oncol. 2015; 2. Cortes, Cancer. 2015; 3. Roboz, J Clin Oncol. 2014; 4. Stahl M, ASH Abst. 1063, Blood. 2016

The Advent of FLT3 Inhibitors

ADMIRAL Study Design



- **Primary endpoint:** OS
- **Secondary endpoints:** EFS, CR, leukemia-free survival, remission duration, composite CR, CR

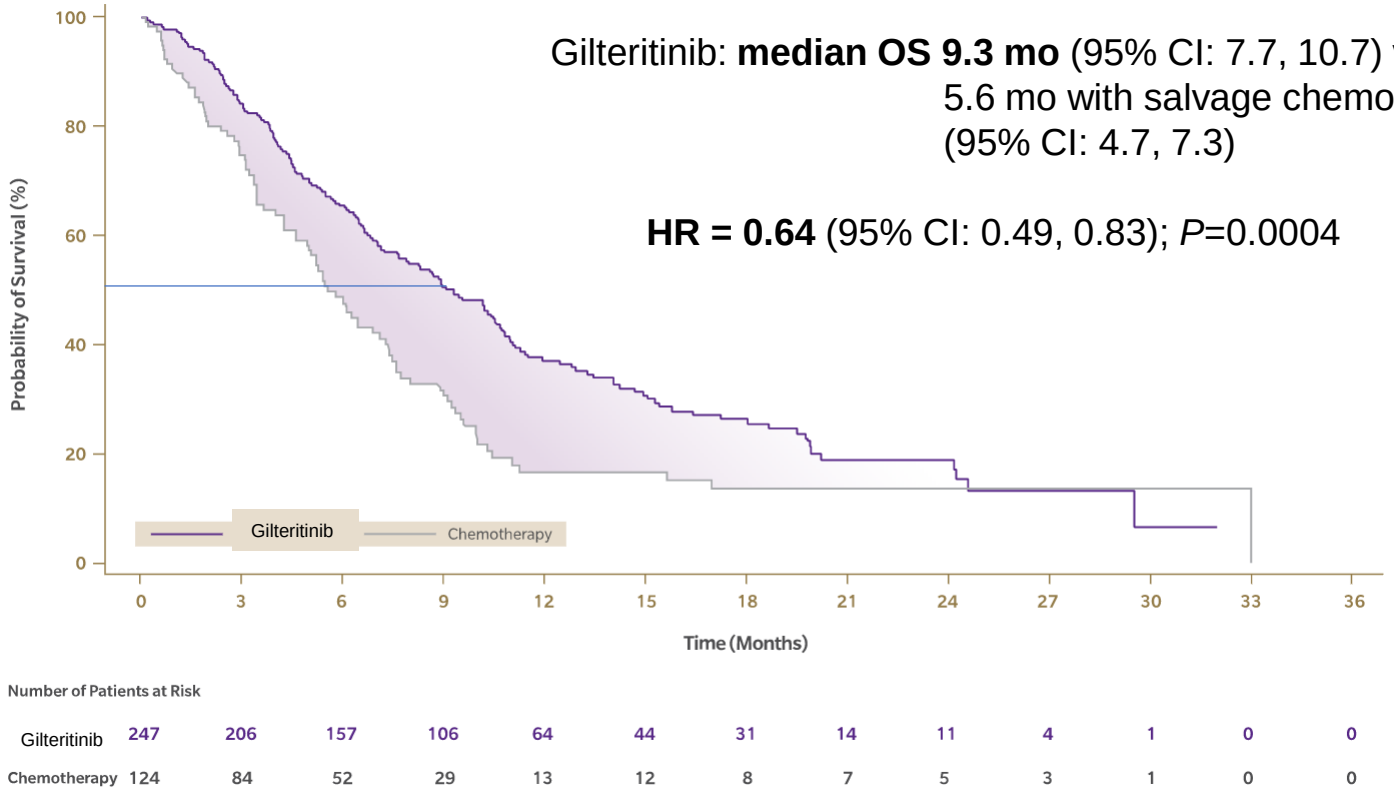
Abbreviations: FLAG-IDA, fludarabine, cytarabine, and granulocyte-colony stimulating factor with idarubicin; HSCT, hematopoietic stem cell transplant; LoDAC, low dose cytarabine; MEC, mitoxantrone, etoposide, and intermediate-dose cytarabine

- Median age: 60 years
- Relapsed AML 59%; Refractory AML 41%
- Distribution of molecular aberrations:
  - FLT3 ITD 88%, FLT3 TKD 9%, FTL3 ITD and TKD 4%

Perl, AACR Abst. CT184, Cancer Res. 2019

ADMIRAL Study

Primary Endpoint: Overall Survival (Interim Analysis)



Gilteritinib: **median OS 9.3 mo** (95% CI: 7.7, 10.7) vs. 5.6 mo with salvage chemotherapy (95% CI: 4.7, 7.3)

HR = 0.64 (95% CI: 0.49, 0.83); *P*=0.0004

Perl, AACR Abst. CT184, Cancer Res. 2019

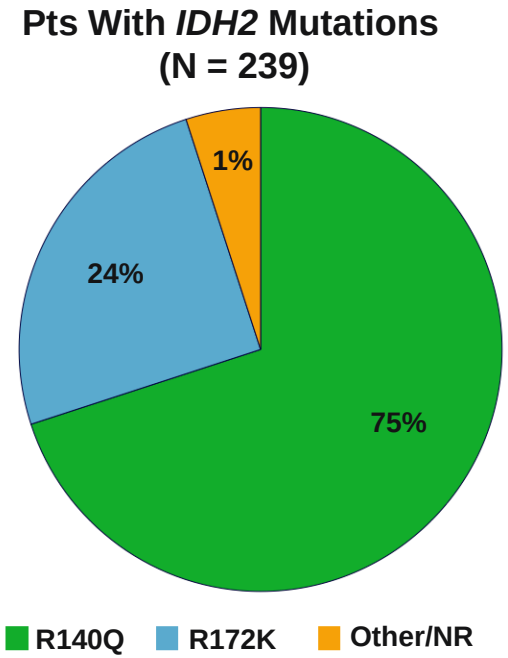
ADMIRAL Study
CRc Rates and Duration (Final Analysis)

Characteristics	Gilteritinib N=247	Salvage Chemotherapy N=124
CRc Rate (%)		
Median	54.3% (47.8-60.6)	21.8% (14.9-30.1)
Duration of CRc (95% CI), weeks		
Median	**4.6** (3.7-7.7)	Not estimable (NE) (1.8-NE)

Perl, AACR Abst. CT184, Cancer Res. 2019; Xospata® official physician website (www.xospatahcp.com)

The Advent of Isocitrate Dehydrogenase (IDH) Inhibitors: Pro-differentiating Effect in AML in Pts with IDH mutations

IDH2 Inhibitor Enasidenib (AG-221) in R/R AML Pts with *IDH2* mutations



Response (%) and mOS (mo) in R/R AML Pts	Enasidenib	
	100 mg QD (n = 109)	All Doses* (n = 176)
ORR	38.5%	40.3%
Best response		
▪ CR	20.2%	19.3%
▪ CRp/CRi	6.4%	6.8%
▪ PR	2.8%	6.3%
Median response duration	**5.6 mo**	**5.8 mo**
Median OS^	N/A	9.3 mo

Stein, Blood. 2017

*Enasidenib administered at 50-650 mg QD;
^ Calculated from the time of AML relapse

FDA-approved in August 2017 for relapsed/refractory AML with an *IDH2* mutation

Ivosidenib in R/R AML Pts with *IDH1* mutations

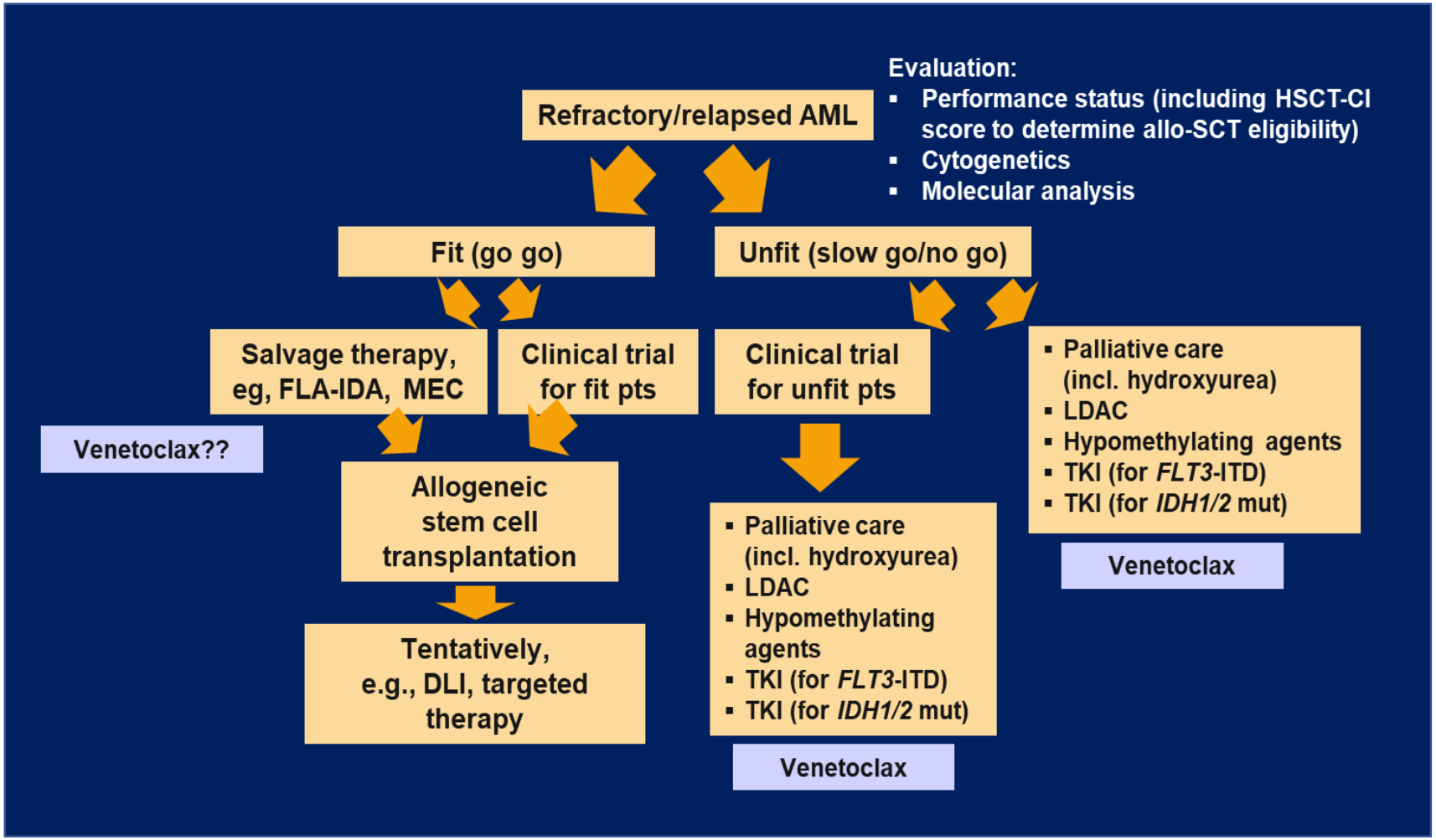
Efficacy Results in Patients Receiving Ivosidenib 500 mg QD (N = 125)	
CR+CRh	30.4%
CR	21.6%
Median duration of CR+CRh	8.2 mo
Median duration of CR	**9.3 mo**
Overall response rate (CR+CRi/CRp+PR+MLFS)	41.6%

- **Toxicities:**
- Most common AEs (n=258): **Diarrhea (33%), leukocytosis (30%), nausea (30%), fatigue (29%), febrile neutropenia (25%)**
- **Differentiation syndrome: 11.2%**

DiNardo. ASH Abst. 725, Blood. 2017

FDA-approved in July 2018 for relapsed/refractory AML with an *IDH1* mutation

Treatment Algorithm for Relapsed/ Refractory AML

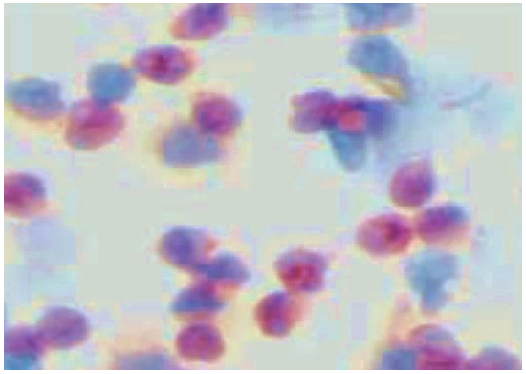


Modified from Thol, Blood. 2015

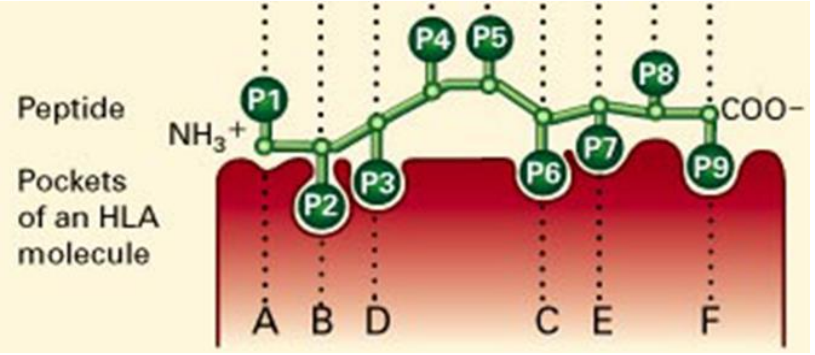
Wilms Tumor 1 (WT1) Protein: A Top-Priority Target for Immunotherapy in AML

- **WT1** is **broadly detectable in hematological malignancies, including AML (where it is densely and almost universally expressed)**[1] **as well as assorted solid tumors**; not found appreciably in adult tissues, which **lowers potential off-target toxicity**

- WT1 is an **optimal target for immunotherapy**[2,3] due to its properties:
  - Intracellular cancer oncofetal antigen
  - Highly expressed, processed, and presented in cancer cells → recognized and killed by specifically immunized T-cells
  - Does not down-regulate or become mutated frequently
  - Expressed on leukemic stem cells



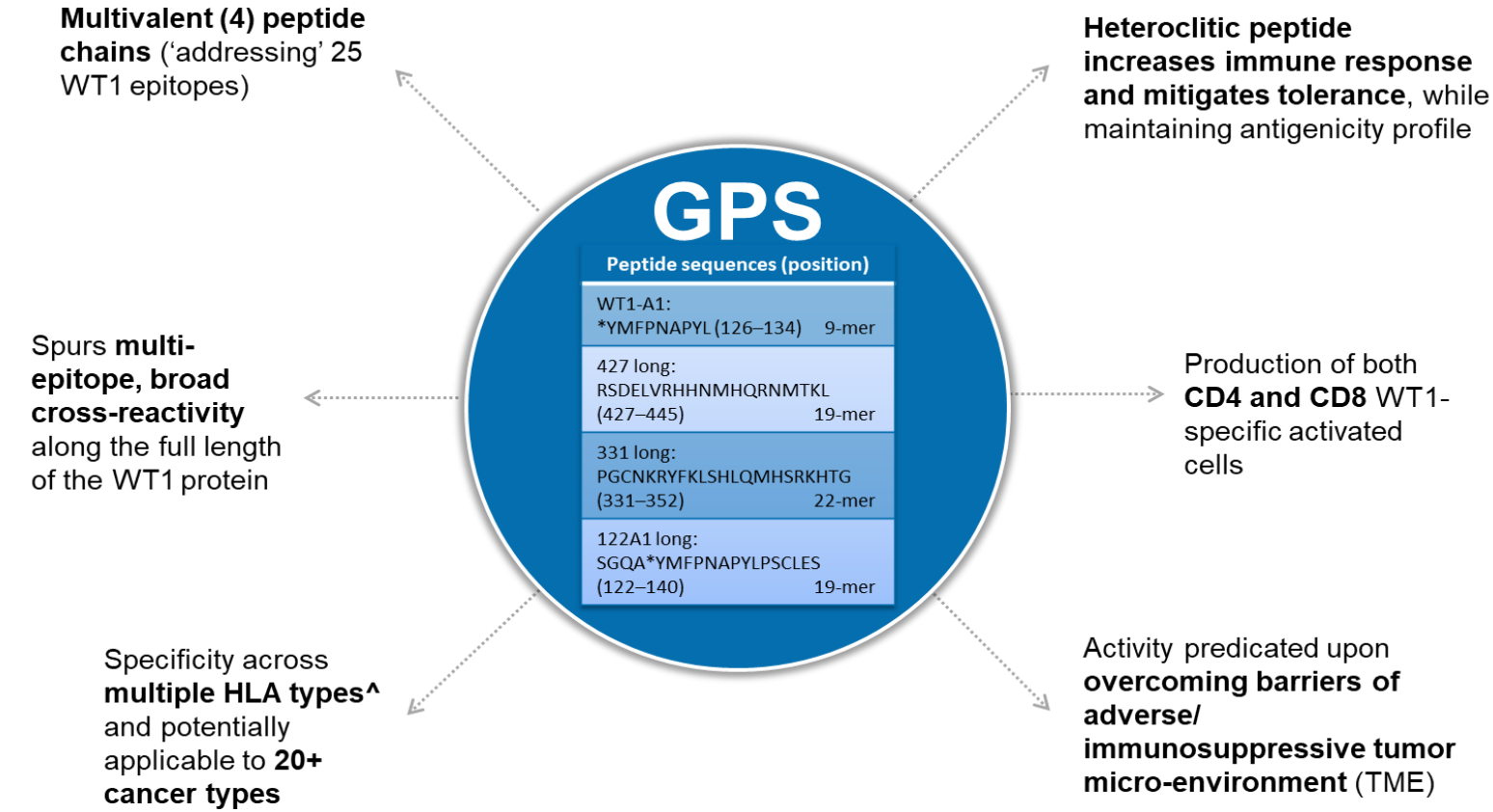
AML blasts stained for WT1 (ESK1 Mab)



Potential to Target Clinically in Settings of Low Disease Burden (Morphologic CR) with Multivalent Anti-WT1 Vaccine (Galinpepimut-S; GPS)

1. Gaiger, Leukemia. 1998; 2. Dao & Scheinberg, Best Pract Res Clin Haematol. 2008; 3. Nishida & Sugiyama, Methods Mol Biol. 2016

Galinpepimut-S (GPS): Peptide Vaccine with Uniquely Differentiated Properties as an IO Agent in AML



*: Mutated peptide (native sequence has R instead of Y);
^: Predicted to be reactive with 10 MHC-type I [HLA-A & -B] and 15 MHC-Type II [HLA-DRB1-XX] molecules)

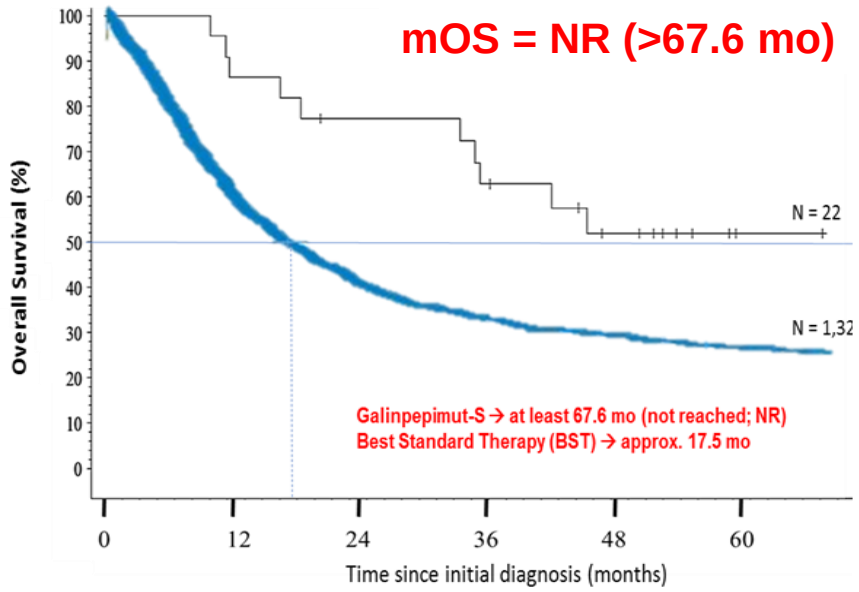
Pinilla-Ibarz, Leukemia. 2006; Gomez-Nunez, Leuk Res. 2006; May, Clin Cancer Res. 2007; Maslak, Blood. 2010; Krug, Cancer Immunol Immunother. 2010

IO: immuno-oncology

GPS: Impressive Clinical and Immune Response Data when Administered as post-CR Maintenance in AML

CR1 Setting

OVERALL SURVIVAL (ALL AGES)

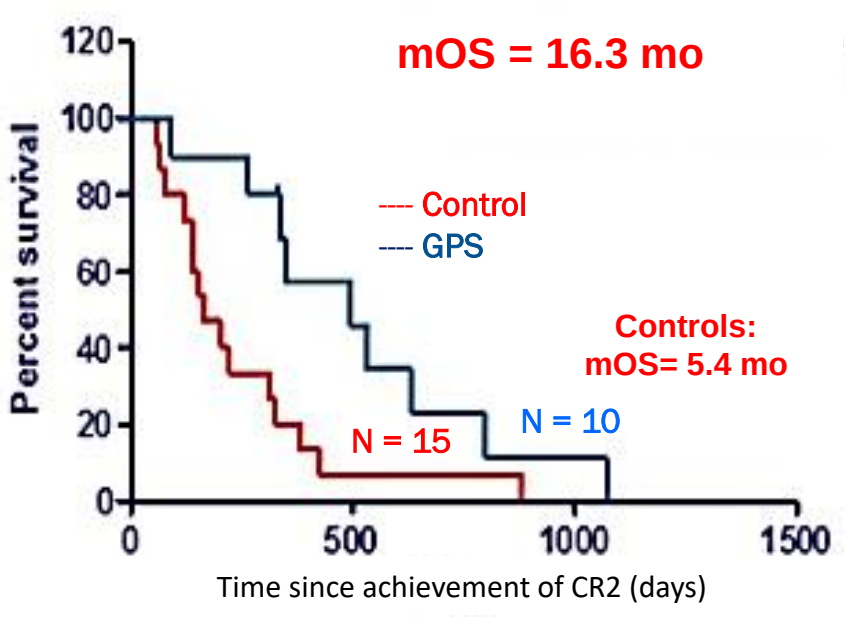


Source for hist controls (blue curve):
Walter, J Clin Oncol. 2010

Maslak, Blood Adv. 2018; SELLAS, Data on file

CR2 Setting

OVERALL SURVIVAL (MEDIAN AGE = 74)



Brayer, Am J Hematol. 2015

CR: complete remission; mo: months; CR1: first complete response; CR2: second complete response

Previously Reported Outcomes in Matching Control Populations

CR1 Setting; Patients Older than 65 yrs

	Ph2 GPS study	Smith, 2011	Lowenberg, 2009	Pollyea, 2013	Kantarjian, 2013	Freeman, 2013
Median OS (mo)	35.3	9.5 (**3.74 X**)	Not provided	15.8 (**2.25 X**)	13.8 (**2.57 X**)	12 (**2.96 X**)
Landmark OS rate @ 2-Yr (%)	61%		16% (**3.75 X**)			
Landmark OS rate @ 3-Yr (%)	46%		13% (**3.54 X**)		20% (**2.3 X**)	
Median PFS (mo)	15.1		10.5 (**1.44 X**)			
Landmark PFS rate @ 2-Yr (%)	31%		20% (**1.55 X**)			

Smith, Blood Rev. 2011; Lowenberg, N Engl J Med. 2009; Pollyea, Haematologica. 2013; Kantarjian, Blood. 2010; Freeman, J Clin Oncol. 2013; Maslak, Blood Adv. 2018; SELLAS, data on file.

N.B.: All median survival times and landmark rates calculated from the time of initial AML diagnosis.

CR2 Setting; Patients of Any age

	GPS (MCC) Brayer, 2015	Controls* (MCC) Brayer, 2015	Armistead 2007	Faderl 2008	Breems 2005	Price 2011	Jabbour 2012	Rowe 2005
Median OS (mo)	16.3	5.4	5.6	4.4	~6.0	6.6	7.4	~3.5

*contemporaneously treated, post-hoc matched controls; all other controls are historical (i.e., originate from the literature)

Brayer, Am J Hematol. 2015; Armistead, Blood. 2007; Faderl, Cancer. 2008; Breems, J Clin Oncol. 2005; Price, Leuk Res. 2011; Jabbour, Clin Lymphoma Myeloma Leuk. 2012; Rowe, Blood. 2005; SELLAS, Data on file.

N.B.: All median survival times calculated from the time of achievement of CR2.

CR: complete remission; mo: months; CR1: first complete response; CR2: second complete response; PFS: progression-free survival; OS: overall survival, GPS: galinpepimut-S; Yr: year; X: fold (increase of GPS-associated value vs. comparator); MCC: Moffitt Cancer Center study

Galinpepimut-S WT1 Vaccine: Randomized Pivotal Phase 3 Study in AML Patients for Maintenance Therapy After CR2/CR2p

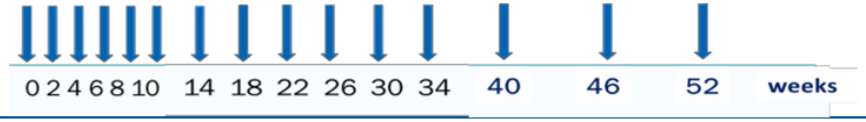
- AML in CR2 post-2nd line Rx in patients ≥ 18 yrs (incl. CR2p, but with adequate WBC counts)
- Ineligible/unable to undergo Allo-SCT
- ~50 centers (US/EU)
- Three Stratification axes:
  - CR2 vs CR2p status
  - cytogenetics risk category at initial diagnosis (poor vs all other, incl. unknown)
  - Duration of historical CR1 (<12/>12 months)

R

1:1

- Galinpepimut-S (200 µg of each peptide x 4; total 800 µg)
- Montanide (500 µl/ dose)
- GM-CSF (sargramostim; Leukine® ; 70 µg/dose; d-2 & d0)

Schedule of Administration*

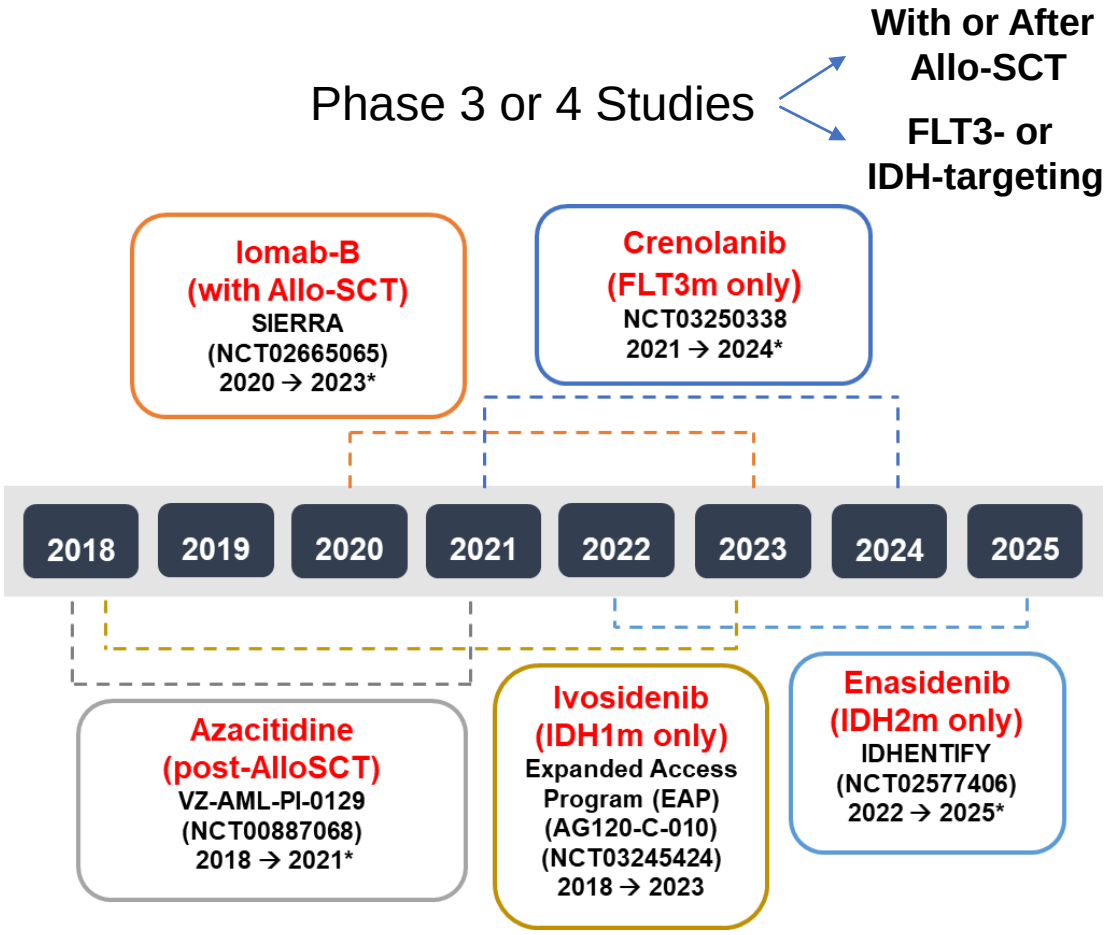


- Best Available Therapy (BAT) – 4 predefined choices
  - Clinician's choice: Observation (incl. hydroxyurea palliation); Venetoclax; HMAs; Low-dose Ara-C
  - Therapy duration: up to 52 wks

- Primary Endpoint: Median Overall Survival (mOS)
- Secondary Endpoints
  - Toxicity
  - Efficacy (LFS; MRD)
- Exploratory Endpoints
  - Immune Response (IR) Assessment (Antigen-Specific and General)
  - Tumor Microenvironment Markers

CR: complete remission;
GM-CSF: granulocyte-macrophage colony stimulating factor;
HMAs: hypomethylating agents;
LFS: leukemia-free survival;
MRD: minimal residual disease;
Wks: weeks

AML Competitive Landscape For Agents to Be Given After Second Line Rx



Phase 2 Studies

With or After Allo-SCT

- Plerixafor (Mozobil)
- Azacitidine (+ DLI)
- ALT-803 (haplo NK cells)
- MG4101 (NK cells)

Other Agents (non-IO), *but with Expectedly high AE burden*

- Selinexor (+ fludarabine + AraC)
- Lenalidomide + MEC
- Selinexor + Sorafenib

Immuno-Oncology (IO) Agents

- Avelumab (anti-PDL1) + Azacitidine

Galinpepimut-S (GPS)
(WT1 vaccine)

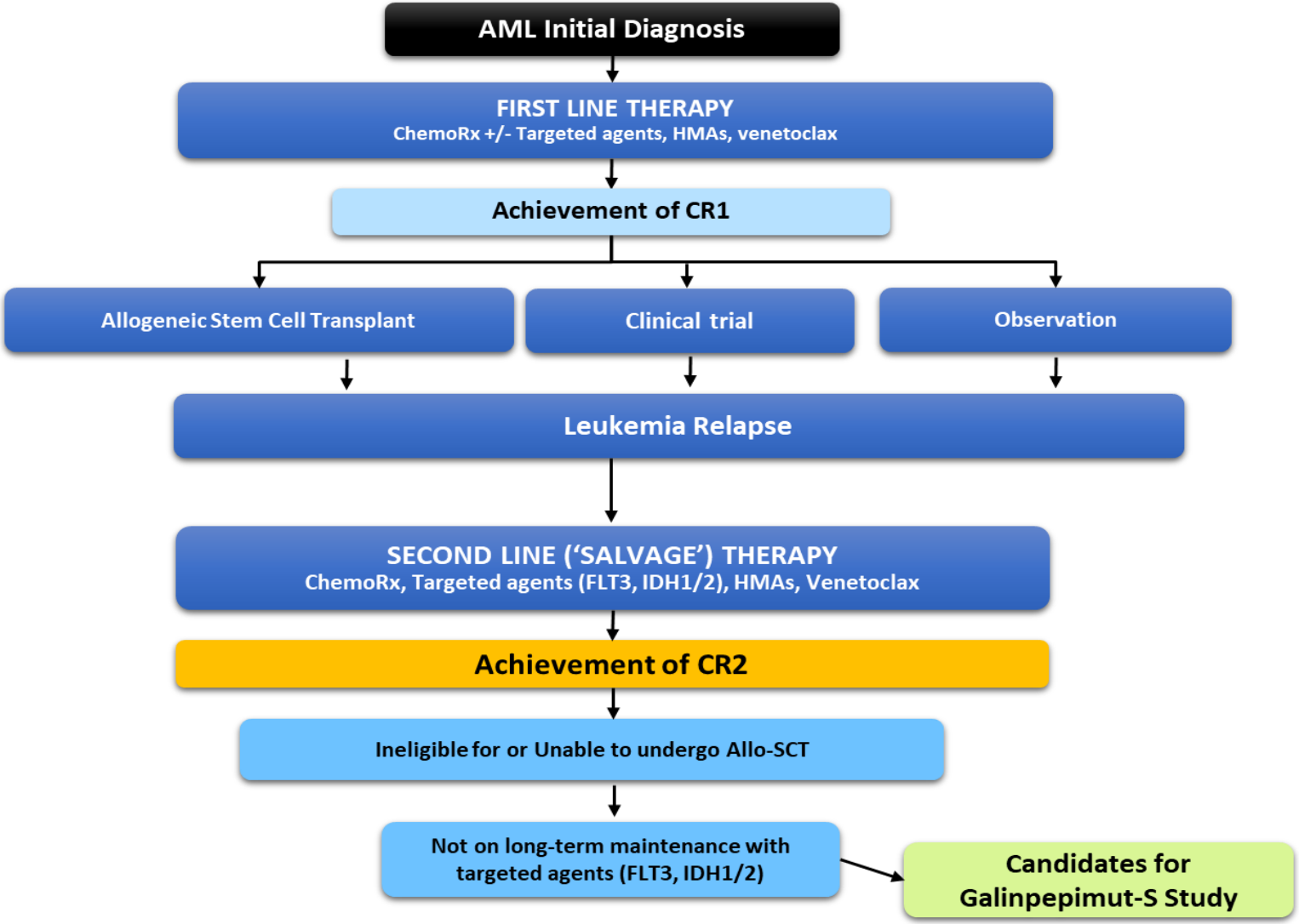
- ✓ **IO Agent with Expectedly Low AE Burden**
- ✓ **Not Associated with Allo-SCT**
- ✓ **Not for molecularly preselected patient populations**

*Launch dates for prospective market entrants were based on the assumptions of 1. positive study results and 2. a study duration of 3 years

Allo-SCT: allogeneic stem cell transplantation; DLI: donor lymphocyte infusion; IO: immuno-oncology; MEC: mitoxantrone, etoposide, and cytarabine; NK: natural killer cells

Patient "Flow" Towards Post-CR2 Maintenance in AML

→ Candidate Position of GPS: A Potential New Treatment Paradigm



Evolving Treatment Landscape for Patients Achieving CR2 after Salvage Therapy for R/R AML

Conclusions and Key Take-away Points

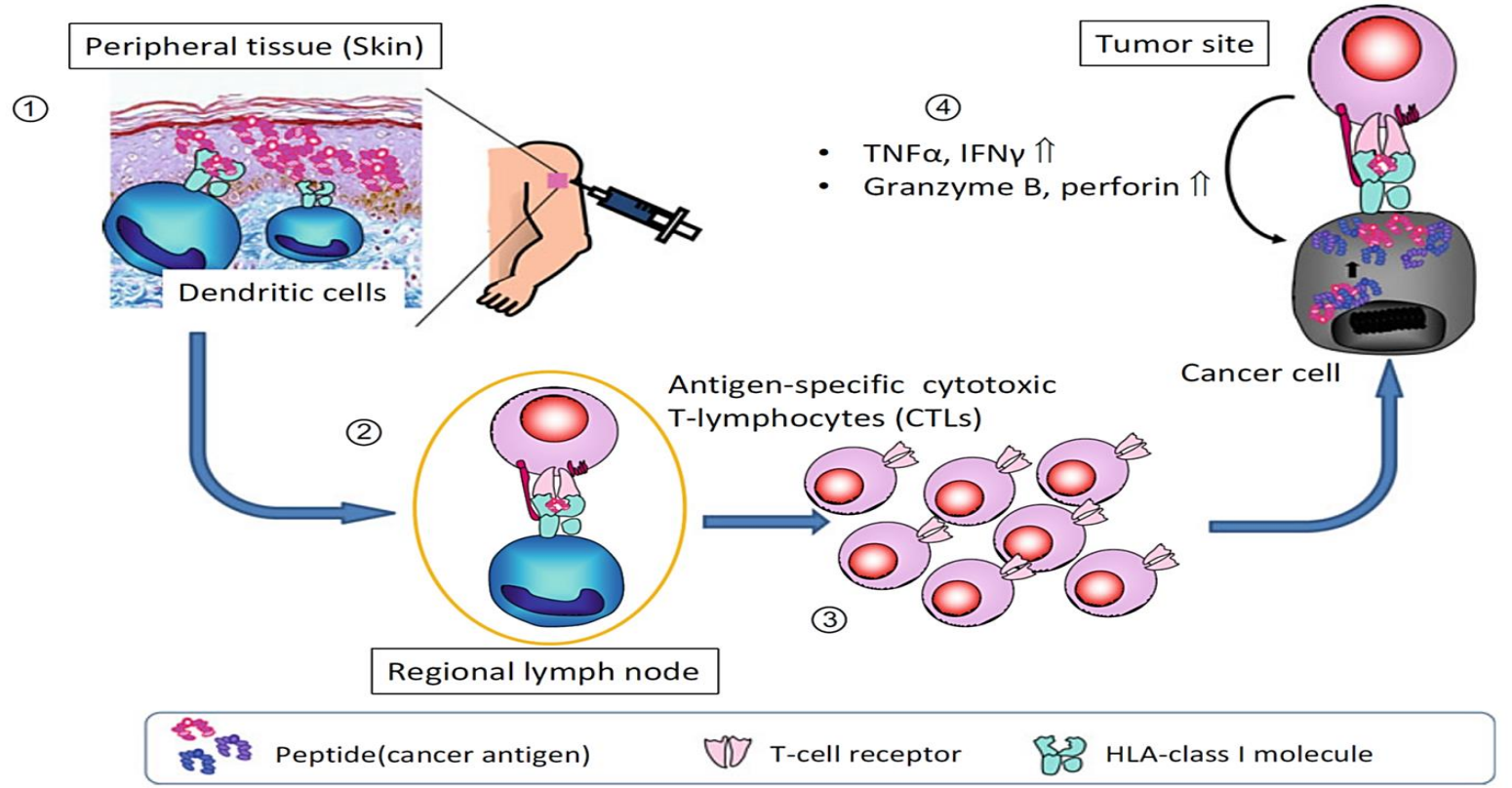
- R/R AML remains a huge unmet clinical need
  - Newly introduced 2nd line therapies have led to modest improvements in molecularly predefined populations (FLT3, IDH mut), with notable adverse event burden
  - A significant proportion of relapsed AML pts are ineligible for or unable to undergo allo-SCT
- Essentially all late development agents targeting patients after CR2 are given with or after allo-SCT or in molecularly pre-defined populations (FLT3, IDH mut)
- Promising clinical and immune response data from the Ph2 galinpepimut-S (GPS) AML studies strongly support its further development in a pivotal randomized Ph3 study in CR2 patients in R/R AML, with the potential for its results – if positive – to be practice-changing

Cancer Vaccines

Javier Pinilla-Ibarz, MD, PhD
Senior Member & Director of Immunotherapy
Department of Malignant Hematology
Moffitt Cancer Center
Tampa, Florida

MOFFITT CANCER CENTER

General Mechanism of Action of Therapeutic Cancer Vaccines



Cancer cells express some antigens recognized by the host immune system, and present the peptide derived from this antigen/HLA class I complex on the cell surface. Antigen-specific cytotoxic lymphocytes that are elicited by peptide-based cancer vaccines recognize peptide/HLA class I complexes via the T-cell receptor (TCR)
1. Injection of cancer antigen and immune adjuvant; 2. Migration to lymph node and presentation of cancer antigen to T-cells; antigen-specific cytotoxic T-lymphocytes (CTLs); 3. Proliferation and differentiation of T-lymphocytes; 4. Cytotoxicity mediated by antigen-specific CTLs

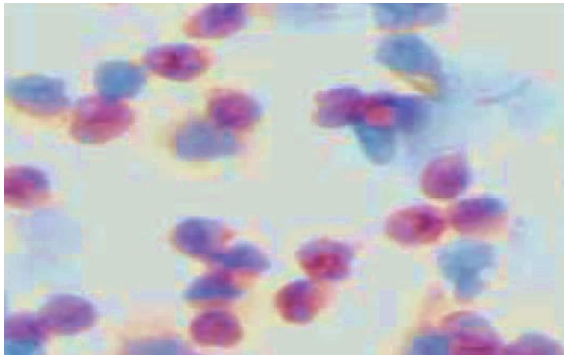
Nishida & Sugiyama, Methods Mol Biol. 2016

Wilms Tumor 1 (WT1) Protein: A Top-Priority Target for Immunotherapy

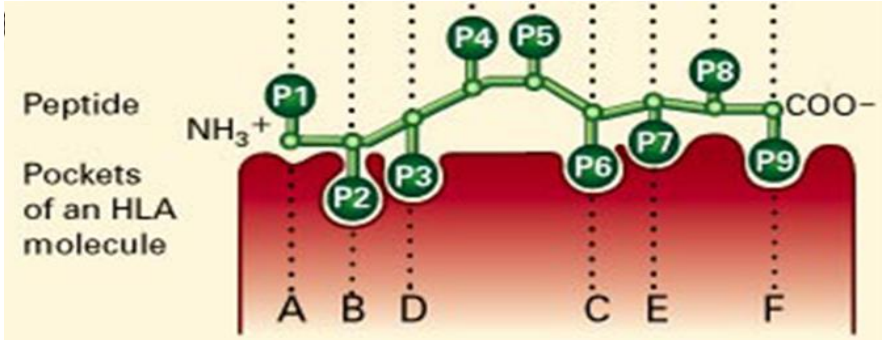
- **WT1** is **broadly detectable in hematological malignancies, including AML (where it is densely and almost universally expressed)**[1] **as well as assorted solid tumors**; not found appreciably in adult tissues, which **lowers potential off-target toxicity**

- **WT1** was highest ranked by a 2009 National Cancer Institute pilot program[2] for the prioritization of cancer antigens for immunotherapy with the **potential to treat 20 or more cancer types**

- WT1 is an **optimal target for immunotherapy**[3,4] due to its properties:
  - Intracellular cancer oncofetal antigen, which is induced during the oncogenic process, emerging as an oncogene
  - Highly expressed, processed, and presented in cancer cells, which get then recognized and killed by specifically immunized T-cells
  - Does not down-regulate or become mutated frequently and thus specifically immunized T cells remain reactive and tumor cells do not escape immune attack
  - Also expressed on cancer progenitor (or stem) cells



AML blasts stained for WT1 (ESK1 Mab)

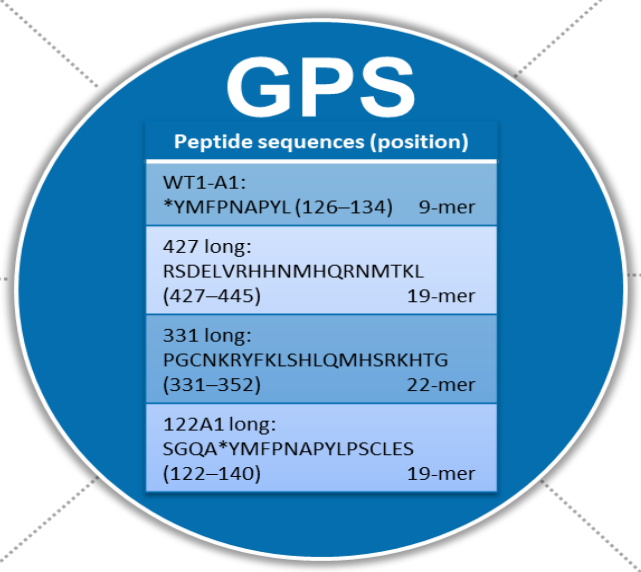


1. Gaiger, Leukemia. 1998; 2. Cheever, Clin Cancer Res. 2009; 3. Dao & Scheinberg, Best Pract Res Clin Haematol. 2008; 4. Nishida & Sugiyama, Methods Mol Biol. 2016

GPS: Novel Peptide Mixture Engineered for Differentiated Immunotherapy

Multivalent (4) peptide chains ('addressing' 25 WT1 epitopes)

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



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

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

Specificity across **multiple HLA types^** and potentially applicable to **20+ cancer types**

Activity predicated upon **overcoming barriers of adverse/ immunosuppressive tumor micro-environment** (TME)

*: Mutated peptide (native sequence has R instead of Y);
^: Predicted to be reactive with 10 MHC-type I [HLA-A & -B] and 15 MHC-Type II [HLA-DRB1-XX] molecules)

Pinilla-Ibarz, Leukemia. 2006; Gomez-Nunez, Leuk Res. 2006; May, Clin Cancer Res. 2007; Maslak, Blood. 2010; Krug, Cancer Immunol Immunother. 2010

GPS has Shown Activity Across Multiple HLA types, Potentially Allowing for Treatment of Global Pt populations

Composition and Immunobiological Features of GPS

Peptide Sequences (position)	Computationally Predicted Binding to HLA	Immune Response
WT1-A1: *YMFPNAPYL (126–134)	A0201, A0301, A2402, B1501, B3901	CD8+ CTLs
427 long: RSDELVRHHNMHQRNMTKL (427–445)	B1501, B3901, B0702, B08, B2705, B4001, B5801, and numerous HLA-DRB1-XX	CD4+ T cells
331 long: PGCNKRYFKLSHLQMHSRKHTG (331–352)		CD4+ T cells
122A1 long: SGQA*YMFPNAPYLPSCLES (122–140)	A0201, A0301, A2402, B1501, B3901, B0702, B08, B2705, B4001, B5801, and numerous HLA-DRB1-XX	CD4+ and CD8+ T cells

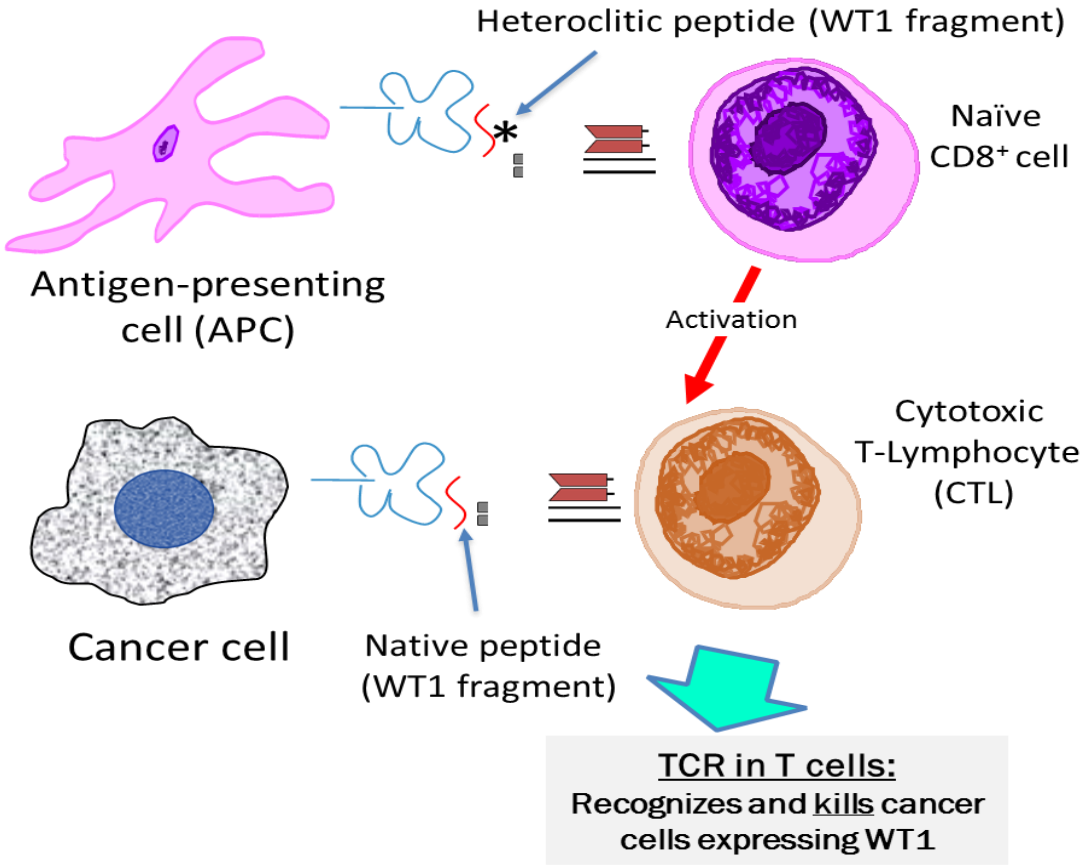
aa, amino acids; CD, cluster of differentiation; CTLs, cytotoxic T lymphocytes; GPS, galinpepimut-S; HLA, human leukocyte antigen; WT1, Wilms' tumor protein 1.
*Mutated peptide (native sequence has R instead of Y).

Galinpepimut-S addresses 25 WT1 epitopes predicted to be reactive with 10 HLA-A and HLA-B Alleles (MHC-type I) and numerous HLA-DRB1-XX Molecules (MHC-Type II)
** Heteroclitic peptides are highlighted with green arrows **

Pinilla-Ibarz, Leukemia. 2006; Gomez-Nunez, Leuk Res. 2006; May, Clin Cancer Res. 2007; Maslak, Blood. 2010; Krug, Cancer Immunol Immunother. 2010

GPS: Heteroclitic Technology-Based, First-in-Class Peptide Vaccine with Direct Anti-Cancer Immunizing Properties

- GPS is a mixture of 2 native and 2 synthetic (heteroclitic) WT1 peptide sequences
- Heteroclitic peptides:
  - A. have higher affinity for HLA
  - B. are prone to break tolerance and
  - C. generate a strong and prolonged response to the native peptide sequence (of the cognate target antigen) expressed by cancer cells

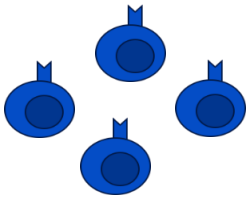


Pinilla-Ibarz, Leukemia. 2006; May, Clin Cancer Res. 2007; Krug, Cancer Immunol Immunother. 2010

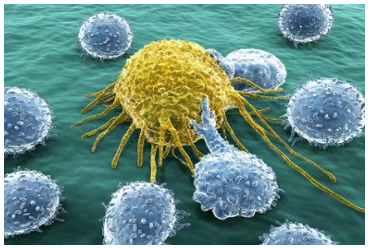
TCR: T-cell receptor

GPS Immunization is Associated with Epitope Spreading[1,2]: A Key Element for a Clinically Successful Cancer Immunotherapy

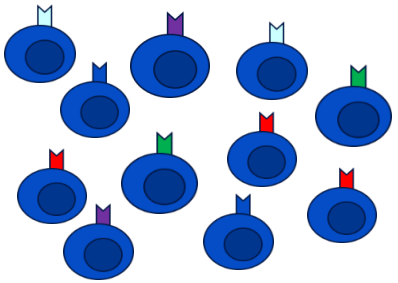
GPS-specific T-Tells recognize and kill the tumor cell



Tumor cell death releases new antigens into the tumor microenvironment



New antigens cause creation of T-cells specific for a broader set of antigens vs which the host was not initially immunized against



- Reactivity of lymphocytes from pts treated with GPS tested against a collection of overlapping peptide epitopes of the entire WT1 protein (~230 fragments)
- For CD8+, exposure of patient cells to these peptides at baseline do not trigger IFN responses – therefore, **no WT1-specific CD8 cells exist in the host prior to galinpepimut-S administration**
- After galinpepimut treatment, not only are there peptide-specific CD8+ T cells, but there are also CD8+ (and CD4+) T-cells reactive to WT1 peptide **epitopes for which the host was not specifically immunized**
- For this to happen, there would have had to be active cancer cell killing, release and presentation of WT1 peptide fragments, processing of additional WT1 epitopes by the immune synapse, and production of a broader, *de novo* expanded, repertoire of CD8+ clones specific to epitopes not included in the galinpepimut-S mixture

Multifunctional cross-epitope T-cell reactivity

→ Epitope spreading effect

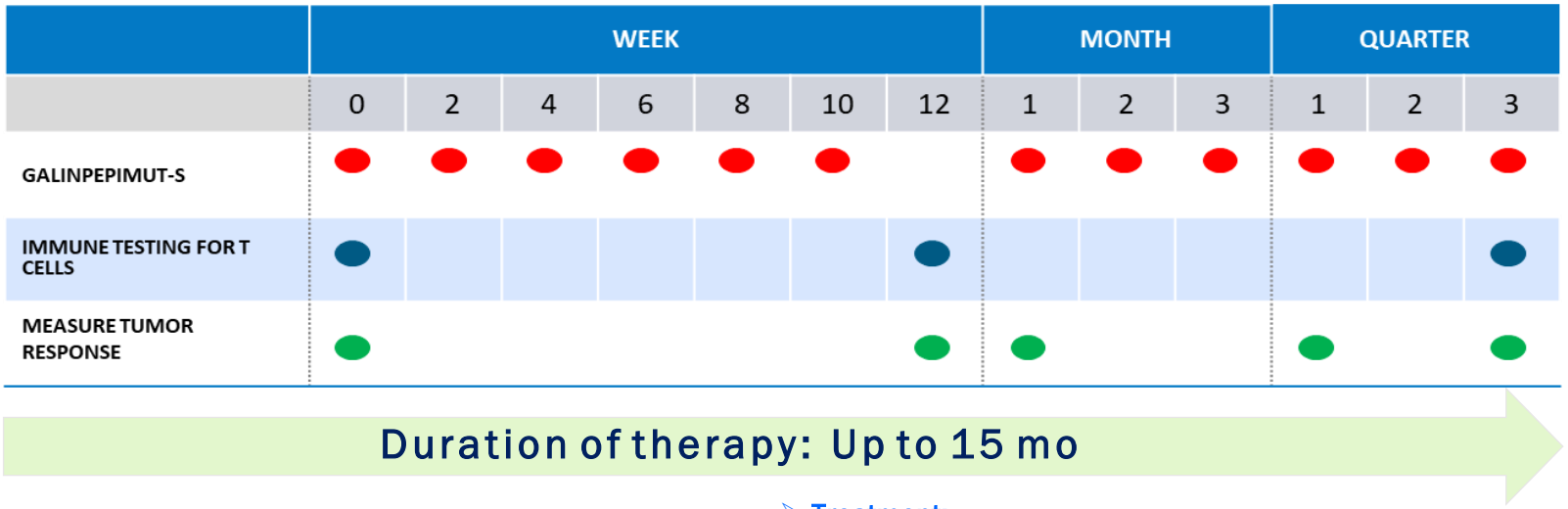
1. Koehne, Soc Hematol Oncol (SOHO) Mtg. Abst. MM-252, 2017; 2. Koehne, EBMT Mtg. Oral presentation 0132, 2018.

Comparison Among WT1-Targeting Vaccines

Parameters of Interest	DSP-7888 (nelatimotide/ adegramotide) Dainippon	OCV-501 Otsuka	GPS (Galinpepimut-S) SELLAS
Number of Peptides	2	1	4
WT1 Amino Acids	235-243, 126-133	335-350	126-134^, 427-445, 331-352, 122-140^
Heteroclitic	Yes	No	Yes
HLA Coverage (disclosed)	HLA-A*02:01, HLA-A*02:06 or HLA-A*24:02	HLA-DRB1-01:01, *04:05, *15:01, *15:02, *08:03, or *09:01	HLA-A-201, A301, A24:02, B39:01, B15:01, B08, B07:02, B27:05, B40:01, B58:01, and numerous DRB1:xx types
Adjuvant Used	Montanide	Montanide	Montanide
MHC Class I/II	I and II	II only	I and II
AML Clin Development Status	N/A	Ph2 (Japan, South Korea and Taiwan Only)	Ph3 registration-enabling study starting imminently
Other settings	MDS, Recurrent GBM (Ph2 with Bevacizumab), Advanced solid malignancies	N/A	Multiple myeloma, mesothelioma, ovarian (with Nivo), basket trial with Pembro in 5 indications (CRC, Ovarian, SCLC, TNBC, AML)

^ Heteroclitic sequences within the GPS mixture

Ph1 (Pilot)[1] and Ph2[2] Study Design in AML pts GPS Maintenance Rx in CR1



➢ **Eligibility:**

- Age > 18 y
- AML in first complete response (CR1)
- Completion of induction and post-remission therapy
- Have documented WT1-positive disease at CR1 (Phase 2)
  - **All patients harbored MRD(+) disease prior to GPS administration by WT1 mRNA transcript detection despite persistence of morphologic stringent CR**

➢ **Treatment:**

- **GPS (s.c. administration):**
  - **Four WT1 peptides (200 mg each; total amount of GPS mixture per administration: 800 mg)**
  - **Montanide (1:1 volume) adjuvant**
- **GM-CSF (Sargramostim; 70 mcg, s.c.; on days -2 and 0)**
- Patients may then continue monthly if immune response seen and no disease progression
- Follow up every 2 mo for up to 3 yrs after end of treatment

BOOSTER TREATMENTS WERE USED TO MAXIMIZE THE OPPORTUNITY FOR A PROLONGED WINDOW OF BENEFIT AND WILL ALSO BE USED IN THE PLANNED PIVOTAL PHASE 3 STUDY (IN CR2 PATIENTS)

[1] Maslak, Blood. 2010 and [2]Maslak, Blood Adv. 2018

Positive Ph 2 Clinical Results in AML (in CR1)[1]

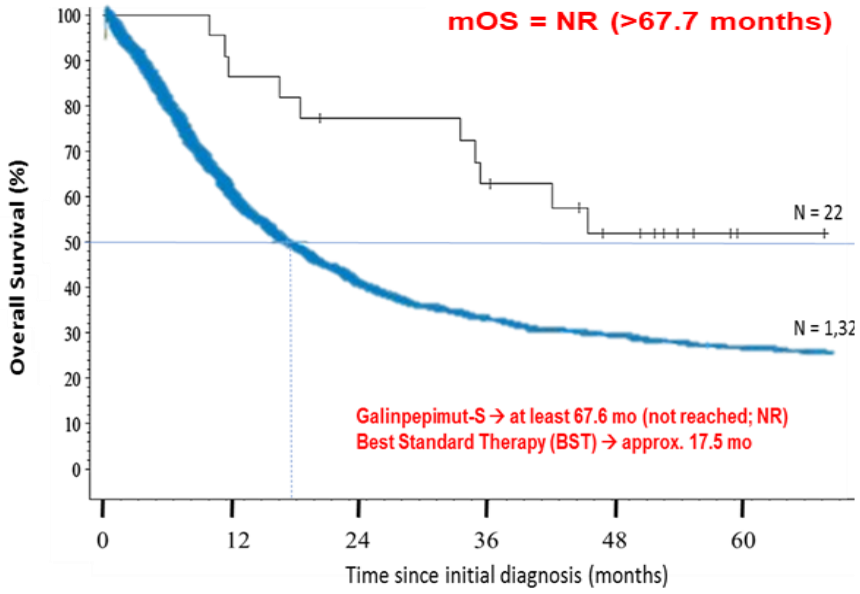
- Primary endpoint of 3-year OS > 34% was met → 47.4%
- Prolonged median overall survival: **67.6 months** (all ages) (vs current SOC of 17.5 - 25 mo)
- Aggregate population of patients ≥ 60 years (Phase 3 population): median overall survival (mOS) = **35.3 months** in Phase 2 (vs SOC of ~ 14 mo in the elderly)
  - Patients ≥ 60 years in CR1 demonstrated statistically significant 3-yr OS rate vs. predefined threshold
- **88%** of patients had evidence of antigen-specific immune response (IR), either CD8+ or CD4+, to any of the 4 peptides in GPS after vaccination at any time tested
  - **64%** of patients had **persistent antigen-specific IR, mainly CD4+**, to any of the 4 peptides in GPS after vaccination at both early and late time-points
- **CD4+ responses seen across all HLA-Class II subtypes tested**
- No discernable effect of HLA allelic type expression on clinical outcomes
- No discernable effect of baseline risk stratification profile by cytogenetics* on clinical outcomes for favorable and intermediate-risk patients, incl. those with normal karyotype
- **No Grade 3 or worse systemic side effects** were observed

* According to the European LeukemiaNet (ELN) prognostic scoring system (Doehner, Blood. 2017)

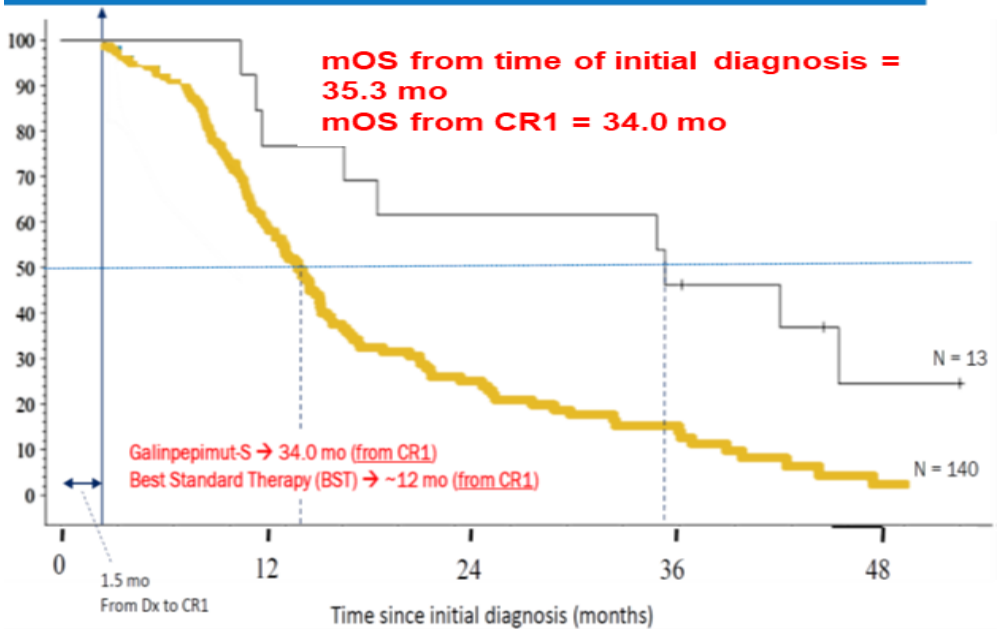
[1]Maslak, Blood Adv. 2018; SELLAS, Data on file

GPS: Phase 2 Study- Overall Survival Results in AML (in CR1)[1,2]

ALL AGES



AGE ≥ 60 YRS



Source for hist controls (blue curve):
Walter RB, et al. J Clin Oncol. 2010; 28:1766-71.

Source for hist controls (yellow curve):
Freeman SD, et al. *J Clin Oncol. 2013;* 31:4123-31

Mo: months; CR1: first complete response
MRD: minimal residual disease

- K-M log-rank analysis from time of initial diagnosis
- Overlap with historical control data for purpose of general illustrative comparison

- Pts in the Freeman cohort comparable to the GPS study
→ Elderly subgroup:
- 60+ yrs, AML in CR1, MRD+ (at the time of CR1)

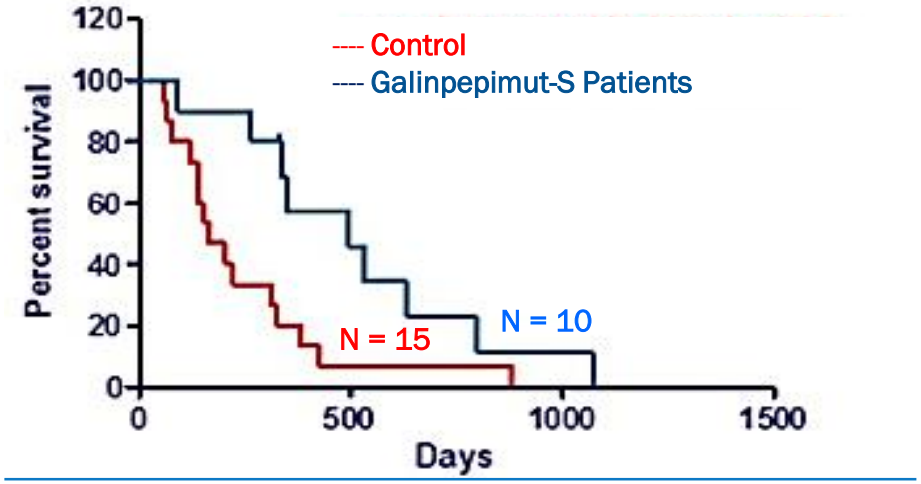
PHASE 2 PRIMARY ENDPOINT POSITIVE: MULTIPLE-FOLD INCREASE IN OVERALL SURVIVAL*

*versus carefully selected, comparable historical control populations

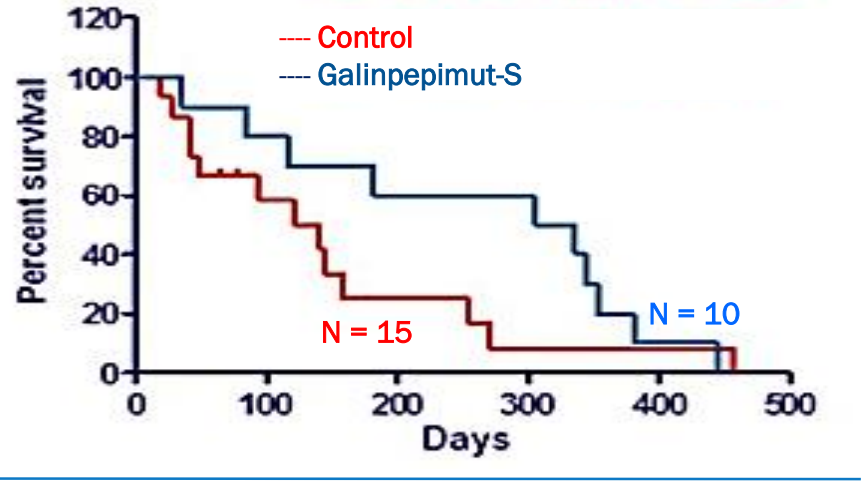
1. Maslak, Blood Adv. 2018; 2. SELLAS, data on file

GPS Pilot Study (Moffitt CC) – Efficacy Results[1]
Maintenance in Adult CR2 AML Patients with WT1(+) Disease
(After Completion of salvage therapy with adequate reconstitution of blood counts)

OVERALL SURVIVAL



RELAPSE-FREE SURVIVAL



- AML patients receiving ≥ 2 administrations of GPS (n=10) compared to group of paired patients in CR2 **contemporaneously treated** at MCC during a similar time period (n=15)
- **Overall survival (OS)** in GPS-treated individuals significantly greater vs. the compared group, **16.3 mo vs. 5.4 mo** (p = 0.0175)

1. Brayer, Am J Hematol. 2015

CR2: second complete remission; GPS: galinpepimut-S; mo: months; CC: Cancer Center

GPS Pilot Study (Moffitt CC)
Maintenance in Adult CR2 AML Patients: Other Key Results[1]

Evaluable N=10

- Median age: 74 yrs
- All pts had documented MRD (+) status at time of study entry
- Mean interval between achievement of CR2 status and first GPS administration = **2.7 mo**
- **Median leukemia (relapse)-free survival (mLFS) = 10.5 mo**
- No patients underwent allo-HSCT on either arm

MRD: minimal residual disease; CR2: second complete remission; GPS: galinpepimut-S; mo: months; CC: Cancer Center; MDS: myelodysplastic syndrome

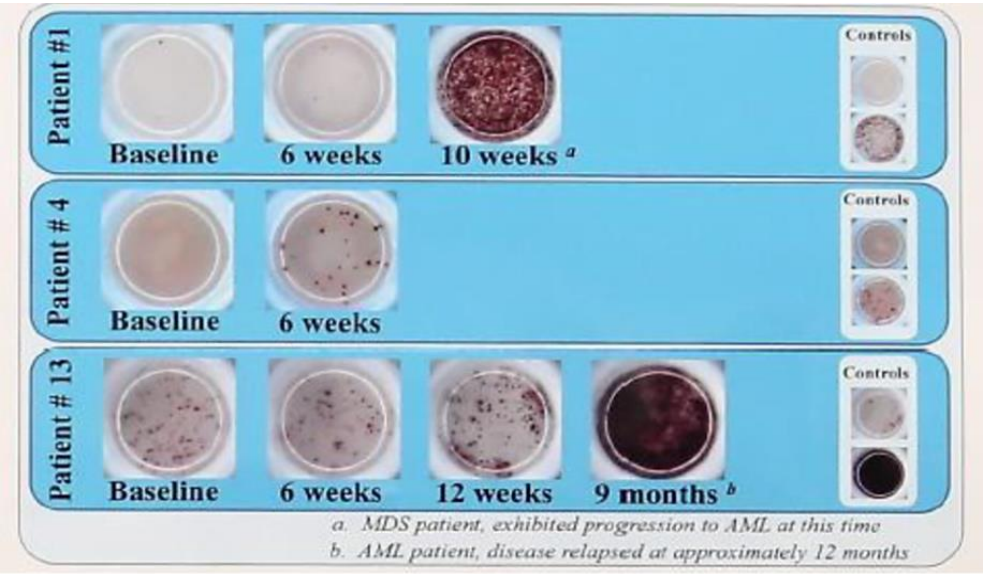
1. Brayer, Am J Hematol. 2015

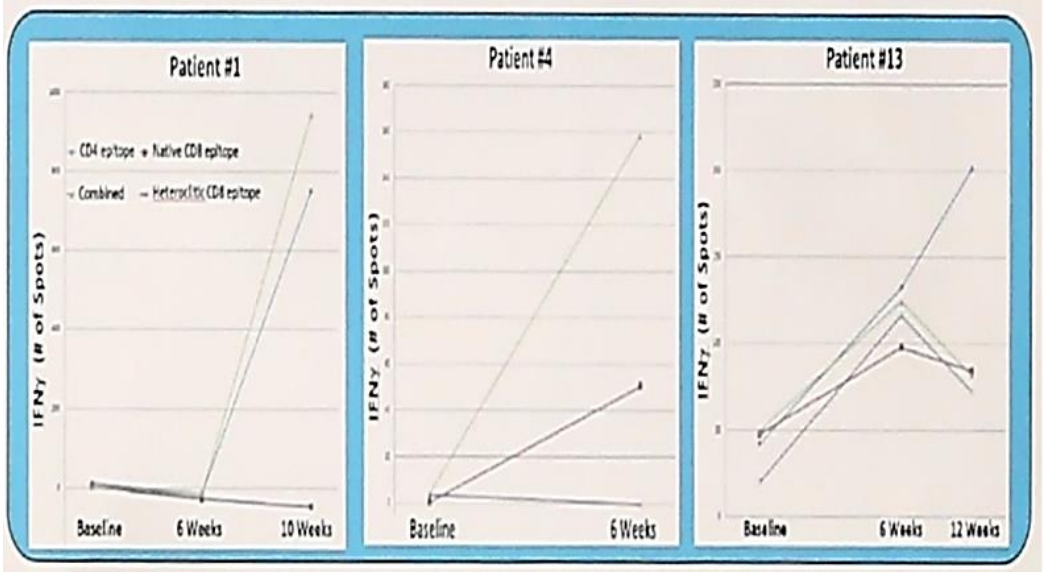
Drug-Related Adverse Events (N=16)*

Toxicity	Grade 1/2	Grade 3/4
Fatigue	3 (18·75%)	0
Generalized weakness	1 (6·67%)	0
Anorexia	1 (6·67%)	0
Flushing/hot flashes	1 (6·67%)	0
Pain	2 (12·5%)	0
Leukopenia	2 (12·5%)	1 (6·67%)
Anemia	1 (6·67%)	0
Thrombocytopenia	1 (6·67%)	0
Hematoma/abnormal bleeding	2 (12·5%)	0
Nausea	2 (12·5%)	0
Emesis	1 (6·67%)	0
Diarrhea	1 (6·67%)	0
Bloating	1 (6·67%)	0
Transaminitis	1 (6·67%)	0
Hyperbilirubinemia	1 (6·67%)	0
Cough	1 (6·67%)	0
Rash	1 (6·67%)	0
Local injection site reaction	6 (37·5%)	0
Pruritis	1 (6·67%)	0

*Safety analysis included 10 pts with AML in CR2 and 6 pts with MDS

GPS Pilot Study (Moffitt CC): Vaccine Induces Antigen-Specific IFNγ Production by Patients' T-Cells[1]



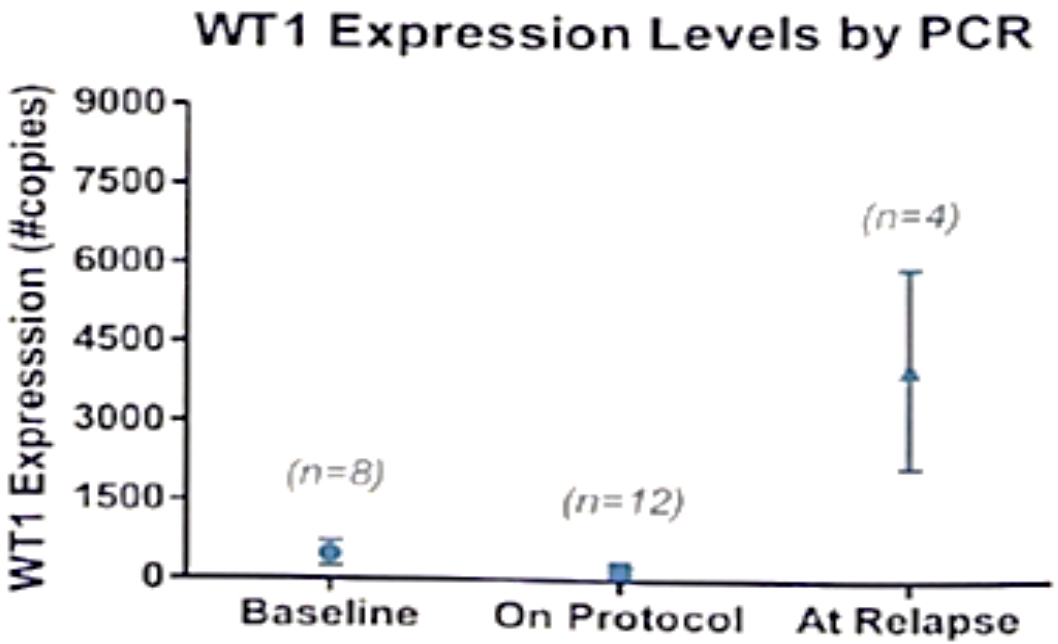


CD3+ lymphocytes isolated from peripheral blood samples at predefined time points were restimulated in culture against all peptides combined. After 2 rounds of expansion, responses against the individual native CD8 epitope, heteroclitic CD8 eptitope, CD4 epitope, and combination of all 4 peptides were measured by IFNγ ELISPOT. **(A)** depicts ELISPOT responses of 3 patients to combined peptide.

1. Brayer, ASCO Abst. 3089, J Clin Oncol. 2014

CC: Cancer Center; ELISPOT: enzyme-linked immune absorbent spot (assay); IFNγ: interferon-gamma

GPS Pilot Study: Patients who Continued on Per-Protocol Vaccinations were Able to Maintain Molecular Remission (MRD measured by WT1 PCR)



WT1 expression increases with disease recurrence. WT1 transcripts were measured by qRT-PCR to determine expression levels at baseline, at specified time points according to trial design, and upon relapse (when available, not a predetermined time point in the study design).

1. Brayer, ASCO Abst. 3089, J Clin Oncol. 2014

MRD: minimal residual disease; GPS: galinpepimut-S
qRT-PCR: quantitative real-time polymerase chain reaction

Competitive Immunotherapy Landscape in AML

Manufacturer	Name of Agents/Product with Immunologically-mediated MOA*	Class
Actinium Pharmaceuticals	Iomab-B CD45	Anti-CD45-RAI conjugate - Myeloablative agent -- prior to Allo-SCT
Amgen	AMG 330 & AMG 673	anti-CD33/CD3 BiTE antibodies
	AMG 427	FLT3/CD3 BiTE
BMS	BMS-936564	anti-CXCR4 MAb
Celgene	GEM-333 (acquired from GemoAb)	Anti-CD33/CD3 bispecific antibody
Celyad - Ono	CYAD-01	CAR-T against NKG2D
Dainippon Sumitomo Pharma (DSP)/ Boston Biomedical	DSP-7888 (adegramotide/ nelatimotide)	WT1 vaccine
Fortress Biotech	CNDO-109	Allogeneic tumor activated NK cells (TANK lymphocytes)
Glycostem Therapeutics	oNKord®	Umbilical cord blood (UCB) progenitor cells-derived NK cells
Immune Pharmaceuticals/ Vector Therapeutics	Histamine dihydrochloride (CEPLENE®)	NOX2 inh (IL2 action potentiator; co-administered with IL2)
Innate Pharma	Lirilumab (IPH2102/ BMS-986015)	Anti-KIR Mab
MacroGenics/ Servier	MGD006	anti-CD123/CD3 Dual Affinity ReTargeting (DART®) BITE
Merus N.V.	MCLA-117	anti-CLEC12A/CD3 Biclonics® molecule
Otsuka	OCV-501	WT1 vaccine
Sellas Life Sciences Group	Galinpepimut-S (GPS)	WT1 vaccine

* Excludes various individualized cell therapies (e.g., neoantigen CAR T-cells), combination approaches with immune synapse modulators (e.g., checkpoint blockers [PD1/PDL1 inhibitors]) and agents administered in conjunction with or after allogeneneic hematopoietic stem cell transplant (allo-SCT)

Key Take-Away Points

- ✓ GPS is a Sophisticated First-in-Class Heteroclitic, non-HLA-Restricted Peptide Vaccine, Specifically Designed to Induce both CD8+ and CD4+ Immunoresponses
- ✓ GPS has Multiple Innovative Properties Optimal for both the Current and Future Immuno-Oncology Landscape in AML and other malignancies
- ✓ Overall Survival in the Phase 2 AML (CR1) trial was **Multiples Fold** Longer than Predicted; Positive Efficacy Signal by both OS and PFS in the CR2 Maintenance Setting was also seen
- ✓ Consistent Immune Response Profile and Evidence of Epitope Spreading
- ✓ The GPS Clinical Program Results in Aggregate Provided Solid Rationale for the Design of a Pivotal Phase 3 Trial in AML for CR2 maintenance in Patients who have Successfully Completed Salvage (2nd Line) Therapy. This Phase 3 Study has Completed FDA Review and is to be Initiated Imminently
- ✓ Clinical Development Opportunities as Both Monotherapy Maintenance Therapy (in MRD settings) and –due to the Agent's Low Toxicity Burden and MOA- in Combination with Checkpoint Inhibitors and other Immuno-Oncology Therapies (to address measurable advanced disease)

Phase 3 trial of GPS in AML (CR2 Setting) Clinical Overview

Nicholas J. Sarlis, MD, PhD
Chief Medical Officer

New York City, NY - 15 November 2019

Clinical Study Introduction

A **R**andomized, Open-Label Study of the **E**fficacy and Safety of **G**alinpepimut-S (GPS) Maintenance Monotherapy Compared to Investigator's Choice of Best Available Therapy in Subjects with **A**cute Myeloid **L**eukemia Who Have Achieved Complete Remission After Second-Line Salvage Therapy (**CR2**)

The **REGAL** Study (SLSG18-301)

- Phase 3 – Pivotal (Registration-enabling)

Target population

- AML patients (any age) who have successfully achieved their second morphological complete remission – with or without adequate platelet recovery - (CR2/CR2p) (after 2nd line therapy excluding targeted agents for specific molecular aberrations*) who are ineligible for or unable to undergo allo-HSCT

*FLT3 internal tandem duplication (ITD), FLT3 mutations, IDH1 or IDH2 mutations
Allo-SCT: allogeneic stem cell transplantation

Study Objectives

Primary Endpoint

- Comparison of the efficacy (**median Overall Survival; mOS**) of **GPS monotherapy (active arm)** vs. Investigator's choice of **Best Available Therapy** (**BAT** - **control arm**) in the maintenance setting post-CR2/CR2p

Secondary Endpoints

- ***Toxicity***:
  - Safety & tolerability of GPS (to determine the risk-benefit ratio)
- ***Efficacy***:
  - Leukemia-Free Survival (LFS)
  - OS rate (%) at 6, 9 and 12 months (landmark)
  - LFS rate (%) at 6, 9, and 12 months (landmark)
  - Minimal residual disease (MRD) burden by multigene assay (NHLBI)

Exploratory Endpoints

- ***Immune Response (IR) Assessment***:
  - Antigen (WT1 Peptide)-Specific T-cell (CD8/CD4) IR & Epitope Spreading (Peripheral blood) – GPS arm only[1]
  - Non-Specific Immunocyte Frequency and Distribution Dynamics Over Time (in Bone Marrow) [2] (by IHC assay)
- ***Tumor Microenvironment Markers***:
  - Pro-inflammatory molecular "signatures" over time (in Bone Marrow Stroma)[3]

1: by multicytokine flow cytometry; 2: By Immunohistochemistry (IHC) for specific immunocyte types & subpopulations;
3. by tissue microassays (TMA) RNA expression assays

Trial Schema and Design: N=116

- AML in CR2 post-2nd line Rx in patients ≥ 18 yrs (incl. CR2p, but with adequate WBC counts)
- Ineligible/unable to undergo Allo-SCT
- ~50 centers (US/EU)
- Three Stratification axes:
  - CR2 vs CR2p status
  - cytogenetics risk category at initial diagnosis (poor vs all other, incl. unknown)
  - Duration of historical CR1 (<12/>12 months)

R

1:1

- Galinpepimut-S (200 µg of each peptide x 4; total 800 µg)
- Montanide (500 µl/ dose)
- GM-CSF (sargramostim; Leukine® ; 70 µg/dose; d-2 & d0)

Schedule of Administration*



- Best Available Therapy (BAT) – 4 predefined choices
  - Clinician's choice: Observation (incl. hydroxyurea palliation); Venetoclax; HMAs; Low-dose Ara-C
  - Therapy duration: up to 52 wks*

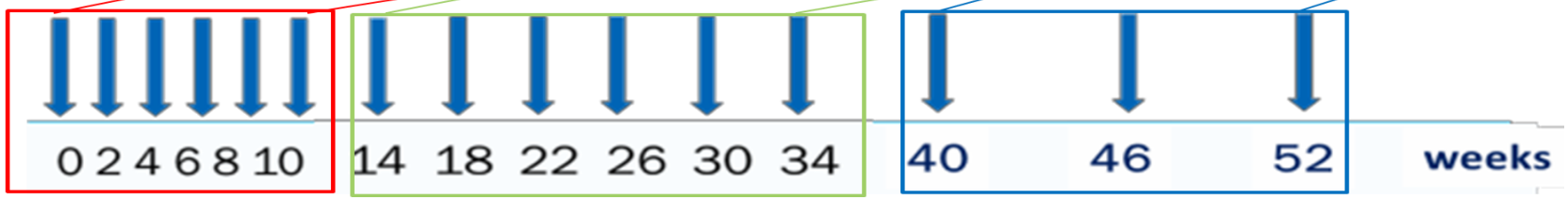
- Follow-up duration: up to 9 months
- OS and PFS to be assessed every month during the off-treatment follow-up period for pts who have completed 1 yr of therapy in either arm

*Assumes no disease progression; this corresponds to up to 15 vaccine doses in the GPS arm

Study Treatments

Active Arm: GPS Administration Schedule

Treatment Phase:	Induction Phase	Early Boosters	Late Boosters
Weeks:	0, 2, 4, 6, 8, 10	14, 18, 22, 26, 30, 34	40, 46, 52



Control Arm (Physician Choice):

All drugs are administered per label/ NCCN/ ASCO/ ASH/ EHA guidelines, per standard of care

- **Stratum 1**: Observation[1]
- **Stratum 2:** Low-dose Cytarabine (Ara-C) (LDAC)[2]
- **Stratum 3**: Hypomethylating Agent
  - ✓ Decitabine[3]
  - ✓ Azacitidine[4]
- **Stratum 4**: Venetoclax[5] - **monotherapy only allowed**

1. Palliative use of hydroxyurea is allowed; dose titrated to control of leukocytosis in acutely relapsing pts; 2. 20 mg twice a day SC on days 1-10; repeat cycle q.28 - 42 days (depending on blood counts); 3. 5-day regimen: 20 mg/m² continuous IV infusion (CIVI) over 1 hr qd x 5 days, repeat cycle q.28 days OR 3-day regimen: 15 mg/m² CIVI over 3 hr q8h x 3 days; repeat q.42 days; 4. 7-day regimen: 75 mg/m² SC or IV qd x 7 days; repeat q.28 day; 5. Dose ramp-up phase (D1: 100 mg PO qd → D2: 200 mg PO qd → D3: 400 mg PO qd), Day 4 and beyond: 400 mg – 600 mg PO qd until disease progression or unacceptable toxicity

Statistical Considerations (Top-Line)

- Planned number of deaths is 105 (out of a total N of 116) at the time of Final Analysis (FA)
- At least **90% power** under an assumed hazard ratio **(HR) of 0.52**, based on a **mOS** of 5.4 mo (BAT) vs. 10.4 mo (GPS) (**92.6% relative difference**)
- Overall 1-sided significance level (***P***) of **0.025**
- One **pre-planned interim analysis (IA)** by an independent data monitoring committee (IDMC) for efficacy after the **first 80 events**
- **In order to declare statistical significance, one needs to either observe a HR of <0.60 at interim analysis, or a HR of <0.675 at final analysis**
- The interim analysis is expected to occur approximately 5 months after the last subject has been randomized

U.S. & Global Lead



Hagop Kantarjian, MD
Distinguished Professor
Head, Dept. of Leukemia
M.D. Anderson Cancer Center
Houston, TX, USA

EU Lead



Gert Ossenkoppele, MD, PhD
Professor of Hematology
VU University Medical Center
Head, HOVON Network
Amsterdam, The Netherlands

Current Operational Status

- Study design and statistics discussed and precleared with FDA
- Global full-service CRO contracted and fully engaged
  - Worldwide Clinical Trials; www.worldwide.com
- Reach out process initiated in multiple sites in all selected countries (US, Germany, Belgium, Netherlands, Poland, Czech Republic)
- 85+ Site Investigators contacted and in the process of engagement
- First clinical site (US) successfully selected and IRB submissions ongoing

Thank you

ΣELLAS
LIFE SCIENCES GROUP

PD-1 blockade alone, in combination with vaccines, and the rationale for its combination with Galinpepimut-S:

Results to-date and ongoing clinical studies

Jeffrey S. Weber, MD, PhD

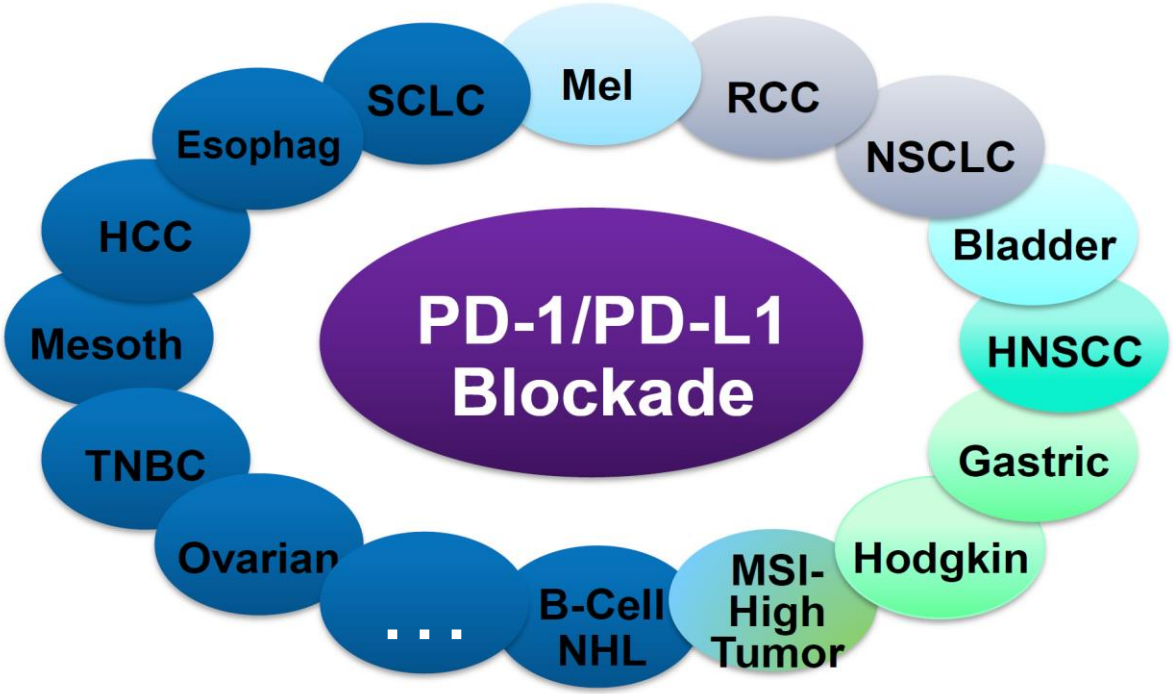
Deputy Director, Laura & Isaac Perlmutter Cancer Center

Co-Director, Melanoma Program & Head of Experimental Therapeutics

NYU/Langone Health

New York, NY

PD-1/PDL1 Blockade is an Established Therapeutic in Oncology with Registrations in Multiple Cancers: The End of the Beginning…



- **It is now being applied in earlier stages of disease:**

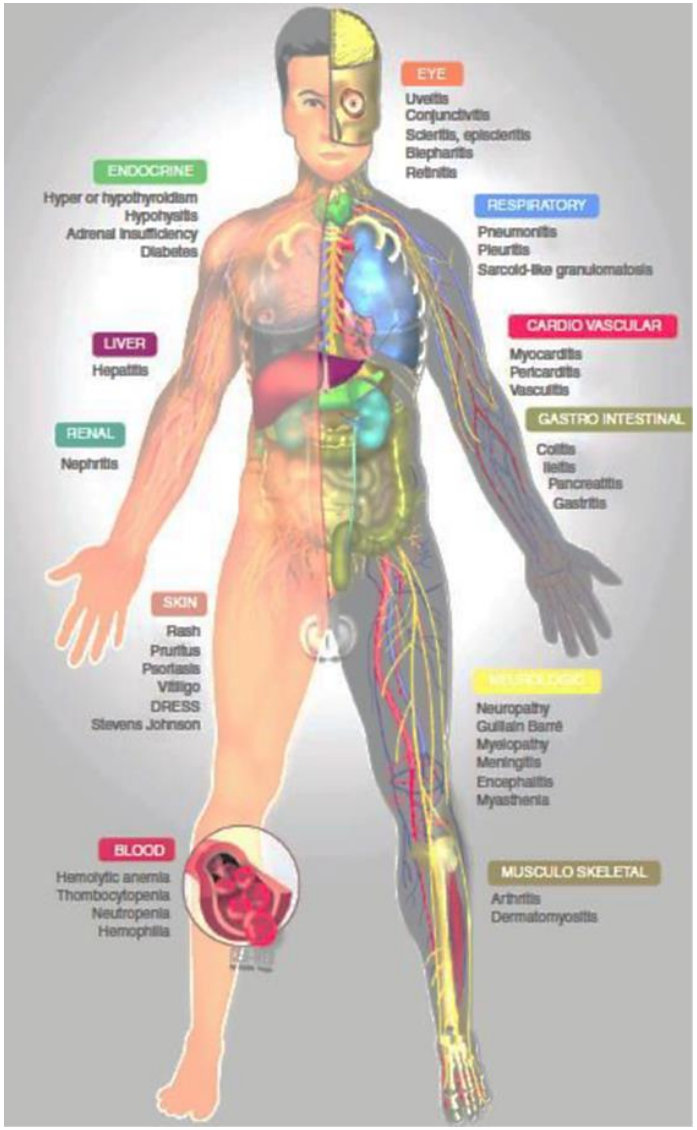
Metastatic Refractory Disease → Metastatic/Advanced Disease 1st Line → Adjuvant Therapy in Low Tumor Burden/NED Settings

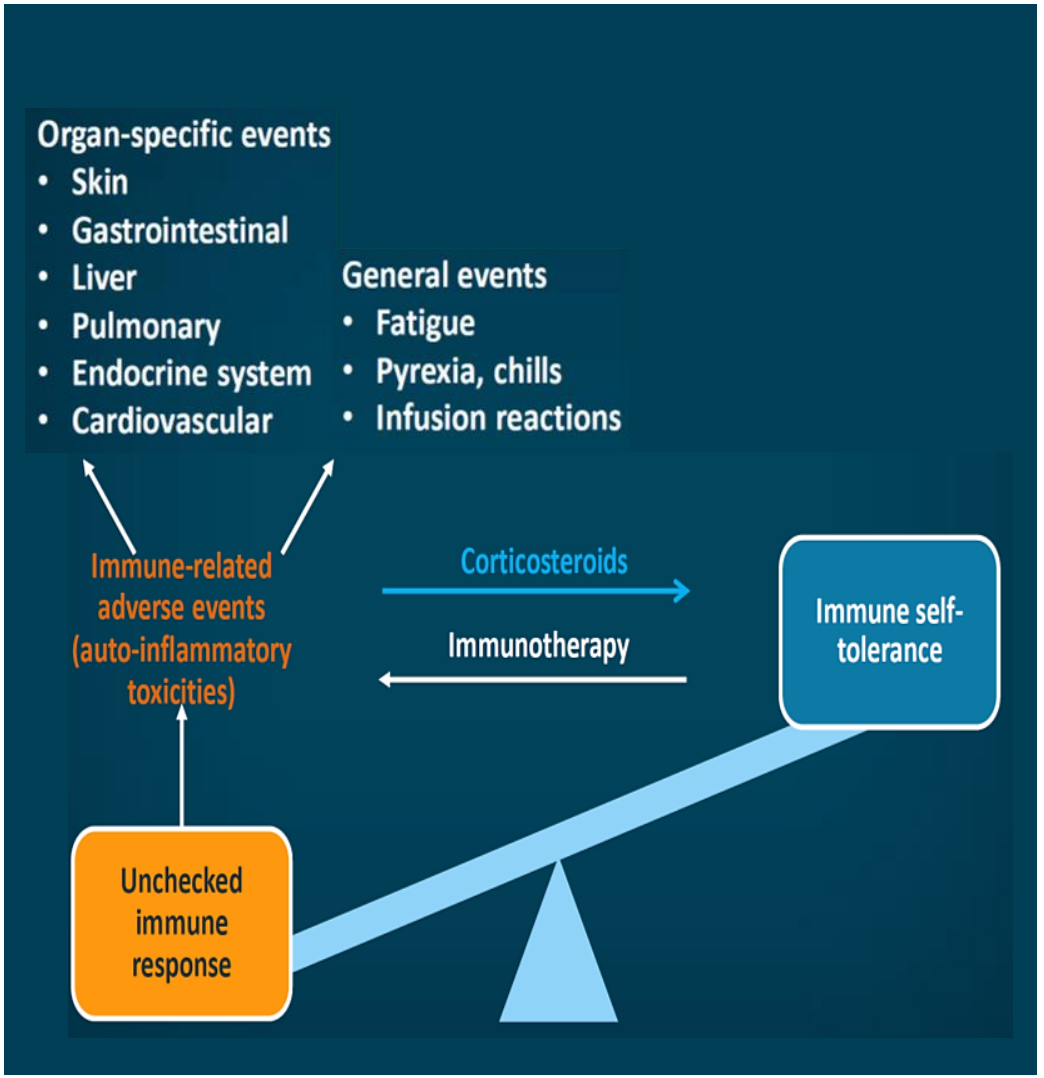
- **Combination Therapies** (Eight hundred trials on-going) –

N.B.: Not all based on a solid immunobiological rationale!
(lots of empiricism)

The bad news: PD-1/PDL1 Blockade: Continued Challenges

Immune-related Adverse Events (irAEs)

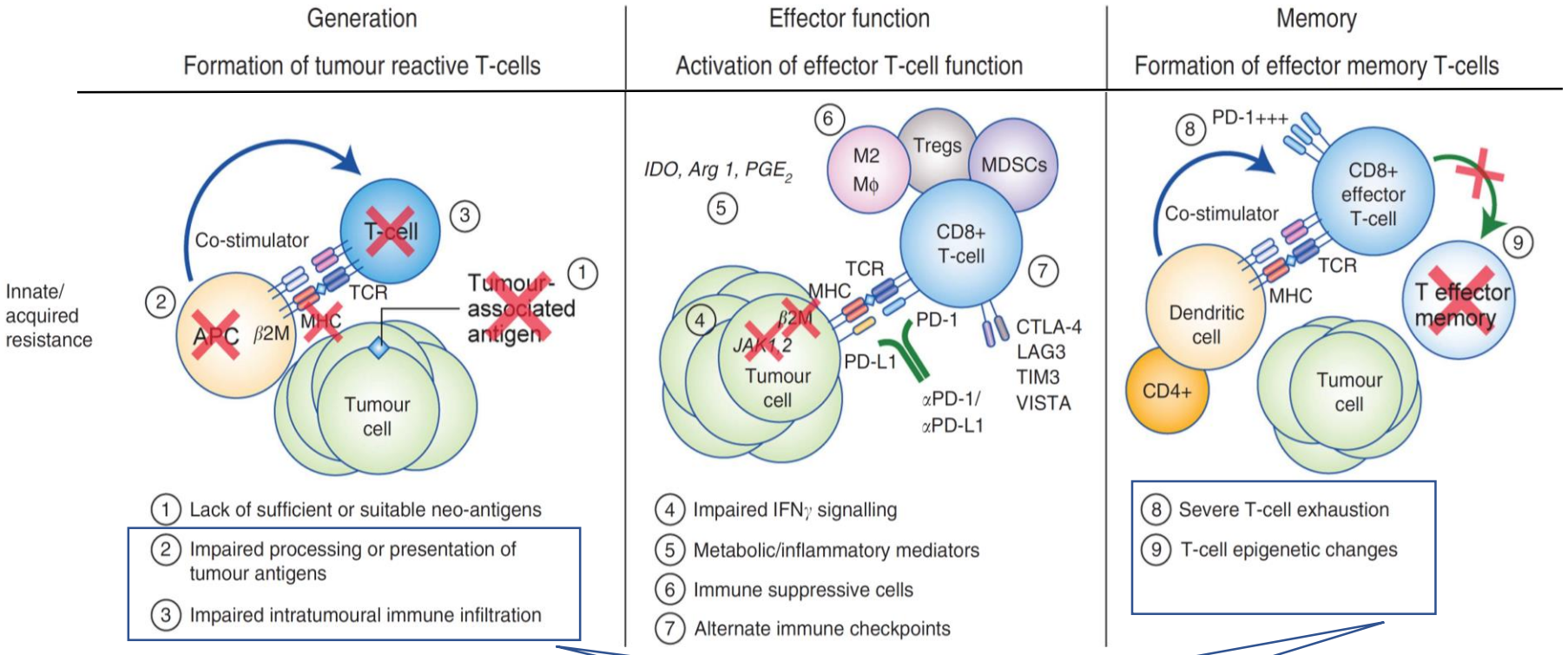




Champiat, Ann Oncol. 2016

The bad news: PD-1/PDL1 Blockade: Continued Challenges

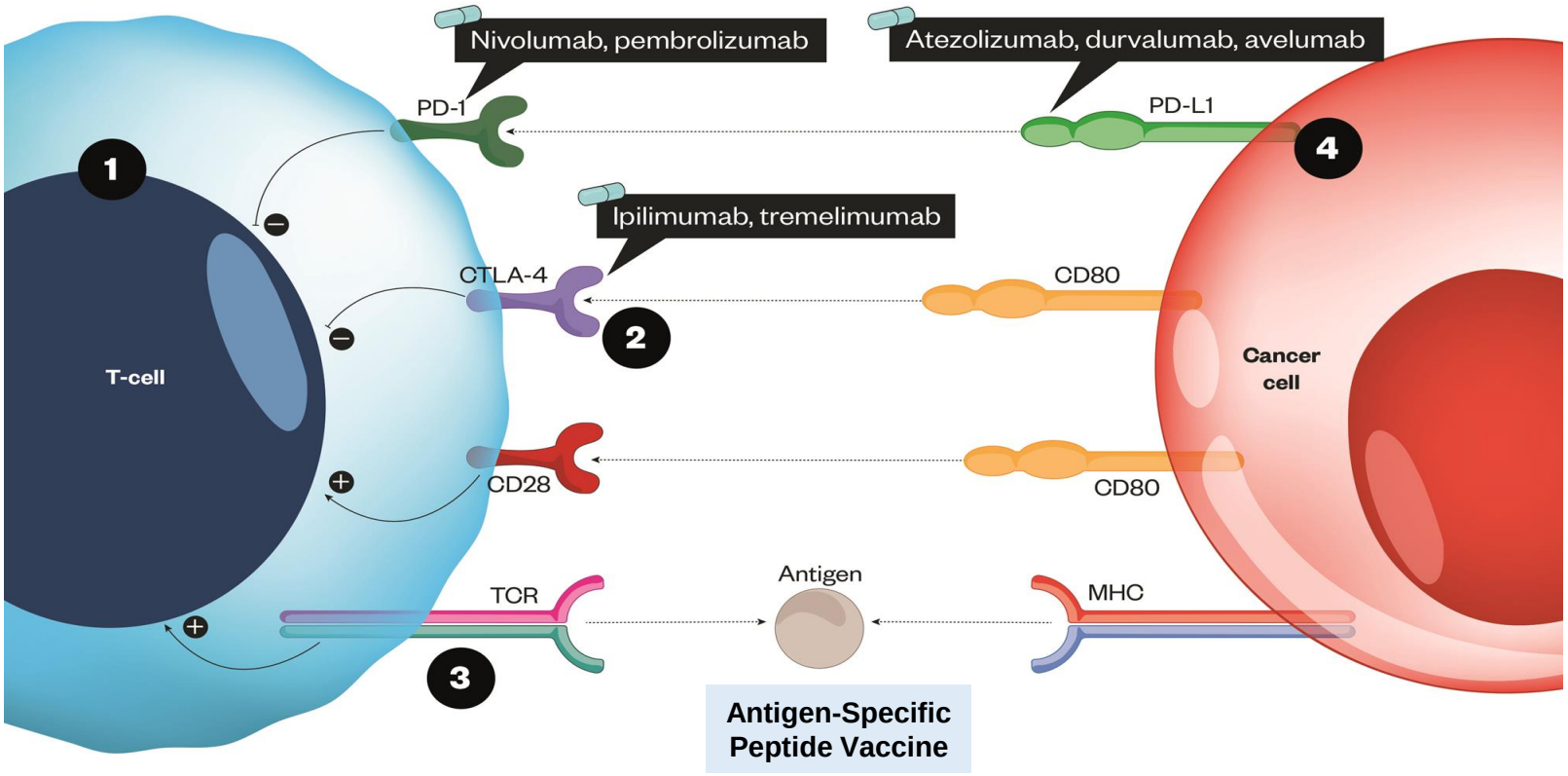
Resistance to CPI Effect →
Key Mechanism Underlying the Lack of Universal Clinical Efficacy of CPIs Across Indications/Tumor Types



Where oncologic vaccines may help

Modified from Jenkins, Br J Cancer. 2018

Molecular Locus of Action of Various IO Therapies
The Basis for Synergy Between CPIs and Cancer Vaccines



The T-cell receptor (TCR) binds to an antigen found on the MHC on the surface of the cancer cell
(1) Stimulatory response activates T cells to remove cancer cells (positive circles). A co-stimulatory receptor (CD28) binds to a ligand (CD80), resulting in an increased immune response toward the cancer cell
(2) CTLA-4 has a stronger affinity to CD80, thus competing with the co-stimulatory pathway to inhibit the response and 'switch it off'
(3) When a strong TCR stimulus emerges, CTLA-4 is upregulated and transported to the cell surface; similar processes occur with PD-1
(4) Checkpoint inhibitors (CPIs) act by blocking the inhibitory response by targeting CTLA-4, PD-1 or the ligand PD-L1

Modified from Evans, Pharmaceut J. 2018

CPI: checkpoint inhibitor

Paradigms For Clinical Uses of Cancer Vaccines

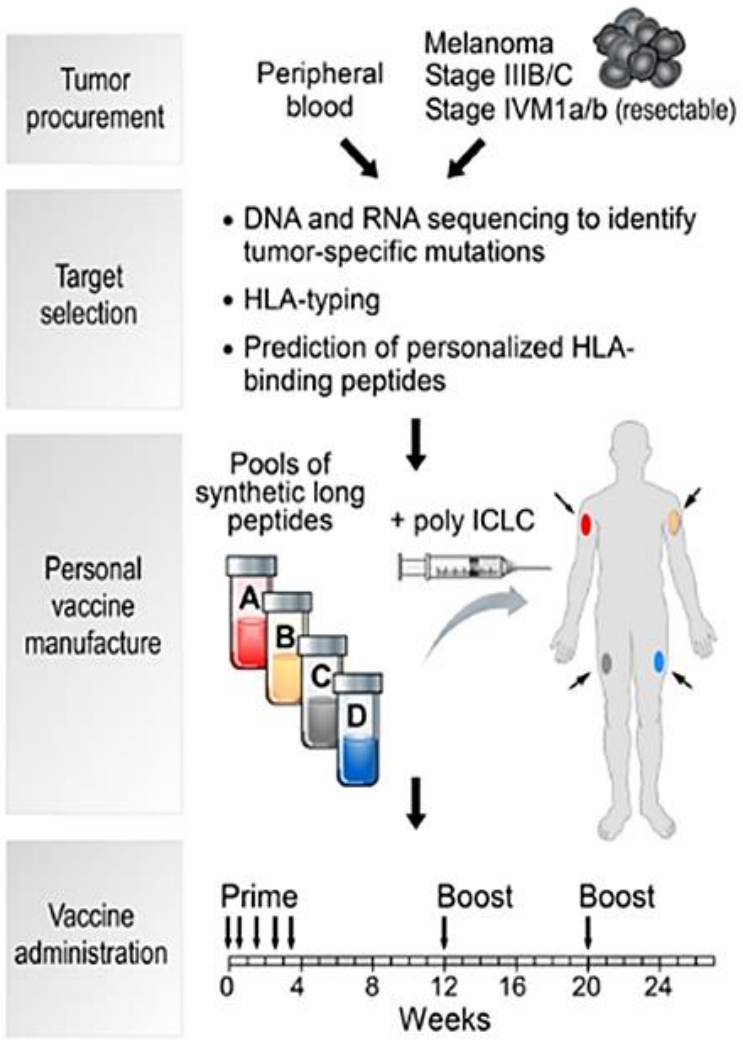
- AS **MONOTHERAPY OR IN COMBINATION WITH APPROVED ADJUVANT IMMUNOTHERAPIES** IN THE MAINTENANCE/ ADJUVANT SETTING

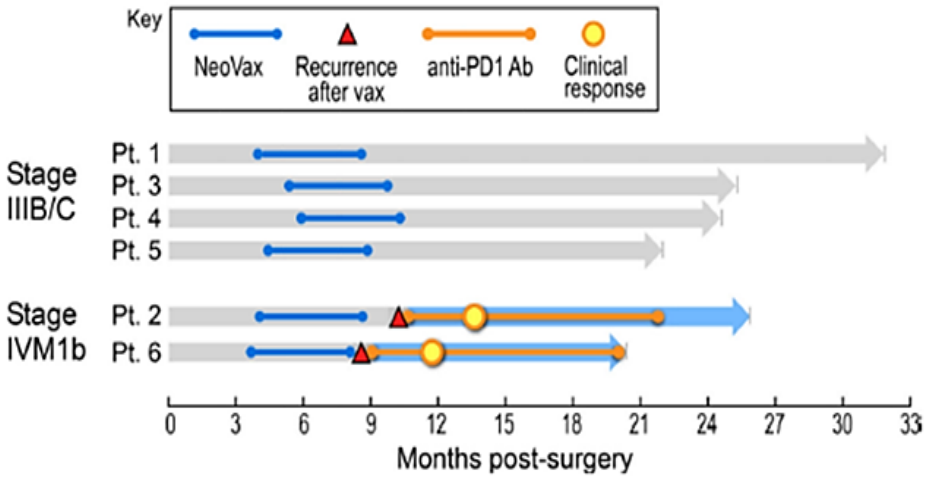


- **IN COMBINATION WITH IMMUNOTHERAPIES** TO TREAT MEASURABLE/ MACROSCOPIC ADVANCED DISEASE

- Clinical trials studying the effect of the combination of cancer vaccines plus immuno-oncology (IO) agents vs. IO agents alone
- Strong preclinical/ immunobiological rationale (in most cases)
- What are the existing clinical data for vaccines +/- PD-1 blockade?

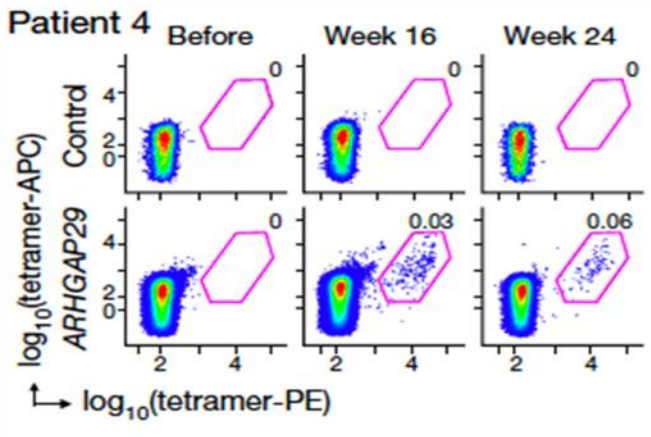
PD-1 blockade with Neoantigen Peptide Vaccine

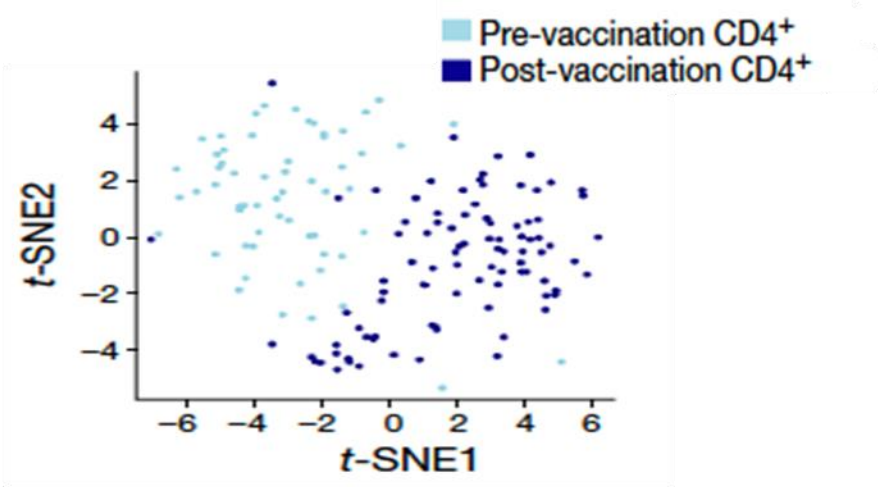


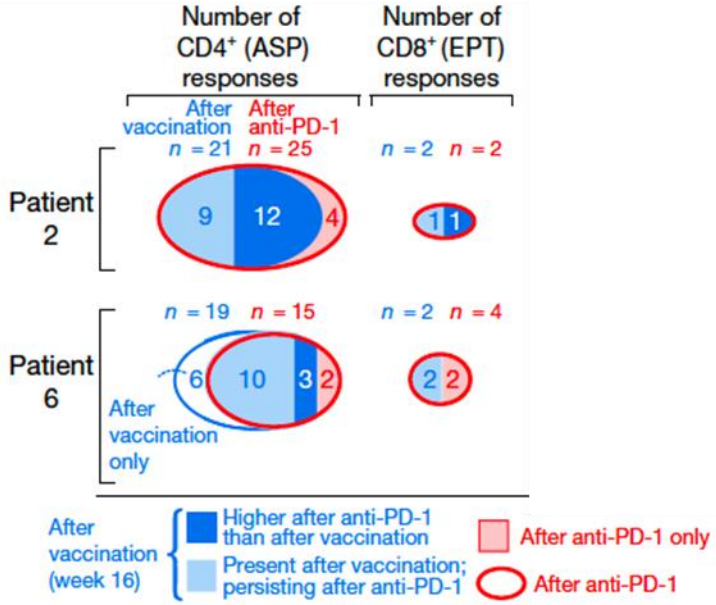


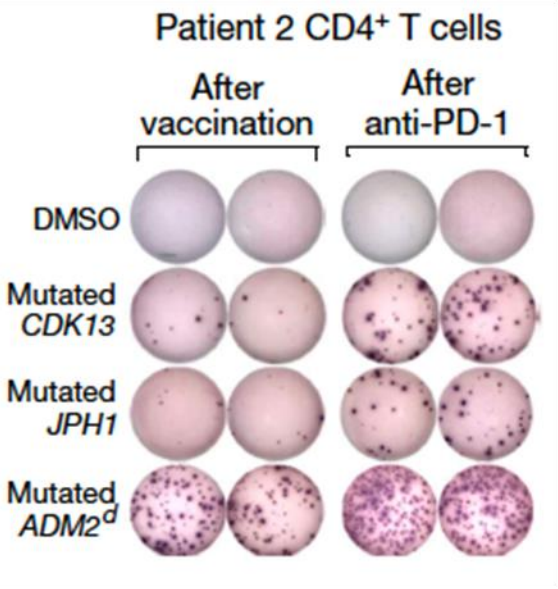
Ott, Nature. 2017

Peptide T-cell Responses After PD-1 Blockade



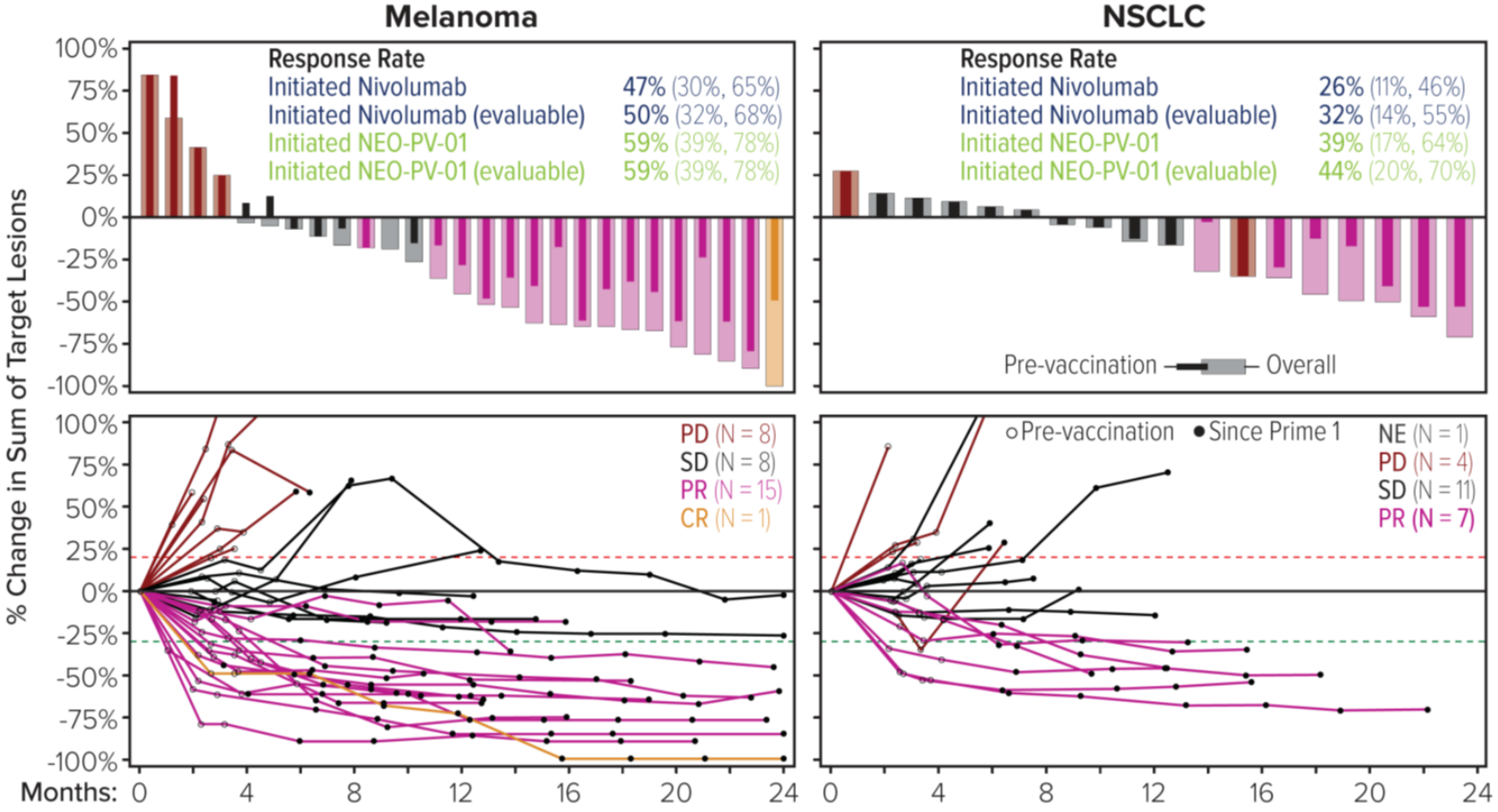






Ott, Nature. 2017

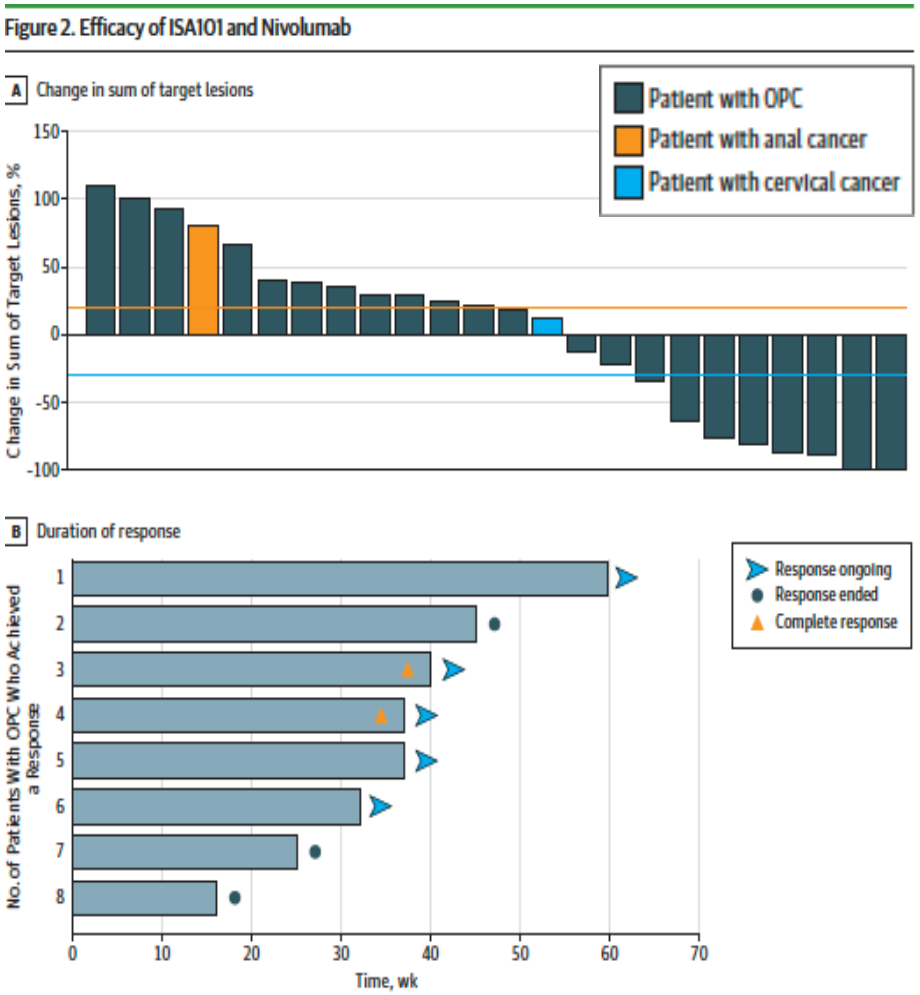
Ph1 Study of Peptide Vaccine (from NEON) Plus Nivolumab in Melanoma and NSCLC - Does Vaccine Increase PD-1's Clinical Benefit?



Ott. Abst. P437, SITC 2019

HPV Long Peptide Vaccine + PD-1 blockade in Oropharyngeal Cancer (OPC)[1]

Response per RECIST, version 1.1	No. (%)					
		Patients With Oropharyngeal Cancer				
	All Patients (N = 24)	All (n = 22)	Platin-Refractory Disease (n = 17)	Cetuximab-Refractory Disease (n = 8)	Platin- and Cetuximab-Refractory Disease (n = 6)	Received Second-line Treatment (n = 12)
Overall response rate	8 (33)	8 (36)	6 (35)	5 (63)	3 (50)	5 (42)
Complete response	2 (8)	2 (9)	2 (12)	1 (13)	0	2 (17)
Partial response	6 (25)	6 (27)	4 (24)	4 (50)	3 (50)	3 (25)
Stable disease	3 (13)	2 (9)	1 (6)	0	1 (17)	1 (8)
Disease control rate[b]	11 (46)	10 (45)	7 (41)	5 (63)	4 (67)	6 (50)
Progression of disease	13 (54)	12 (55)	10 (59)	3 (38)	2 (33)	6 (50)



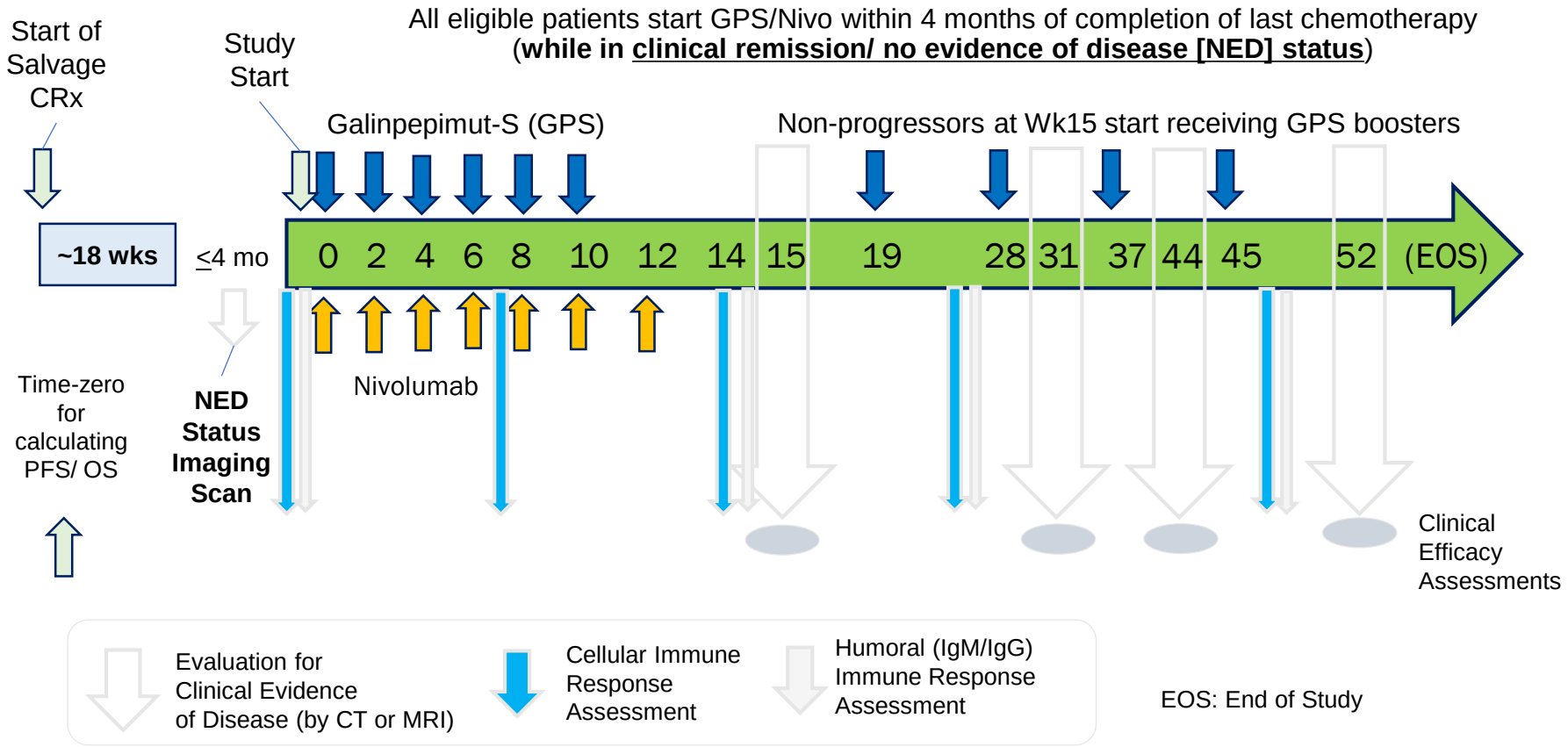
- 33% ORR is better than expected
- 14-18% ORR with PD-1 alone[2,3]

1. Massarelli, JAMA Oncol. 2018; 2. Seiwert, Lancet Oncol. 2016 (Keynote-012 Study);
3. Cohen, Lancet. 2019 (Keynote-040 results)

Galinpepimut S (GPS) + Nivolumab Pilot Study in Ovarian Cancer

Patients with WT1(+) Recurrent Ovarian Cancer in 2nd or Greater Remission

Study Schema (Open Label)

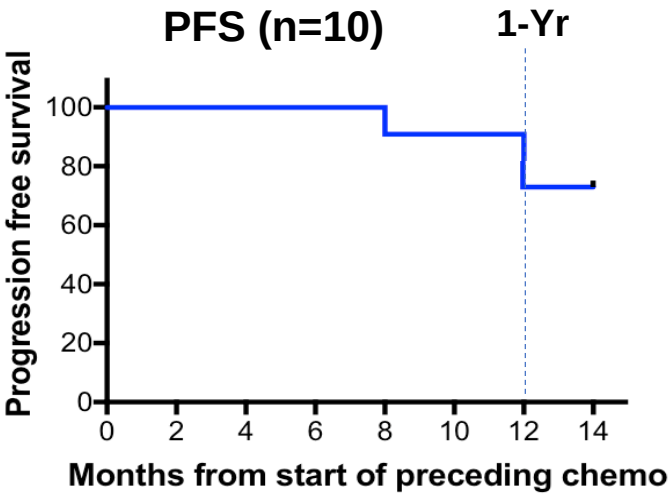


O'Cearbhaill, ASCO 2018 Abst. 5553, J Clin Oncol. 2018; SELLAS, data on file.

GPS + Nivolumab Pilot Study in Ovarian Cancer: 2nd/3rd Line Therapy, Clinical Results[1]

- Patient Characteristics:
  - N = 11
  - 7 pts were in second remission and 4 pts were in third remission

- Clinical activity
  - **Landmark 1-year PFS rate = 70%** in pts who received >1 dose of GPS + nivolumab (n=10)
  - Historical PFS rates[2-4] do not exceed 50% in this setting[1]
  - **Landmark 2-year PFS rate = at least 30%** in pts who received >1 dose of GPS + nivolumab (n=10) [5]
  - Historical PFS rates[2-4] range between 3-10% in this setting[5]



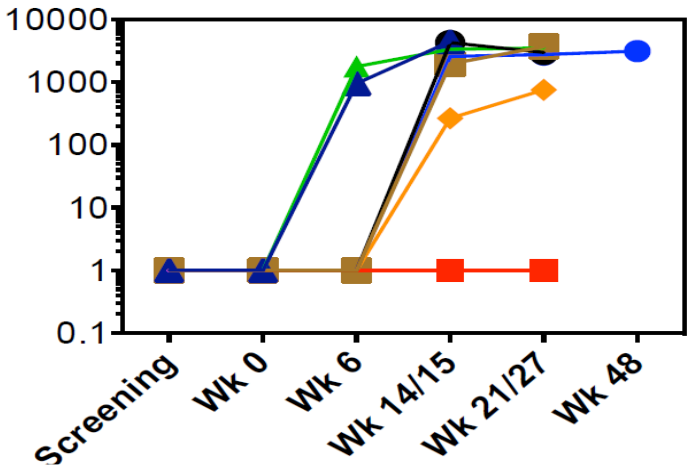
- Safety – **Tolerable AE profile – No worrisome tox 'signal'**[1,5]
  - Most frequent TRAEs:
    - Injection site reaction (G≤1), joint pain (G≤2) and fatigue (G≤2)
  - DLT in one patient, with G3 myositis (incl. cardiac involvement); resolved
    - AE known to be associated with the use of nivolumab

1. O'Cearbhaill, ASCO 2018 Abst. 5553, J Clin Oncol. 2018; 2. Parma, Lancet, 2003;
3. Harrison, Gynecol Oncol. 2007; 4. Sabbatini, Gynecol Oncol. 2010; 5. SELLAS, data on file (updated PFS analysis; Nov. 2019)

GPS + Nivolumab Pilot Study in Ovarian Cancer: Immunologic Results

- Immune responses
  - **WT1-specific IgG observed in 86% of pts** (wks 6 – 27)
  - CD4 and CD8 T-cell responses also observed (wks 6 – 15)
- IgG reactivity was seen both against all 4 individual peptides within the GPS mixture as well as – importantly- the **full-length (FL) WT1 protein**, consistent with **multi-epitope B-cell reactivity** akin to **'epitope spreading'** (observed previously with GPS in myeloma) [1,2]

WT1-specific IgG titers over time



- The timing and titers of WT1-specific IgG were consistent with **IgM-to-IgG isotype switching** by B-cells, which means that GPS was able to activate both T-cell costimulatory signals as a response to the tumor antigen[3,4] (in this case, WT1). This is a marker of effective immunization.

1. Koehne, EBMT Mtg, 2018; 2. Koehne. ASCO Mtg 2017; 3. Wykes, J Immunol. 1998; 4. Wykes & MacPherson, Immunology. 2000

O'Cearbhaill, ASCO 2018 Abst. 5553, J Clin Oncol. 2018

GPS + Nivolumab Pilot Study in Ovarian Cancer:

Peripheral Blood Lymphocyte Subpopulation Dynamics & T-cell Surface Activation Marker Distribution *(non-antigen-specific)*

GPS + Nivolumab administration was associated with time-dependent:

- **Decrease in the expression of PD-1 in both CD4 and CD8 T-cells**, consistent with a PD1-blocker therapy effect
- **Enrichment in Ki-67+, PD-1+, and granzyme B (GzB)+ T_{em} (effector memory*) cell subset of both CD4 and CD8**
- **Proliferation of subsets of CD38+ and (GzB)+ cells**, as assessed by Ki-67 expression)
- The above findings reflect activation of the immune cascade, and are generally consistent with **effective immunization against a tumor antigen (in this case WT1)** with the combination

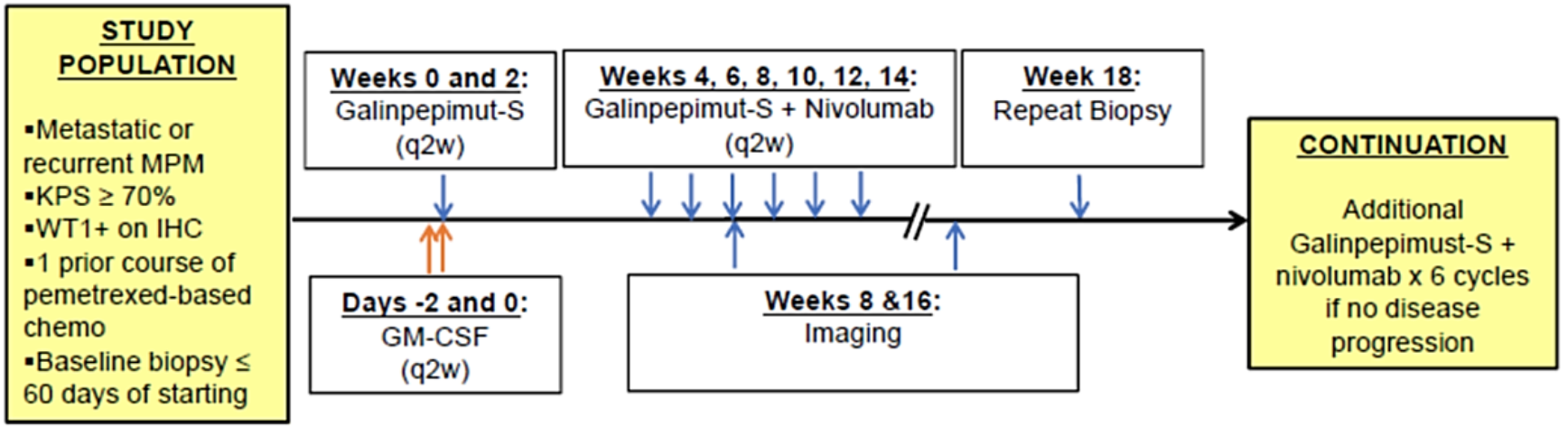
*CD45(-); CCR7(-)

Phillip Wong, PhD (Immune Monitoring Core Facility, MSKCC) and SELLAS, Data on file

GPS + Nivolumab Pilot Study in Malignant Pleural Mesothelioma (MPM)

Study Schema

Single-arm Pilot study in relapsed (2nd line) or refractory MPM (Study # MSK17-654; NCT04040231)



Key Study Features

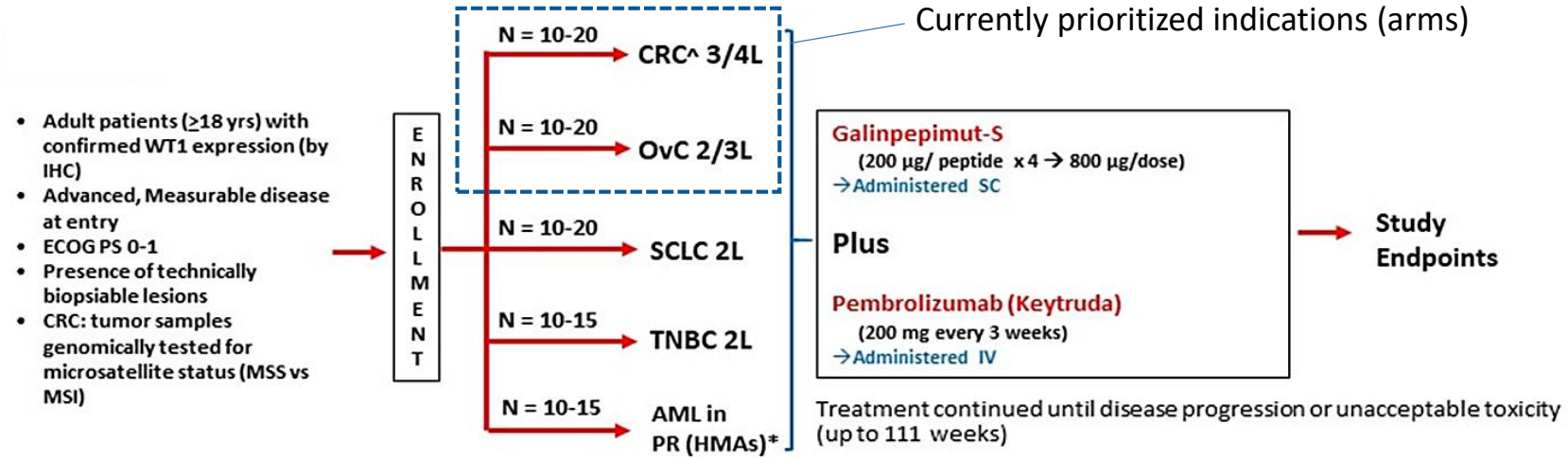
- Principal Investigator: Marjorie Zauderer, MD (MSKCC)
- Independent-Sponsored Trial (IST); supported by SELLAS and BMS
- Initial target N = 10 pts
- Study Status
  - Fully activated on 31-Jul-2019
  - Currently patients are being screened for study entry

Merck Combo Study Pembrolizumab + Galinpepimut-S in 5 tumor types:

SLSG17-201 / MRK KN 770 (NCT03761914) - 'Basket' type, U.S. only study
Initiated and Currently On-going

Schema

Open label, non-comparative, multicenter, multi-arm combination trial; N = 90



Primary Endpoints:

- Safety
- ORR (RECIST) (solid tumors)
- Morphologic CR (incl. CRi/CRp) (AML)

Secondary Endpoints:

- TTR, TTNT, DOR

Exploratory Endpoints:

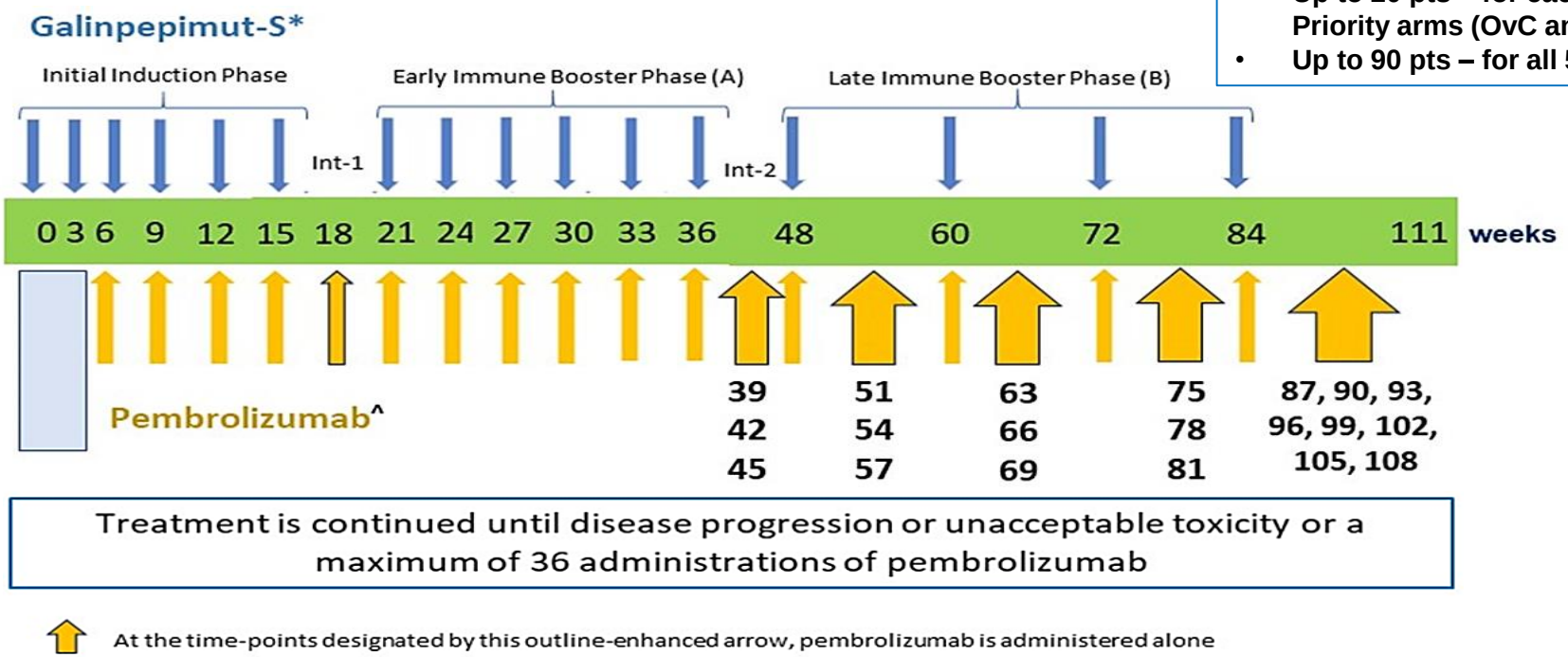
PFS, OS • ORR (iRECIST)(solid tumors) & % MRD(-) rate (AML)
Immune Response (IR) and Pembrolizumab PD Correlates
- Peripheral Blood:
  - GPS-relevant WT1-specific CD8 and CD4
  - Complete T cell phenotypic quantication
- Tumor tissue (for solid tumors) or bone marrow (for AML)
  - WT1-specific CD8 and CD4 distribution
  - MDSC, Treg and TAMs distribution
  - PD-L1 and inflammatory gene-signature array expression

^: focus will be genomically microsatellite-stable (MSS); *: Allotransplant non-eligible

N.B.: Study is conducted under a CTSA with Merck (known as MSD outside the United States and Canada; tradename of Merck & Co., Inc., Kenilworth, N.J., USA)

Merck Combination Study: Investigational Therapy Schedule

- **Up to 20 pts – for each of the Priority arms (OvC and CRC)**
- **Up to 90 pts – for all 5 arms**



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GPS + Checkpoint Inhibitors
Potential for Synergistic Effective Immunotherapy Across Multiple Tumor Types

Conclusions and Key Take-away Points

- PD-1 antibodies have clinical activity across multiple histologies, inducing responses with long duration
- Multiple lines of evidence, now clinical, suggest that PD-1 blockade will add or synergize with vaccine approaches
- Encouraging clinical and pre-clinical immune data from the GPS + NIVO trial in ovarian cancer support further development of the combination of GPS with a checkpoint inhibitor in multiple tumor types



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