MELANOMA bridge 2021

Virtual meeting
December 2nd - 4th, 2021

Nemvaleukin Alfa (ALKS 4230) Monotherapy in Patients With Advanced Melanoma: ARTISTRY-1

Karl Lewis

CONFLICT OF INTEREST STATEMENT

I hereby declare that I do not conduct activities that would involve a conflict of interest with CME-accreditable training, but that in the past 2 (two) years I have received the funding listed below from the following sources:

1. Consulting: Regeneron, Merck, Pfizer, Sanofi
2. Research grants: Regeneron, Merck, Pfizer/Array, Bristol Myers Squibb, Incyte, Kartos, Iovance, Genentech, Oncosec, Senhwa, Replimune, Ultimovacs, Nektar, Seattle Genetics, Alkermes

Nemvaleukin Alfa (ALKS 4230) Monotherapy in Patients With Advanced Melanoma: ARTISTRY-1

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*At time of study

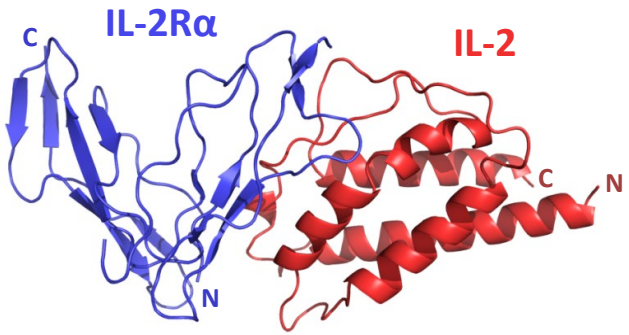
Advanced Melanoma Represent Tumor Types With High Unmet Needs

- Despite improved outcomes with CPI therapy in patients with melanoma, ~50% of patients do not respond to CPI monotherapy and ~40% do not respond to combinations[1]
- A subset of responders ultimately progress and have limited treatment options, underscoring a high unmet need for novel treatments with durable benefit
- Mucosal melanoma remains particularly difficult to treat, with response rates to frontline CPI monotherapy of 23% and progression-free survival times of ~3 months, compared with 41% and 6 months, respectively, for cutaneous melanoma[2,3]
- High-dose IL-2 was one of the first immunotherapies to be approved for the treatment of metastatic melanoma[4]

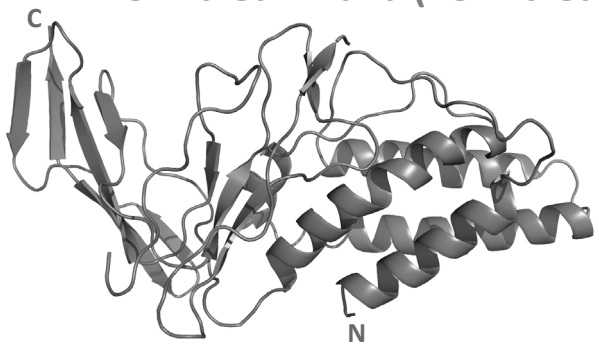
CPI, checkpoint inhibitor; IL-2, interleukin-2.

1. Gellrich FF, et al. *J Clin Med*. 2020;9:223. 2. Tyrrell H, Payne M. *Melanoma Manag*. 2018;5(3):MMT11. 3. D'Angelo SP, et al. *J Clin Oncol*. 2017;35(2):226-235.
4. Rosenberg S, et al. *J Immunol*. 2014;192:5451-5458.

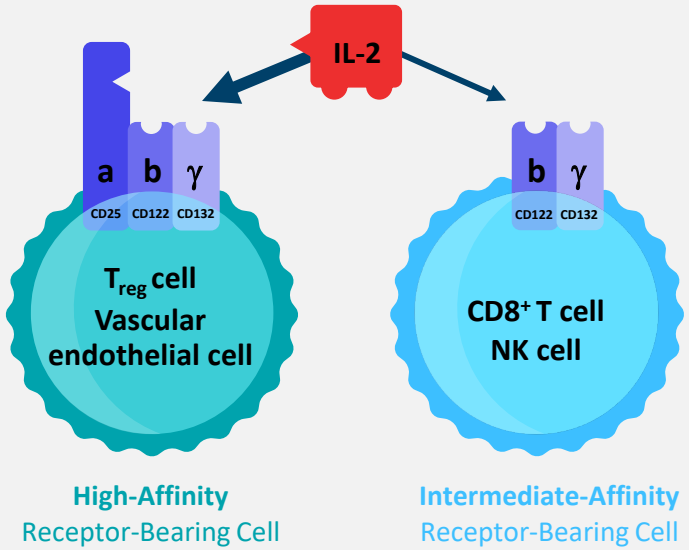
Nemvaleukin Alfa: a Novel, Engineered Cytokine



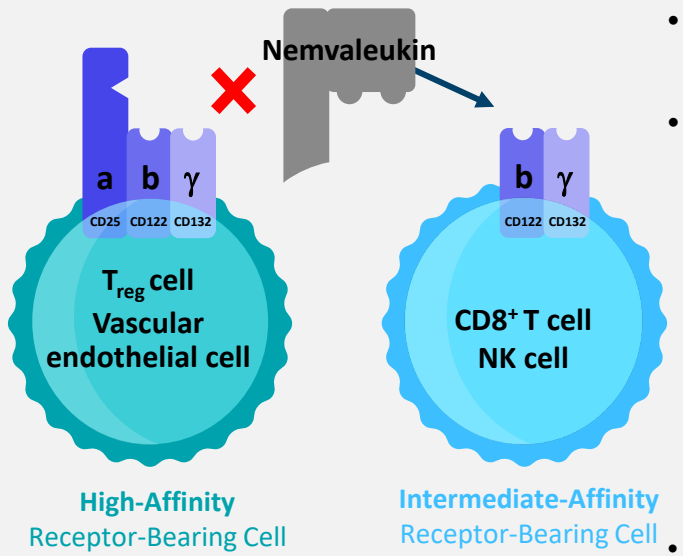
Nemvaleukin alfa (nemvaleukin, ALKS 4230)



- Stable fusion protein that is intrinsically active immediately upon systemic entry
- Does not require metabolic activation or degrade to native IL-2



- IL-2 potently activates the high-affinity IL-2R, which is preferentially expressed on immunosuppressive T_{regs} and vascular endothelial cells
- Preferential activation of the high-affinity IL-2R by high-dose IL-2 leads to expansion of T_{regs}, which may counteract antitumor activity and activate vascular endothelial cells that are associated with a high incidence of acute toxicities, including capillary leak syndrome



- Nemvaleukin is sterically occluded from binding the high-affinity IL-2R
- Nemvaleukin is designed to selectively bind the intermediate-affinity IL-2R
  - For preferential activation and expansion of tumor-killing $CD8^+$ T cells and NK cells, with minimal expansion of T_{regs}
  - To mitigate toxicities associated with the preferential binding of IL-2 to the high-affinity IL-2R
- Nemvaleukin therapy leads to increases in both peripheral and intratumoral immune effector cells

IL-2, interleukin-2; IL-2R, IL-2 receptor; NK, natural killer; T_{reg}, regulatory T cells.

Lopes JE, et al. *J Immunother Cancer*. 2020;8(1):e000673. doi: 10.1136/jitc-2020-000673.

Potential for Nemvaleukin for the Treatment of Advanced Melanoma

- In preclinical studies, antitumor activity of multiple agents, including chemotherapy, CPIs, and TKIs, was enhanced when each was used in combination with nemvaleukin[1-3]
- In clinical studies, responses were observed with nemvaleukin monotherapy and in combination with pembrolizumab in various tumor types, including breast, cervical, head and neck, gastrointestinal, genitourinary, lung, platinum-resistant ovarian cancers, melanoma, and renal cell carcinoma[4,5]
- Here we describe the antitumor activity of nemvaleukin monotherapy from the ARTISTRY-1 trial that led to the US FDA granting nemvaleukin Fast Track Designation for the treatment of mucosal melanoma
- The FDA has also granted nemvaleukin Orphan Drug Designation for the treatment of mucosal melanoma
- The phase 2 ARTISTRY-6 study of nemvaleukin monotherapy in patients with advanced mucosal or advanced cutaneous melanoma is now enrolling

CPI, checkpoint inhibitor; FDA, Food and Drug Administration; TKI, tyrosine kinase inhibitor.

1. Losey HC, et al. American Association for Cancer Research 2017 Annual Meeting. Abstract 591. 2. Lopes JE, et al. American Association for Cancer Research 2020 Annual Meeting. Abstract 2202. 3. Pan Y, et al. European Society for Medical Oncology 2021 Congress. Abstract 3326. 4. Boni V, et al. *J Clin Oncol*. 2021;39(Suppl 15):abstr 2513. 5. Hamid O, et al. *J Clin Oncol*. 2021;39(Suppl 15):abstr 2552.

ARTISTRY-1 Study Design

Part A: Monotherapy
Nemvaleukin dose escalation

- **Objectives:** Determine safety/tolerability of nemvaleukin, maximum tolerated dose, and RP2D
- Dose cohorts: 0.1 µg/kg to 10.0 µg/kg

RP2D:
6 µg/kg/d

Part B: Monotherapy
Nemvaleukin dose expansion

- **Objectives:** Characterize safety profile and antitumor activity by ORR of nemvaleukin at RP2D
- **Cohorts:** Advanced, refractory melanoma or RCC

Safety run-in
Nemvaleukin + pembrolizumab combination

Part C: Combination therapy
Nemvaleukin + pembrolizumab (200 mg)

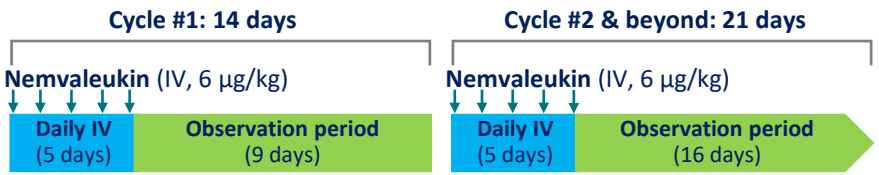
- **Objectives:** Characterize safety profile and antitumor activity by ORR of nemvaleukin in combination with pembrolizumab
- **Cohorts:** Mixed tumor types based on PD-(L)1 indication and prior treatment history at 3 µg/kg nemvaleukin
- Additional tumor-specific cohorts at 6 µg/kg nemvaleukin

Rollover[a]

Melanoma cohort: Key eligibility criteria

- Advanced melanoma
- Malignancy refractory to/intolerant of established therapies known to provide clinical benefit
- CPI pretreated
- ECOG PS 0-1 with life expectancy ≥3 months
- Adequate hematologic reserve, hepatic function, and renal function

Dosing regimen



CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; PD-(L)1, programmed death (ligand) 1; RCC, renal cell carcinoma; RP2D, recommended phase 2 dose.
[a]Disease progression (after ≥2 cycles) or stable disease (after ≥4 cycles).

ClinicalTrials.gov Identifier: NCT02799095.

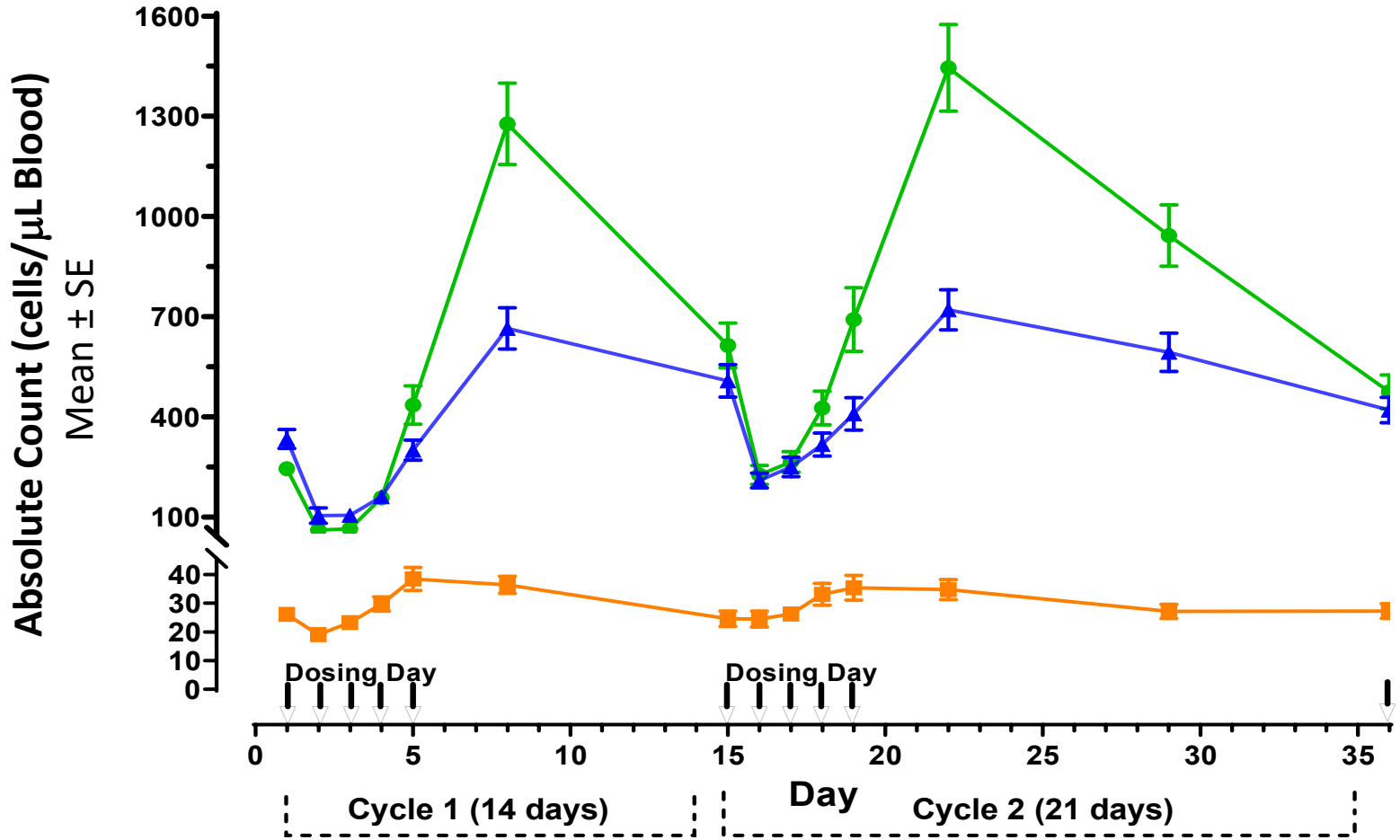
Part B Melanoma Cohort: Patient Baseline Characteristics

Characteristic	N = 47[a]
Age, years	
Median (range)	66 (37-82)
Race, n (%)	
White	42 (89)
Asian	5 (11)
ECOG PS, n (%)	
0	23 (49)
1	24 (51)
Histology, n (%)	
Cutaneous	30 (64)
Mucosal	7 (15)
Uveal	6 (13)
Acral	4 (9)
Prior lines of therapy, n	
Median (range)	3 (1-6)

ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]Safety population.

Part B, melanoma cohort.
Data cutoff date: August 31, 2021

Nemvaleukin Induced Robust Expansion of CD8+ T and NK Cells With Minimal Effect on T_{regs}



N = 46 (biomarker population)

Total NK Cells

Total CD8+ T Cells

FOXP3+ T_{regs}

NK, natural killer; SE, standard error; T_{regs}, regulatory T cells.

Part B, melanoma cohort.
Data cutoff date: August 31, 2021

Safety of Nemvaleukin in Patients With Melanoma

Event, n (%)	N = 47[a]
Any AE, regardless of causality	46 (98)
Grade 1 or 2 nemvaleukin-related AE	45 (96)
Grade 3 or 4 nemvaleukin-related AE	35 (75)
Nemvaleukin-related SAE	6 (13)
AEs leading to discontinuation	2 (4)
AEs leading to death	0

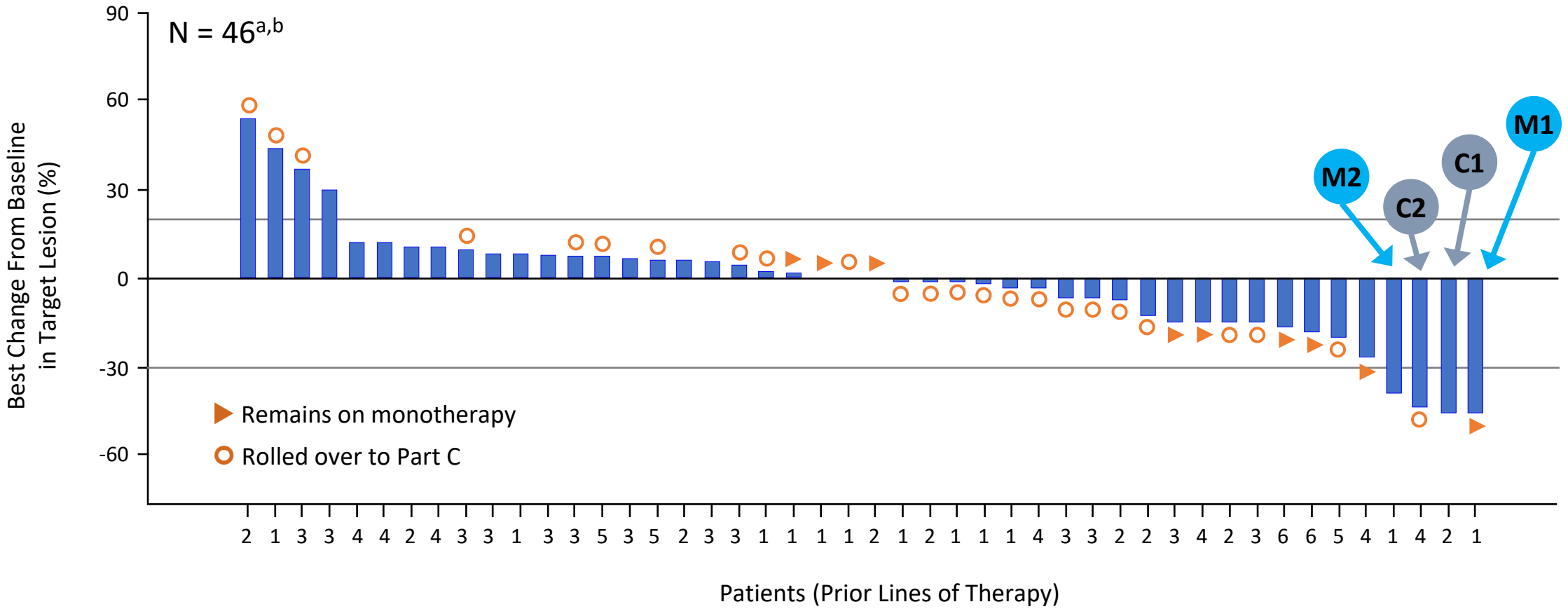
AE, n (%)	Patients with ≥30% AEs (all grades, regardless of causality)	Patients with grade ≥3 nemvaleukin-related AEs
Pyrexia	32 (68)	1 (2)
Nausea	24 (51)	0
Chills	21 (45)	2 (4)
Neutropenia	21 (45)	19 (40)
Hypotension	20 (43)	2 (4)
AST increased	18 (38)	3 (6)
ALT increased	17 (36)	3 (6)

- Most related AEs were grade 1/2 and represent symptoms typically associated with cytokine therapy
- Grade 3/4 related AEs were mostly laboratory abnormalities
  - Transient, asymptomatic, and resolved spontaneously or with nemvaleukin dose interruption
- 2 patients had AEs leading to treatment discontinuation
  - 1 with confusional state (unrelated)
  - 1 with failure to thrive (possibly related)
- No additional safety signals observed in patients who rolled over to Part C

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious AE.
[a]Safety population.

Part B, melanoma cohort.
Data cutoff date: August 31, 2021

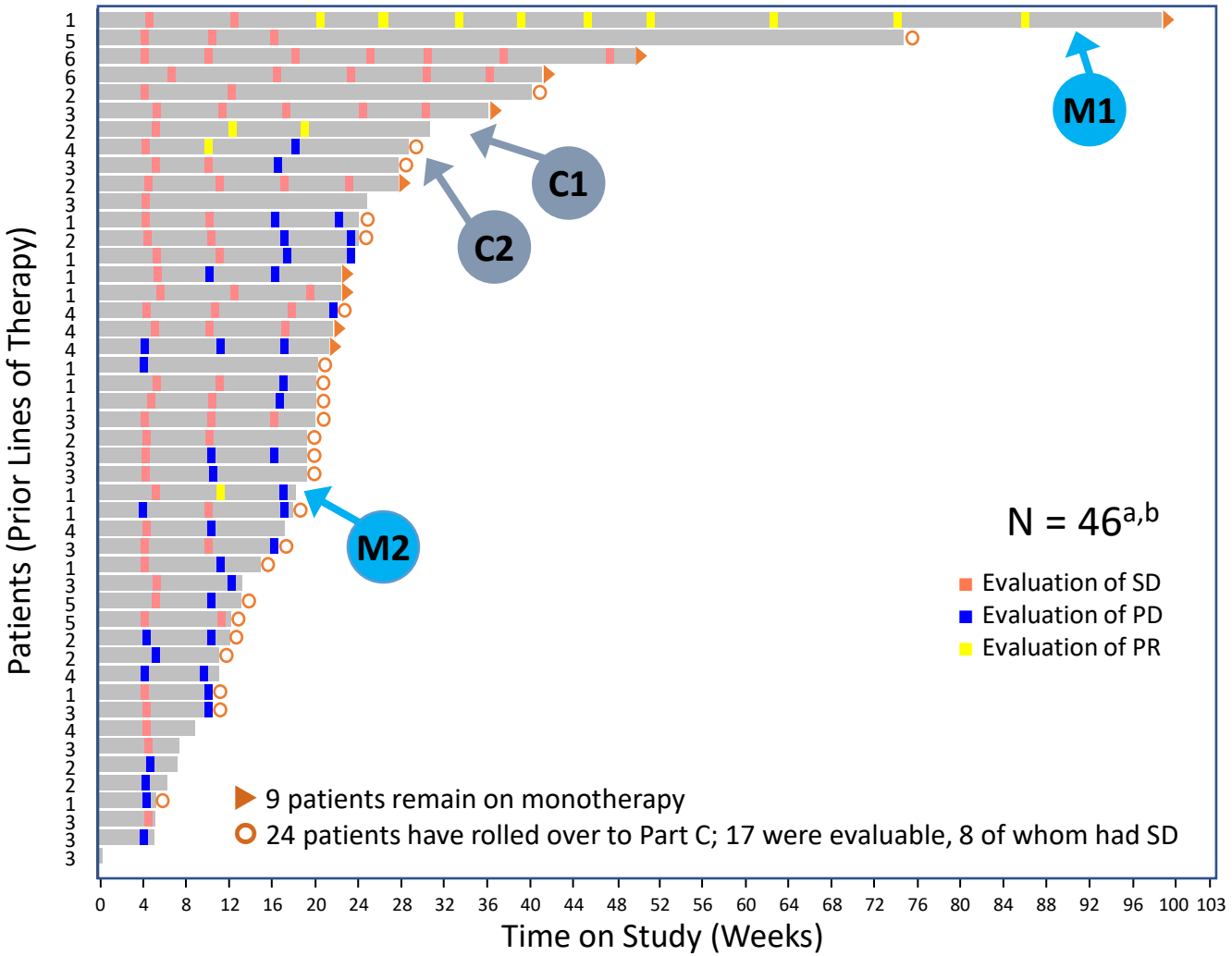
Best Change From Baseline of Target Lesion Sum in Response to Nemvaleukin Monotherapy



[a]Efficacy-evaluable population.
[b]1 patient with mucosal melanoma discontinued prior to first scan (patient request).

Part B, melanoma cohort.
Data cutoff date: August 31, 2021

Antitumor Activity of Nemvaleukin Monotherapy



Summary of patient experience

Melanoma tumor subtype	Number of regimens: Prior therapy	Best overall response	Max. reduction of target lesions (%)	Time on therapy (weeks)
M1 Mucosal	1: Adjuvant nivolumab	PR	46 ↓	101 ▶
M2 Mucosal	1: Adjuvant nivolumab	uPR	39 ↓	18
C1 Cutaneous	2: Adjuvant ipilimumab, pembrolizumab	PR	46 ↓	30
C2 Cutaneous	4: Atezolizumab/cobimetinib, nivolumab, melanoma vaccine AGI-101H, CBP/PAC	uPR	44 ↓	19 (Part B) + 9 (Part C)

- Of 6 evaluable patients with mucosal melanoma, 2 had PR and 2 had SD
- Of 30 evaluable patients with cutaneous melanoma, 2 had PR and 22 had SD

CBP, carboplatin; max, maximum; PAC, paclitaxel; PD, progressive disease; PR, partial response; SD, stable disease; uPR, unconfirmed PR.
[a]Efficacy-evaluable population.
[b]1 patient with mucosal melanoma discontinued prior to first scan (patient request).

Part B, melanoma cohort.
Data cutoff date: August 31, 2021

Target Lesion Decrease in Patient With Cutaneous Melanoma

C1

2017
53-yo woman diagnosed with cutaneous melanoma

Aug 2017 – Aug 2019
Adjuvant ipilimumab

Jun – Nov 2020
Pembrolizumab
(best response SD)

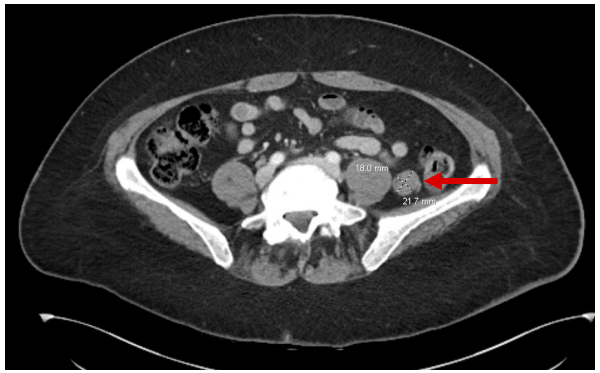
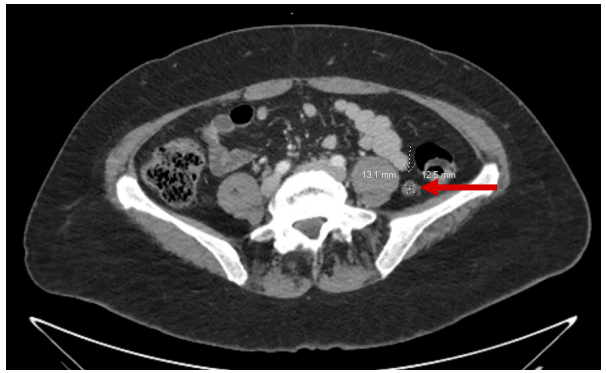
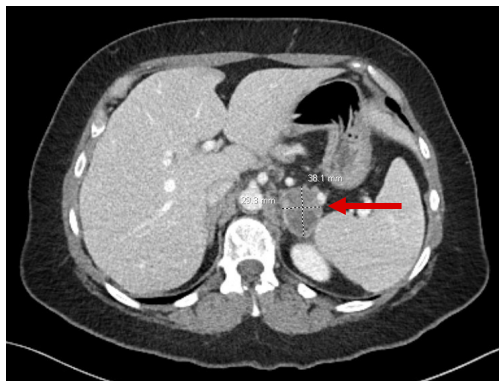
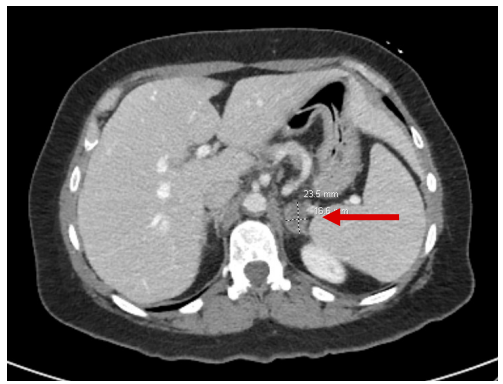
Feb – Jun 2021 (20+ wks)
Nemvaleukin 6 µg/kg

2017 2018 2019 2020 2021

Jul – Sep 2020
Radiation therapy

Apr 2021
Best response
PR

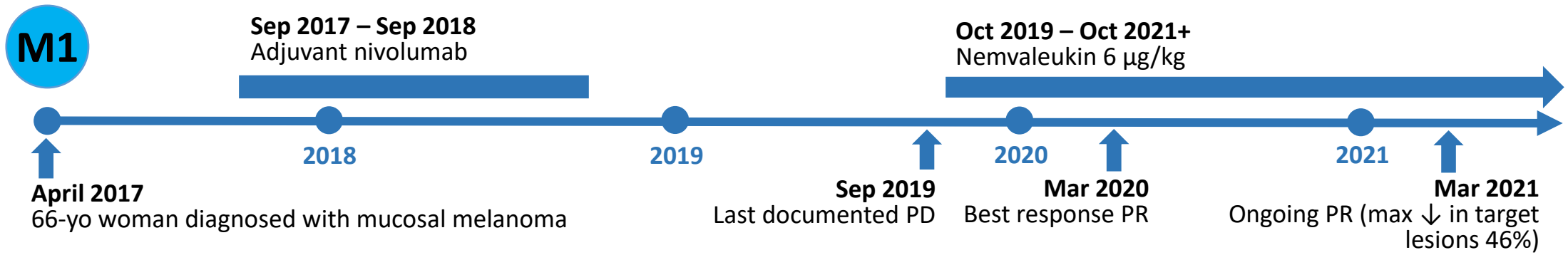
Jun 2021
PR confirmed
(max ↓ in target lesions 46%)

	Screening 1/11/2021	**Cycle 6 6/12/2021**
Pelvic lesion[a]		
Adrenal lesion[a]		

PR, partial response; RT, radiation therapy; SD, stable disease; yo, year-old.
[a]3 total target lesions.

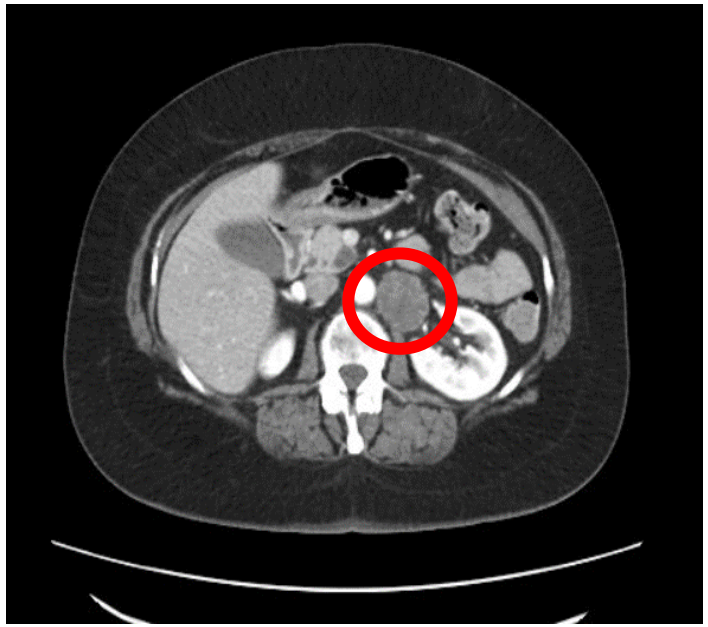
Part B, melanoma cohort.
Data cutoff date: August 31, 2021

Target Lesion Decrease in Patient With Mucosal Melanoma

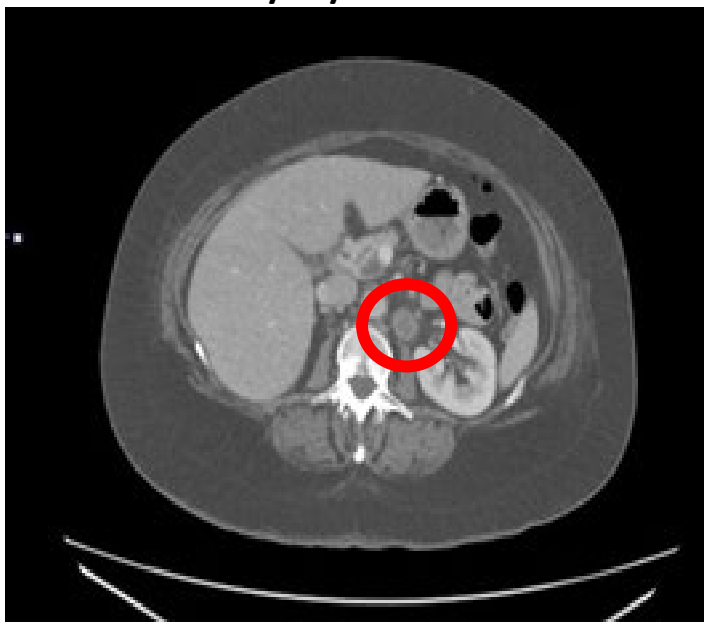


1 of 2 target lymph node lesions

Screening 10/9/2019



Cycle 16 9/21/2021



PD, progressive disease; PR, partial response; yo, year-old.

Part B, melanoma cohort.
Data cutoff date: August 31, 2021

Global Study in Mucosal and Cutaneous Melanoma Is Now Enrolling

ARTISTRY-6: A phase 2, global, multicenter, cohort study of nemvaleukin monotherapy administered SC in patients with advanced cutaneous melanoma or IV in patients with advanced mucosal melanoma who have previously received anti–PD-(L)1 therapy

Actively recruiting
Locations:

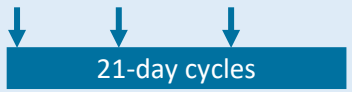
Korea, USA, Australia, Asia, Europe, and Canada

Key eligibility criteria

- Unresectable or metastatic cutaneous or mucosal melanoma
- Patient has received anti–PD(L)-1 ± anti–CTLA-4 therapy
- No more than 2 prior systemic therapies
- Measurable disease per RECIST v1.1
- ECOG PS 0-1

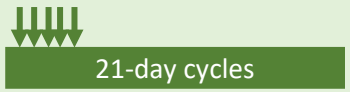
Cohort 1

Cutaneous melanoma (N = 40)
Nemvaleukin SC 3 mg



Cohort 2

Mucosal melanoma (N = 70)
Nemvaleukin IV 6 µg/kg



Treatment until progression

Key endpoints (independent of cohort)

- ***Primary:*** ORR per RECIST v1.1 (by independent central review)
- ***Key secondary:*** DOR, PFS, DCR, TTR per RECIST v1.1 (by independent central review)

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, overall response rate; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SC, subcutaneous; TTR, time to response.

ClinicalTrials.gov Identifier: NCT04830124.

Conclusions

- In ARTISTRY-1, nemvaleukin monotherapy was well tolerated
- Nemvaleukin monotherapy has shown antitumor activity in CPI-experienced patients with advanced cutaneous or mucosal melanoma
  - 2 of 6 patients with mucosal melanoma had partial responses, with 1 patient remaining on treatment for 23+ months
- Data from ARTISTRY-1 informed the FDA's decision to grant nemvaleukin Fast Track Designation for mucosal melanoma
- The FDA has also granted nemvaleukin Orphan Drug Designation for the treatment of mucosal melanoma
- The phase 2 ARTISTRY-6 study (NCT04830124) is evaluating nemvaleukin monotherapy in advanced mucosal or cutaneous melanoma
- Evaluations of nemvaleukin in additional tumors and in combination are being explored[a]

CPI, checkpoint inhibitor; FDA, Food and Drug Administration.

[a]The phase 3 ARTISTRY-7 study will evaluate nemvaleukin in combination with pembrolizumab in platinum-resistant ovarian cancer.

Acknowledgments

- The authors would like to thank all of the patients who are participating in this study and their families
- The study is sponsored by Alkermes, Inc.
- Medical writing and editorial support was provided by Parexel and funded by Alkermes, Inc.