Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies

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Presenter Disclosure Information

Amod Sarnaik, MD

The following relationships exist related to this presentation:

- Consulting or Advisory Role: ***B4CC, Iovance Biotherapeutics***
- Research Funding: ***Genentech (Inst); Iovance Biotherapeutics (Inst); Provectus (Inst)***
- Patents, Royalties, Other Intellectual Property: ***Compositions and methods for improving tumor-infiltrating lymphocytes for adoptive cell therapy, filed March 20, 2014 U.S. Patent Application No. 61/955,970 and second Application No. 61/973,002 (Inst)***

This study is sponsored by Iovance Biotherapeutics, Inc.

Iovance C-144-01: Background

- There are currently no approved agents for patients with metastatic melanoma whose disease progressed after immune checkpoint inhibitors (ICIs) and BRAF/MEK inhibitors
- In patients who are either primary refractory or develop resistance to ICI, retreatment with ICIs or chemotherapy has demonstrated poor objective response rate (ORR) between 4%-10%[1-2] and a median OS of ~7-8 months[3-4]
- Adoptive cell therapy utilizing tumor-infiltrating lymphocytes (TIL) has demonstrated antitumor efficacy with durable long-term responses in heavily pretreated patients[5]
- **C-144-01** (NCT02360579) is a global Phase 2, open-label, multicohort, multicenter study:
  - Investigational agent: centrally manufactured and cryopreserved autologous TIL product, lifileucel (LN-144)
  - Patient population: unresectable or metastatic melanoma who have progressed on checkpoint inhibitors and BRAF/MEK inhibitors (if BRAF mutant)
  - Manufacturing method: central manufacturing of cryopreserved TIL, 22 day duration, Gen 2

[1] Larkin J, Minor D, D'Angelo S, et al. Overall Survival in Patients With Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in CheckMate 037: A Randomized, Controlled, Open-Label Phase III Trial. *J Clin Oncol.* 2018;36:383-90.
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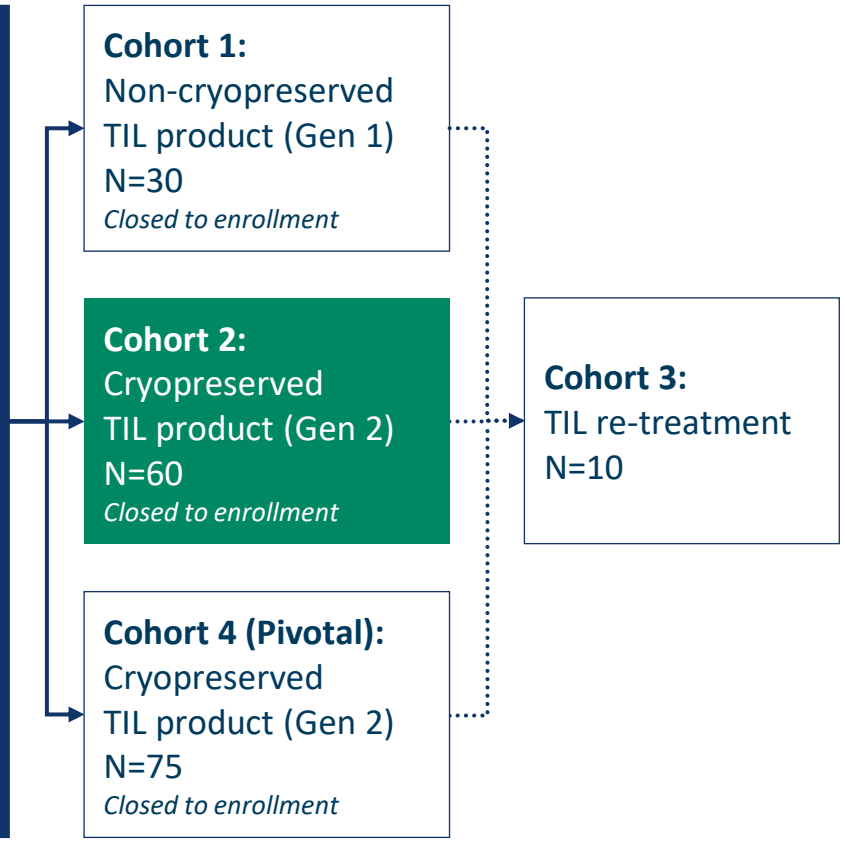
Iovance C-144-01 Study Design

Phase 2, multicenter study to assess the efficacy and safety of autologous Tumor Infiltrating Lymphocytes (lifileucel) for treatment of patients with metastatic melanoma (NCT02360579)

Patient Population:

Unresectable or metastatic melanoma treated with at least 1 systemic prior therapy including a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF or BRAF/MEK



Cohort 2 Endpoints:

- Primary: Efficacy defined as investigator-assessed Objective Response Rate (ORR) following RECIST 1.1
- Secondary: Safety and efficacy

Other Key Eligibility Criteria:

- One tumor lesion resectable for TIL generation (~1.5cm in diameter) and ≥ one tumor lesion as target for RECIST 1.1 assessment
- Age ≥ 18 years at the time of consent
- ECOG Performance Status of 0-1

Methods:

- Data Extract: 23 April 2020 for Cohort 2
- Cohort 2 Safety and Efficacy sets: 66 patients who underwent resection for the purpose of TIL generation and received lifileucel infusion

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C-144-01 Cohort 2 Patient Characteristics

CHARACTERISTIC	Cohort 2, N=66, (%)
Gender, n (%)	
Female	27 (41)
Male	39 (59)
Age, years	
Median	55
Min, Max	20, 79
Prior therapies, n (%)	
Mean # prior therapies	3.3
Anti-CTLA-4	53 (80)
Anti-PD-1	66 (100)
BRAF/MEK	15 (23)
Progressive Disease for at least 1 prior therapy	
Anti-CTLA-4	41 (77[(1)])
Anti-PD-1	65 (99)
Baseline ECOG score, n (%)	
0	37 (56)
1	29 (44)

CHARACTERISTIC	Cohort 2, N=66, (%)
BRAF Status, n (%)	
Mutated V600	17 (26)
Wild Type	45 (68)
Unknown	3 (5)
Other	1 (2)
Baseline LDH (U/L)	
Median	244
1-2 times ULN	19 (29)
> 2 times ULN	8 (12)
Target Lesions Sum of Diameter (mm)	
Mean (SD)	106 (71)
Min, Max	11, 343
Number of Target and Non-Target Lesions (at Baseline)	
>3	51 (77)
Mean (SD)	6 (2.7)
Patients with Baseline Liver and/or Brain Lesions	28 (42)

Cohort 2 patients have:

- 3.3 mean prior therapies, ranging from 1-9
- High tumor burden at baseline: 106 mm mean sum of diameters of the target lesions

(1) The denominator is the 53 patients who received prior anti-CTLA-4.

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Study Overview and Procedures

1 → 2 → 3 → 4 → 5 → 6

Patient Intake

Surgical Resection

The process begins with surgical resection of a tumor lesion (~1.5 cm in diameter). The tumor lesion is shipped to a Central GMP facility and undergoes a 22-day process that generates a cryopreserved TIL infusion product.

TIL were generated from **skin, lymph nodes, liver, lung, peritoneal, musculo-skeletal, breast, and other organs.**

NMA-LD

Patient undergoes nonmyeloablative lymphodepletion: Cyclophosphamide followed by fludarabine.

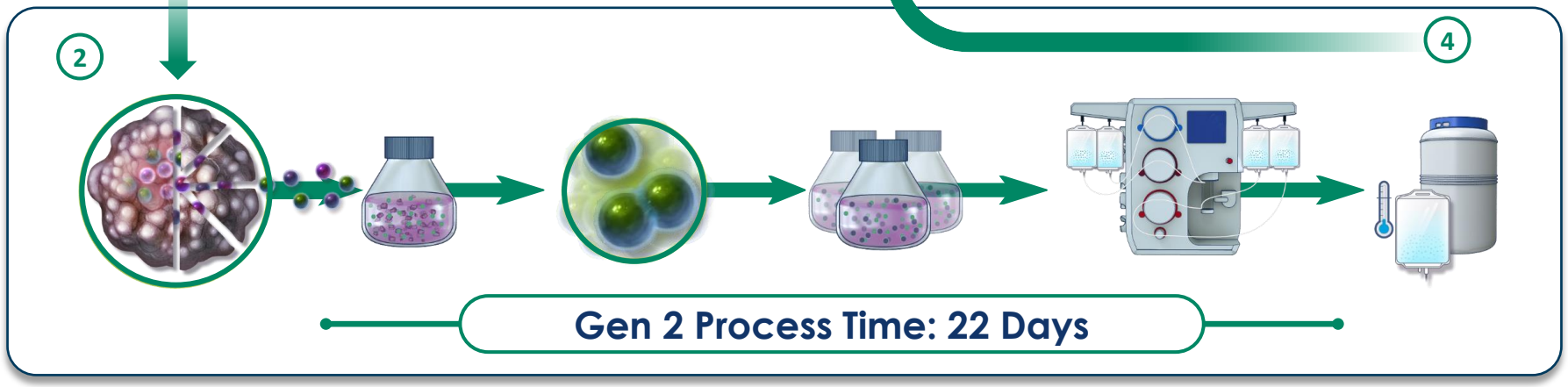
TIL Infusion

Patient receives one time treatment of expanded and activated lifileucel TIL product infusion.

IL-2 Infusions

Following lifileucel, patients complete a short course of up to 6 doses of interleukin-2 (IL-2) infusions , to enhance the antitumor activity of the TIL.

Recovery/Discharge



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Iovance C-144-01 Cohort 2 Safety:

Treatment Emergent Adverse Events (≥ 30%)

PREFERRED TERM	Cohort 2 (N=66)		
	Any Grade, n (%)	Grade 3/4, n (%)	Grade 5, n (%)
Number of patients reporting at least one Treatment-Emergent AE	66 (100)	64 (97.0)	2 (3.0)*
Thrombocytopenia	59 (89.4)	54 (81.8)	0
Chills	53 (80.3)	4 (6.1)	0
Anemia	45 (68.2)	37 (56.1)	0
Pyrexia	39 (59.1)	11 (16.7)	0
Neutropenia	37 (56.1)	26 (39.4)	0
Febrile neutropenia	36 (54.5)	36 (54.5)	0
Hypophosphatemia	30 (45.5)	23 (34.8)	0
Leukopenia	28 (42.4)	23 (34.8)	0
Fatigue	26 (39.4)	1 (1.5)	0
Hypotension	24 (36.4)	7 (10.6)	0
Lymphopenia	23 (34.8)	21 (31.8)	0
Tachycardia	23 (34.8)	1 (1.5)	0

*One death was due to intra-abdominal hemorrhage considered possibly related to TIL and one was due to acute respiratory failure assessed as not related to TIL per investigator assessment.
Patients with multiple events for a given preferred term are counted only once using the maximum grade under each preferred term.
Treatment-Emergent Adverse Events refer to all AEs starting on or after the first dose date of TIL up to 30 days.

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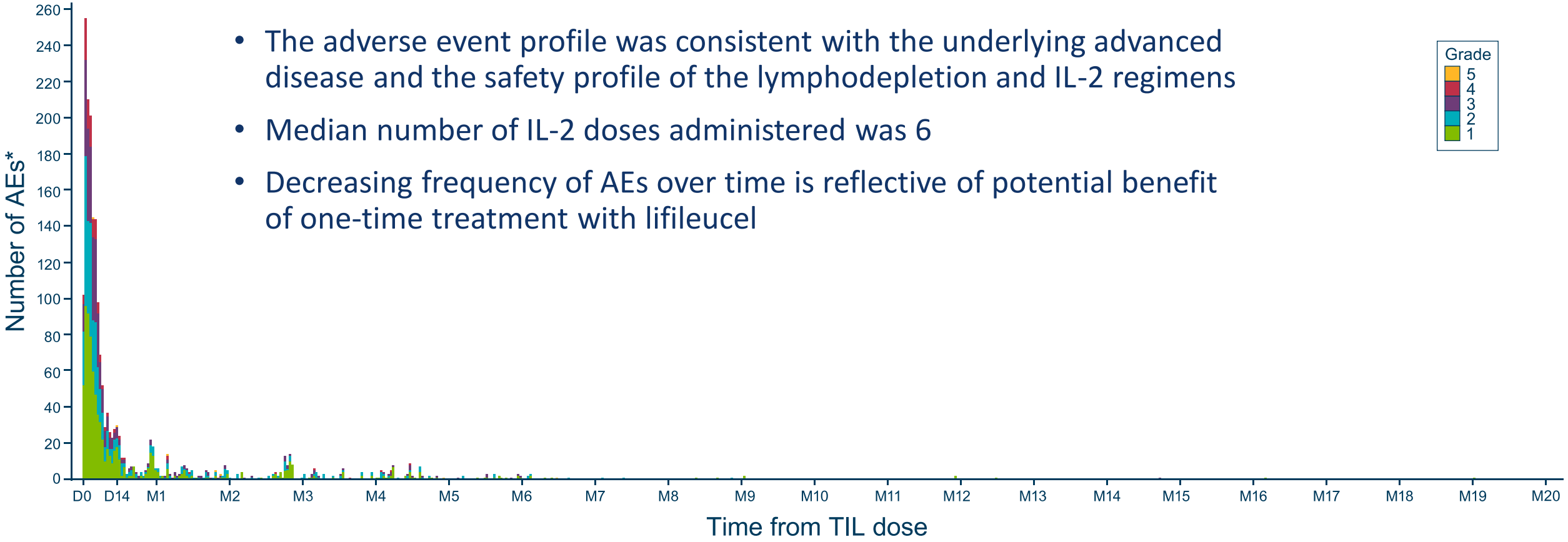
C-144-01 Cohort 2 Safety:

Adverse Events over Time

- The adverse event profile was consistent with the underlying advanced disease and the safety profile of the lymphodepletion and IL-2 regimens
- Median number of IL-2 doses administered was 6
- Decreasing frequency of AEs over time is reflective of potential benefit of one-time treatment with lifileucel



*The number of AEs is cumulative and represent the total number of patients dosed.

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C-144-01 Cohort 2 Efficacy

RESPONSE	PATIENTS, N=66 n (%)
Objective Response Rate	**24 (36.4)**
Complete Response	2 (3.0)
Partial Response	22 (33.3)
Stable Disease	29 (43.9)
Progressive Disease	9 (13.6)
Non-Evaluable[(1)]	4 (6.1)
Disease Control Rate	53 (80.3)
Median Duration of Response	**Not Reached**
Min, Max (months)	2.2, 26.9+

- After a median study follow-up of 18.7 months, median DOR was still not reached (range 2.2, 26.9+)
- Response was seen regardless of location of tumor resected
- Mean number of TIL cells infused: 27.3×10^9

[(1)] NE due to not reaching first assessment.

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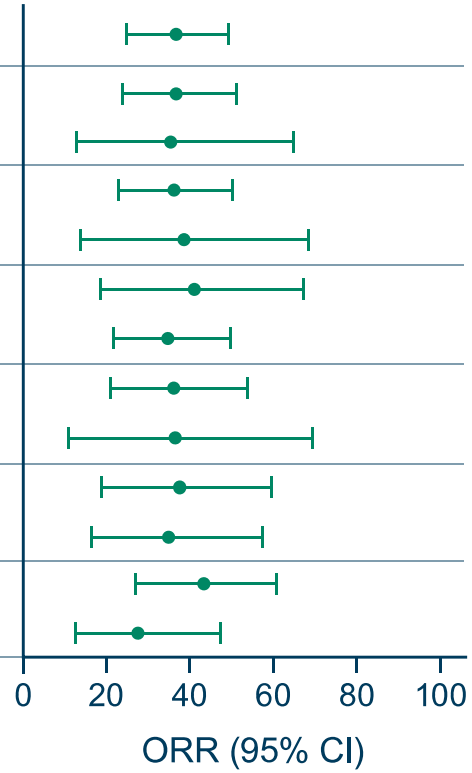
C-144-01 Cohort 2 ORR By Subgroup

Subgroup		n/N	ORR	95% CI
Overall		24/66	36.4	(24.9, 49.1)
Age Group	<65	19/52	36.5	(23.6, 51.0)
	≥65	5/14	35.7	(12.8, 64.9)
Prior Anti-CTLA-4 Use	Yes	19/53	35.8	(23.1, 50.2)
	No	5/13	38.5	(13.9, 68.4)
BRAF Mutation Status	V600 or V600K Mutated	7/17	41.2	(18.4, 67.1)
	Non-mutated	17/49	34.7	(21.7, 49.6)
PD-L1 Status (TPS ≥1% vs <1%)	≥1%	13/36	36.1	(20.8, 53.8)
	<1%	4/11	36.4	(10.9, 69.2)
PD-L1 Status (TPS ≥5% vs <5%)	≥5%	9/24	37.5	(18.8, 59.4)
	<5%	8/23	34.8	(16.4, 57.3)
Baseline ECOG	0	16/37	43.2	(27.1, 60.5)
	≥1	8/29	27.6	(12.7, 47.2)



Responses were demonstrated:

- Across a wide age range
- Even in patients who have progressed on prior anti-CTLA-4 or prior BRAF
- Regardless of the BRAF mutational status
- Equally in patients with PD-L1 low or high levels

CI, Confidence interval.
95% CI is calculated using the Clopper-Pearson Exact test.

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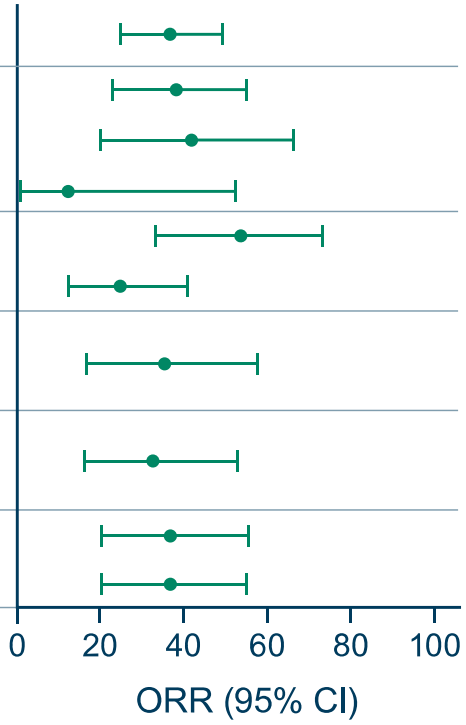
C-144-01 Cohort 2 ORR By Subgroup

Subgroup		n/N	ORR	95% CI
Overall		24/66	36.4	(24.9, 49.1)
Baseline Lactate Dehydrogenase	≤ ULN	15/39	38.5	(23.4, 55.4)
	1-2 x ULN	8/19	42.1	(20.3, 66.5)
	>2 x ULN	1/8	12.5	(0.3, 52.7)
Baseline Target Lesion Sum of Diameters	<70 mm	14/26	53.8	(33.4, 73.4)
	≥70 mm	10/40	25.0	(12.7, 41.2)
Patients with Baseline Liver Lesion		8/23	34.8	(16.4, 57.3)
Patients with Baseline Brain and/or Liver Lesion		9/28	32.1	(15.9, 52.4)
Time from Stop of Anti-PD-1/ PD-L1 to TIL Infustion	≤ median (4.76 months)	12/33	36.4	(20.4, 54.9)
	> median (4.76 months)	12/33	36.4	(20.4, 54.9)



Responses were demonstrated:

- In patients with elevated LDH (1-2x)
- In patients with bulky disease at baseline
- Patients with lesions in liver and/or brain
- Patients post anti-PD-1 regardless of duration of time from the patient's last anti-PD-1/L1

ULN, Upper Limit Normal; CI, Confidence interval.
95% CI is calculated using the Clopper-Pearson Exact test.

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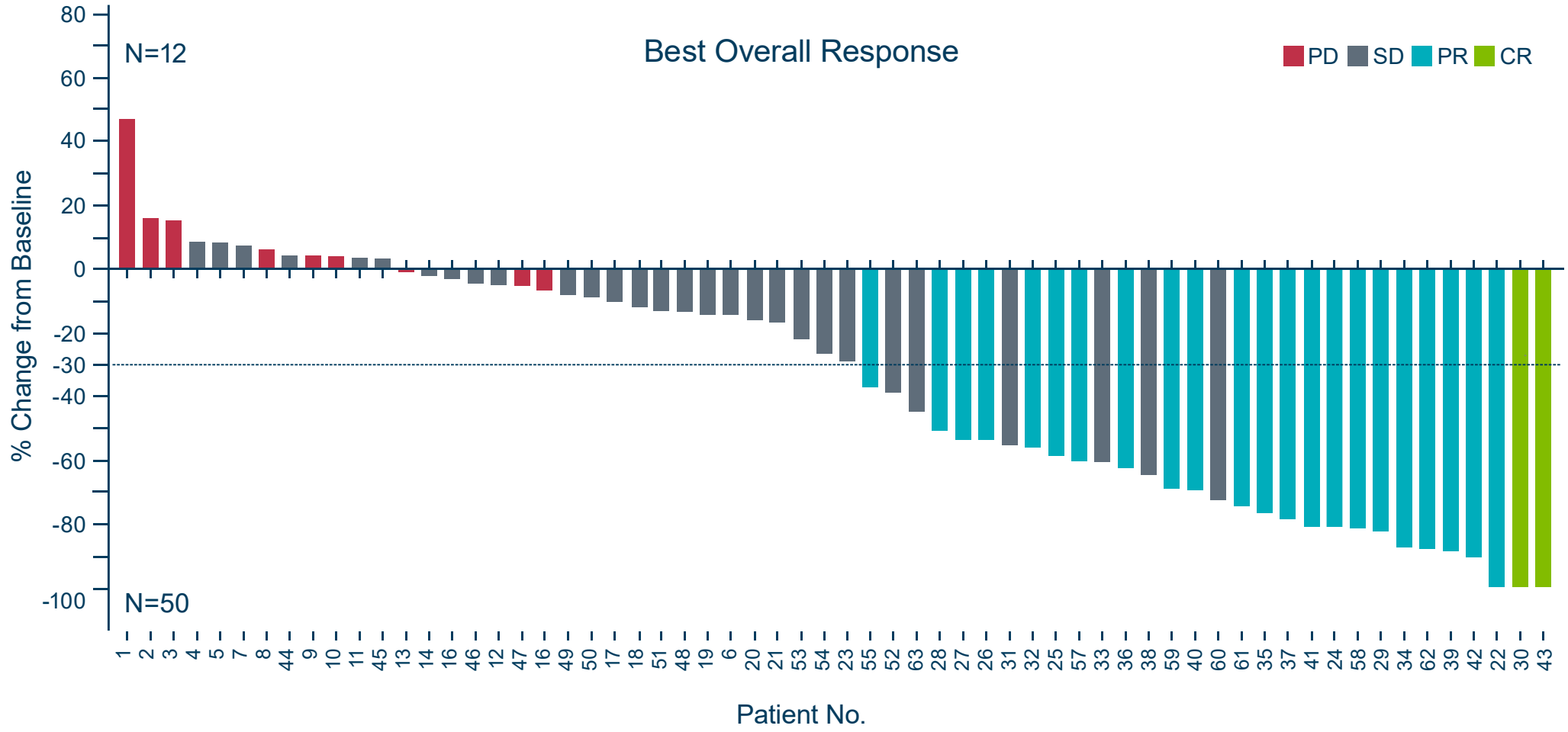
C-144-01 Cohort 2 Efficacy: Best Overall Response

81% (50/62) of patients had a reduction in tumor burden



Three subjects had no post TIL disease assessment due to early death, and one due to start of new anti-cancer therapy.

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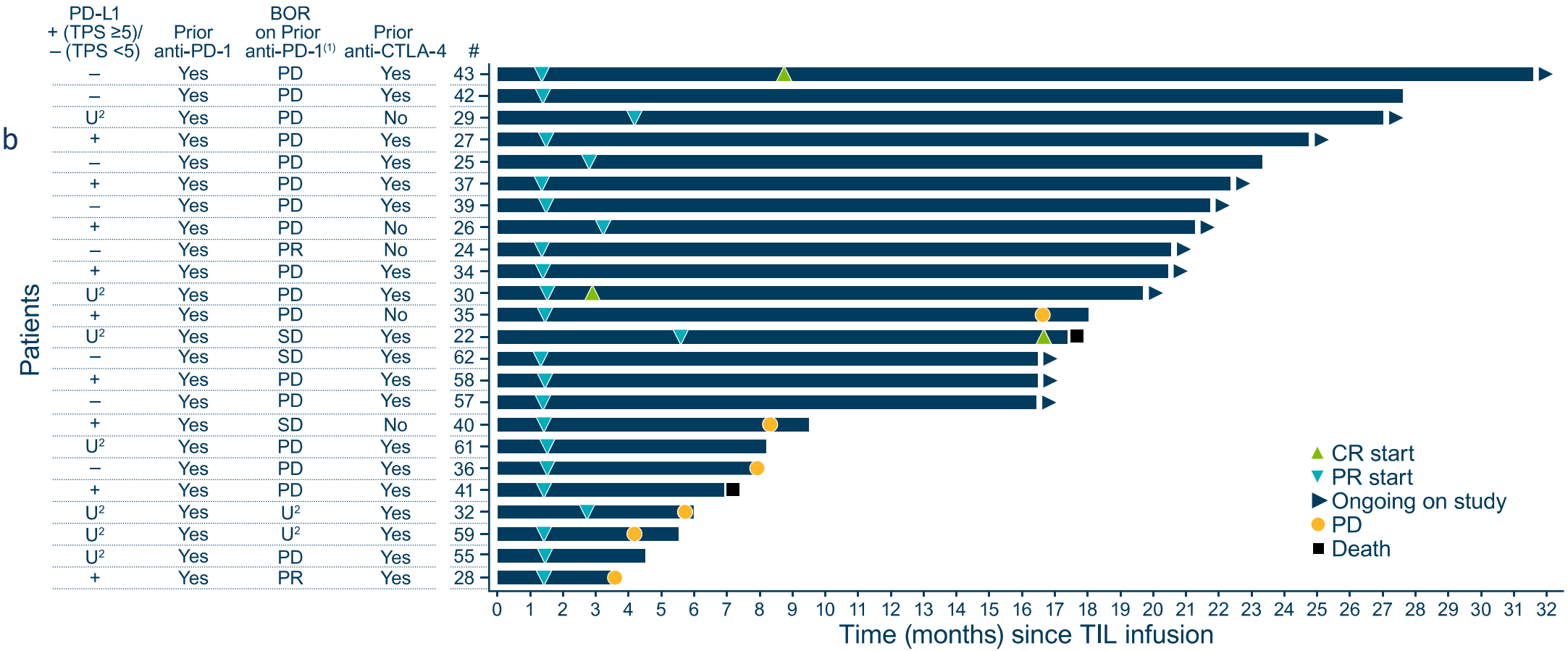
C-144-01 Cohort 2 Efficacy:

Time to Response for Evaluable Patients (PR or Better)

79% of responders had received prior ipilimumab

Responses deepen over time



(1) BOR is best overall response on prior anti-PD-1 immunotherapy
(2) U: unknown
(3) Patient 22 BOR is PR

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C-144-01 Cohort 2: Conclusions

- In heavily pretreated metastatic melanoma patients with high baseline disease burden who progressed on multiple prior therapies, including anti-PD-1 and BRAF/MEK inhibitors, if BRAFV600 mutant, lifileucel treatment results in:
  - 36.4% ORR
  - 80.3% DCR
  - Median DOR was still not reached at 18.7 months of median study follow up
- Responses deepen over time

Lifileucel has demonstrated potential efficacy and durability of response for patients with metastatic melanoma and represents a viable therapeutic option warranting further investigation

Cohort 4 in C-144-01 recently completed enrollment in support of lifileucel registration

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Acknowledgments

- The authors would like to thank the patients and their families for participation in the study
- The authors would also like to acknowledge the support and dedication of all site team members from all the clinical trial institutions
- The authors would like to acknowledge the Iovance team for their contributions