Primary Analysis of the IGNYTE Registrational Cohort in Anti-PD1 Failed Melanoma

June 6, 2024

Safe Harbor

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Today's Speakers/Q&A Panel

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Today's Agenda

- Data Summary
- ASCO 2024 Recap: IGNYTE 12-month Investigator-assessed Data
- Topline IGNYTE Primary Analysis by Independent Central Review
- Progress to BLA
- Q&A

Data Summary

- Strong primary analysis data: ORR of 33.6% (mRECIST 1.1) and 32.9% (RECIST 1.1) by independent central review
  - Improvement versus investigator-assessed ORR of 32.1% (mRECIST 1.1)
- Median DOR >35 months; 100% of responses last >6 months (from baseline)
  - DOR by independent central review consistent with investigator assessment
- Phase 3 confirmatory study (IGNYTE-3) with first patient expected to be enrolled in Q3 2024; BLA submission planned for 2H 2024

*N=140

ASCO Recap: Anti-PD1 Failed Melanoma Patients from the IGNYTE Clinical Trial

Options are Limited in Melanoma Following Progression on Anti-PD1 Therapy

- Further single agent anti-PD1 for patients having confirmed PD on prior anti-PD1 gives a response rate of 6-7%[1,2]
- Nivolumab + ipilimumab is a potential option[3,] but toxicity is high[4-5]
- Anti-LAG3 plus anti–PD1 has not demonstrated meaningful efficacy in the anti–PD1 failed setting[6]
- For BRAF mutant tumors, BRAF-targeted therapy responses are generally transient[7]
- T-VEC + pembrolizumab has limited activity outside of the adjuvant setting, with no responses seen in patients with visceral disease[8-9]
- TIL therapy for select patients gives response rates of ~30%, but comes with toxicity (nearly all patients have grade 4 toxicity)[10]

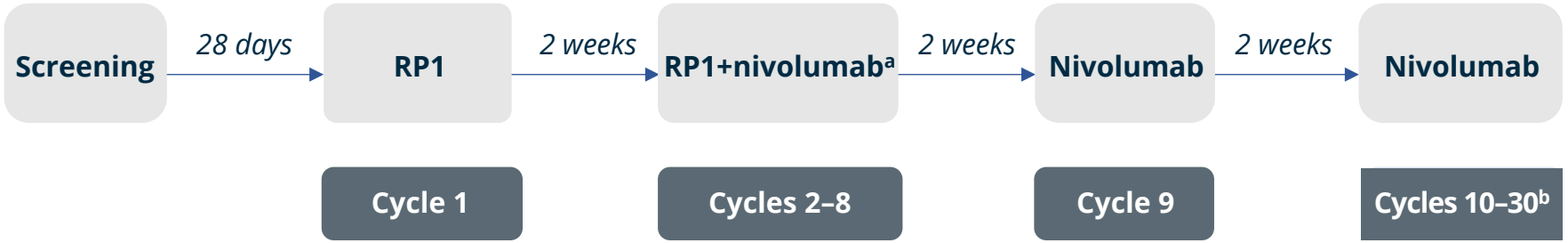
CTLA-4, cytotoxic T-lymphocyte antigen 4; LAG3, lymphocyte-activation gene 3; PD-1, programmed cell death protein 1; TIL, tumor infiltrating lymphocyte

1. Mooradian MJ, et al. Oncology. 2019;33(4):141-8. 2. Beaver JA, et al. Lancet Oncol. 2018;19(2):229-39. 3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Melanoma: Cutaneous. Version 2.2024. 4. Pires da Silva I, et al. Lancet Oncol. 2021;22(6):836-47. 5. VanderWalde AM, et al. Presented at the American Association of Cancer Research Annual Meeting 2022. New Orleans. 6. Ascierto PA, et al. J Clin Oncol. 2023;41(15)2724-35. 7. Dixon-Douglas JR, et al. Curr Oncol Rep. 2022;24(8):1071-9. 8. Gastman B, et al. J Clin Oncol. 2022;40(16_suppl):9518. 9. Hu-Lieskovan S, et al. Cancer Res. 2023;83(7_suppl):3275. 10. US Food and Drug Administration. BLA clinical review and evaluation - AMTAGVI. BLA 125773. Updated February 6, 2024. Accessed May 31, 2024].https://www.fda.gov/media/176951/download.

IGNYTE Study Design
Anti-PD1 Failed Melanoma Cohort

Anti–PD1 failed melanoma cohort

(140 pts; 16 pts treated in prior cohorts: Total=156)



Primary objectives
- Safety and tolerability
- Efficacy as assessed by ORR using modified RECIST 1.1 criteria

Secondary objective
DOR, CR rate, DCR, PFS, by central & investigator review, ORR by investigator review, and 1-year and 2-year OS

Key eligibility criteria

Confirmed progression while on prior anti-PD1 therapy[c]

At least 8 weeks of prior anti–PD1, confirmed progression while on anti–PD1; anti–PD1 must be the last therapy before clinical trial. Patients on prior adjuvant therapy must have progressed while on prior adjuvant treatment.

Primary analysis to be conducted when all patients have ≥ 12 months follow up

[a]Dosing with nivolumab begins at dose 2 of RP1 (C2D15). [b]Option to reinitiate RP1 for 8 cycles if criteria are met. c. Non-neurological solid tumors CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; LD, longest diameter; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; pfu, plaque-forming unit; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline Clinical Characteristics

A 'real world' anti-PD1 failed melanoma population was enrolled

- Good representation of each of the sub-groups of patients who progress on prior anti-PD1 therapy

Patients, n (%)	All patients (N = 156)
Age (median [range])	62 (21-91)
Sex	
Female	52 (33.3)
Male	104 (66.7)
Stage	
IIIb/IIIc/IVM1a	75 (48.1)
IVM1b/c/d	81 (51.9)
Prior therapy	
Anti–PD1 only as adjuvant therapy	39 (25.0)
Anti–PD1 not as adjuvant therapy	117 (75.0)
Anti–PD1 & anti–CTLA-4	74 (47.4)
Received BRAF-directed therapy	17 (10.9)

Patients, n (%)	All patients (N = 156)
Other disease characteristics	
Primary resistance to prior anti–PD1[a]	105 (67.3)
Secondary resistance to prior anti–PD1[b,c]	51 (32.7)
BRAF wt	103 (66.0)
BRAF mutant	53 (34.0)
LDH ≤ULN	105 (67.3)
LDH >ULN	50 (32.1)
LDH unknown	1 (0.6)

Median follow up is 15.4 months (range 0.5-55.5)

Data cutoff: March 8th 2024. [a]Primary resistance: Progressed within 6 months of starting the immediate prior course of anti–PD-1 therapy; [b]Secondary resistance: Progressed after 6 months of treatment on the immediate prior course of anti-PD-1 therapy; [c]Includes 2 pt unknown resistance status. CTLA-4, cytotoxic T-lymphocyte antigen 4; LDH, lactate dehydrogenase; PD-1, programmed cell death protein 1; ULN, upper limit of normal; wt, wild-type.

Efficacy

Investigator assessed data with all patients having at least 12 months follow up

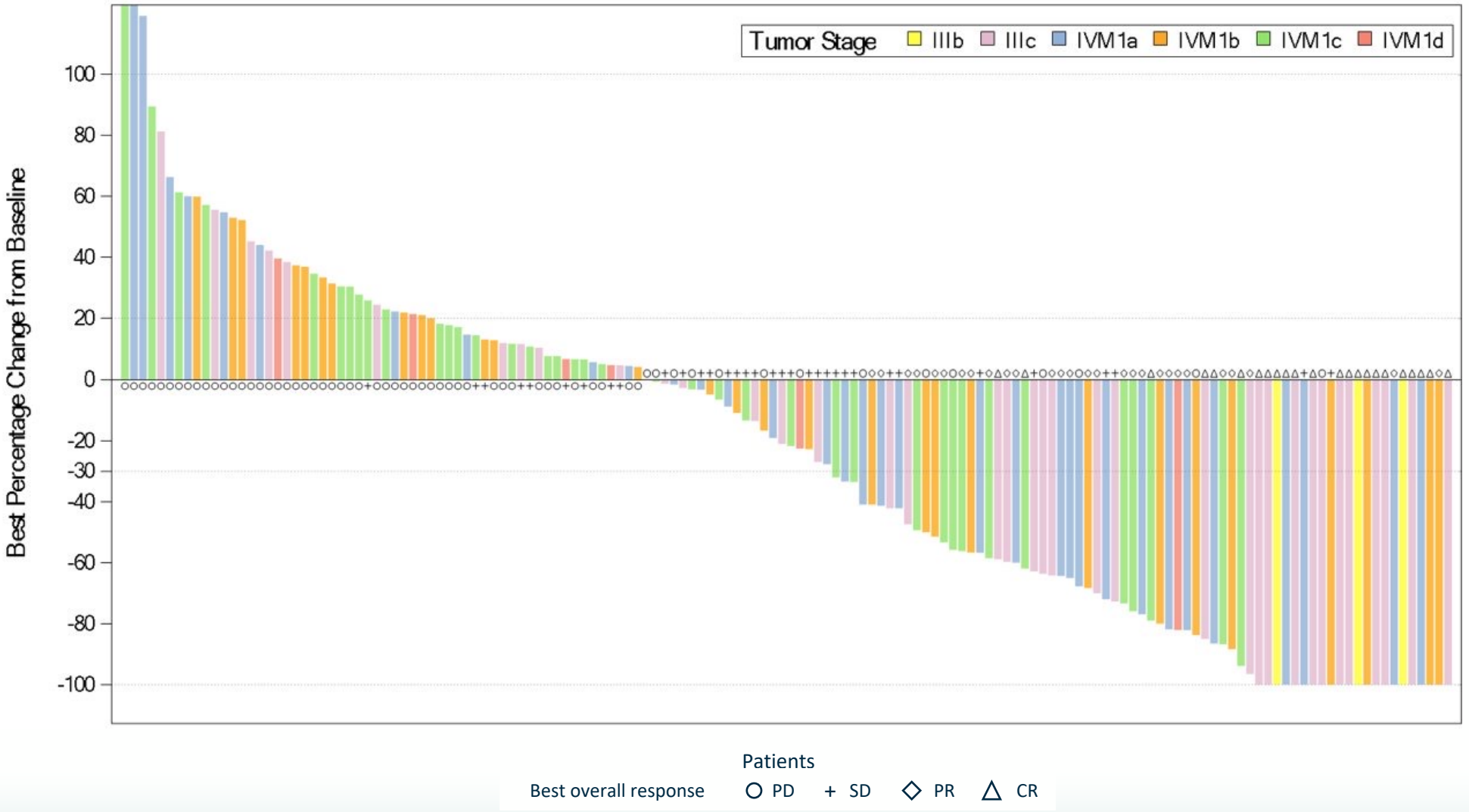
BOR n (%)	All patients enrolled in IGNYTE						
	All patients (n = 156)	Prior single-agent anti–PD1 (n = 82)	Prior anti–PD1/CTLA-4 (n = 74)[a]	Stage IIIb-IVM1a (n = 75)	Stage IVM1b-d (n = 81)	1º resistance to anti–PD1 (n = 105)	2º resistance to anti–PD1 (n = 51)[b]
CR	23 (14.7)	18 (22.0)	5 (6.8)	18 (24.0)	5 (6.2)	18 (17.1)	5 (9.8)
PR	28 (17.9)	13 (15.9)	15 (20.3)	13 (17.3)	15 (18.5)	18 (17.1)	10 (19.6)
SD	34 (21.8)	18 (22.0)	16 (21.6)	19 (25.3)	15 (18.5)	17 (16.2)	17 (33.3)
PD	63 (40.4)	31 (37.8)	32 (43.2)	24 (32.0)	39 (48.1)	47 (44.8)	16 (31.4)
ORR	**51 (32.7[c])**	**31 (37.8)**	**20 (27.0)**	**31 (41.3)**	**20 (24.7)**	**36 (34.3)**	**15 (29.4)**

[a]Eight patients were treated with sequential anti-CTLA-4 and anti-PD1 (ORR for prior combined anti-CTLA-4/anti-PD1 was 25.8%). [b]Includes one patient with unknown resistance status. [c]ORR for the 140-patient registration intended cohort was 32.1%

- 1 in 3 patients achieved an objective response (32.7%)
- Consistent ORR across subgroups, including:
  - 27% ORR in patients who had prior anti–PD1 & anti–CTLA-4
  - 34% ORR in patients who are primary resistant to their prior anti-PD1 therapy

Data cutoff: March 8th 2024. BOR, best overall response; CR, complete response; CTLA-4, cytotoxic T-lymphocyte antigen 4; PD-1, programmed cell death protein 1; PD, progressive disease; PR, partial response; ORR, objective response rate; SD, stable disease.

Depth of Response

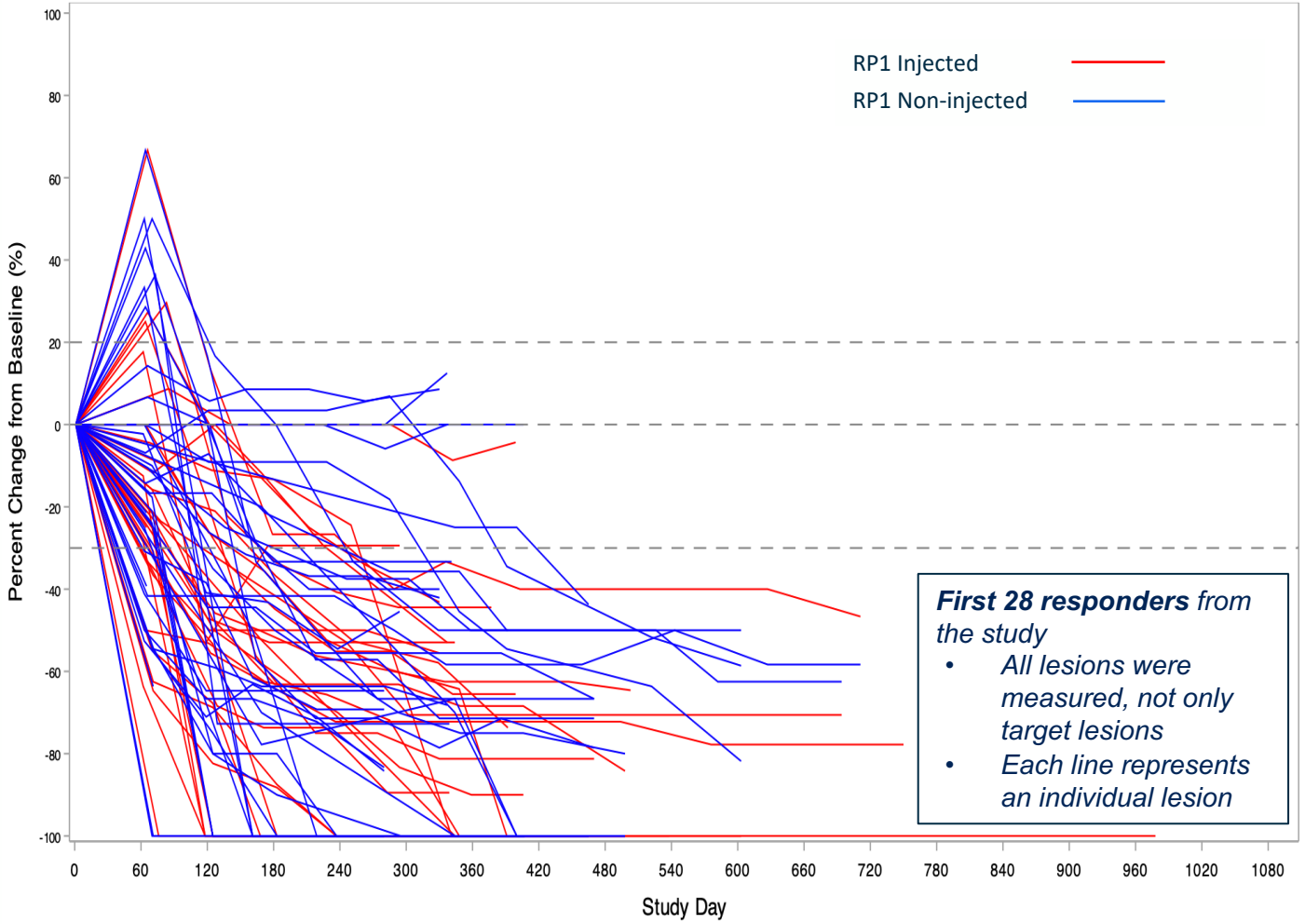


- Target lesions were reduced in >50% of patients
- Responses were seen across disease stages, including CRs in patients with **stage IVM1b/c disease**

Data cutoff: March 8th 2024. The target lesion response is shown for patients with at least one post-baseline assessment. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

Responses are Systemic

Change in size of individual injected and non-injected lesions

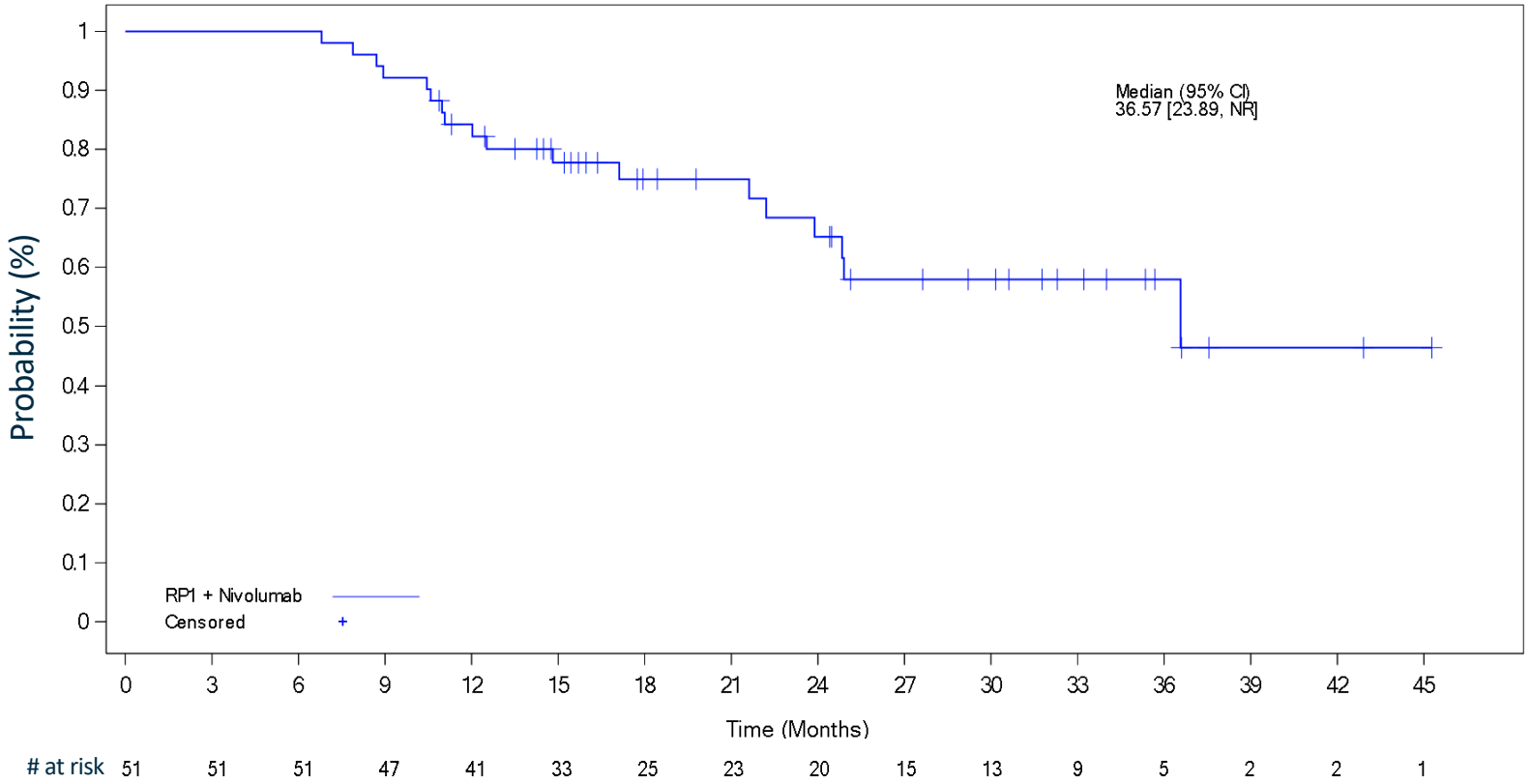


- 70.4% of responding patients had non-injected lesions
- Injected and non-injected lesions responded with similar duration and kinetics
- Depth of response independent of injection status

Responses in non-injected lesions demonstrate systemic benefit

Includes both target and non-target lesions for RECIST assessment, measured from CT/MRI scans for radiologically assessable lesions (responders from the first 75 patients enrolled into the registration intended cohort). 58/75 patients had at ≥ 1 non-injected lesion, of whom 15 achieved a response based on those lesions only (excludes possible response in injected lesions); ORR of 25.9% on the basis of non-injected lesions only. First presented at ASCO 2023.

Duration of Response
From baseline



>6 months	>12 months	>18 months	>24 months
100%	84.2%	74.9%	65.2%

The median follow up for responders is 27.9 months (range 10.5-55.5)

- Responses are durable, with a **median DOR** of **36.6 months**

Data cutoff: March 8th 2024. Duration of response defined as time from baseline to end of response for responders. DOR, duration of response.

Safety: Treatment-related AEs (N = 156)

Preferred term, n (%)	TRAEs occurring in >5% of patients				
	Grade 1–2	Grade 3	Grade 4	Grade 5	Total (N = 156)
Chills	53 (34.0)	1 (0.7)	0	0	53 (34.0)
Fatigue	51 (32.7)	2 (1.3)	0	0	52 (33.3)
Pyrexia	49 (31.4)	0	0	0	49 (31.4)
Nausea	35 (22.4)	0	0	0	35 (22.4)
Influenza-like illness	30 (19.2)	0	0	0	30 (19.2)
Injection-site pain	23 (14.7)	0	0	0	23 (14.7)
Diarrhea	21 (13.5)	1 (0.6)	0	0	21 (13.5)
Vomiting	21 (13.5)	0	0	0	21 (13.5)
Headache	20 (12.8)	0	0	0	20 (12.8)
Pruritus	20 (12.8)	0	0	0	20 (12.8)
Asthenia	13 (8.3)	1 (0.6)	0	0	14 (9.0)
Arthralgia	11 (7.1)	1 (0.7)	0	0	11 (7.1)
Myalgia	11 (7.1)	0	0	0	11 (7.1)
Decreased appetite	9 (5.8)	1 (0.6)	0	0	10 (6.4)
Rash	9 (5.8)	1 (0.6)	0	0	10 (6.4)

RP1 combined with nivolumab continues to be a generally well tolerated regimen

- Predominantly grade 1 and 2 constitutional-type side effects
- Low incidence of grade 3 and 4 events
- No grade 5 events

Additional grade 3 and 4 events <5%
Grade 3: Two each of rash maculo-papular and hypophysitis; 1 each of tumor pain, infusion-related reaction, muscular weakness, abdominal pain, amylase increased, dermatitis bullous, eczema, immune-mediated enterocolitis, immune-mediated hepatitis, paresthesia, acute left ventricular failure, arthritis, cancer pain, enterocolitis, extranodal marginal zone B-cell lymphoma (MALT type), hyponatremia, injection site necrosis, left ventricular dysfunction, memory impairment, meningitis aseptic, edema, palmar-plantar erythrodysesthesia syndrome, peripheral sensory neuropathy, radiculitis brachial, sinus arrhythmia, tricuspid valve incompetence, and type 1 diabetes mellitus

Grade 4: One each of lipase increased, alanine aminotransferase increased, blood bilirubin increased, cytokine release syndrome, myocarditis, and hepatic cytolysis, splenic rupture

Data cutoff: March 8th 2024. MALT, mucosa-associated lymphoid tissue; TRAE, treatment-related adverse event.

Conclusions

- RP1 combined with nivolumab in melanoma patients who had confirmed progression on prior anti-PD1 continues to show:
  - Deep and durable, systemic responses
  - A favorable safety profile, with generally ‘on target’ and transient grade 1–2 side effects indicative of systemic immune activation
- 1 in 3 patients experienced a response (ORR: 32.7%)
  - 27% ORR in patients had prior anti–PD1/anti–CTLA-4
  - 34% ORR in patients who had primary resistance to their immediate prior anti-PD1 therapy
  - Clinically meaningful activity was seen across all enrolled subgroups
  - 55% of patients experienced clinical benefit (CR + PR + SD)
- Responses were highly durable
  - All patients followed for at least 12 months
  - All responses lasted at least 6 months, with median DOR >36 months

Topline Data for the IGNYTE Registrational Cohort in Anti-PD1 Failed Melanoma Assessed by Independent Central Review

Strong IGNYTE Primary Analysis Data by Independent Central Review

Overall Response Rate (registration-intended cohort: n=140) (%)		
Investigator Assessment	**Independent Central Review[1]**	
Modified* RECIST 1.1 **32.1%**	**Primary Endpoint** **Modified* RECIST 1.1** **33.6%**	**RECIST 1.1**** **32.9%**

* Confirmation of PD requires further tumor increase from the first observation of PD; responses can be captured at any time up until next anti-cancer therapy[2]
** Requested by FDA, with confirmation of PD required; responses not included in ORR after the first confirmed PD
All patients with at least 12 months follow up

Data cutoff: March 8th 2024. Median follow up for the 140 patients in the registration intended cohort is 15.8 months (range 0.5-47.6); [1]Each central reviewer selects their own target lesions without knowledge of RP1 injection status. [2]This was to allow for the potential for prolonged pseudo-progression (>1 scan interval) before response; however, in practice the pseudo-progression seen was transient (generally <1 scan interval)

Patient Example

Prior atezolizumab+cobimetinib, ipilimumab, SX682 (CXCR-inhibitor)+ atezolizumab, ipilimumab+nivolumab

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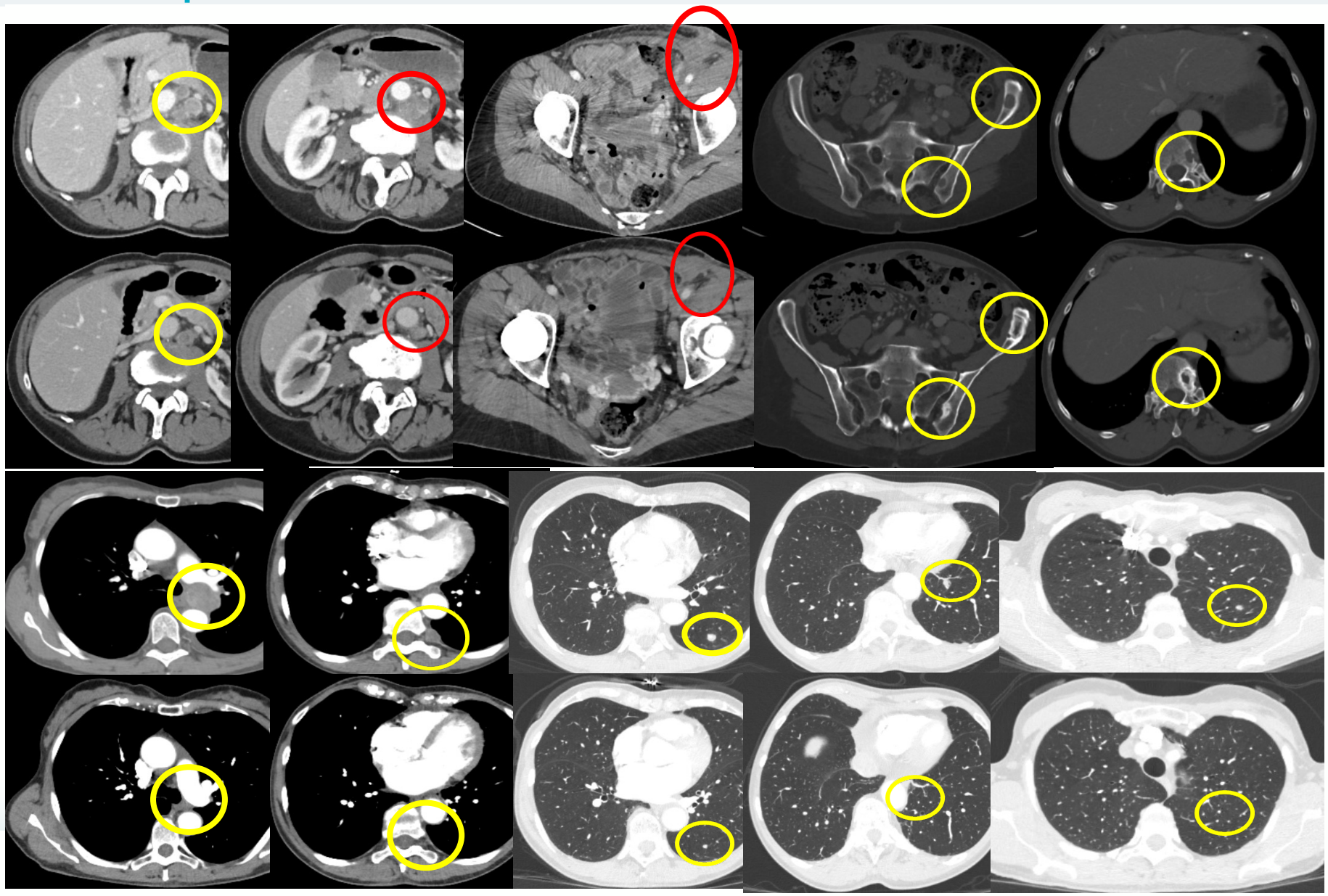


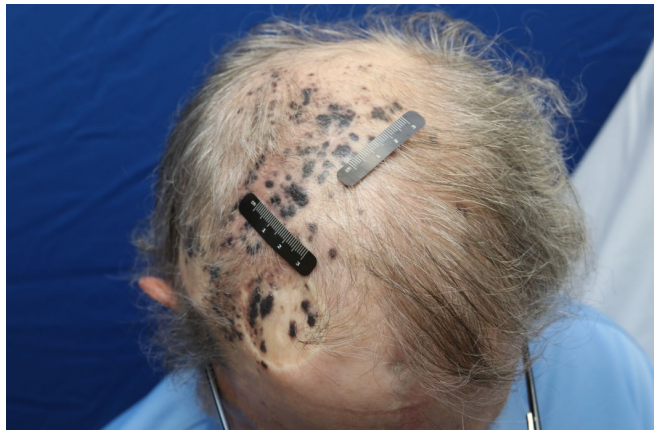
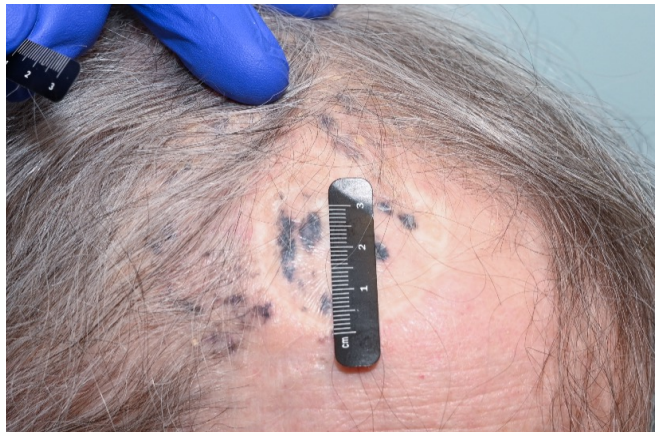
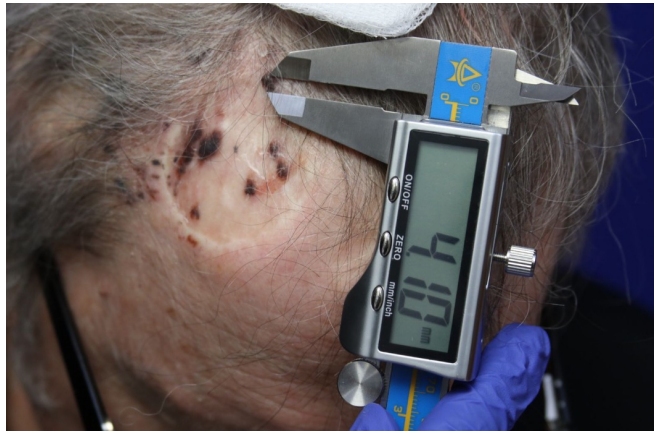
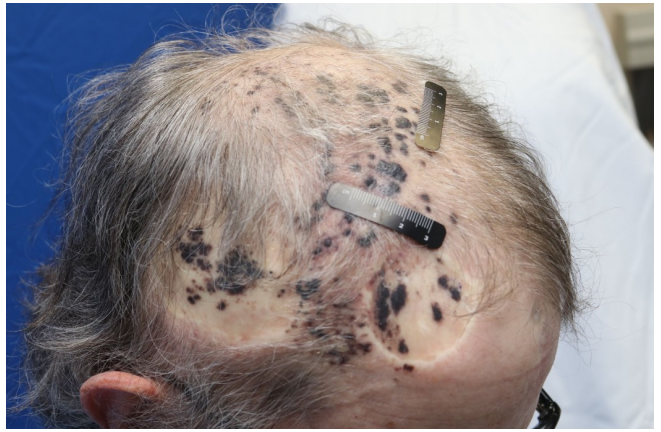
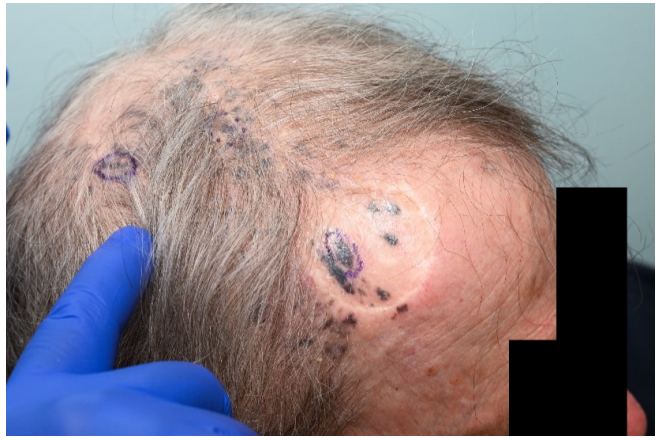
Responses in uninjected distant and visceral tumors including healing of lytic bone lesions (increasing sclerosis & new internal bone formation seen)

RP1 injected
Non-injected

Patient Example

Prior pembrolizumab (1L), encorafenib+binimetinib (2L), and nivolumab+relatlimab (3L)

Replimune®

Baseline	4 months	15 months
		
		

IGNYTE Data Shows Clinically Meaningful Benefit

- One third of patients respond (ORR: 33.6%)
- Responses are durable
  - 100% last >6 months, median DOR >35 months (from baseline)
- RP1 combined with nivolumab continues to be a generally well tolerated regimen
  - Predominantly grade 1/2 constitutional-type side effects
  - Low incidence of grade 3 and 4 events; no grade 5 events
- Full data to be submitted for presentation at an upcoming medical congress

Progress to BLA

IGNYTE Data and Phase 3 Confirmatory Trial Incorporates FDA Feedback

Type B meeting in 2021

A real-world population, representative of the IO progressed landscape should be enrolled

Patients should have confirmed progression while **on** anti-PD1 therapy, with minimum 8 weeks exposure

Responses should be durable

Clinically meaningful activity should be seen across all melanoma sub-groups enrolled

Responses should be demonstrably systemic, i.e. of both injected and uninjected lesions

Type C meeting in Sept 2023

FDA acknowledged that the IGNYTE population represents one of unmet need

Contribution of components demonstrated by reference to the literature*

Centrally reviewed data by RECIST 1.1 and mRECIST 1.1

All patients followed for at least 12 months (protocol primary analysis timepoint)

All responding patients followed for at least 6 months from response initiation

Phase 3 confirmatory study will be underway by BLA submission

*The response rate for further single agent anti-PD1 for patients having confirmed PD on prior anti-PD1 is expected to be 6-7%; Ribas et al Lancet Oncology 2018 (19), Hodi et al JCO 2016 (34)

IGNYTE-3: Confirmatory Phase 3 Trial Design*

RP1 and Nivolumab in Ipi-Nivo Pretreated Patients

Advanced cutaneous melanoma

Progressed on anti-PD1 AND anti-CTLA-4 OR not candidates for anti-CTLA-4

Up to 2 prior lines of systemic therapy for advanced disease

BRAF mutant patients must have been treated with BRAF/MEK-directed therapy[1]

N=~400

Randomized 1:1

RP1 + Nivolumab

Treatment of Physician's Choice (TPC)

- *Nivolumab-Relatlimab (Opdualag)*
- *Chemotherapy (DTIC, TMZ, paclitaxel/nab-paclitaxel)*
- *Rechallenge with anti-PD1 monotherapy (nivolumab or pembrolizumab)*

Primary Endpoint
Overall Survival

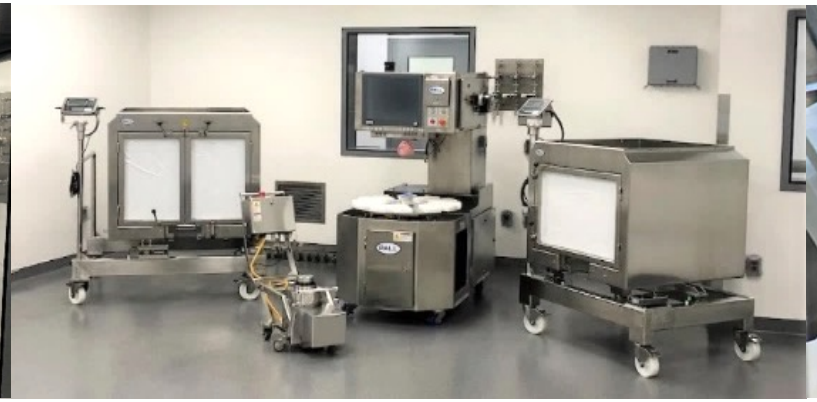
Key Secondary Endpoints
Progression Free Survival and Objective Response Rate

[1] For BRAF mutant patients prior BRAF/MEK-directed therapy is required unless deemed not clinically indicated at investigator's discretion due to documented concurrent medical condition or prior toxicity; *ClinicalTrials.gov ID: NCT6264180

Manufacturing on Track to Support RP1 BLA and Commercialization

Commercial scale in-house manufacturing established

- Type C meeting with FDA confirmed alignment on Chemistry, Manufacturing and Controls (CMC) plans to support RP1 BLA submission
- 63,000 square foot state-of-the-art facility for GMP manufacturing in Framingham, MA
  - RP1 BLA consistency lot runs complete
  - Commercial inventory build underway
- Scale expected to be sufficient to cover global commercialization of RP1 and RP2
- Commercially attractive cost of goods & 'off the shelf' product practicality



U.S. Melanoma RP1 Patient Opportunity

Compelling potential option for a broad range of anti-PD1 failed patients

Anti-PD1 failed melanoma

~13K patients[1]

1L prior adjuvant

2L+ BRAF WT

2L+ BRAF MT

Addresses a high unmet need in anti-PD1 failed settings

RP1+nivolumab is well positioned to be the **first option for patients who progress on a PD1-based regimen** (in adjuvant or 1L setting), given:

1. Deep & durable responses
2. Safety profile
3. Ease of administration

Source: [1]Melanoma US treated patient population for 2030 based on CancerMPact® Patient Metrics, Cerner Enviza (available from www.cancermpact.com Accessed 15 Oct 2023), with adjustments to future 2L+ treatment rates based on primary market research.

RP1 Well Positioned for BLA Submission and Commercialization

- Strong IGNYTE primary endpoint ORR data by independent central review of 33.6% (mRECIST 1.1)
- Durable responses: 100% last >6 months, median DOR >35 months (from baseline)
- Manufacturing on track to support RP1 BLA & global commercialization
  - Type C meeting with FDA confirmed alignment on CMC plans
- First patient expected to be enrolled in the phase 3 confirmatory study (IGNYTE-3) in Q3 2024, with BLA submission planned for 2H 2024
- Attractive commercial RP1 opportunity in anti-PD1 failed melanoma
  - Significant patient population and unmet need
  - Compelling risk:benefit profile

Thank You