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Phase 2 Trial of Mocetinostat in Combination with Durvalumab in NSCLC Patients (Pts) with Progression on Prior Checkpoint Inhibitor Therapy

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Presenter Disclosure Information

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The following relationships exist related to this presentation:

Advisory board for Nektar Therapeutics

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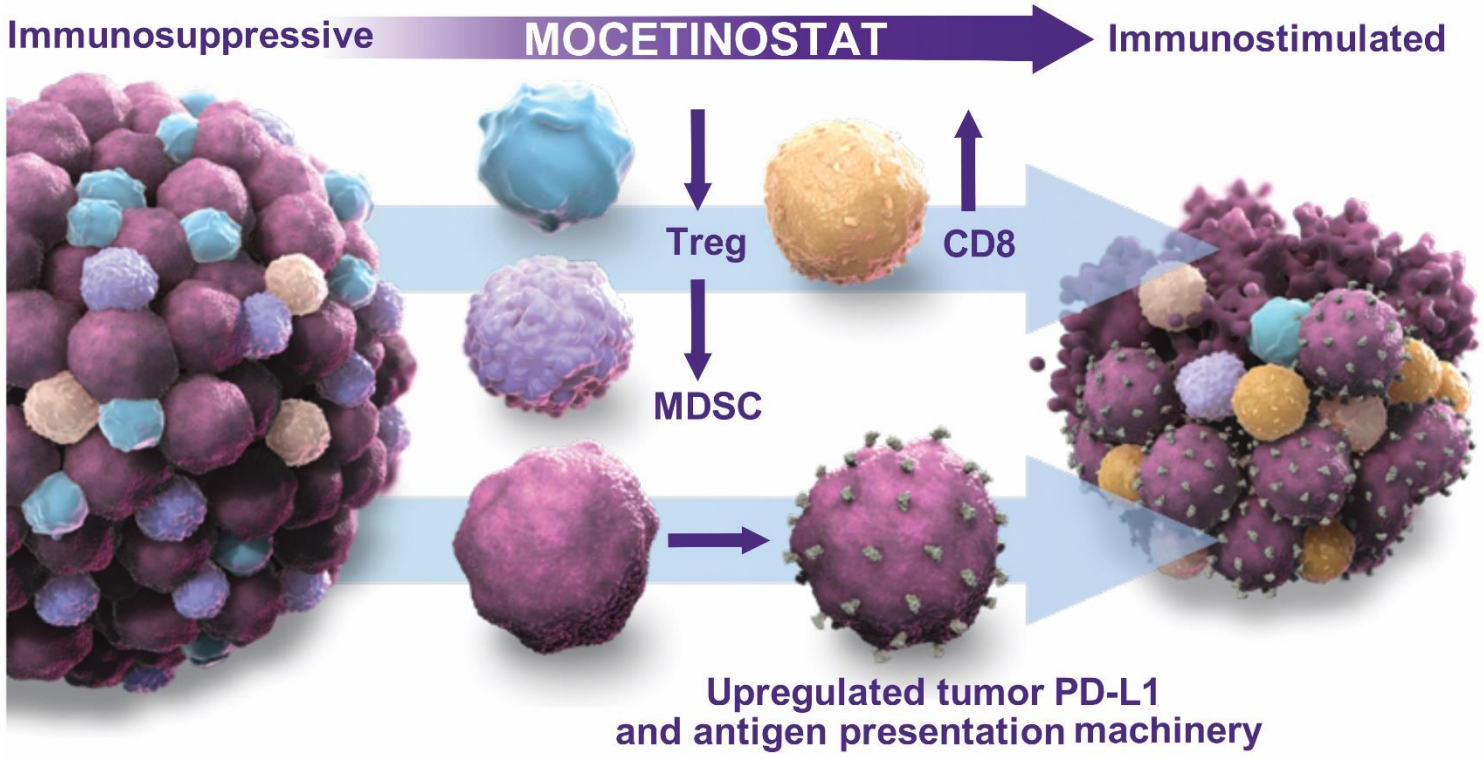
There will be discussion about the use of products for non-FDA approved indications in this presentation.

0103-020 Background

Mocetinostat: Class I and IV HDAC Inhibitor
Immuno-supportive effects in the Tumor Microenvironment (TME**)**



Given the pleiotropic immune activating effects of moceotinostat, the combination of mocetinostat and the PD-L1 blocking mAb durvalumab was tested in NSCLC patients with checkpoint inhibitor therapy (CIT) naïve disease or had progressive disease after prior CIT

0103-020 Phase 2 Design

- Phase 1/2 study evaluating the tolerability and clinical activity of mocetinostat in combination with durvalumab
- ORR in accordance with RECIST 1.1 is the primary clinical benefit endpoint
- Predictive Probability Design for assessment of enrollment expansion in each stage and treatment arm

- Phase 1- Increased doses of mocetinostat administered (50, 70, 90 mg three times weekly [TIW]) in combination with 1500 mg durvalumab on day 1 of each 28-day cycle
- 7-day lead in with mocetinostat monotherapy prior to combination treatment

			Stage 1	Expand after Indicated Responses	Stage 2
Any Histology NSCLC Receipt of previous platinum doublet or immunotherapy for advanced disease	Checkpoint Naive (CIT-N)	**No/Low PD-L1 Expression**	**n=9**	**≥ 1**	**n=8**
		High PD-L1 Expression	**n=17**	**≥ 6**	**n=27**
	Checkpoint Experienced (CIT-E)	**Prior Clinical Benefit**	**n=9**	**≥ 1**	**n= 8**
		No Prior Clinical Benefit	**n=9**	**≥ 1**	**n= 8**

0103-020 Study Objectives and Key Eligibility

PRIMARY OBJECTIVES

- Determine RP2D dose of mocetinostat in combination with durvalumab
- Objective Response Rate (ORR) by RECIST 1.1
    - Investigator Assessed

SECONDARY OBJECTIVES

- Safety and tolerability, PK for mocetinostat and durvalumab, incidence of anti-drug antibodies to durvalumab
- Evaluate mocetinostat effect on tumor cell, PD-L1 expression during a 7-day lead-in with mocetinostat monotherapy

KEY PHASE 2 ENTRY CRITERIA

- NSCLC with metastatic or unresectable, locally advanced disease
- Receipt of at least one platinum-based doublet or immunotherapy regimen
- If Checkpoint experienced (CIT-E) most recent treatment must have included a checkpoint inhibitor; If no prior checkpoint received (CIT-N) biopsy required to determine PD-L1 expression status
- ECOG performance status of 0 or 1

0103-020 Patient Population

PHASE 2 PATIENT POPULATION

Patients with advanced or metastatic NSCLC and receipt of ≥ 1 platinum-containing doublet.

Four population cohorts:

1. Immunotherapy naïve, no/low PD-L1 expression (<25% of tumor cells)*
2. Immunotherapy naïve, high PD-L1 expression (≥25% of tumor cells)*
3. Prior clinical benefit with PD-L1 or PD-1 inhibitor treatment followed by progression.
4. Prior treatment with PD-L1 or PD-1 inhibitor with progression within 16 weeks of initiation of treatment.

**SP-263 CDx Assay*

0103-020 Patient Characteristics

Phase 2 Safety Population N=63		
Age, years	Median (range)	68.0 (27-88)
Sex, n (%)	Male	33 (52)
	Female	30 (48)
Race, n (%)	Caucasian	51 (81)
	Black	5 (8)
	Asian	4 (6)
	Other	3 (5)
Smoking, n (%)	Lifetime Non-smoker	8 (13)
	Current Smoker	8 (13)
	Former Smoker	47 (75)
ECOG PS, n (%)	0	16 (25)
	1	47 (75)
Lines of prior therapy, n (%)	One	22 (35)
	Two	29 (46)
	Three +	12 (19)

*Data cut off 02-Oct-2018

Phase 2 Enrollment by Cohort	
Cohort 1	18
Cohort 2	3
Cohort 3	23
Cohort 4	19

0103-020 Safety: Most Frequent (≥10%) Treatment-Related (Mocetinostat and/or Durvalumab)

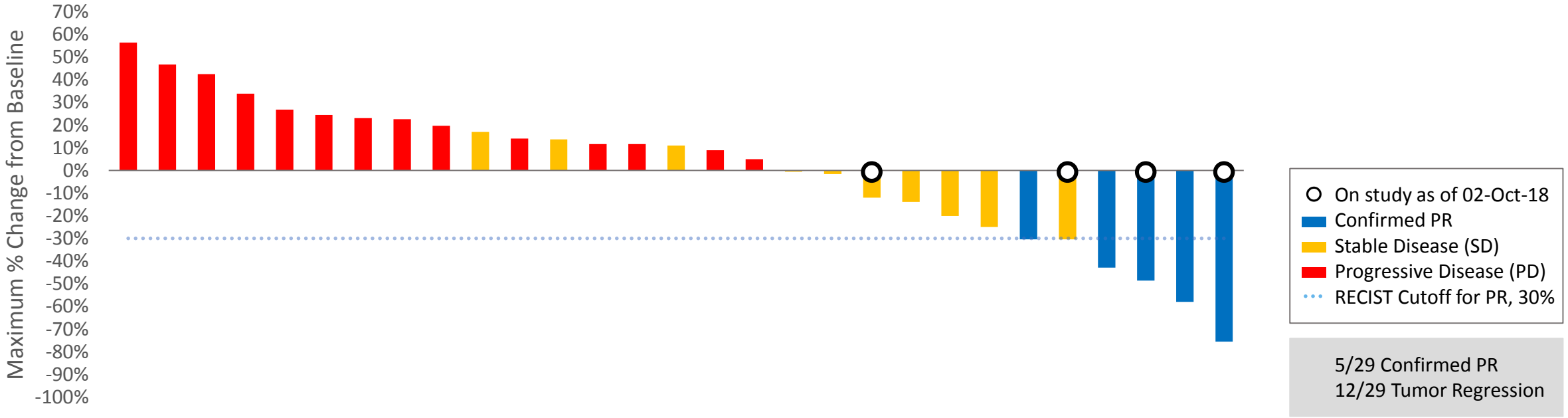
Adverse Event (Preferred Term)	Phase 2 Safety Population N=63	
	All Grades n (%)	Grade ≥3 n (%)
Fatigue	25 (40)	6 (10)
Nausea	22 (35)	1 (2)
Diarrhea	18 (29)	2 (3)
Decreased appetite	15 (24)	0
Vomiting	8 (13)	0
Cardiac disorders*	5 (8)	3 (5)

*Includes adverse events of atrial fibrillation, cardiac tamponade, pericardial effusion, and pericarditis
As of 02 October 2018 – all Phase 2 patients including CIT-Experienced and CIT-Naïve.

0103-020 Clinical Activity

PRELIMINARY MAXIMUM RESPONSE IN NSCLC PATIENTS WHO FAILED PRIOR CHECKPOINT THERAPY

(Clinical Activity Evaluable Patients, N=29)

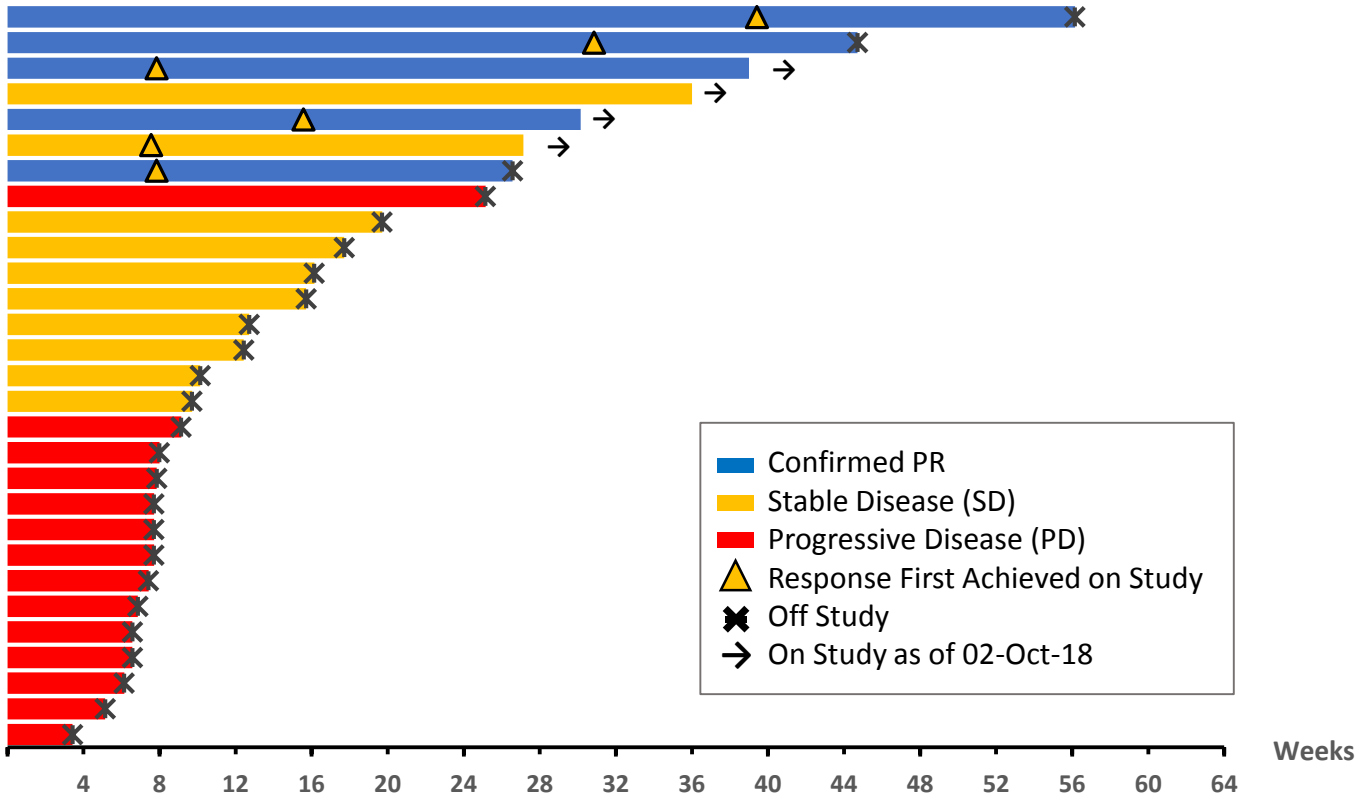


5/29 Confirmed PR
12/29 Tumor Regression

0103-020 Duration on Treatment

PRELIMINARY DURATION OF TREATMENT IN STUDY 0103-020 BY BEST OVERALL RESPONSE*

(Clinical Activity Evaluable Patients, N=29)



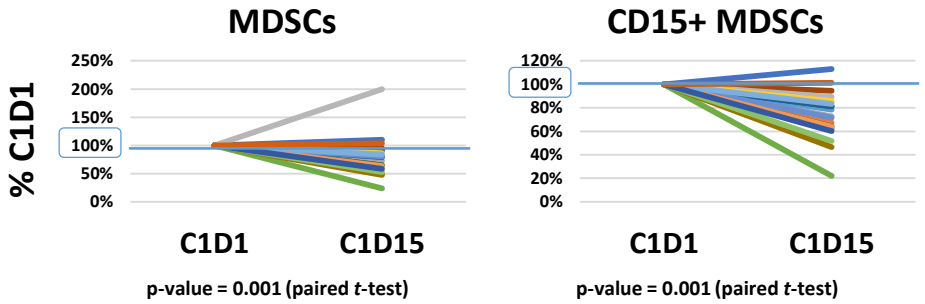
*Preliminary Kaplan-Meier estimate of median Duration of Response > 5 months

0103-020 Biomarkers

BIOMARKERS – FLOW CYTOMETRY ON CIRCULATING IMMUNE CELLS

MDSCs and granulocytic MDSCs decreased in patients at C1D15 vs C1D1

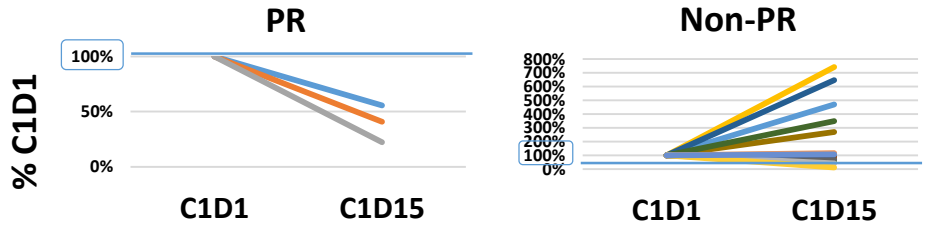
MDSCs: Lin-HLA-DRlow/-CD33+CD11b+
Granulocytic MDSCs: Lin-CD15+HLA-DRlow/-CD33+CD11b+



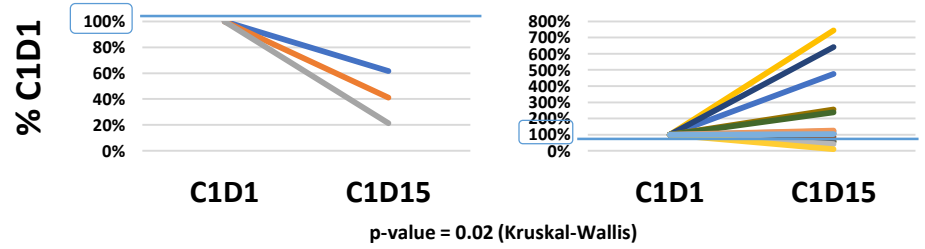
Monocytic MDSCs and CD14+ HLA-DR low/- Lin- monocytes decreased at C1D15 vs C1D1 in PR vs Non-PR

Monocytic MDSCs: CD14+HLA-DRlow/-CD33+CD11b+Lin-

CD14+, HLA-DR low/-, Lin- Monocytes



CD14+ MDSCs



0103-020 Summary

- The combination of mocetinostat and durvalumab showed clinical activity with 5/29 confirmed PRs in patients with progression on prior checkpoint inhibitor therapy.
- The clinical efficacy between Prior Benefit and No Prior Benefit cohorts are similar to date.
- Preliminary Kaplan-Meier estimate of median Duration of Response > 5 months.
- Tolerable safety profile with manageable AEs.
- Reduction of circulating MDSCs evident in patients.
- Reduction of circulating CD14+ MDSCs observed in patients with PR.
- Enrollment into the study opened in June 2016 and is ongoing in the United States.