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NEW PATHWAYS TO SMARTER MEDICINE™

SITC 2019

Nektar Therapeutics Investor & Analyst Call

November 10, 2019

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Today's Speakers

Dr. Adi Diab

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Nektar Therapeutics

Dr. Stina Singel

Vice President,
Oncology Clinical
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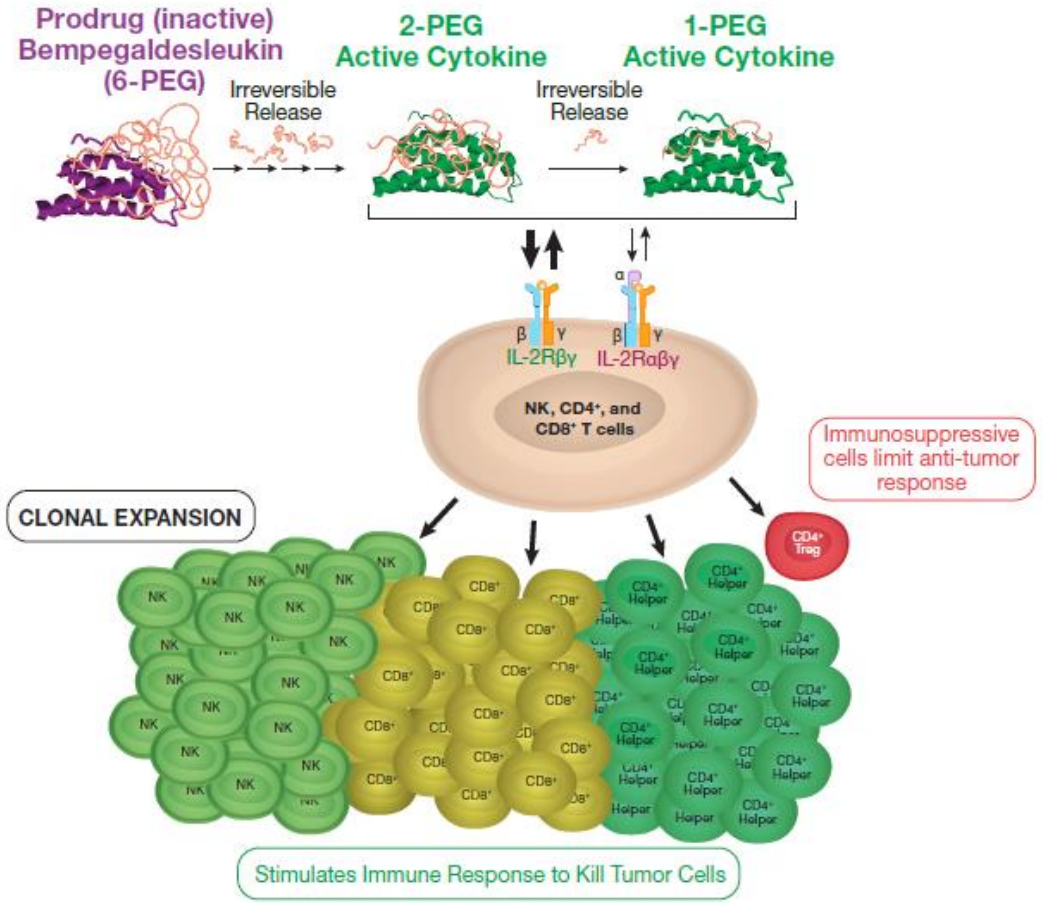
Background: Bempegaldesleukin Preferential Signaling Through the IL-2 Receptor Pathway

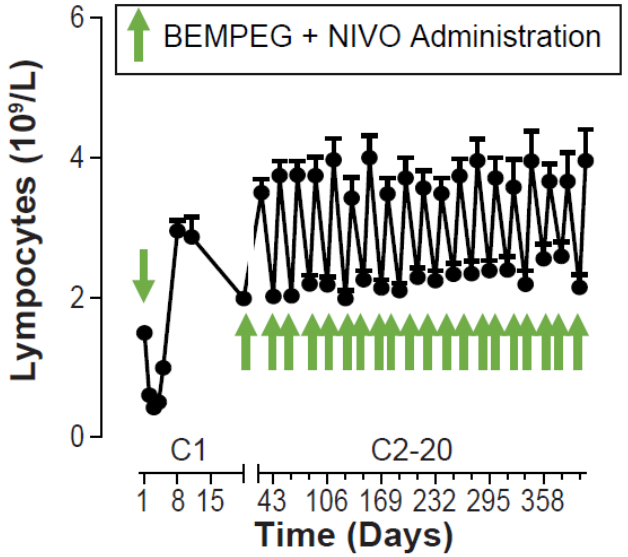


- Bempegaldesleukin (BEMPEG; NKTR-214): is a CD122-preferential IL-2 pathway agonist shown to increase tumor-infiltrating lymphocytes, T cell clonality and PD-1 expression[1,2]
- BEMPEG plus checkpoint inhibitor (CPI) nivolumab (NIVO) has been shown to convert baseline tumors from PD-L1(-) to PD-L1(+)[3-6]
- Low levels of baseline tumor-infiltrating lymphocytes (TILs)[7-9] and T cell–inflammation[10] is predictive of a poor response to CPIs

1. Charych D, et al. *PLoS One.* 2017; 12: e0179431; 2. Bentebibel SE, et al. *Cancer Discov*. 2019;9:711-721; 3. Diab A, et al. SITC 2018. Abstract O4; 4. Siefker-Radtke, et al. ASCO GU 2019. Abstract 388; 5. Hurwitz M, et al. ASCO 2019. Abstract 2623; 6. Tolaney S, et al. CICON 2019. Poster A001; 7. Daud AI, et al. *J Clin Oncol*. 2016;34:4102-09; 8. Daud AI, et al. *J Clin Invest*. 2016;126:3447-52; 9. Tumeh PC, et al. *Nature*. 2014;515:568-71; 10. Ayers M, et al. *J Clin Invest*. 2017;127:2930-2940.

ASCO 2019: Rapid Activation of the Immune System was Observed with BEMPEG and NIVO

Increase in Lymphocytes with Every Treatment Cycle*

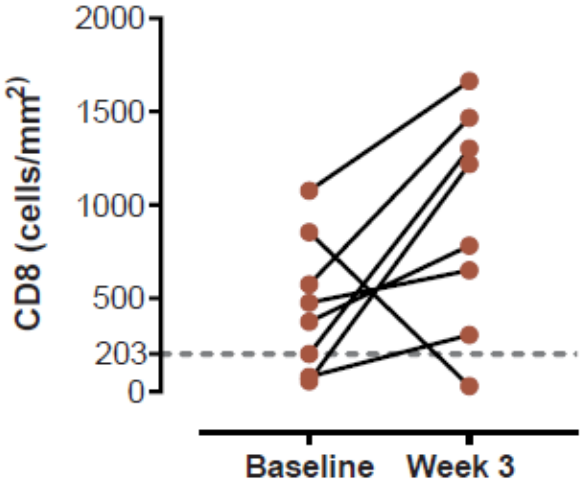


Lymphocyte effects of the BEMPEG + NIVO combination are driven by BEMPEG, as a similar pattern is observed with monotherapy[2]

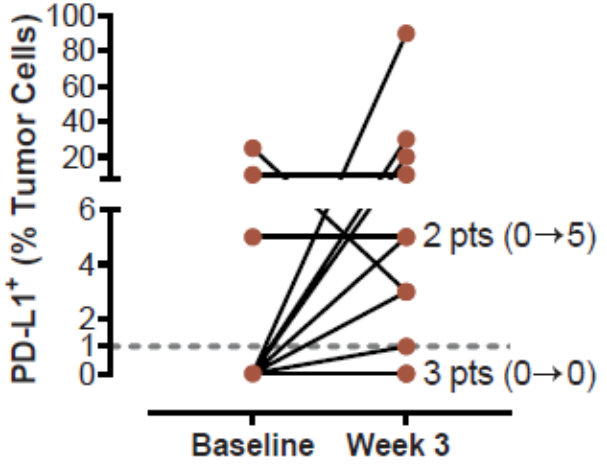
*Lymphocyte levels were obtained from standard hematology analyses. All efficacy evaluable melanoma (n=38) and mUC (n=27) in the BEMPEG + NIVO combination enrolled in PIVOT-02 (n=65, Mean+SD) were included in the analyses.

On-Treatment Increase in TIL and PD-L1

Change in CD8 Infiltrate in MEL[3,^]



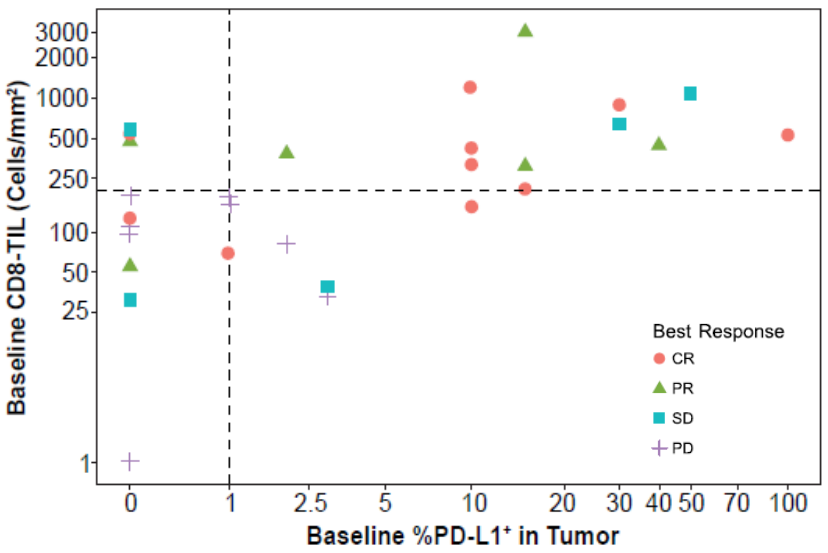
PD-L1 Conversion in UC[4,#]



^IHC for CD8 was obtained by standard methods. All patients with first-line melanoma (1L MEL) with matched Baseline and Week 3 biopsy (n=8) were included in the analyses.
#All patients with 1L urothelial carcinoma (UC) with matched Baseline and Week 3 biopsy (n=13) at time of data cut were included and assessed for PD-L1 expression (DAKO PD-L1 IHC 28-8 pharmDx).

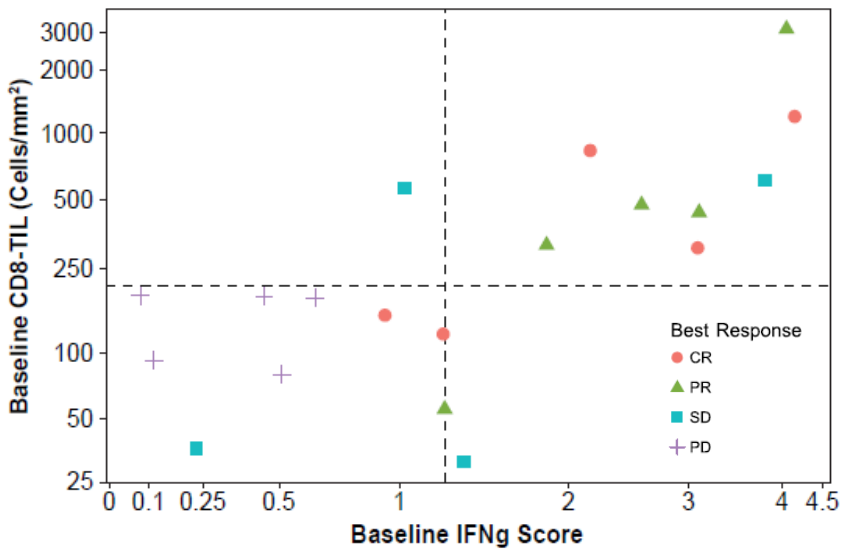
ASCO 2019: In 1L Melanoma, Paired Analyses Show Encouraging Response Rate in Patients with Favorable and Unfavorable Tumor Microenvironment (TME)*

CD8-TIL vs %PD-L1⁺



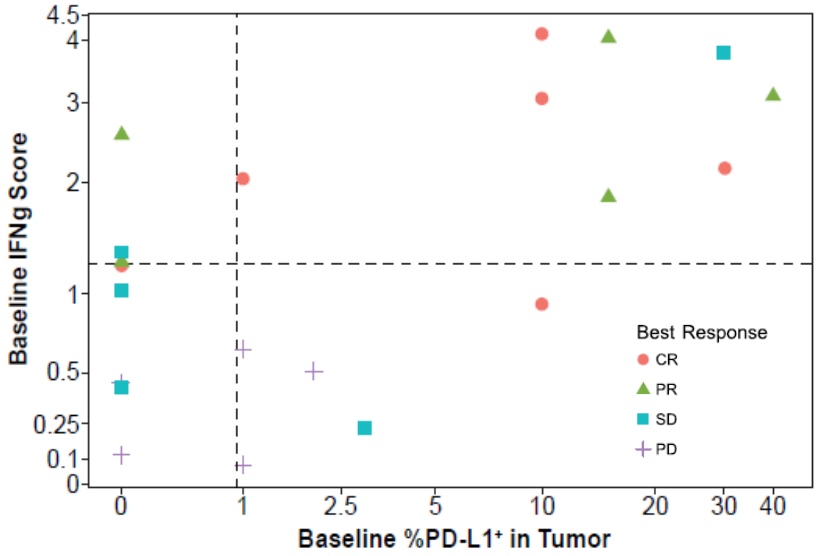
	PD-L1 Neg	PD-L1 Pos
CD8⁺TIL ≥Median	67% (2/3)	**83% (10/12)**
CD8⁺TIL <Median	**29% (2/7)**	29% (2/7)

CD8-TIL vs IFNg



	IFNg <Median	IFNg ≥Median
CD8⁺TIL ≥Median	0% (0/1)	**88% (7/8)**
CD8⁺TIL <Median	**25% (2/8)**	50% (1/2)

IFNg vs %PD-L1⁺

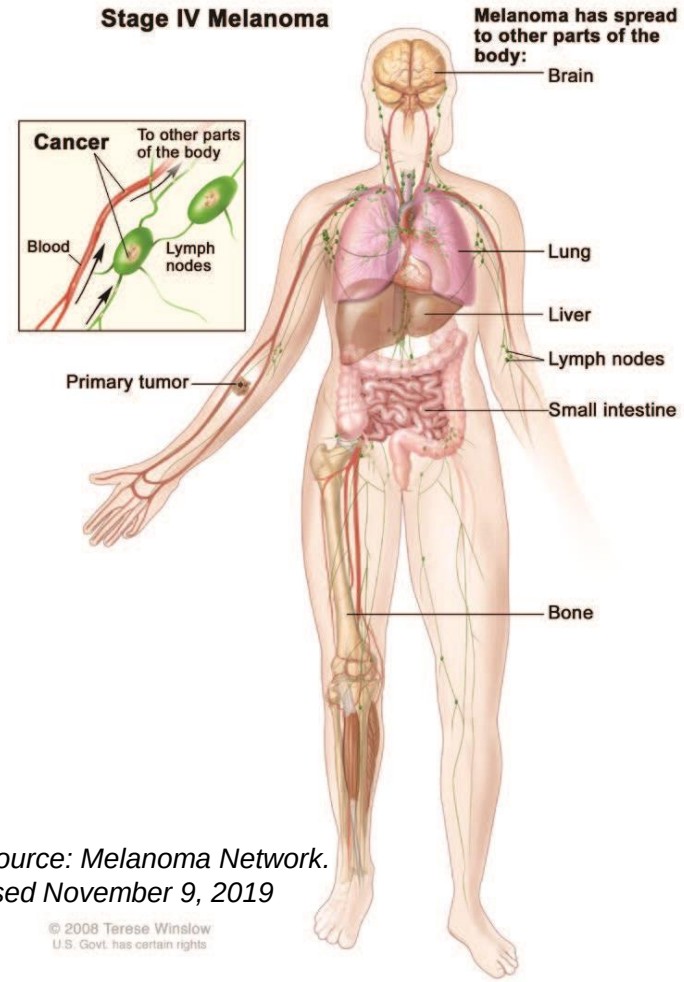


	PD-L1 Neg	PD-L1 Pos
IFNg ≥Median	67% (2/3)	**88% (7/8)**
IFNg <Median	**20% (1/5)**	20% (1/5)

*Unfavorable TME is dened as low/low by TILs/PD-L1, IFNg/TILs, and IFNg/PD-L1[8-10]
2x2 tables are based on median cutoffs of CD8-TIL and IFNg (≥ vs <), and PD-L1 (≥1% vs <1%)
Median: 203 cells/mm² (CD8⁺TIL); 1.2 (IFNg)
Spearman correlation on scale from 0-1 was 0.51 (CD8-TIL and PD-L1), 0.68 (IFNg and CD8-TIL), 0.55 (IFNg and PD-L1)
Dotted line marks the median cutoff (CD8-TIL and IFNg) or negative/positive status (PD-L1)

Hurwitz et. al, ASCO 2019; Abstract #2623/Poster Board #267

Immunotherapy in Metastatic (Stage IV) Melanoma



Data source: Melanoma Network. Accessed November 9, 2019

- Stage IV melanoma has metastasized (spread) to other places throughout the body, such as the brain, lungs, liver, or gastrointestinal (GI) tract.[1]
- Immunotherapy (immune checkpoint inhibitors (CPI) and IL-2) has improved survival in metastatic melanoma[1]
- However, a majority of metastatic patients continue to experience disease recurrence within five years.[2]
- Thus, more effective immunotherapy options such as combination therapies are needed to delay disease progression and prolong OS.[2]
  - Range of complete response rates:
    - PD-1 monotherapy: 9%[3,4] (at 12 months) to 18%[5] (at 4 years)
    - PD-1 in combination with CTLA-4: 9%[4] (at 12 months) to 22%[6] (at 5 years)

1. Melanoma Research Alliance. Accessed October 31, 2019
2. Decision Resources Group – Malignant Melanoma; October 2018
3. 12 month Nivolumab & Nivolumab+Ipilimumab: N Engl J Med. 2015 Jul 2; 373(1): 23–34.; Published online 2015 May 31. doi: 10.1056/NEJMoa1504030
4. Package Insert: Opdivo – Bristol-Myers Squibb (Revised: 5/2019)
5. 4 year Nivolumab & Nivolumab+Ipilimumab: https://doi.org/10.1016/S1470-2045(18)30700-9; Available online 22 October 2018.
6. 5 year Nivolumab & Nivolumab+Ipilimumab: 2019 NEJM Larkin et al.

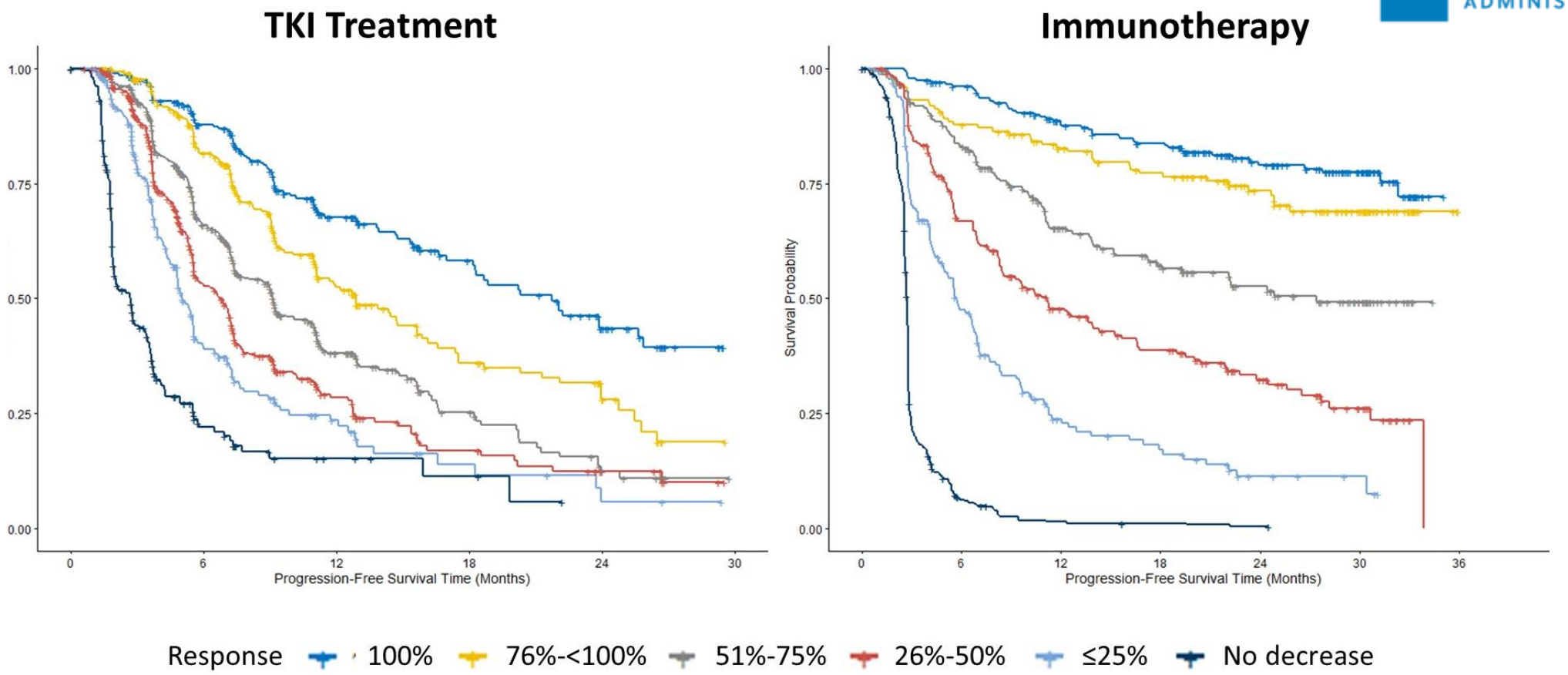
Breakthrough Therapy Designation Granted for BEMPEG + NIVO for Patients with Metastatic Melanoma

- BEMPEG + NIVO received Breakthrough Therapy Designation on July 29th, 2019 from the FDA for patients with previously untreated, unresectable or metastatic melanoma
- BTD programs receive intensive FDA guidance during drug development and BLA review
  - More frequent meetings, timely advice from FDA
- BTD programs also receive FDA organizational commitment with a cross-disciplinary project lead
  - More collaborative multidisciplinary process to guide the efficient drug development
- Advantages of BTD include eligibility for rolling review and Priority Review of BLA

ASCO 2019 Osgood et. al., Retrospective Analysis of Untreated Metastatic Melanoma Patients: Depth of Response (DpR) Correlates with Longer PFS and OS

4,826 patients across 10 randomized controlled trials with previously untreated unresectable or metastatic melanoma

Progression-Free Survival by Reduction Category



Source: 2019 ASCO FDA presentation J Clin Oncol 37, 2019 (suppl; abstr 9508).
"Depth of Response and Survival in Advanced or Metastatic Melanoma", Osgood, C., et al.

ASCO 2019 Osgood et. al., Retrospective Analysis of Untreated Metastatic Melanoma Patients: Depth of Response (DpR) Correlates with Longer PFS and OS

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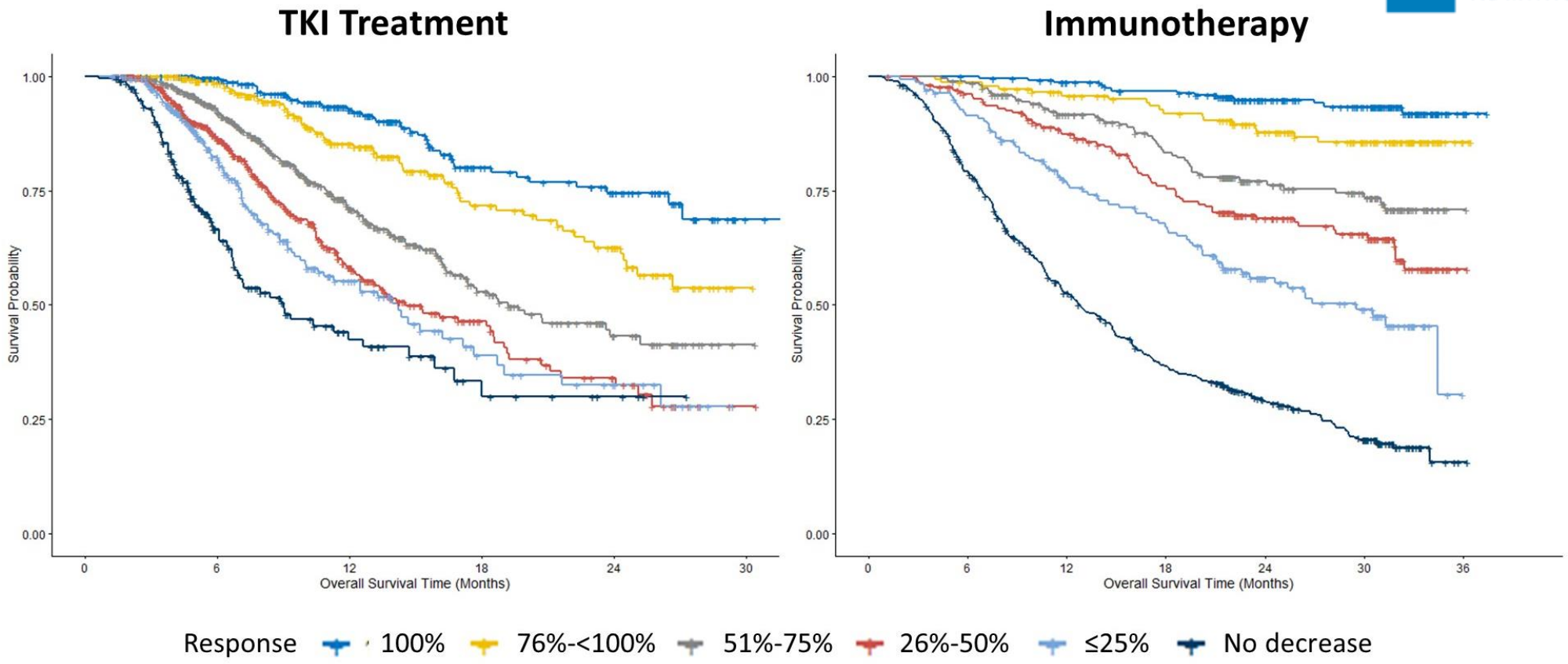
Overall Survival by Reduction Category



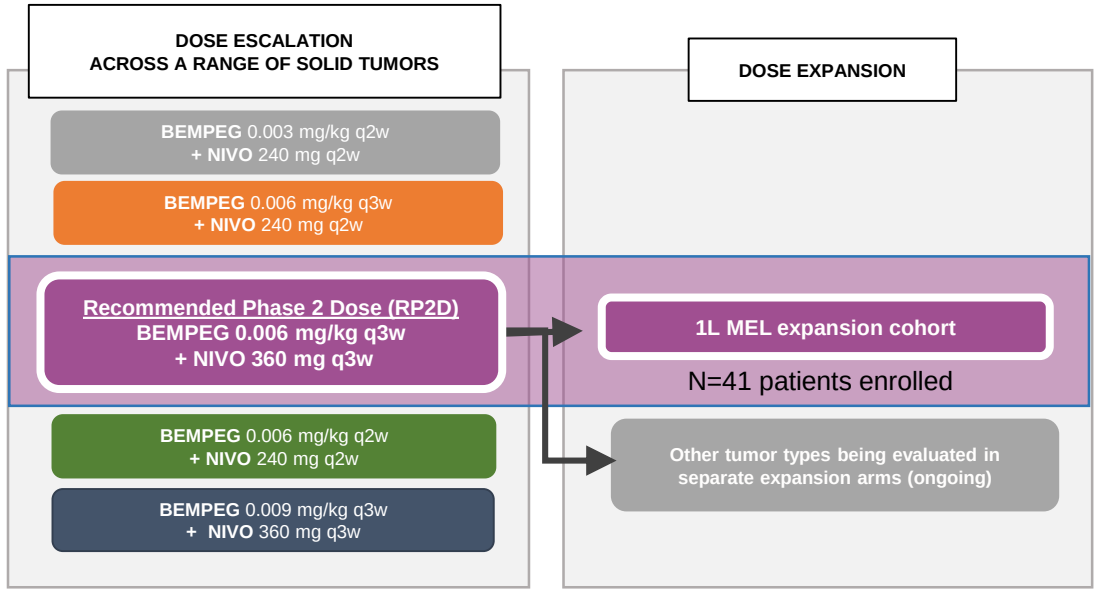
Source: 2019 ASCO FDA presentation J Clin Oncol 37, 2019 (suppl; abstr 9508).
"Depth of Response and Survival in Advanced or Metastatic Melanoma", Osgood, C., et al.

PIVOT-02 Study Schema

NCT02983045

Key MEL Inclusion Criteria

- **1L Metastatic Melanoma (with known BRAF status)**
- **IO naïve**
- **Measurable disease per RECIST v1.1**
- **ECOG PS 0-1**



Primary endpoints:

- Safety and tolerability
- ORR per RECIST assessed every 8 weeks*
- Efficacy evaluable per protocol defined as patients with ≥ 1 post baseline scan

Secondary and exploratory endpoints:

- Duration of response, OS, PFS, clinical benefit rate, PK
- Biomarker analyses in blood and tumor

- **41 MEL patients enrolled and received at least one dose of BEMPEG plus NIVO**
- **As of Sept 25, 2019, 38 patients were efficacy evaluable defined as patients with ≥1 post-baseline scan (3 patients discontinued prior to first scan due to an unrelated TEAE [n=1] and patient decision [n=2])**

*Tumors were assessed by blinded independent central radiology (BICR) and local investigator. BICR was used for this analysis, which required radiologic imaging scans to be submitted to a central location and reviewed by independent radiologists who are not involved in the treatment of the patients.
ECOG PS: Eastern Cooperative Oncology Group Performance Score; MEL: melanoma; RECIST: response evaluation criteria in solid tumors; TEAE: Treatment-emergent adverse events; SOC: standard of care

Patient Demographics and Disease Characteristics

	Total (n=41)
Sex	
Female	17 (41.5%)
Male	24 (58.5%)
Age (years)	
Median (Range)	63 (22-80)
ECOG Performance Status	
0	32 (78.0%)
1	9 (22.0%)
PD-L1 status*	
Positive ≥1%	24 (58.5%)
Negative <1%	14 (34.1%)
Unknown	3 (7.3%)

	Total (n=41)
BRAF status	
Mutant (V600E, V600K)	13 (31.7%)
Wild-Type or non-V600 mutation	27 (65.9%)
Unknown	1 (2.4%)
LDH‡	
Normal	29 (70.7%)
Elevated >ULN#	12 (29.3%)
Stage (7th edition AJCC)	
M1a	5 (12.2%)
M1b	16 (39.0%)
M1c	20 (48.8%)
Liver metastases**	
Yes	11 (26.8%)
No	30 (73.2%)

*PD-L1 status determined by Dako PD-L1 IHC 28-8 pharmDx on fresh or archival tumor; for patients with insufficient tumor tissue for central analysis, local pathology data for PD-L1 status at baseline were substituted. 1 pt previously reported as negative confirmed PD-L1 positive (<5%). **1 patient with liver metastases not evaluable for efficacy.
‡Based on maximum value prior to dosing
#8 patients with ≥ 2X ULN

Treatment-Related Adverse Events (TRAEs) at RP2D

Preferred Term[1]	Total (N=41)
Grade 3-4 Treatment-Related AEs	7 (17.1%)#
Acute kidney injury	2 (4.9%)
Atrial fibrillation*	2 (4.9%)
Dizziness, dyspnea, hypoxia, hyperglycemia, hypernatremia	1 each (2.4%)
Grade 1-2 Treatment-Related AEs (>30% listed below)	
Flu like symptoms**	33 (80.5%)
Rash***	29 (70.7%)
Fatigue	27 (65.9%)
Pruritus	20 (48.8%)
Nausea	19 (46.3%)
Arthralgia	18 (43.9%)
Decreased appetite	15 (36.6%)
Myalgia	15 (36.6%)
Any imAE (Grade ≥3) (Nephritis and renal dysfunction, diabetes mellitus/hyperglycemia treated with insulin)	2 (4.9%)
Patients who discontinued BEMPEG or NIVO due to a TRAE (Cerebrovascular accident, edema peripheral, blood creatinine increased, malaise, pharyngitis)	5 (12.2%)
Treatment-Related Deaths	0 (0%)

The combination of BEMPEG plus NIVO is well tolerated, and treatment-related adverse events (TRAEs) are similar to what was previously reported at ASCO 2019

Data Cutoff Date: 25SEP2019. imAE: Immune-mediated adverse events. Per protocol, safety evaluable is defined as patients with ≥ 1 dose of study treatment. (1) Patients are only counted once under each preferred term using highest grade. #Pts with 2 or more G3-4 TRAEs are only counted once. *1 patient with previous history of atrial fibrillation since 2015; 1 patient experienced atrial fibrillation 1 month after last dose of study drug. **Flu-like symptoms included the following preferred terms: chills, influenza, influenza-like illness, pyrexia. ***Rash included the following preferred terms: erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash

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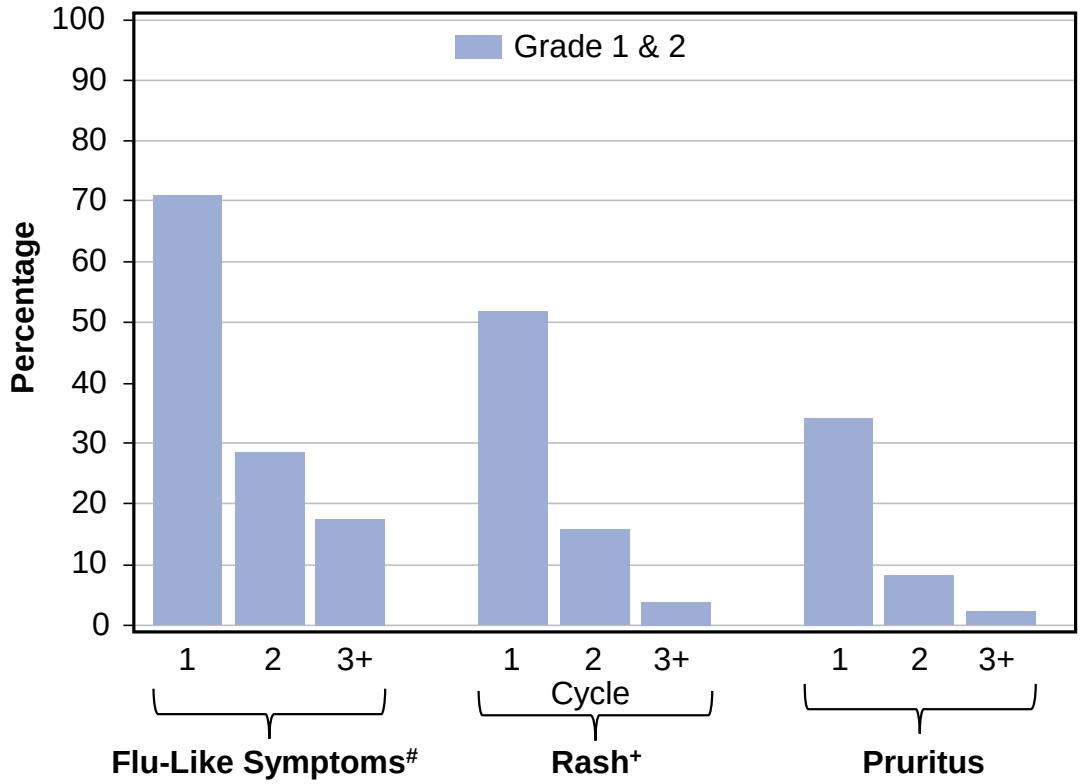
Cytokine-Related AEs: Decreased Frequency with Continued Dosing*

- Hydration guidelines[1] effective: no Grade ≥3 TRAEs of hypotension were observed in cohort
- Cytokine related AEs decreased with subsequent cycles of treatment
  - All were low grade (no Grade ≥3 or higher)
  - Easily managed with NSAIDs/OTCs[1,2]
  - No dose delays, dose reductions or study discontinuations due to cytokine related AEs
- Prodrug design of NKTR-214 accounts for lower frequency of cytokine-related AEs compared to high dose IL-2[1,3]

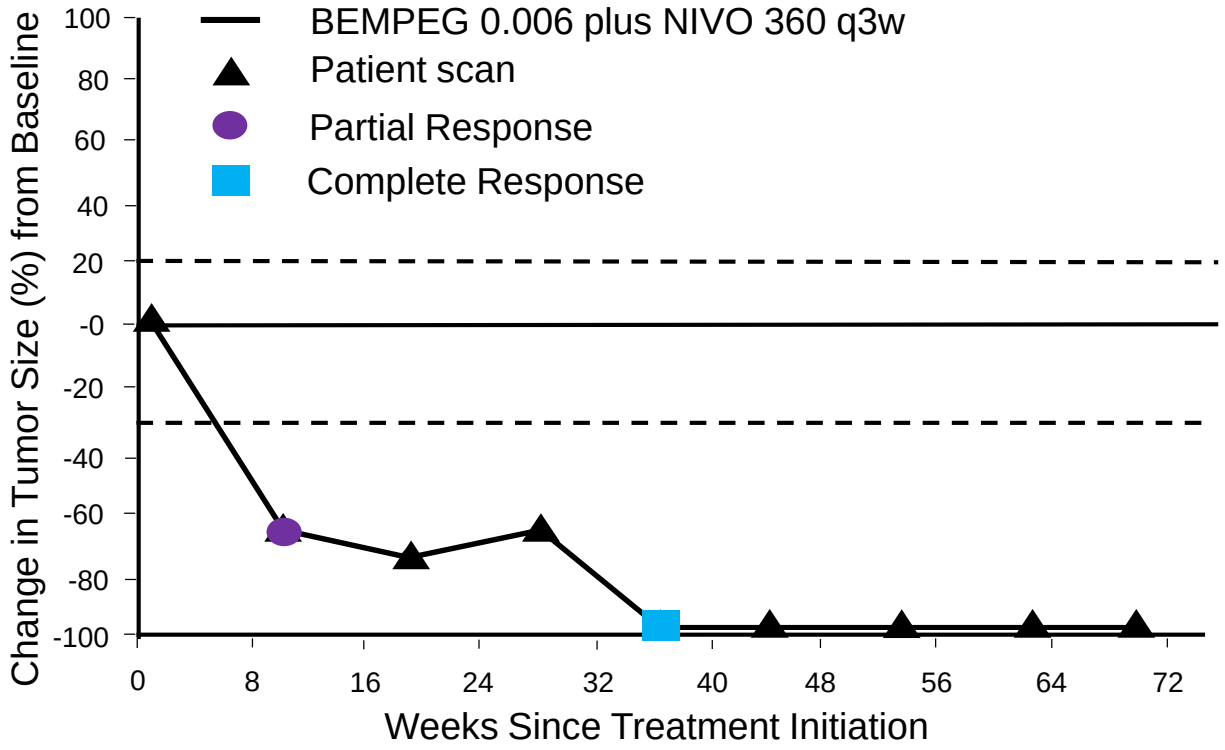


*Cycle 1 includes 41 pts, Cycle 2 includes 39 pts, Cycles 3+ includes ≤ 37 pts.
Cycle 3+ symptoms equals average of % per cycle for cycles 3-33.
#Includes the following preferred terms: chills, influenza like illness, pyrexia, influenza.
†Includes the following preferred terms: erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash papular, rash pruritic, rash pustular, rash vesicular, and exfoliative rash

1. Bentebibel SE, et al. Cancer Discov. 2019;9:711-721; 2. Diab A, et al. SITC 2018. Abstract O4; 3. Dutcher JP, et al. J Clin Oncol. 1991;9:641-8

Patient with 1L Melanoma and Ongoing Response

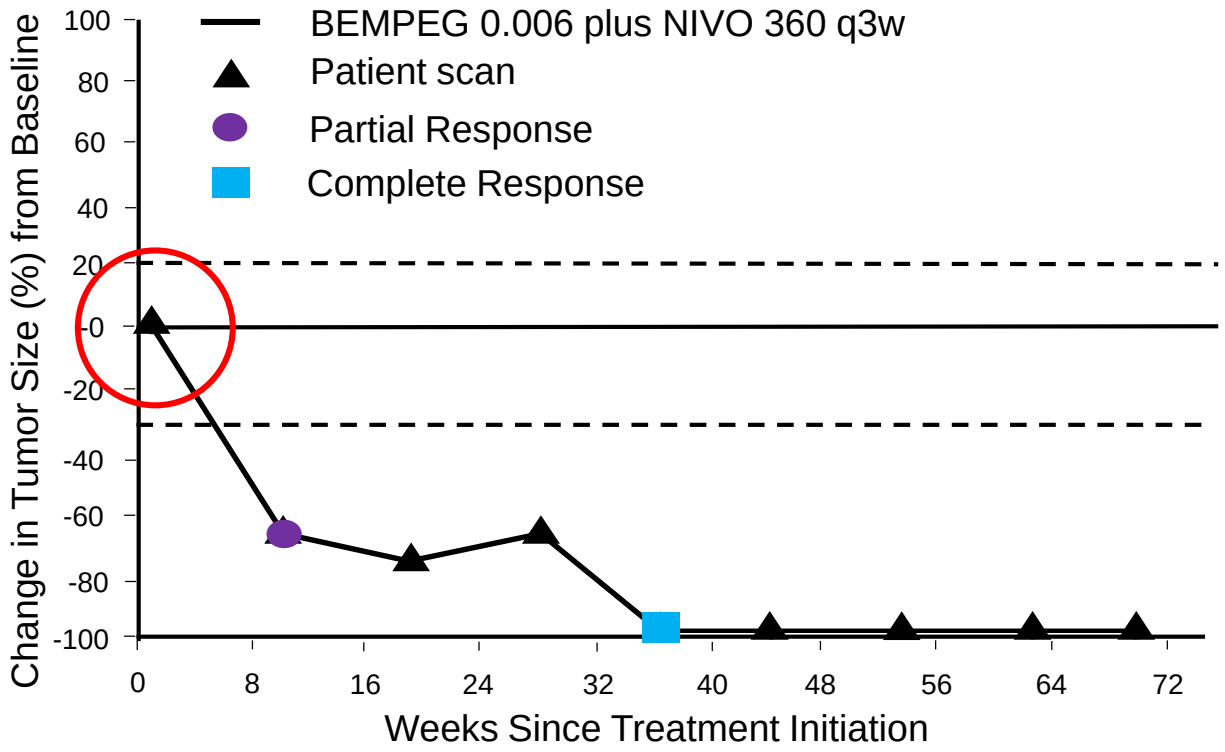
Age	Sex	Metastatic Diagnosis	PD-L1 Status	Baseline SLD (mm)	Best % Change from Baseline	Overall Response	TTR (mo)	EOT
74	Male	Sept 2013: Mel T2aN0, Stage 1B Jan 2018: Metastatic MEL Feb 2018: Treatment initiated	+	44	-100.0	CR	PR (2.1)	Ongoing



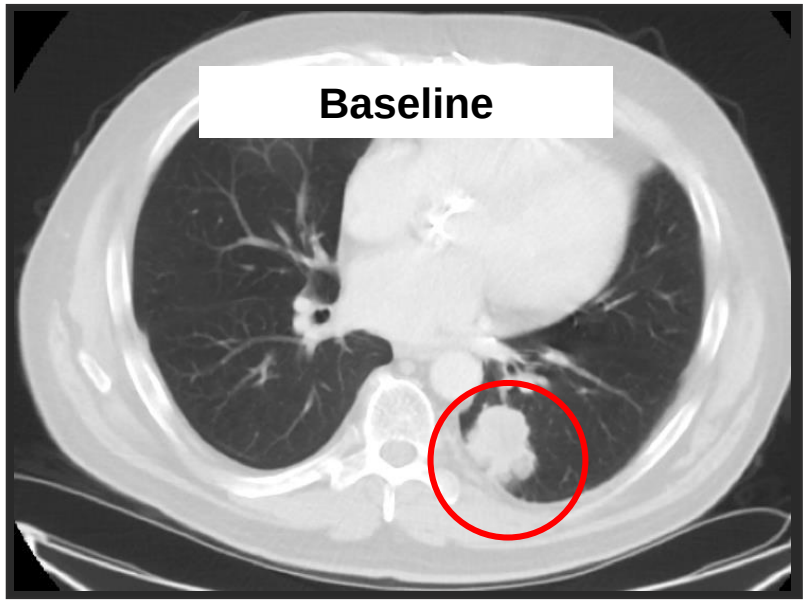
Related/Possibly Related SAE: None
BEMPEG Related AEs (Grade ≥3): None
Combination Related (Grade ≥3): None

Patient with 1L Melanoma and Ongoing Response

Age	Sex	Metastatic Diagnosis	PD-L1 Status	Baseline SLD (mm)	Best % Change from Baseline	Overall Response	TTR (mo)	EOT
74	Male	Sept 2013: Mel T2aN0, Stage 1B Jan 2018: Metastatic MEL Feb 2018: Tx initiated	+	44	-100.0	CR	PR (2.1)	Ongoing



	Lesion Description	Baseline
Target Lesion	Exam/Scan Date	2/20/2018
	T1: Lung - Left Upper Lobe	44
	Sum of the Diameters (% Change from Baseline)	-
Overall Response	RECIST 1.1 from Site	-



Patient with 1L Melanoma and Ongoing Response

Age	Sex	Metastatic Diagnosis	PD-L1 Status	Baseline SLD (mm)	Best % Change from Baseline	Overall Response	TTR (mo)	EOT
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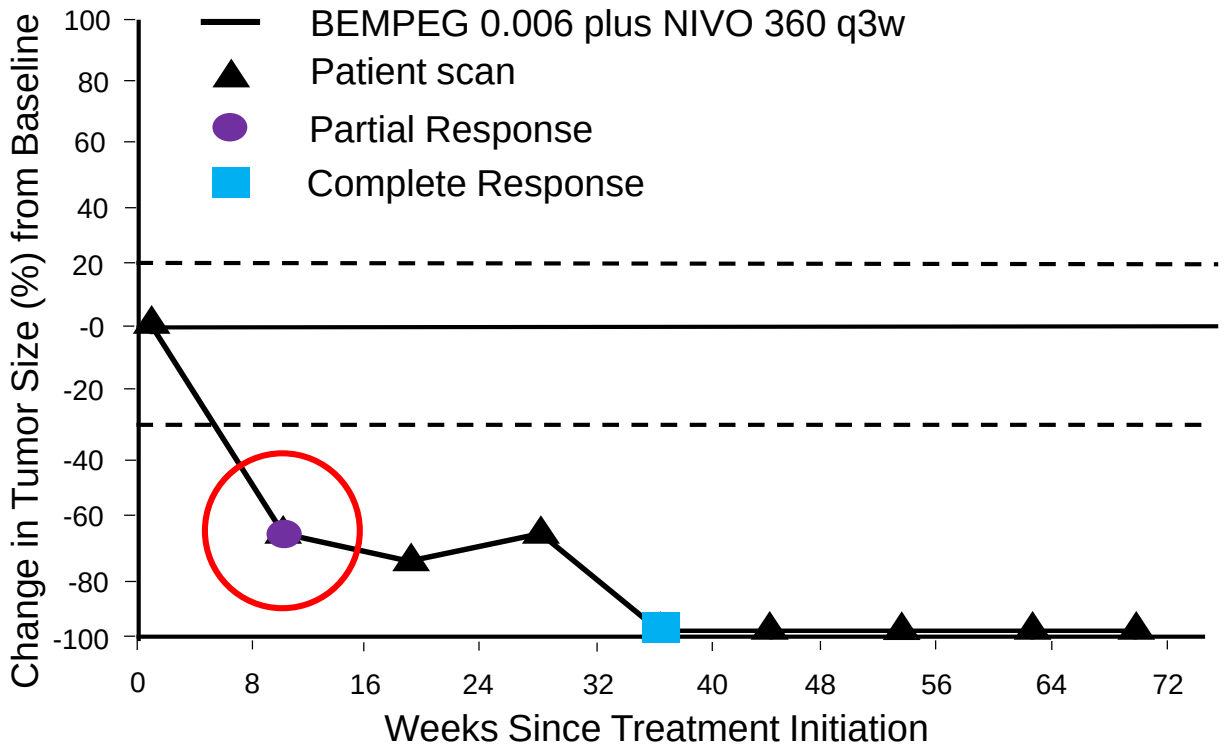
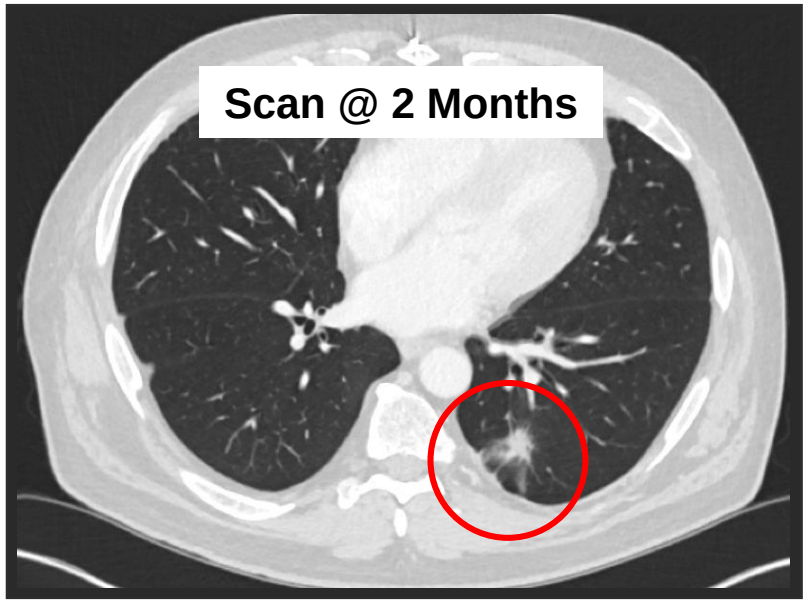
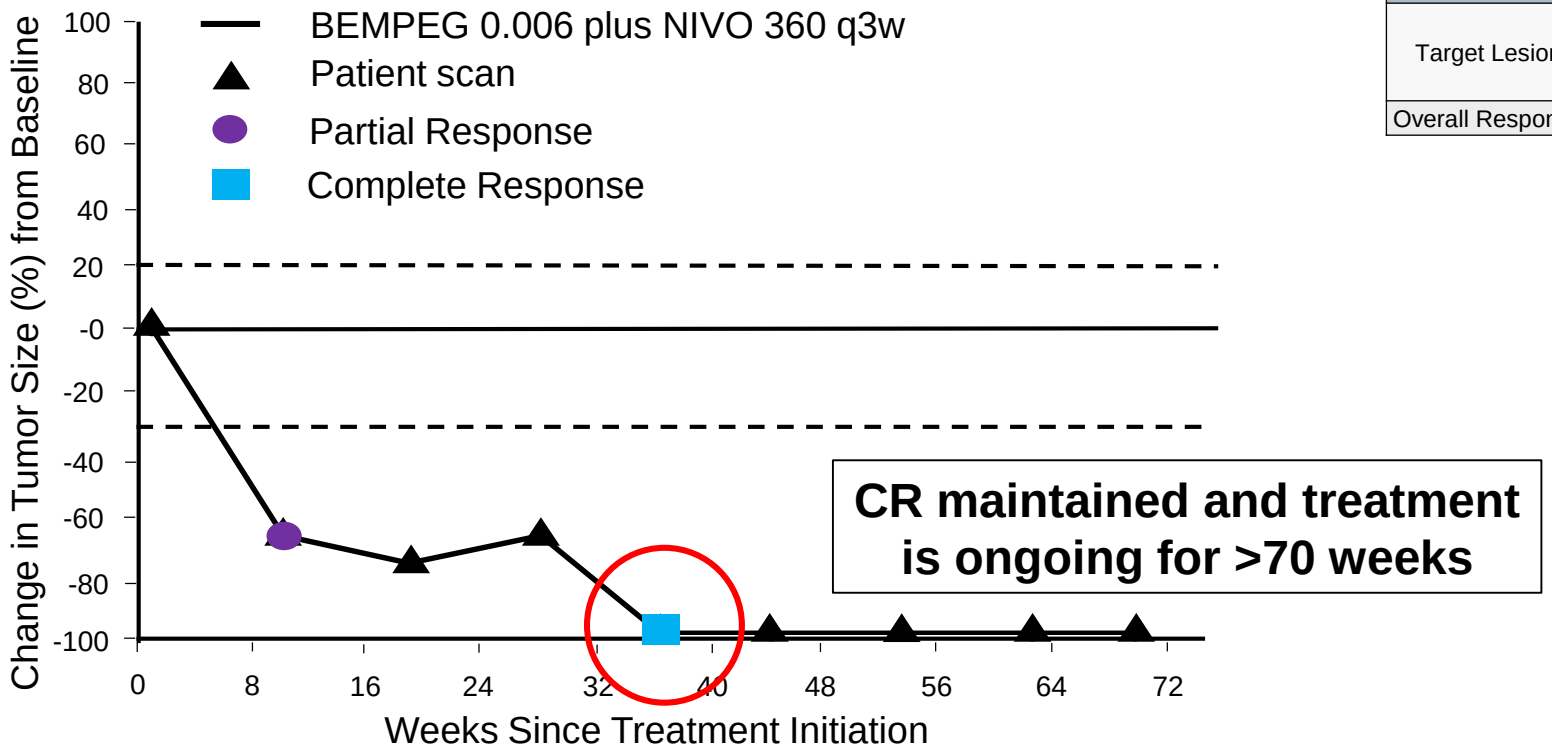


	Lesion Description	Baseline	Scan 1
Target Lesion	Exam/Scan Date	2/20/2018	4/24/2018
	T1: Lung - Left Upper Lobe	44	14
	Sum of the Diameters (% Change from Baseline)	-	-68%
Overall Response	RECIST 1.1 from Site	-	PR



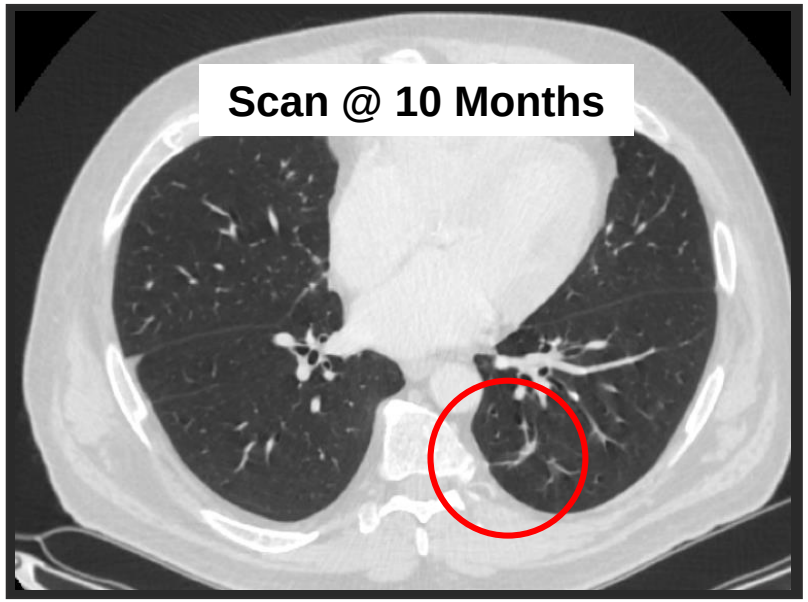
Patient with 1L Melanoma and Ongoing Response

Age	Sex	Metastatic Diagnosis	PD-L1 Status	Baseline SLD (mm)	Best % Change from Baseline	Overall Response	TTR (mo)	EOT
74	Male	Sept 2013: Mel T2aN0, Stage 1B Jan 2018: Metastatic MEL Feb 2018: Tx initiated	+	44	-100.0	CR	PR (2.1)	Ongoing

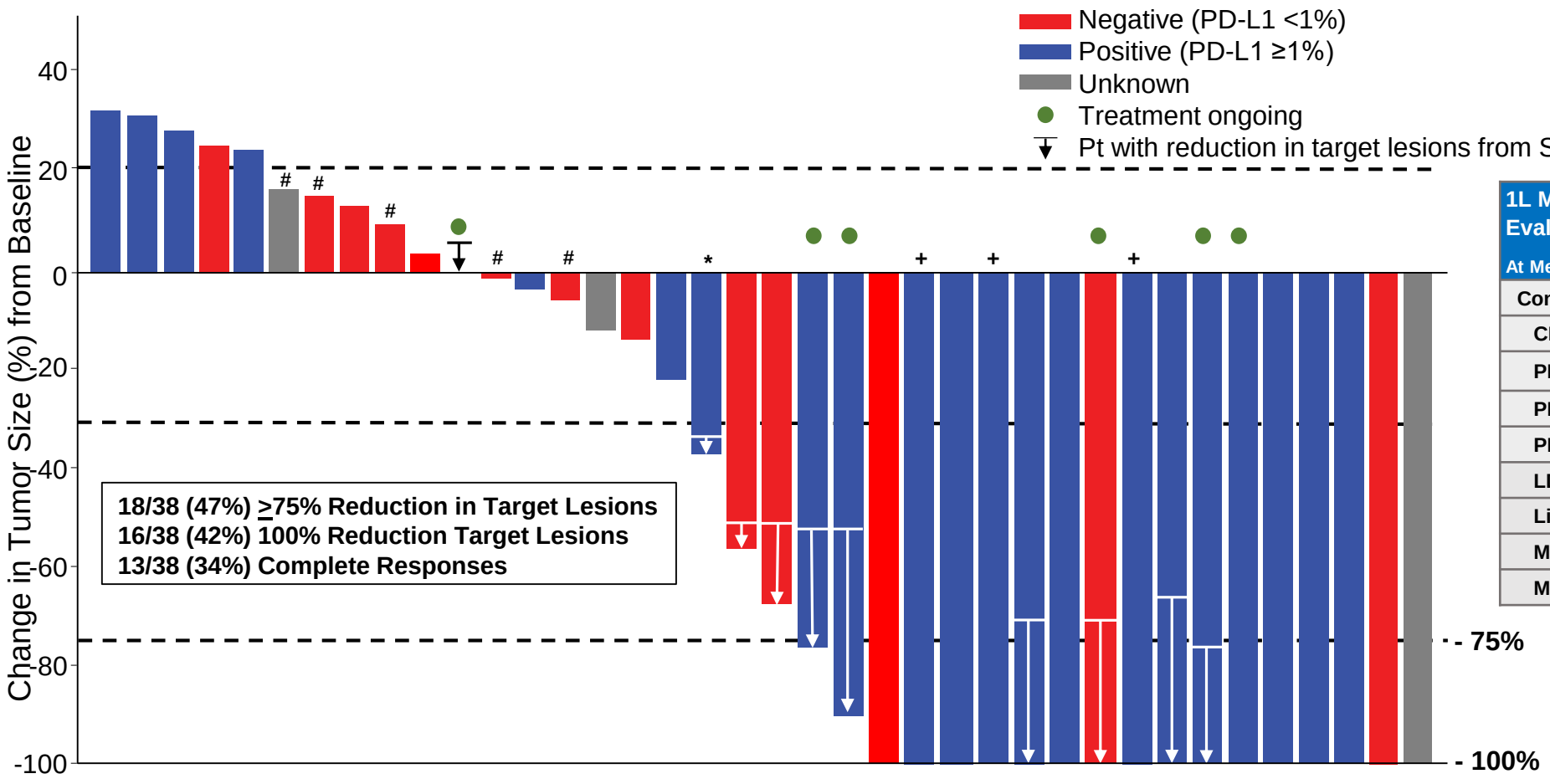


CR maintained and treatment is ongoing for >70 weeks

	Lesion Description	Baseline	Scan 5
Target Lesion	Exam/Scan Date	2/20/2018	12/17/2018
	T1: Lung - Left Upper Lobe	44	0
	Sum of the Diameters (% Change from Baseline)	-	-100%
Overall Response	RECIST 1.1 from Site	-	CR



Stage IV IO-Naïve 1L Melanoma Cohort at RP2D Best Overall Response by Independent Radiology: SITC 2019

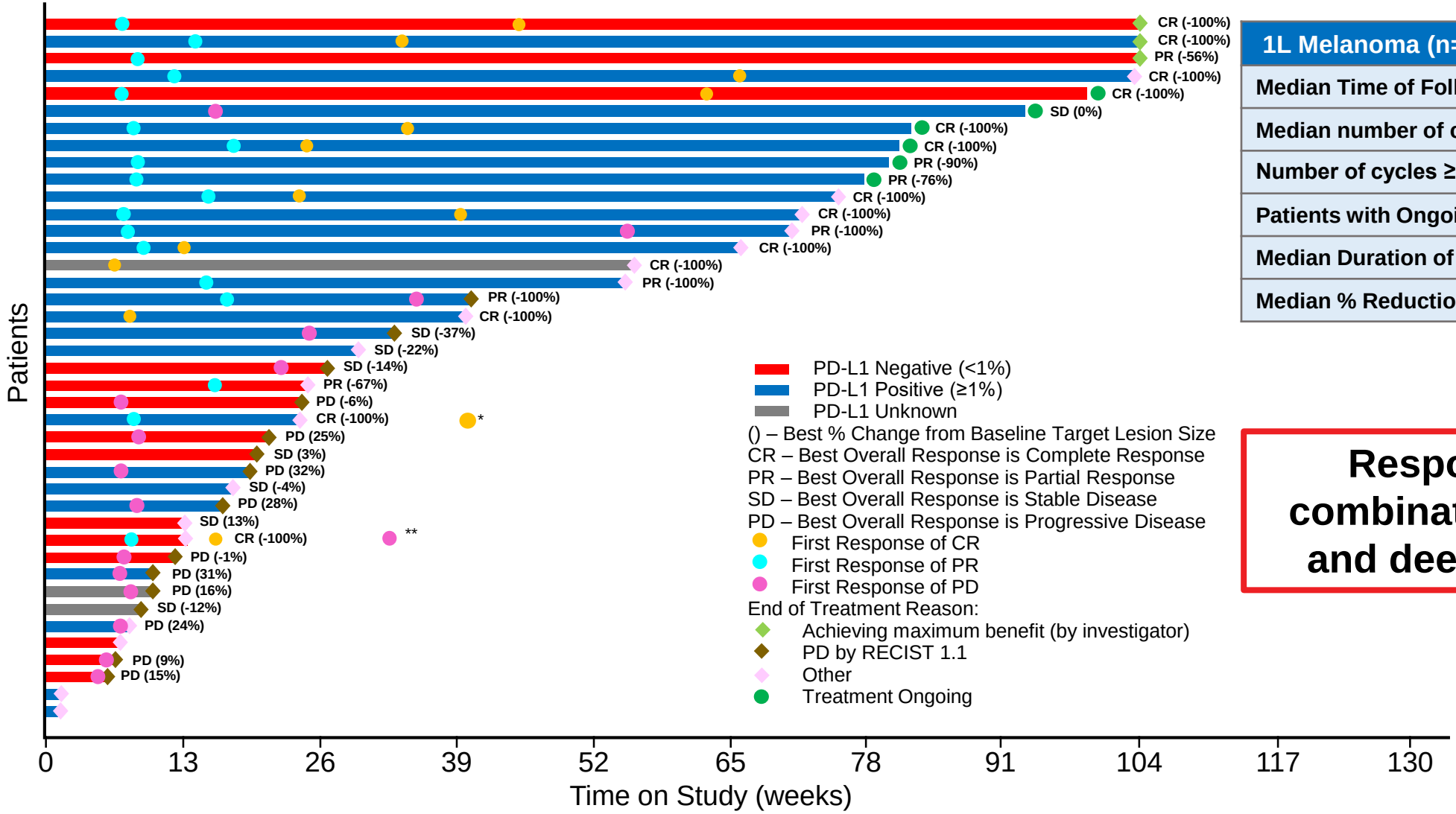


1L Melanoma (n=38 Efficacy Evaluable) At Median 18.6 Months of Follow-up:	Overall Response Rate
Confirmed ORR (CR+PR)	20 (53%)
CR	13 (34%)
PD-L1 negative (n=13)	5 (39%)
PD-L1 positive (n=22)	14 (64%)
PD-L1 unknown (n=3)	1 (33%)
LDH > ULN (n=11)	5 (45%)
Liver metastases (n=10)	5 (50%)
Median Time to Response (mos)	2.0
Median Time to CR (mos)	7.9

All 5 responders with liver metastases experienced CRs

Data Cutoff Date: 25SEP2019. Response evaluable population includes patients who have measurable disease (per RECIST 1.1) at baseline and also have at least one post-baseline assessment of tumor response and (for Parts 2 and 4) meet eligibility criteria are response evaluable. All objective responses are confirmed. #Best overall response is PD due to non-target lesion progression or presence of new lesion; *Best overall response is SD; +Best overall response is PR. CR for target lesion, non-target lesion still present.

Stage IV 1L Melanoma Cohort: ORR 53% with CR 34%

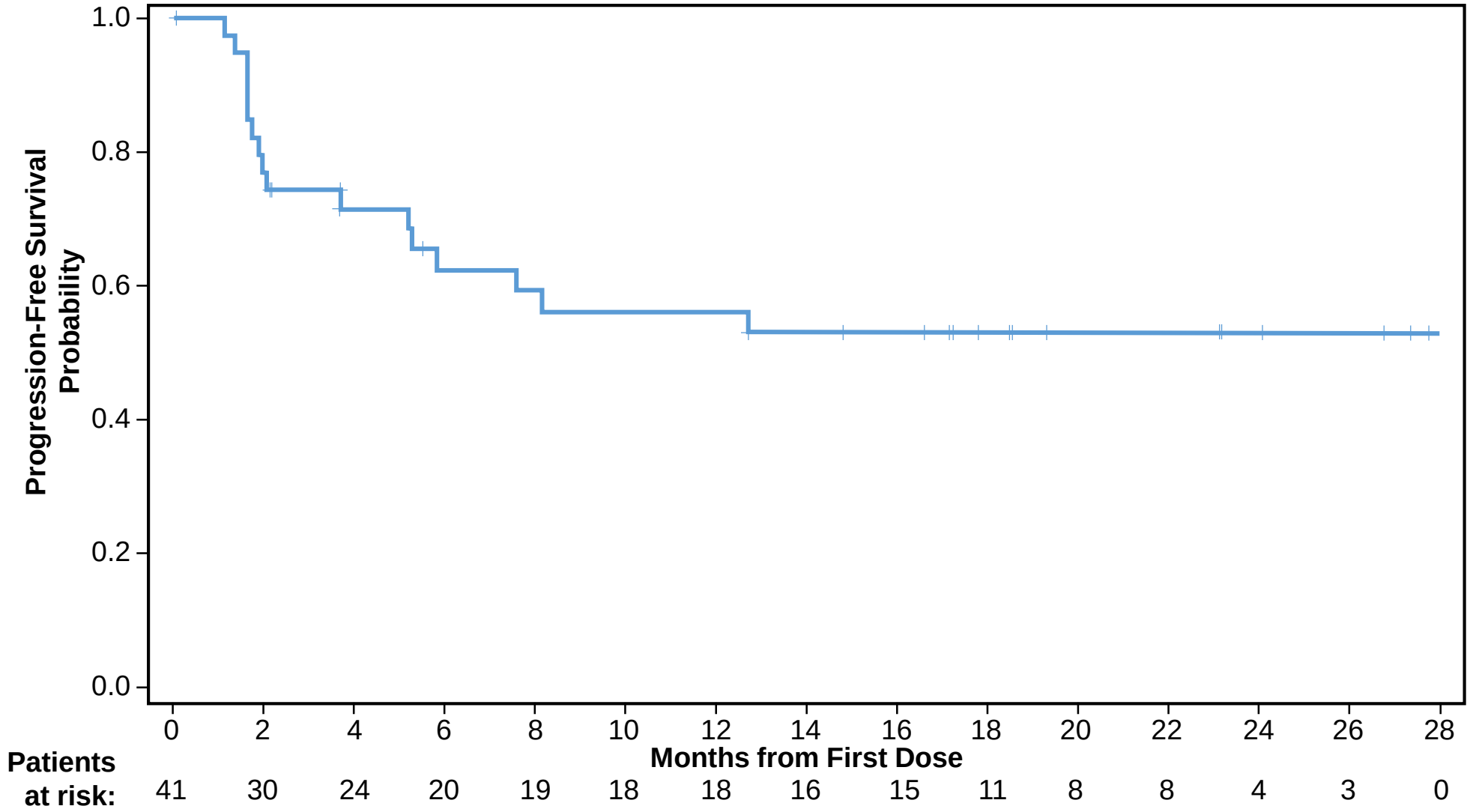


1L Melanoma (n=38)	
Median Time of Follow-Up (months)	18.6
Median number of cycles (range)	9 (1-34)
Number of cycles ≥ 6	29 (70.7%)
Patients with Ongoing Responses	17/20 (85%)
Median Duration of Response (months)	NE
Median % Reduction from Baseline	-61.5%

Responses with the combination were durable and deepened over time

Data Cutoff Date: 25SEP2019. *Pt achieved PR in Mar 2018, EoT in Jul 2018, achieved CR in Oct 2018. **Pt achieved PR in Mar 2018; EoT in May 2018 due to patient decision (QoL issues), achieved CR in May 2018, disease relapse in Sept 2018 due to new lesion (brain)

Kaplan-Meier Estimate of mPFS Not Reached (95% CI: 5.3, NE) at Median Follow-up of 18.6 months



Data Cutoff Date: 25SEP2019

Conclusions

After over 18 months of follow-up, BEMPEG plus NIVO in 1L Melanoma:

- Showed clinical activity with **ORR 53% and CR 34%,** in efficacy-evaluable patients
- Notable response rates were observed **regardless of PD-L1 expression**
- Demonstrated that responses were **durable and deepened over time**
- **Median PFS was not reached**
- BEMPEG plus NIVO is **well tolerated**, and TRAEs are predictable and transient, similar to what was previously reported
- BEMPEG, in combination with NIVO, is being further explored in PIVOT IO 001 Melanoma (NCT03635983), PIVOT-09 RCC (NCT03729245) and PIVOT-10 mUC (NCT03785925)

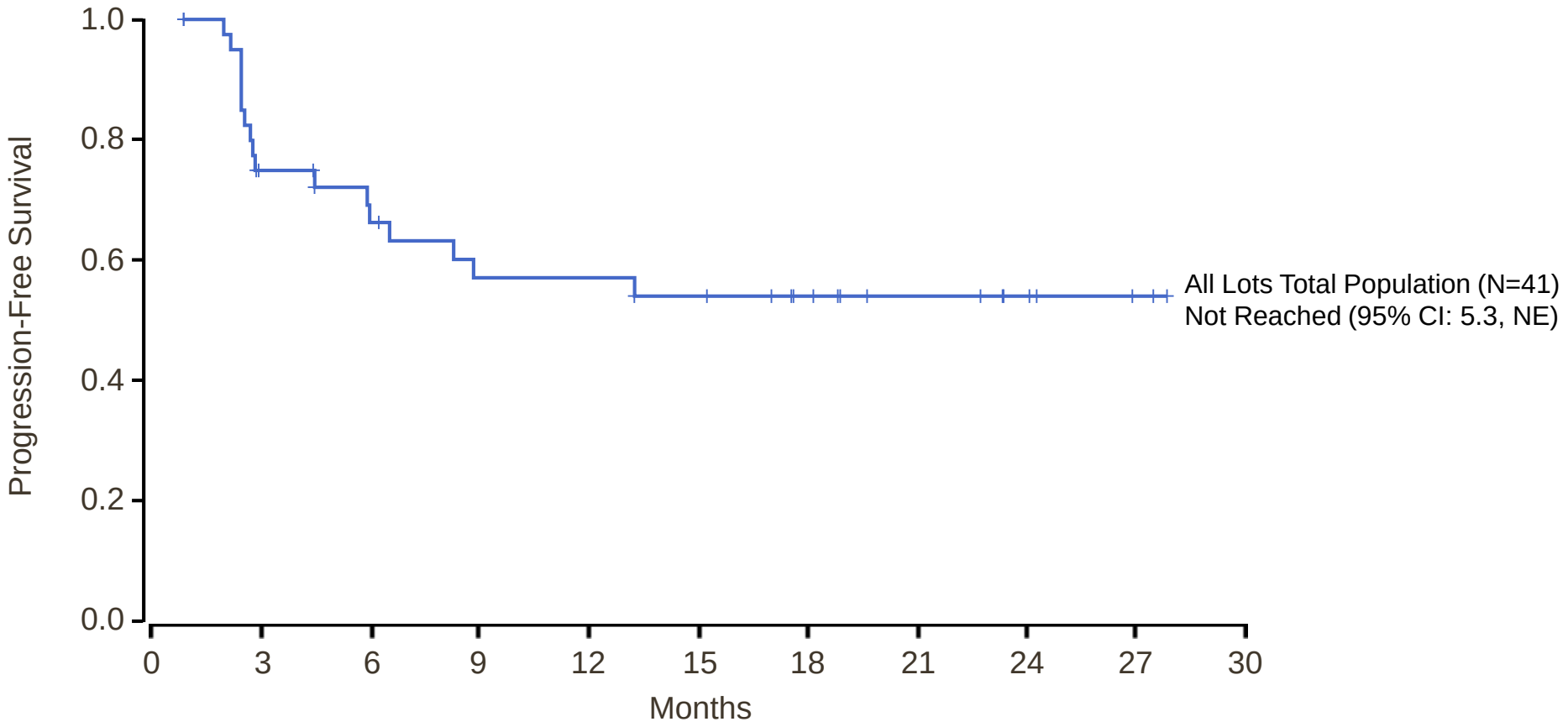
Best Overall Response Rate, CR Rate, and DCR by Manufacturing Lot

	Lots 1&3 N =16 Efficacy Evaluable ≥1 on treatment scan	Lots 2&5 N = 22 Efficacy Evaluable ≥1 on treatment scan
ORR	12 (75.0%)	8 (36.4%)
CR	7 (43.8%)	6 (27.3%)
DCR	15 (93.8%)	13 (59.1%)
Median % Max Reduction of Target Lesions from Baseline Tumor Measurement	-100%	-5%

NEKTAR

*BEMPEG+NIVO data (Sept 25, 2019 BICR Data Cut-off) on file.
**Represents patients who received starting lots of 1 & 3 or 2 & 5

Kaplan-Meier Estimate of mPFS by Manufacturing Lot



*BEMPEG+NIVO data (Sept 25, 2019 BICR Data Cut-off) on file.
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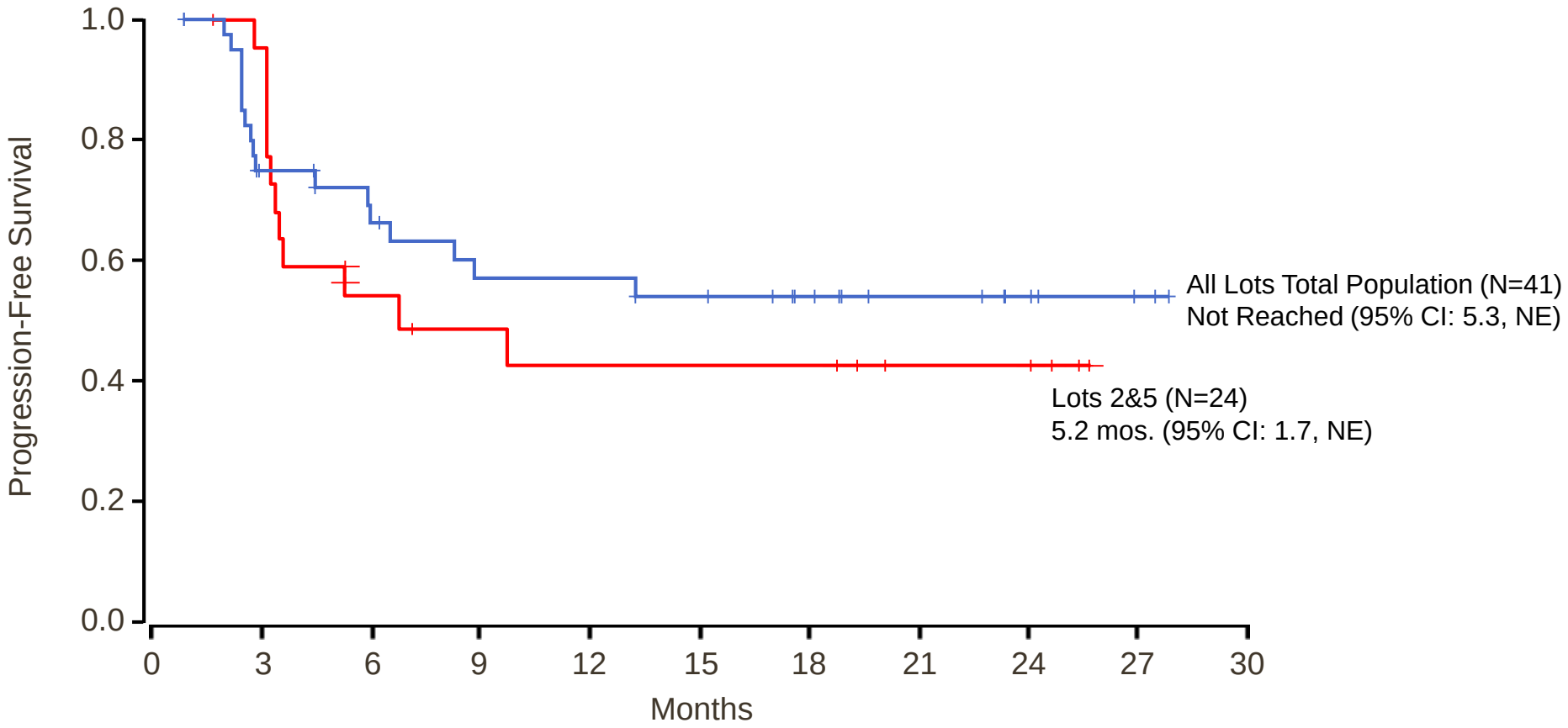
Kaplan-Meier Estimate of mPFS by Manufacturing Lot



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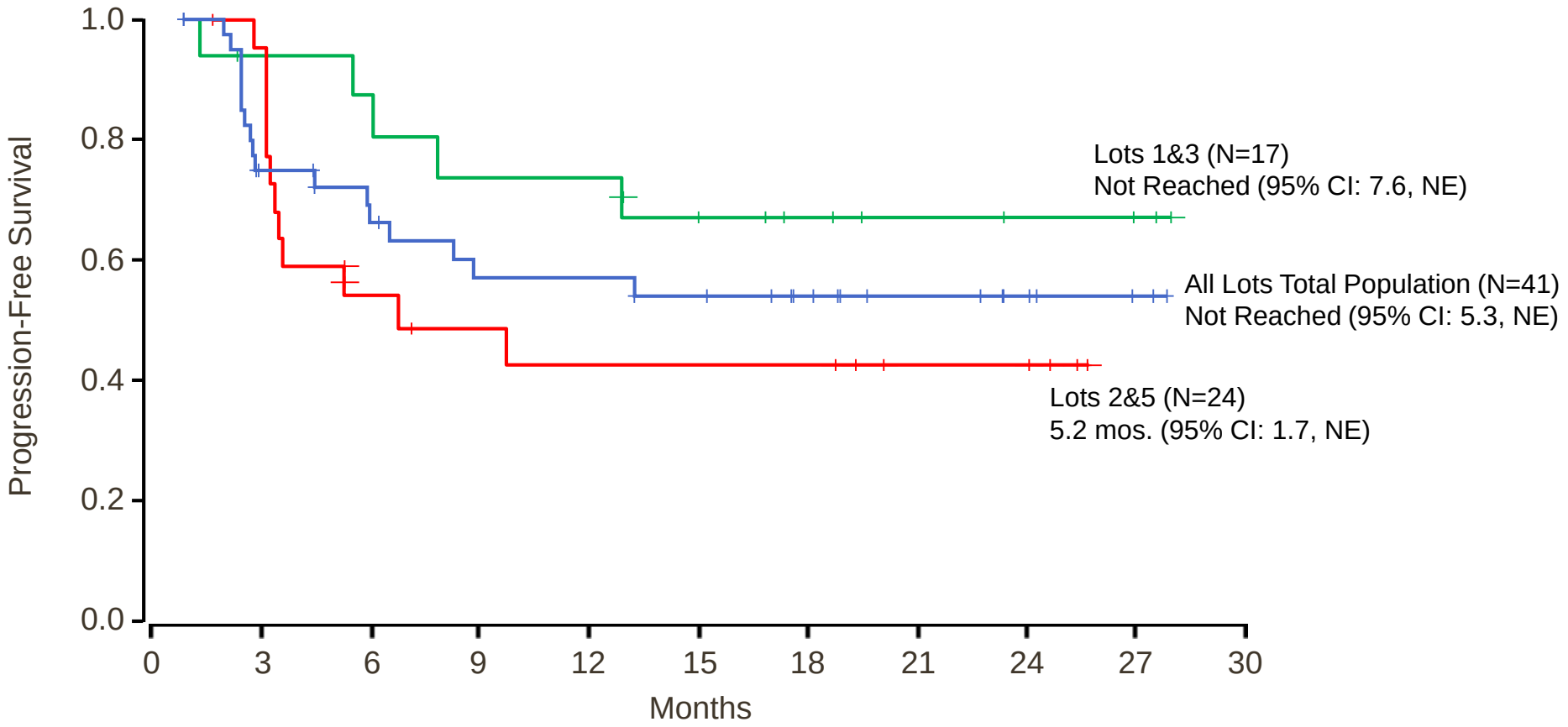
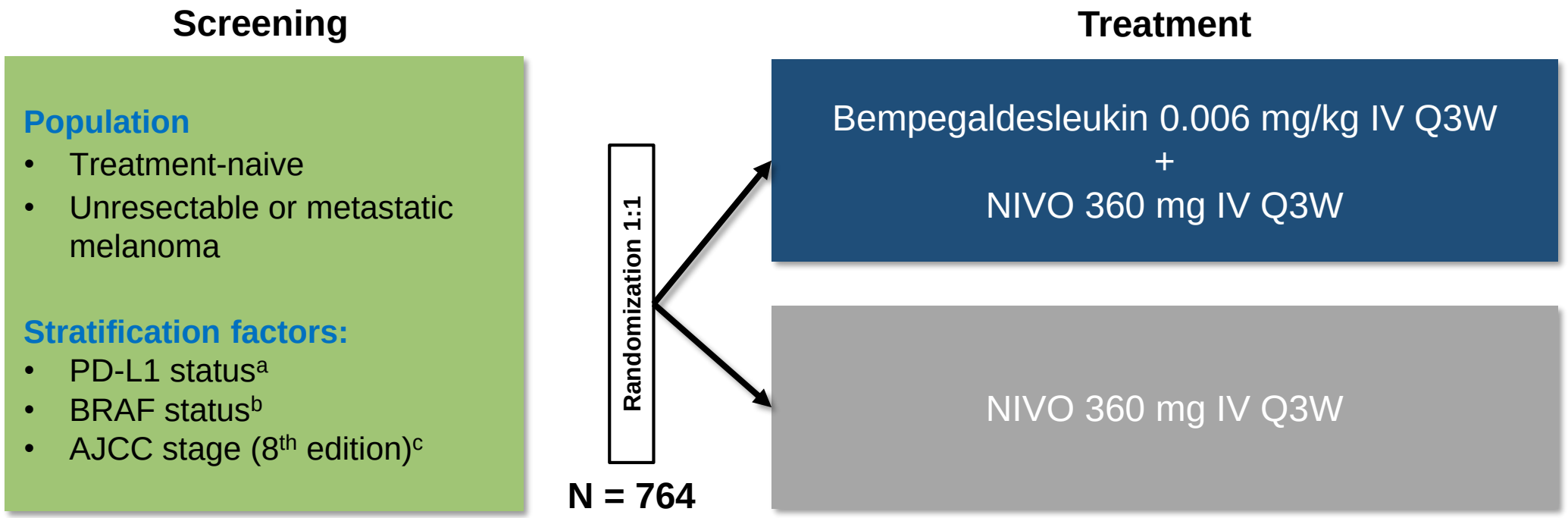
Kaplan-Meier Estimate of mPFS by Manufacturing Lot



*BEMPEG+NIVO data (Sept 25, 2019 BICR Data Cut-off) on file.
**Represents patients who received starting lots of 1 & 3 or 2 & 5

PIVOT IO 001 Study Design

- A Phase 3, Randomized, Open-Label Study of Bempegaldesleukin (BEMPEG) Plus Nivolumab (NIVO) Versus NIVO Monotherapy in Patients With Previously Untreated, Unresectable or Metastatic Melanoma



Primary Endpoints: ORR by BICR, PFS by BICR, OS

[a]Tumor cell PD-L1 expression (≥1% or <1%/Indeterminate) determined using 28-8 pharmDx (Dako, an Agilent Technologies, Inc. company, Santa Clara, CA). [b]V600-mutant vs wild-type. [c]M0/M1 any [0] vs M1 any [1], based on the screening imaging and laboratory test results (lactate dehydrogenase level).

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; IV, intravenous; NIVO, nivolumab; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival;Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors.

Q&A Session