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NEW PATHWAYS TO SMARTER MEDICINE™

5th CRI-CIMT-EATI-AACR Cancer IO Conference

Analyst Call

September 26, 2019

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Today's Speakers

Dr. Sara M. Tolaney

Associate Director, Susan F. Smith Center for Women's Cancers at Dana-Farber Cancer Institute

Dr. Jonathan Zalevsky

Chief Scientific Officer
Nektar Therapeutics

Dr. Mary Tagliaferri

Chief Medical Officer
Nektar Therapeutics

Dr. Stina Singel

Vice President, Oncology Clinical Development
Nektar Therapeutics

Today's Agenda

- Background on Triple Negative Breast Cancer and Treatment
  - Sara M. Tolaney, MD, MPH, Susan F. Smith Center for Women's Cancers at Dana-Farber Cancer Institute
- *"Clinical activity of BEMPEG plus NIVO observed in metastatic TNBC: preliminary results from the TNBC cohort of the Ph1/2 PIVOT-02 study"*
  - Stina Singel, MD, PhD, Nektar Therapeutics
- Presentation of Patient Case Study and Study Conclusions
  - Sara M. Tolaney, MD, MPH, Susan F. Smith Center for Women's Cancers at Dana-Farber Cancer Institute
- Open to Q&A

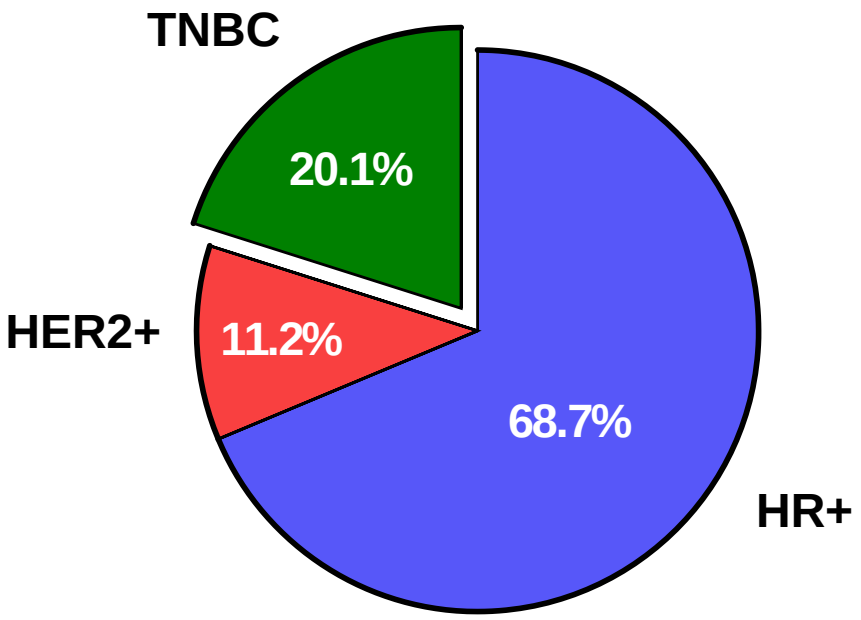
Dr. Sara M. Tolaney

Dr. Sara M. Tolaney joined the staff of Dana-Farber Cancer Institute and Brigham and Women's Hospital in 2008, where she is a medical oncologist and clinical investigator in the Breast Oncology Center. Her research focuses on the development of novel therapies in the treatment of breast cancer.

She received her undergraduate degree from Princeton University in 1998 and her medical degree from UC San Francisco in 2002. She subsequently completed her residency in Internal Medicine at Johns Hopkins University, and fellowships in hematology and medical oncology at Dana-Farber Cancer Institute. She obtained a Masters in Public Health from the Harvard School of Public Health in 2007.

Incidence of Breast Cancer

Breast Cancer Sub-types



Data source: Bioscience Reports (2016) 36, e00432

- Breast cancer is the most common non-cutaneous cancer in the United States (US)
  - 268,600 estimated new cases in women (US) in 2019
    - 15.2% of all new cancer cases
  - 41,760 estimated deaths of women (US) in 2019
    - 6.9% of all cancer deaths
- Breast Cancer is commonly classified by hormone receptor status (HR), as well as human epidermal growth factor receptor 2 (HER2)
  - Triple-Negative Breast Cancer (TNBC) is characterized by tumors that do not express estrogen receptor (ER), progesterone receptor (PR), and lack overexpression of human epidermal growth factor receptor-2 (HER2)
  - TNBC represents up to 20% of all breast cancers worldwide with ~150,000 deaths each year.
- Median overall survival of metastatic TNBC is less than 2 years

Treatment Landscape for Metastatic TNBC

- Because of lack of targeted therapy, standard of care for metastatic TNBC has traditionally been single-agent chemotherapy (such as nab-paclitaxel and weekly paclitaxel)
  - approximately 35% to 45% of patients respond but have a high relapse rate
- CPI monotherapy has shown limited benefit with low objective response rates (ORRs)
  - PD-L1 negative baseline patients ORR: 0% to 5%
  - ≥2L ORR: 5% to 6%
- Checkpoint inhibitor (CPI) therapy in combination with chemotherapy has recently been shown to increase ORR, increase duration of response and prolong survival in metastatic TNBC with PD-L1+ tumors as compared to chemotherapy alone
- More effective immunotherapy combinations are needed to add to CPI, particularly in patients with PD-L1 negative metastatic TNBC
- Approximately 60% of triple negative breast cancer patients have tumors with negative PD-L1 expression leaving a high unmet need for new therapies

1. Adams S, et al. Ann Oncol. 2019;30:397–404.; 2. Dirix LY, et al. Breast Cancer Res Treat. 2018;167:671–686.; 3. Emens LA, et al. JAMA Oncol. 2019;5(1):74.;
4. Schmid P, et al. N Engl J Med. 2018; 379:2108-2121

Single Agent CPI ORR Benchmarks in TNBC

All-lines

Overall

Therapy	Source	N-size	ORR
ATEZO	Emens 2019	(N=115)	9.6%
AVELUMAB	Dirix 2017	(N=58)	5.2%

First-line

Overall

Therapy	Source	N-size	ORR
ATEZO	Emens 2019	(N=21)	24%

PD-L1 (+)

Therapy	Source	N-size	ORR
PEMBRO	Adams 2019	(N=84)	21.5%

PD-L1 (-)

Therapy	Source	N-size	ORR
ATEZO	Emens 2019	NA	0%

Second-line Plus

Overall

Therapy	Source	N-size	ORR
PEMBRO	Adams 2019	(N=170)	5.3%
ATEZO	Emens 2019	(N=94)	6%

PD-L1 (+)

PEMBRO	Adams 2019	(N=105)	5.7%
ATEZO	Emens 2019	(N=91)	12%

PD-L1 (-)

PEMBRO	Adams 2019	(N=64)	4.7%
ATEZO	Emens 2019	(N=21)	0%

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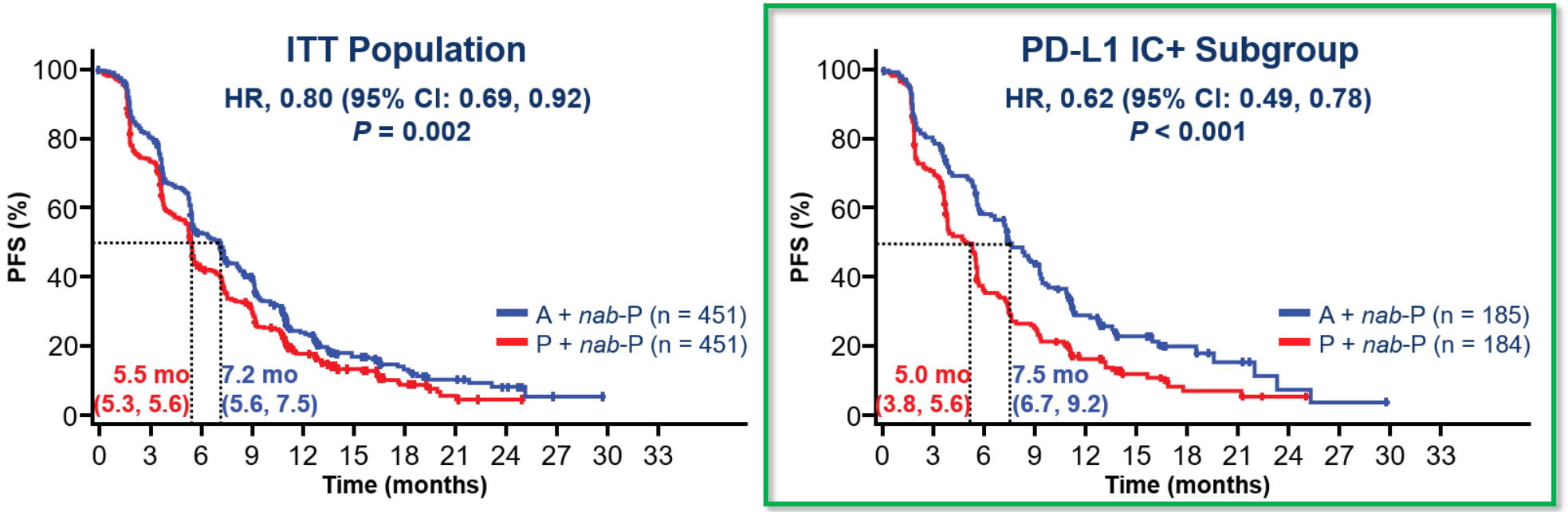
Source: 2019 ASCO IMpassion130 presentation by Dr. Peter Schmid
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative

FDA Approval of Atezolizumab + Nab-Paclitaxel is Limited to the 40% of TNBC Patients with PD-L1+ Tumors

FDA granted accelerated approval of atezolizumab for patients with locally advanced or metastatic triple negative breast cancer that cannot be treated surgically and whose tumors are positive for a protein called PD-L1. (March 2019)

Primary PFS Analysis in the ITT and PD-L1 IC+ Subgroup

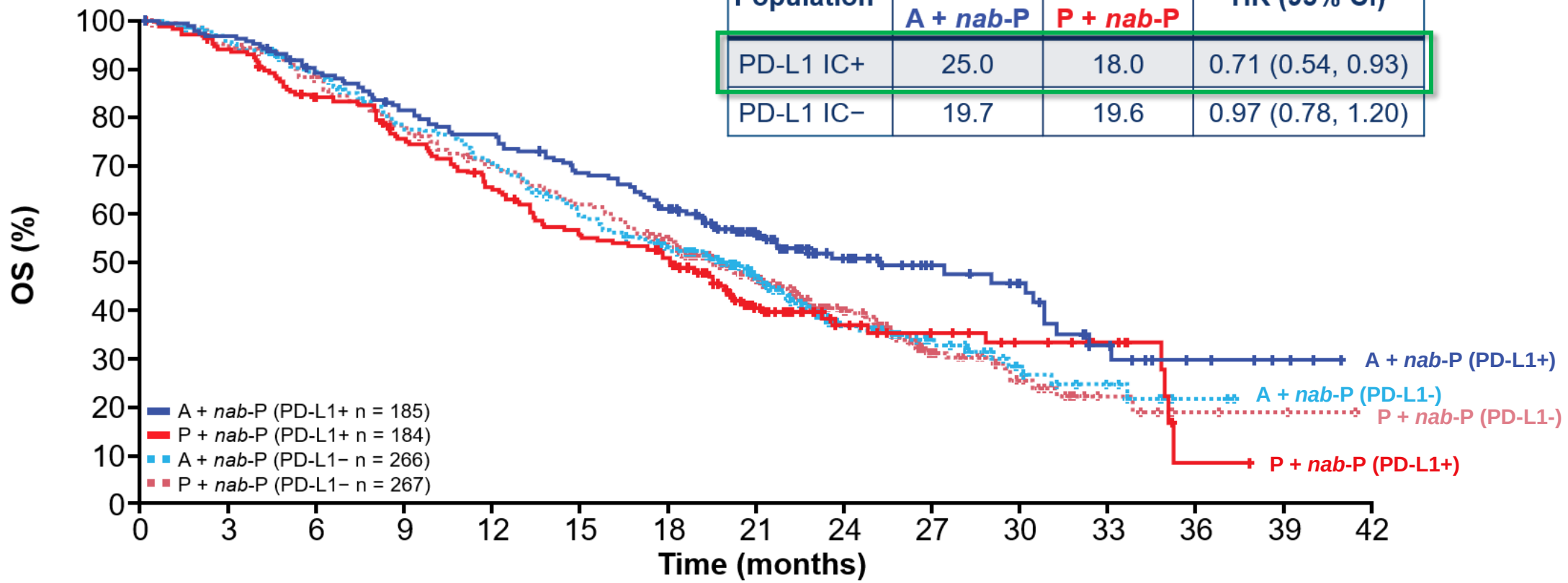


- PFS benefit driven by PD-L1 IC+ patients, as a treatment effect was not observed in PD-L1 IC− patients[1]

Source: 2019 ASCO IMpassion130 presentation by Dr. Peter Schmid
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative

OS Benefit of Atezolizumab + Nab-Paclitaxel is Limited to PD-L1+ Tumors

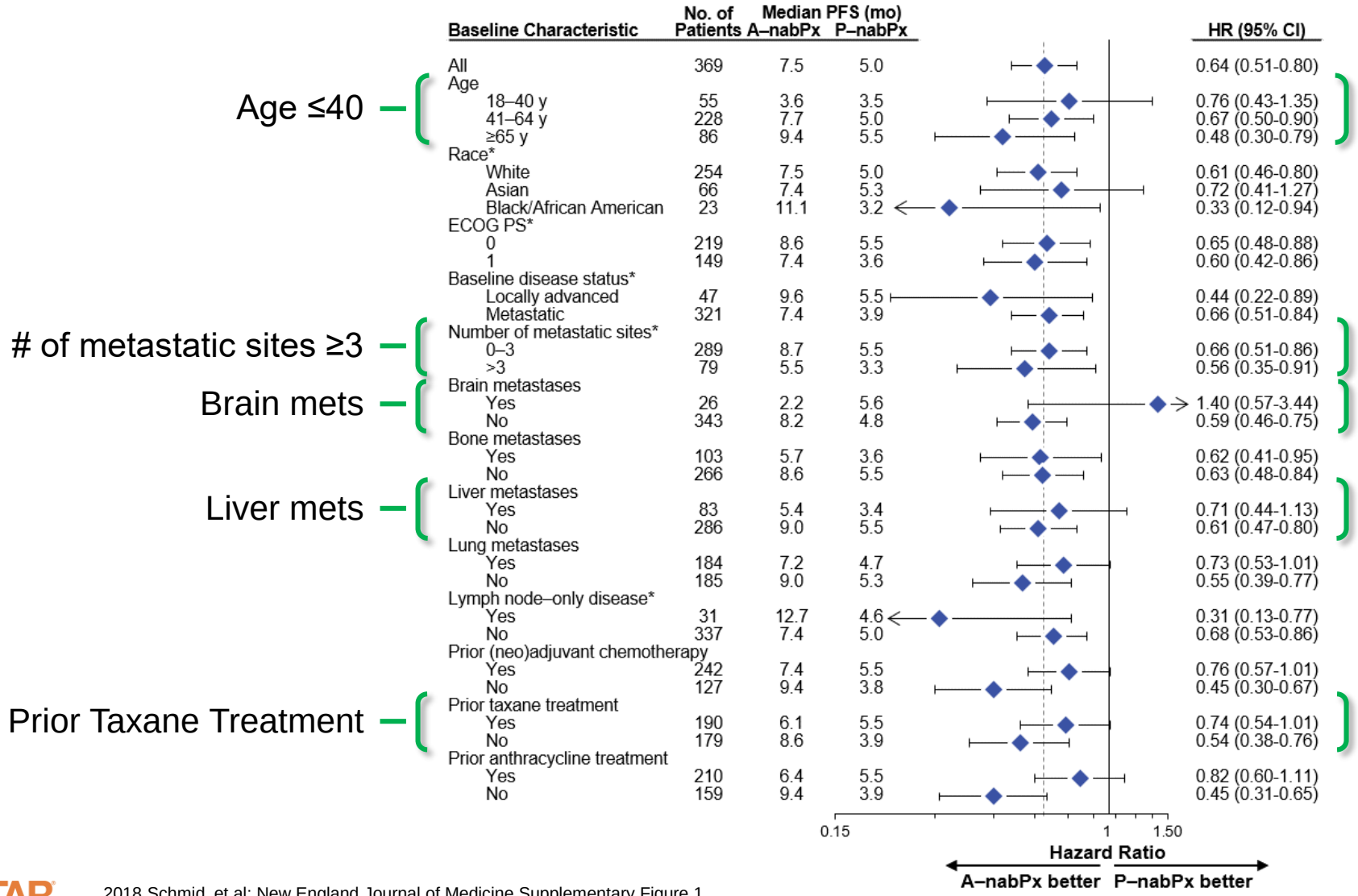
Population	Median OS, mo		HR (95% CI)
	A + *nab*-P	P + *nab*-P	
PD-L1 IC+	25.0	18.0	0.71 (0.54, 0.93)
PD-L1 IC−	19.7	19.6	0.97 (0.78, 1.20)



Approximately 60% of triple negative breast cancer patients have tumors with negative PD-L1 expression leaving a high unmet need for new therapies

Source: 2019 ASCO IMpassion130 presentation by Dr. Peter Schmid
https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-atezolizumab-pd-l1-positive-unresectable-locally-advanced-or-metastatic-triple-negative

Certain Baseline Clinical Factors Associated with Less Benefit from CPI in IMpassion130 PD-L1 Positive Population



2018 Schmid, et al; New England Journal of Medicine Supplementary Figure 1

Clinical activity of BEMPEG plus NIVO observed in metastatic TNBC: preliminary results from the TNBC cohort of the Ph1/2 PIVOT-02 study

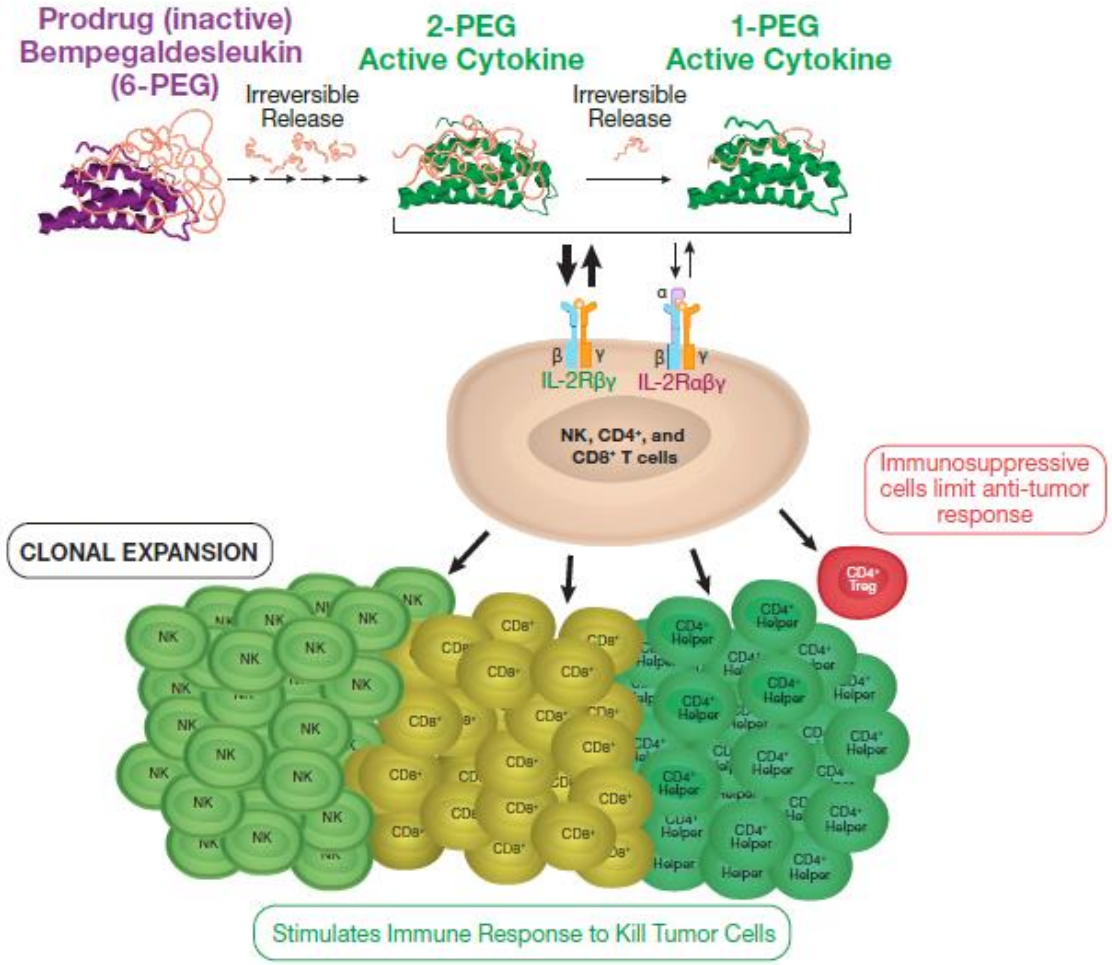
Sara Tolaney[1], Capucine Baldini[2], Alexander Spira[3], Daniel Cho[4], Giovanni Grignani[5], Dariusz Sawka[6], Fabricio Racca[7], Philippe Bedard[8], Annemie Rutten[9], EJ Liao[10], Sunny Xie[10], Sue Currie[10], Wei Lin[10], Mary Tagliaferri[10], Stina Singel[10], Debu Tripathy[11]

1. Dana-Farber Cancer Institute, Boston, MA USA;
2. Institut Gustave Roussy, Villejuif, France;
3. Virginia Cancer Specialists, Fairfax, VA, USA;
4. New York University Langone Medical Center, NYU Cancer Institute, New York, NY, USA;
5. Candiolo Cancer Institute–FPO, IRCCS, Candiolo, Italy;
6. POO Szpital Specjalistyczny w Brzozowie, Brzozów, Poland;
7. Instituto Oncologico Baselga at Hospital Quiron Salud Barcelona, Barcelona, Spain;
8. Princess Margaret Cancer Centre, Toronto, Canada;
9. GZA Ziekenhuizen Campus Sint-Augustinus, Antwerp, Belgium;
10. Nektar Therapeutics, San Francisco, CA, USA;
11. The University of Texas MD Anderson Cancer Center, Houston, TX, USA.

About Bempegaldesleukin (NKTR-214)

Bempegaldesleukin Preferential Signaling Through the IL-2 Receptor Pathway

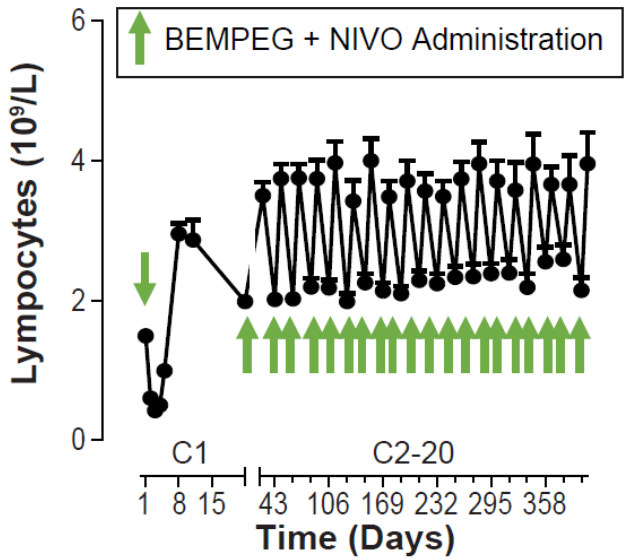
- Bempegaldesleukin (BEMPEG; NKTR-214) is a CD122-preferential IL-2 pathway agonist that has been shown to increase tumor-infiltrating lymphocytes, T cell clonality and PD-1 expression.[1,2]
- BEMPEG combined with the CPI nivolumab (NIVO) has been shown to convert baseline tumors from PD-L1 negative (<1%) to PD-L1 positive (≥1%). [3-5]
- Low levels of baseline tumor-infiltrating lymphocytes (TILs)[6-8] and T cell–inflammation[9] are predictive of a poor response to CPIs.



1. Charych D, et al. PLoS One 2017; 12: e0179431; 2. Bentebibel SE, et al. Cancer Discov May 8 2019 DOI: 10.1158/2159-8290.CD-18-1495; 3. Diab A, et al. Oral presentation at SITC; November 7-11, 2018; Washington, D.C., USA. Abstract #O4; 4. Siefker-Radtke, et al. Poster presentation at ASCO GU; February 13-16, 2019, San Francisco, CA, USA. Abstract #388; 5. Opdivo (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2019; 6. Daud AI, et al. J Clin Oncol 2016; 34:4102-09.; 7. Daud AI, et al. J Clin Invest 2016;126:3447-52.; 8. Tumeh PC, et al. Nature 2014;515:568-71.; 9. Ayers, https://doi.org/10.1172/JCI91190

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

Increase in Lymphocytes with Every Treatment Cycle*

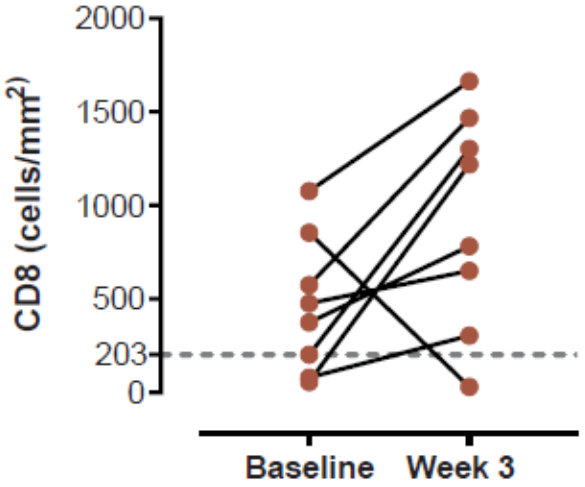


Lymphocyte effects of the BEMPEG + NIVO combination are driven by BEMPEG, as a similar pattern is observed with monotherapy[1]

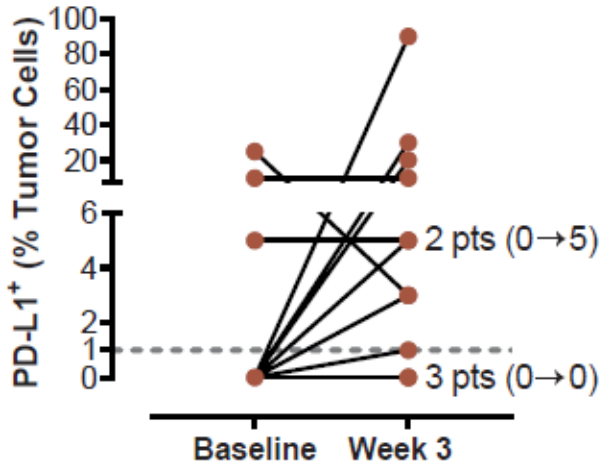
*Lymphocyte levels were obtained from standard hematology analyses. All efficacy evaluable melanoma (n=38) and mUC (n=27) in the BEMPEG + NIVO combination enrolled in PIVOT-02 (n=65, Mean+SD) were included in the analyses.

On-Treatment Increase in TIL and PD-L1

Change in CD8 Infiltrate in MEL[3,^]



PD-L1 Conversion in UC[4,#]



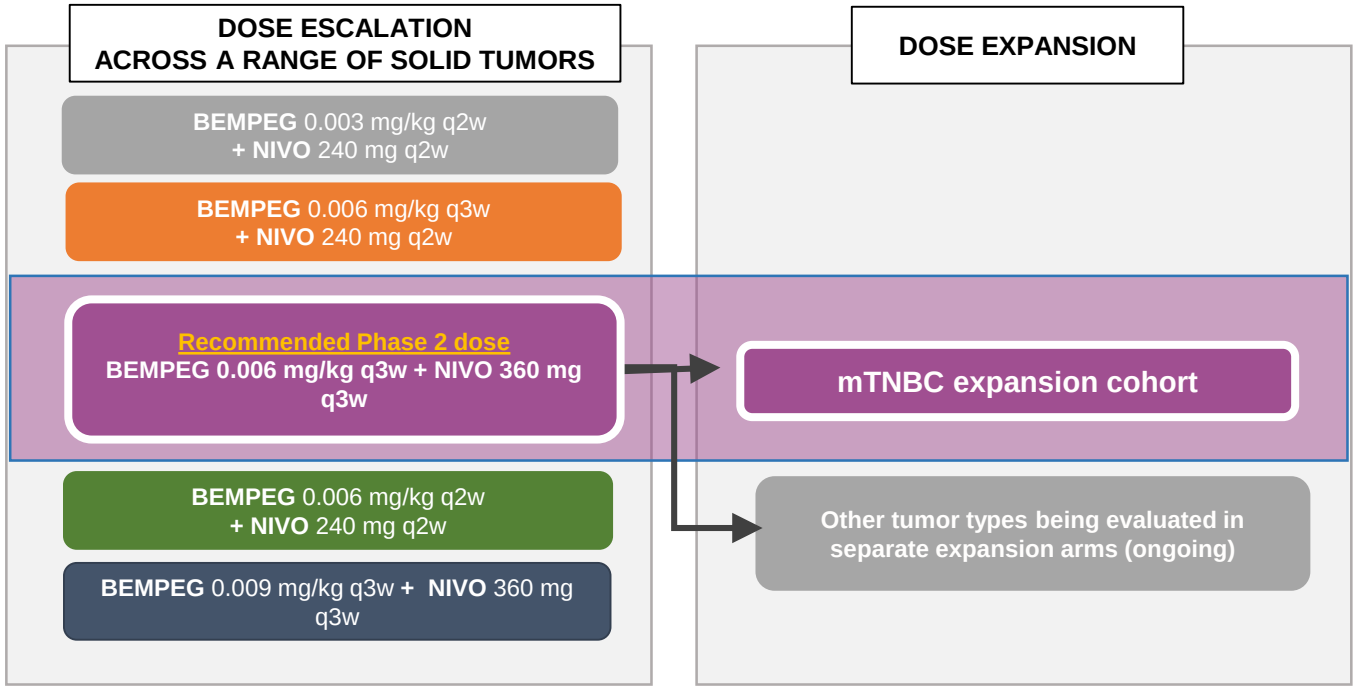
^IHC for CD8 was obtained by standard methods. All patients with first-line melanoma (1L MEL) with matched Baseline and Week 3 biopsy (n=8) were included in the analyses.
#All patients with 1L urothelial carcinoma (UC) with matched Baseline and Week 3 biopsy (n=13) at time of data cut were included and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

Background

- PIVOT-02 is a multicenter, Phase 1/2 study evaluating BEMPEG plus NIVO and includes a cohort of patients with metastatic TNBC
- PIVOT-02 recently reported preliminary clinical and safety data for patients with stage IV metastatic melanoma[1] and metastatic UC[2], demonstrating BEMPEG plus NIVO was well tolerated and demonstrated promising clinical benefit
- Breakthrough Therapy Designation: July 29th, 2019 from the FDA for patients with previously untreated, unresectable or metastatic melanoma
- **Here, we report the first findings BEMPEG plus NIVO in the metastatic TNBC cohort (data cut-off, July 1, 2019)**

1. Diab A, et al., Oral presentation at SITC; 2. Siefker-Radtke, et al., Poster Presentation at ASCO GU

PIVOT-02 Study Schema



Key mTNBC Patient Characteristics

- **Measurable disease per RECIST v1.1**
- **Immuno-oncology therapy naive**
- **ECOG PS 0-1**
- **As of July 1, 2019, 38 patients were efficacy evaluable defined as patients with ≥1 post-baseline tumor assessment (5 patients were not evaluable: 3 had clinical progression and 2 deaths due to progressive disease before the first tumor assessment)**

ECOG PS: Eastern Cooperative Oncology Group Performance Score; RECIST: response evaluation criteria in solid tumors

- Baseline immunohistochemistry (IHC) analysis for PD-L1 was performed using 28-8 pharmDx (Dako) and defined as PD-L1 negative (<1% tumor cell expression) and PD-L1 positive (≥1% tumor cell expression)
- In addition to PD-L1 status, other predictive or prognostic clinical factors assessed included age, disease-free interval (DFI), LDH, number and type of metastatic sites, and prior taxane
- Early relapsers were defined as first line (1L) pts with a metastatic relapse within 12 months of last chemotherapy in early stage setting
- Tumor assessments were performed at screening and every 8 weeks (± 7 days) by Investigator and Independent Central Radiology (ICR)
- Safety and tolerability were assessed by adverse event (AE) analysis reported by CTCAE v4.03

Baseline Patient Demographics and Disease Characteristics

	Total N=43
Age (years)	
Median (Range)	54 (33-76)
≤40	9 (20.9%)
41-64	24 (55.8%)
≥65	10 (23.3%)

ECOG Performance Status	
0	25 (58.1%)
1	18 (41.9%)

PD-L1 status*	
Positive ≥1%	14 (32.6%)
Negative <1%	25 (58.1%)
Unknown	4 (9.3%)

LDH‡	
Normal	25 (58.1%)
Elevated ≥ 1x ULN to <2.5x ULN	13 (30.2%)
Elevated ≥ 2.5x ULN	4 (9.3%)
Unknown	1 (2.3%)

	Total N=43
Line of Metastatic Treatment on Study	
1L	16 (37.2%)
1L, early relapse	8 (18.6%)
2L	26 (60.5%)
3L	1 (2.3%)

Number of Metastatic Organ Sites	
1	8 (18.6%)
2	15 (34.9%)
3	10 (23.3%)
≥4	10 (23.3%)

Sites of Metastatic Disease	
Brain†	2 (4.7%)
Liver	10 (23.3%)
Lung	20 (46.5%)
Bone	10 (23.3%)
Lymph node only	4 (9.3%)

*PD-L1 status determined by 28-8 diagnostic on fresh or archival tumor biopsy
†‡Based on maximum value prior to dosing
†Both pts treated with stereotactic radiation prior to being on study

Treatment-Related Adverse Events (TRAEs) at RP2D

Preferred Term[1]	Total (N=43)[a]
All Treatment-Related Grade 3-4	**11 (25.6%)**
Hypotension	**2 (4.7%)**
Dehydration	**2 (4.7%)**
Myalgia	**2 (4.7%)**
Amylase increased, arthralgia, asthenia, embolic stroke, ejection fraction decreased, flu-like symptoms*, hyponatremia, lipase increased, lymphocyte count decreased, nausea, syncope, vomiting	**1 each (2.3%)**
Treatment-Related, all Grades (>25% listed below)	
Flu-like symptoms**	**34 (79.1%)**
Pruritis	**23 (53.5%)**
Rash**	**23 (53.5%)**
Fatigue	**19 (44.2%)**
Nausea	**18 (41.9%)**
Any imAE (Grade 3)	**1 (2.3%)*** **
Patients who discontinued any study treatment due to a TRAE	**2 (4.7%)**

The combination of BEMPEG plus NIVO is well tolerated, and TRAEs are similar to what was previously reported.[1,2]

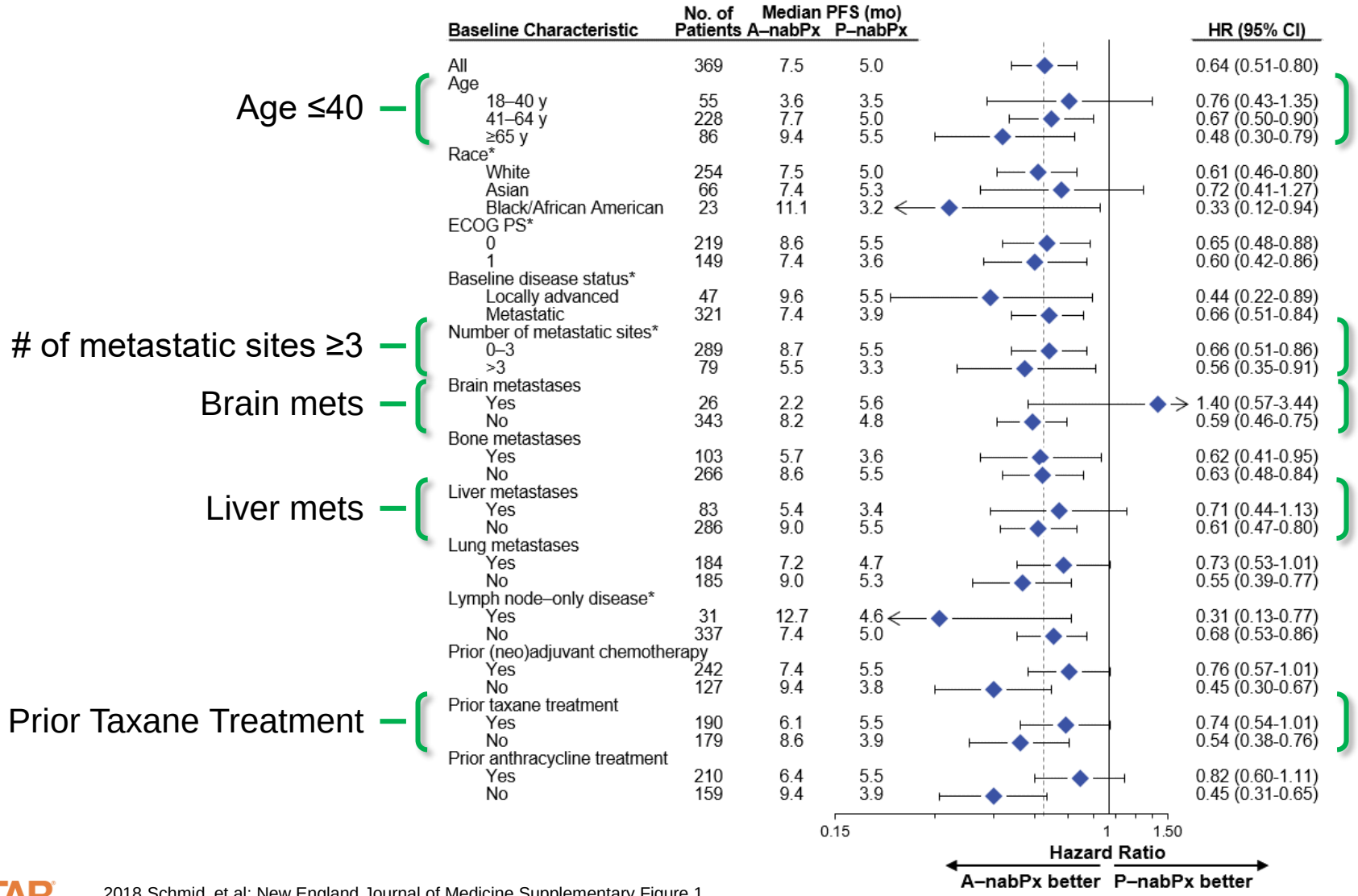
[1] Patients are only counted once under each preferred term using highest grade. [a]N = 43, safety population defined as patients with ≥ 1 dose of study treatment.
*Flu-like symptoms included the following MedDRA PTs: chills, influenza, influenza-like illness, pyrexia.
**Rash included the following MedDRA PTs: erythema, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash maculovesicular, rash papular, rash pruritic, rash pustular, rash vesicular, exfoliative rash. [#] One patient discontinued treatment due to arthralgia. Another patient discontinued treatment due to alkaline phosphatase increased, hypomagnesemia, hyponatremia, lymphocyte count decreased.
***One patient had grade 3 arthralgia

ORR by Investigator Assessment in Efficacy-Evaluable Population

	PDL1 Negative (n=22)	PDL1 Positive (n=12)	PDL1 Unknown (n=4)	Total (N=38)
ORR (CR+PR)	3 (14%)	2 (17%)	0	5 (13%)
CR	0	0	0	0
PR	3 (14%)	2 (17%)	0	5 (13%)
SD	8 (36%)	4 (33%)	0	12 (32%)
DCR (CR+PR+SD)	11 (50%)	6 (50%)	0	17 (45%)
CBR (CR+PR or SD ≥24 weeks)	4 (18%)	3 (25%)	0	7 (18%)
PD	11 (50%)	6 (50%)	4 (100%)	21 (55%)

- All 5 responders had received 1 line of chemotherapy for metastatic TNBC prior to study entry
  - ORR ≥2L was 21% (5/24) with an ORR of 23% (3/13) in PD-L1 negative

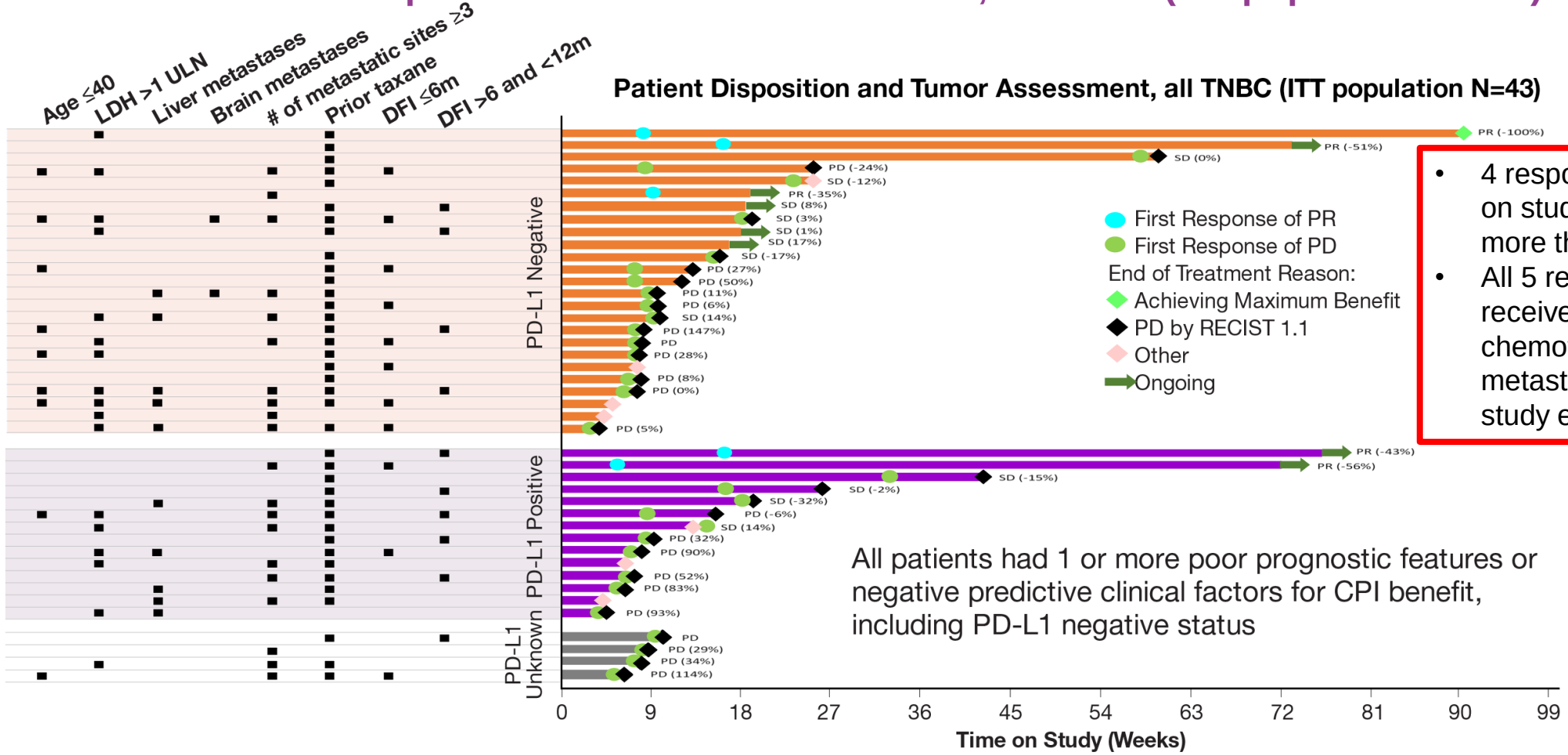
Certain Baseline Clinical Factors Associated with Less Benefit from CPI in IMpassion130 PD-L1 Positive Population



2018 Schmid, et al; New England Journal of Medicine Supplementary Figure 1

Clinical Benefit of BEMPEG + NIVO Appears to Be Regardless of PDL1 Status*

Patient Disposition and Tumor Assessment, all TNBC (ITT population N=43)

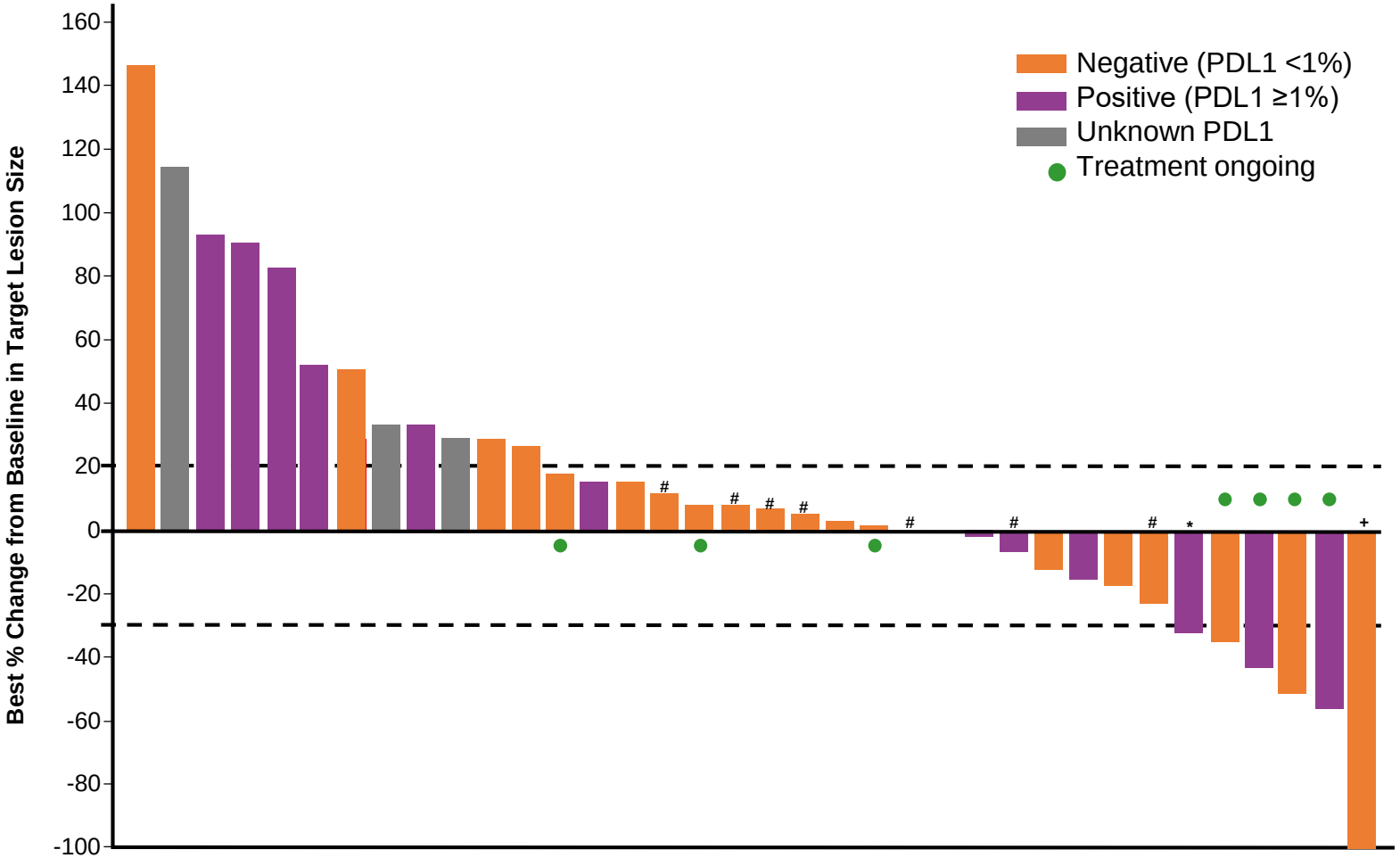


- 4 responders have been on study treatment for more than 72 weeks
- All 5 responders had received 1 line of chemotherapy for metastatic TNBC prior to study entry

*Per protocol, PD-L1 testing was conducted with 28-8 pharmDX
End of treatment is based on date and reason for discontinuation of both BEMPEG and nivolumab, whichever is later. Other reasons for end of treatment include 4 clinical progression, 2 death and 1 due to secondary malignancy. One 1L TNBC patient had tamoxifen as anti-cancer treatment for metastatic treatment.
DFI (disease free interval), defined as early relapsers who are first line (1L) pts with a metastatic relapse within 12 months of last chemotherapy in early-stage setting.

Clinical Benefit of BEMPEG + NIVO by Investigator Assessment (median follow-up 5.8 months)

Best % Change from Baseline in Target Lesion Size, RP2D TNBC (Efficacy Evaluable Population N=38**)



Of the 5 responders:

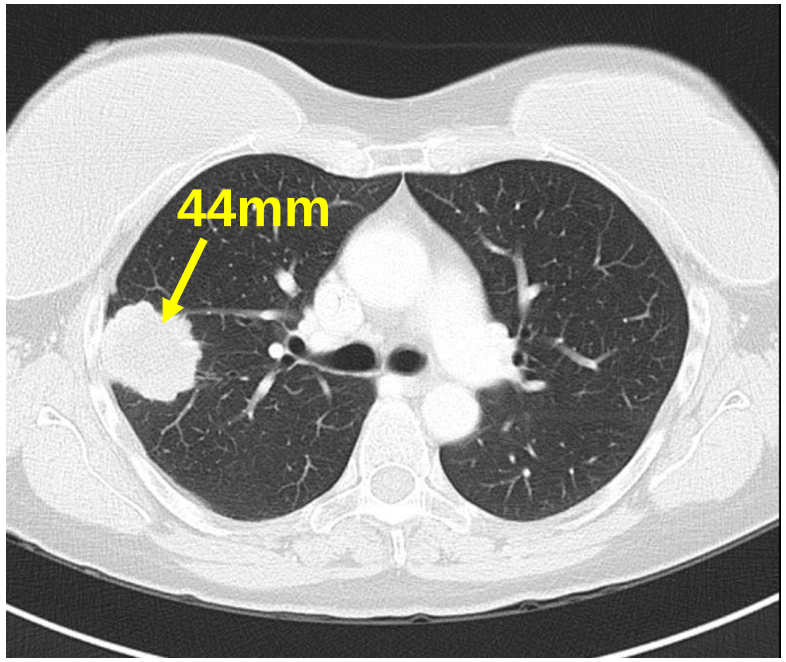
- 4 of 5 responders are ongoing treatment
- 1 responder no longer on treatment achieved maximal clinical benefit and response is continuing at last follow-up

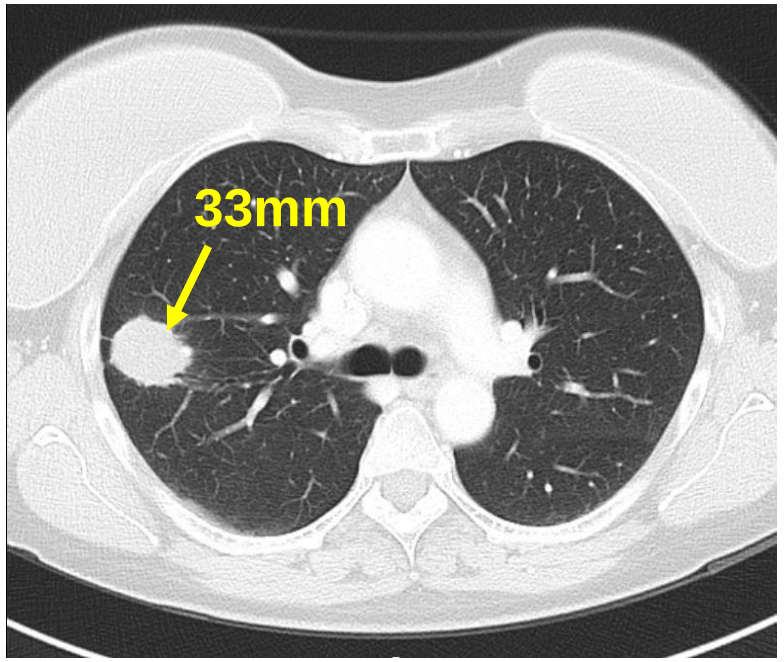
Best overall response is PD due to non-target lesion progression or presence of new lesion; *: Best overall response is SD. + Best overall response is PR. CR of lung lesion, 3 out of 4 bone lesions absent; **2 pts are not presented in the plot due to incomplete target lesion measurements.; 1 pt with unequivocal progression, with multiple back lesions; 1 pt with unequivocal progression of non-target lesions and new pleural deposits.

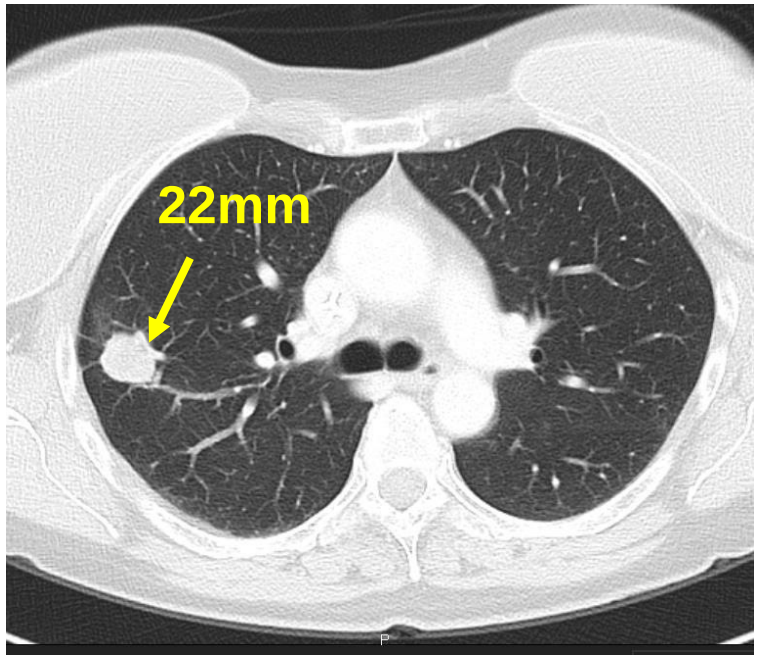
Patient Case Study: 49 Year Old Woman with Metastatic TNBC Refractory to Prior Chemotherapy

- Initial diagnosis: Stage II ER+PR-HER2- in March 2016
  - Mastectomy followed by adjuvant epirubicin/cyclophosphamide and paclitaxel
- Early relapse with metastatic TNBC at only 6 months after completion of chemotherapy in the early disease setting
  - Progressive disease after only 2 months of first-line metastatic treatment with carboplatin plus gemcitabine
- Enrolled to PIVOT-02 study of BEMPEG plus NIVO in January 2018
  - At time of enrollment, patient had pleuritic chest pain requiring medication and was unable to work; tumor biopsy tested PD-L1 positive

Scan History: Lung Lesion (Right Upper Lobe)







Baseline

8 weeks

87 weeks (ongoing treatment and response)

25% reduction of target lesions

50% reduction of target lesions

Target lesion reduction continues (reduced by 50% to date)

Patient Case Study: 49 Year Old Woman with Metastatic TNBC Refractory to Prior Chemotherapy

- Therapy was well tolerated in this patient with any AEs being treated with Tylenol for flu-like symptoms and low dose of prednisone for mild arthralgia
- Patient has returned to work
- PR occurred at second on-treatment scan and continues to deepen over time
- Treatment is ongoing with prolonged response over 18 months

Study Conclusions in Metastatic TNBC

- Clinical activity and prolonged responses were observed in patients with metastatic TNBC who were treated with BEMPEG plus NIVO
    - notably in pts with poor prognostic features or negative predictive clinical factors (LDH, # of metastatic sites, prior taxane, early relapsers) for CPI benefit, including those who were baseline PD-L1 negative
- BEMPEG plus NIVO was well tolerated, with a manageable safety profile
- These data support the future development of BEMPEG plus CPI, with chemotherapy, in metastatic TNBC pts who are baseline PD-L1 negative, have poor prognostic features, and/or are relapsed/refractory to prior chemotherapy regimens
- This study (NCT02983045) and registrational studies in other solid tumor settings are ongoing

Q&A Session