Advances in the Treatment of Triple-Negative Metastatic Breast Cancer

Mohammad Jahanzeb, MD, FACP

Professor of Clinical Medicine, Hematology-Oncology

Medical Director, UM Sylvester Deerfield Campus

Associate Center Director for Community Outreach

Sylvester Comprehensive Cancer Center

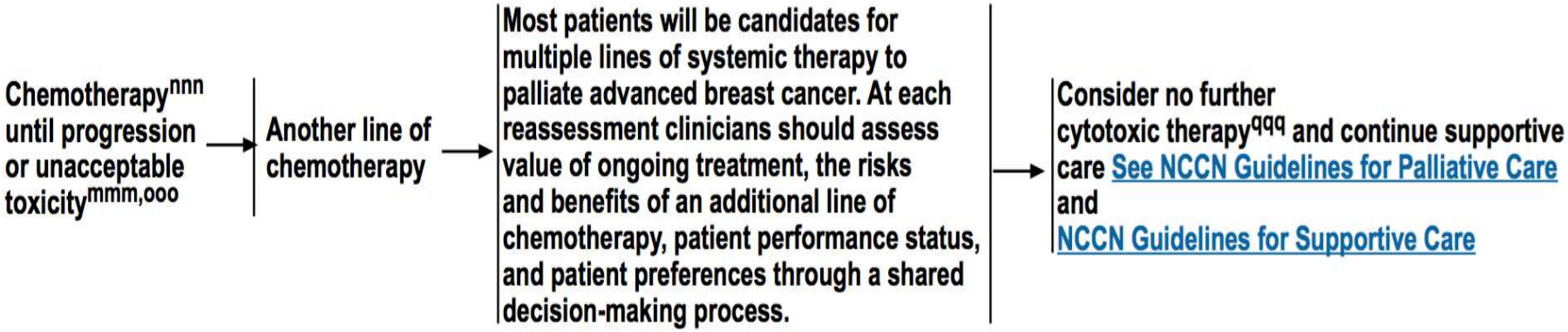
University of Miami, Miller School of Medicine

Triple-negative breast cancer (TNBC)

- Patients with advanced or metastatic TNBC experience poor outcomes relative to patients with other breast cancer subtypes,[1] with a median OS of ≈ 18 months or less[2-4]
- First-line treatment typically includes single-agent taxane or anthracycline chemotherapy, although platinum-gemcitabine doublet is also used[5,6]
- No targeted therapies have improved OS to date
- Checkpoint inhibition may be a useful approach in the treatment of TNBC
  - PD-L1 can inhibit anti-cancer immune responses[7]
  - PD-L1 in TNBC is expressed mainly on tumour-infiltrating immune cells (IC)[8,9]

1. den Brok *BCRT* 2017. 2. Gobbini *EJC* 2018. 3. Yardley *Ann Oncol* 2018. 4. Miles *Ann Oncol* 2013. 5. NCCN 2018. 6. Cardoso *Ann Oncol* 2018.
7. Chen *Immunity* 2013. 8. Sabatier *Oncotarget* 2015. 9. Mittendorf *CIR* 2014.

SYSTEMIC TREATMENT OF RECURRENT OR STAGE IV (M1) DISEASE: ER AND/OR PR NEGATIVE; HER2 NEGATIVE[d]



CHEMOTHERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b]

HER2-Negative

Preferred regimens

- Anthracyclines
  - Doxorubicin
  - Liposomal doxorubicin
- Taxanes
  - Paclitaxel
- Anti-metabolites
  - Capecitabine
  - Gemcitabine
- Microtubule inhibitors
  - Vinorelbine
  - Eribulin
- PARP inhibitors (options for patients with HER2-negative tumors and germline *BRCA1/2* mutation)[d]
  - Olaparib[d] (category 1)
  - Talazoparib[d] (category 1)
- Platinum (option for patients with triple-negative tumors and germline *BRCA1/2* mutation)[d]
  - Carboplatin
  - Cisplatin
- Atezolizumab + albumin-bound paclitaxel (option for patients with PD-L1-positive TNBC)[e]

Other recommended regimens[c]

- Cyclophosphamide
- Docetaxel
- Albumin-bound paclitaxel
- Epirubicin
- Ixabepilone

Useful in certain circumstances[c]

- AC (doxorubicin/cyclophosphamide)
- EC (epirubicin/cyclophosphamide)
- CMF (cyclophosphamide/methotrexate/fluorouracil)
- Docetaxel/capecitabine
- GT (gemcitabine/paclitaxel)
- Gemcitabine/carboplatin
- Paclitaxel/bevacizumab[f]

HER2-Positive[g]

Preferred regimens

- Pertuzumab + trastuzumab + docetaxel (category 1)[h]
- Pertuzumab + trastuzumab + paclitaxel[g]

Other recommended regimens:

- Ado-trastuzumab emtansine (T-DM1)
- Trastuzumab + paclitaxel[h] ± carboplatin
- Trastuzumab + docetaxel[h]
- Trastuzumab + vinorelbine[h]
- Trastuzumab + capecitabine
- Lapatinib + capecitabine
- Trastuzumab + lapatinib (without cytotoxic therapy)
- Trastuzumab + other agents[h,i,j]

[f] Randomized clinical trials in metastatic breast cancer document that the addition of bevacizumab to some first- or second-line chemotherapy agents modestly improves time to progression and response rates but does not improve overall survival. The time-to-progression impact may vary among cytotoxic agents and appears greatest with bevacizumab in combination with weekly paclitaxel.

[g] Trastuzumab and hyaluronidase-oysk injection for subcutaneous use may be substituted for trastuzumab. It has different dosage and administration instructions compared to intravenous trastuzumab. Do not substitute trastuzumab and hyaluronidase-oysk for or with ado-trastuzumab emtansine.

TNBC: Actionable Targets

- **Targeting Oncogenes:**
  - ***BRCA***
  - ***PIK3CA***
- **Targeting key intracellular signaling pathways:**
  - **PI3K/AKT/mTOR Pathway**
  - **Androgen receptor (AR)**
- **Targeting cell-surface markers for selective delivery of potent agents:**
  - **Trop-2 ADC**
  - **LIV-1 ADC**

Approved Drugs

Hematology/Oncology (Cancer) Approvals & Safety Notifications

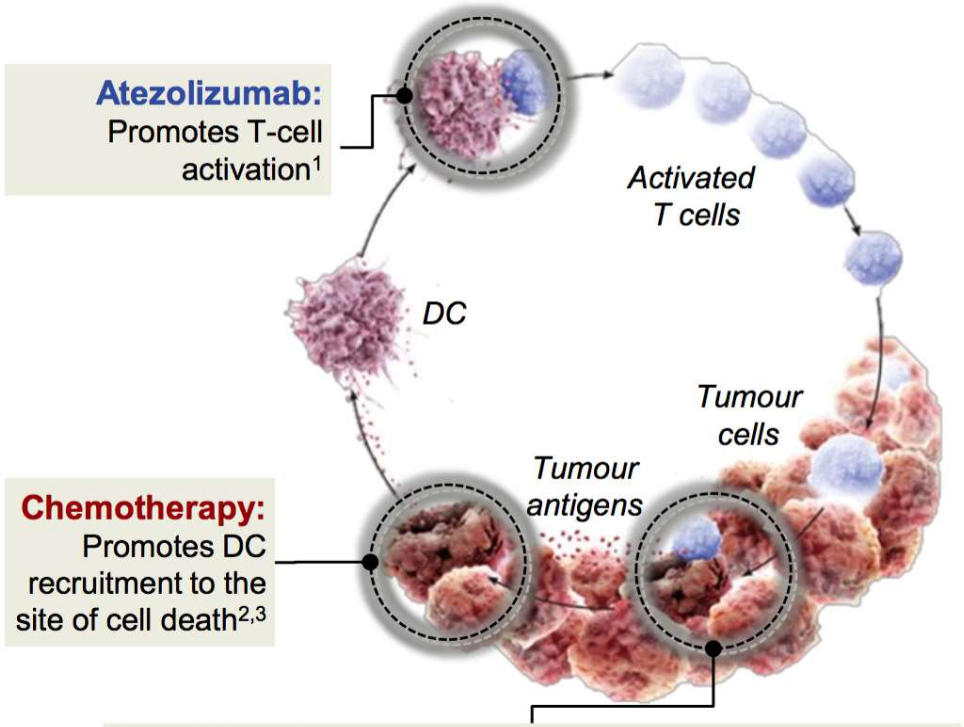
Drug Information Soundcast in Clinical Oncology (D.I.S.C.O.)

Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)

FDA approves atezolizumab for PD-L1 positive unresectable locally advanced or metastatic triple-negative breast cancer

On March 8, 2019, the Food and Drug Administration granted accelerated approval to atezolizumab (TECENTRIQ, Genentech Inc.) in combination with paclitaxel protein-bound for adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] of any intensity covering ≥ 1% of the tumor area), as determined by an FDA-approved test.

Atezolizumab and chemotherapy



- Atezolizumab (anti–PD-L1) monotherapy is approved in the United States, Europe and elsewhere for certain types of metastatic urothelial carcinoma and lung cancer[4]
- In a Phase I study, atezolizumab monotherapy was active in multiple cancers, including TNBC,[5,6] with greater activity in patients whose tumours had PD-L1 IC ≥ 1%[6]
- The addition of chemotherapy can enhance atezolizumab's anti-tumour activity[7,8]
  - In a Phase Ib study in mTNBC, concurrent administration of *nab*-paclitaxel did not inhibit atezolizumab-mediated immunodynamic effects[8]

DC, dendritic cell.

1. Chen *Immunity* 2013. 2. Zitvogel *Immunity* 2013. 3. Emens *CIR* 2015. 4. TECENTRIQ US PI/SmPC 2018. 5. Herbst *Nature* 2014. 6. Emens *JAMA Oncol* 2018. 7. Jotte ASCO 2018. 8. Pohlmann AACR 2018.

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Atezolizumab + Nab paclitaxel

- Immune checkpoint inhibition may be augmented by neoantigen elaboration by chemotherapy (or RT).
  - Nab paclitaxel avoids steroids of other taxanes
- Phase Ib

mTNBC
< 3 prior lines

↓

Atezolizumab (800 iv q2wk)
(held C1 biopsy cohort
+
nab paclitaxel (125 iv 3 wks of 4)

Serial biopsies (n=24):
- **pre-Rx**
- **C1 (no atezo)**
- **C2 (+ atezo)**

Adams et al, ASCO 2016

Phase Ib Atezolizumab + Nab paclitaxel

Table 4. Summary of Best Overall Responses by RECIST v1.1

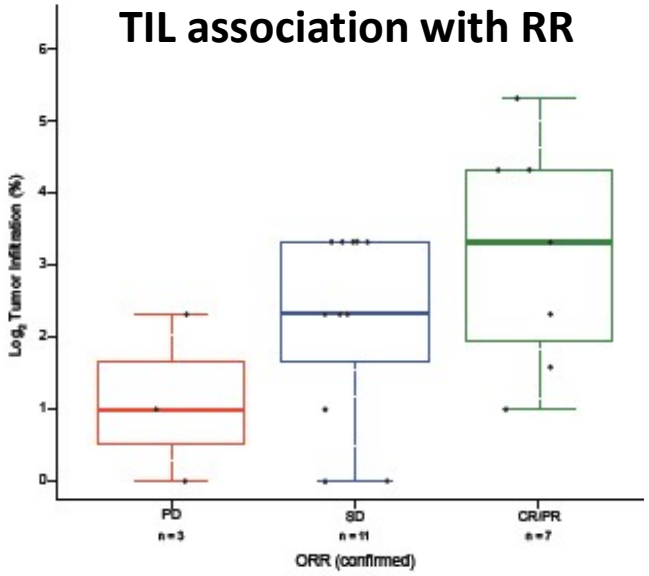
Best Overall Response	First Line (n = 13)	Second Line (n = 9)[b]	Third Line+ (n = 10)[c]	All Patients (N = 32)
Confirmed ORR (95% CI)[a]	46% (19-75)	22% (3-60)	40% (12-74)	38% (21-56)
CR	8%	0%	0%	3%
PR	38%	22%	40%	34%
SD	38%	67%	30%	44%
PD	15%	0%	30%	16%
Missing or NE	0%	11%	0%	3%

Table 2. Treatment-Related Grade 3-4 Adverse Events Occurring in > 1 Patient (> 5%)[a]

Adverse Event, n (%)	Grade 3-4 ≥ 5% N = 32	All Grade N = 32
All	22 (69%)	32 (100%)
Neutropenia and decreased neutrophil count	15 (47%)	21 (66%)
Thrombocytopenia and decreased platelet count	3 (9%)	5 (16%)
Anemia	2 (6%)	7 (22%)
Decreased white blood cell count	2 (6%)	3 (9%)
Diarrhea	2 (6%)	13 (41%)

Adams et al, ASCO 2016

TIL association with RR



IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m² IV
- On days 1, 8 and 15 of 28-day cycle

RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

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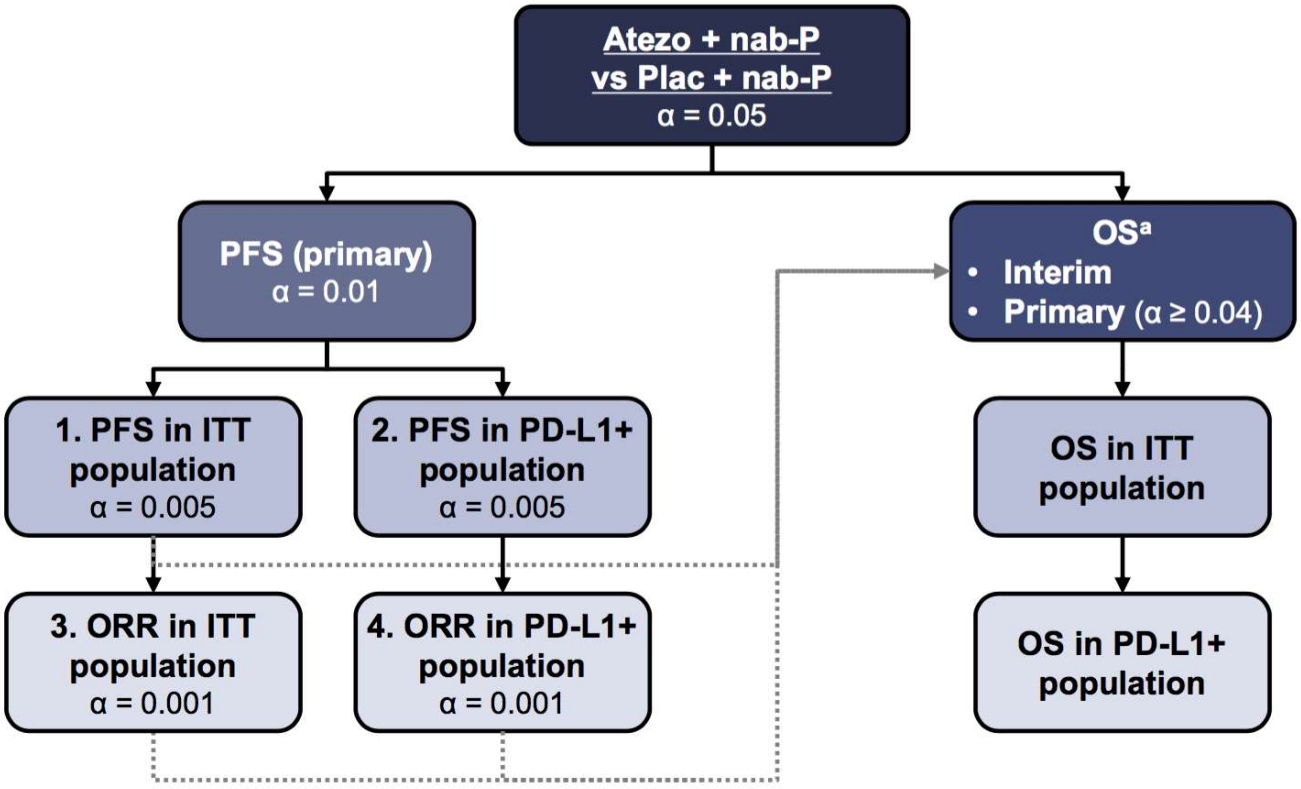
IMpassion130 statistical testing



- Primary PFS analysis (PFS tested in ITT and PD-L1+ populations)
- First interim OS analysis (OS tested in ITT population, then, if significant, in PD-L1+ population)

[a] α recycled if PFS/ORR testing is significant. Hazard ratio (HR)/*P* value–stopping boundaries are dependent on the OS analysis timing.

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IMpassion130 baseline characteristics

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Female, n (%)	448 (99%)	450 (100%)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
Other/multiple	20 (4%)	26 (6%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284 (63%)	286 (63%)
Prior taxane	231 (51%)	230 (51%)
Prior anthracycline	243 (54%)	242 (54%)

Characteristic	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Metastatic disease, n (%)	404 (90%)	408 (91%)
No. of sites, n (%)[d]		
0-3	332 (74%)	341 (76%)
≥ 4	118 (26%)	108 (24%)
Site of metastatic disease, n (%)		
Lung	226 (50%)	242 (54%)
Bone	145 (32%)	141 (31%)
Liver	126 (28%)	118 (26%)
Brain	30 (7%)	31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
PD-L1+ (IC), n (%)	185 (41%)	184 (41%)

Data cutoff: 17 April 2018. [a] Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. [b] Of n = 450 in each arm. [c] ECOG PS before start of treatment was 2 in 1 patient per arm. [d] Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm arm.

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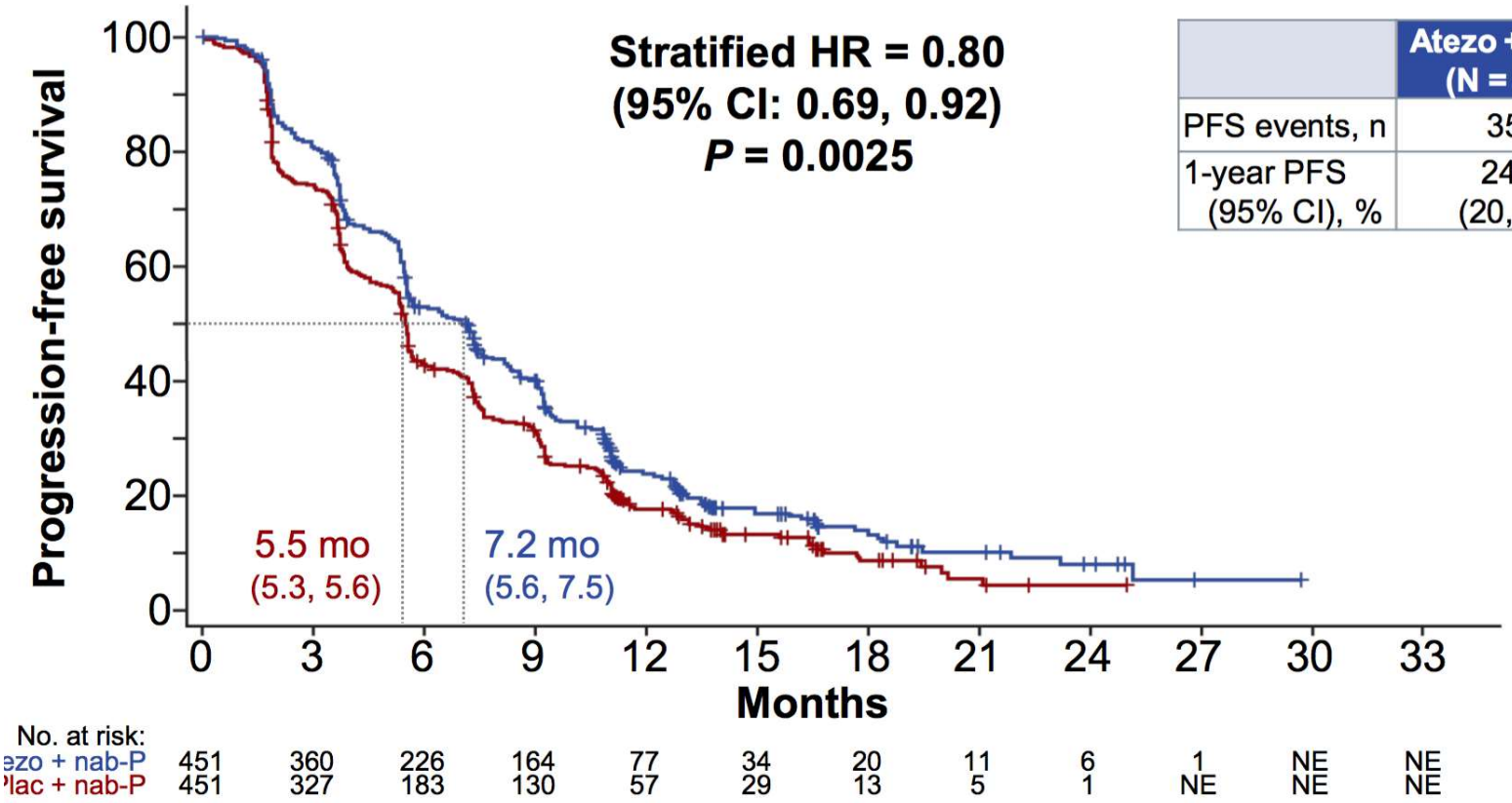
Primary PFS analysis: ITT population



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
PFS events, n	358	378
1-year PFS (95% CI), %	24% (20, 28)	18% (14, 21)

NE, not estimable. Data cutoff: 17 April 2018. Median PFS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

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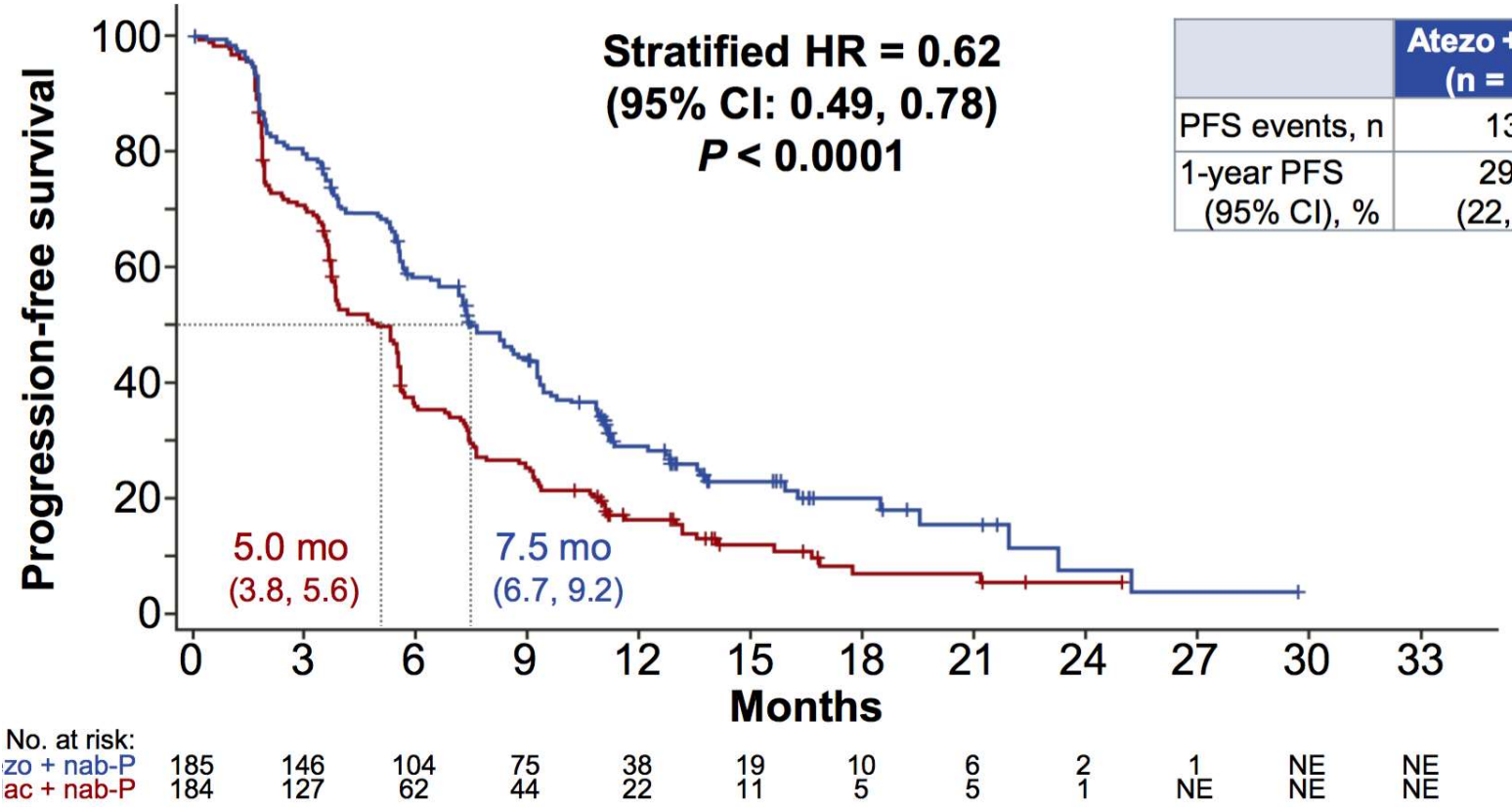
Primary PFS analysis: PD-L1+ population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
PFS events, n	138	157
1-year PFS (95% CI), %	29% (22, 36)	16% (11, 22)

Data cutoff: 17 April 2018.

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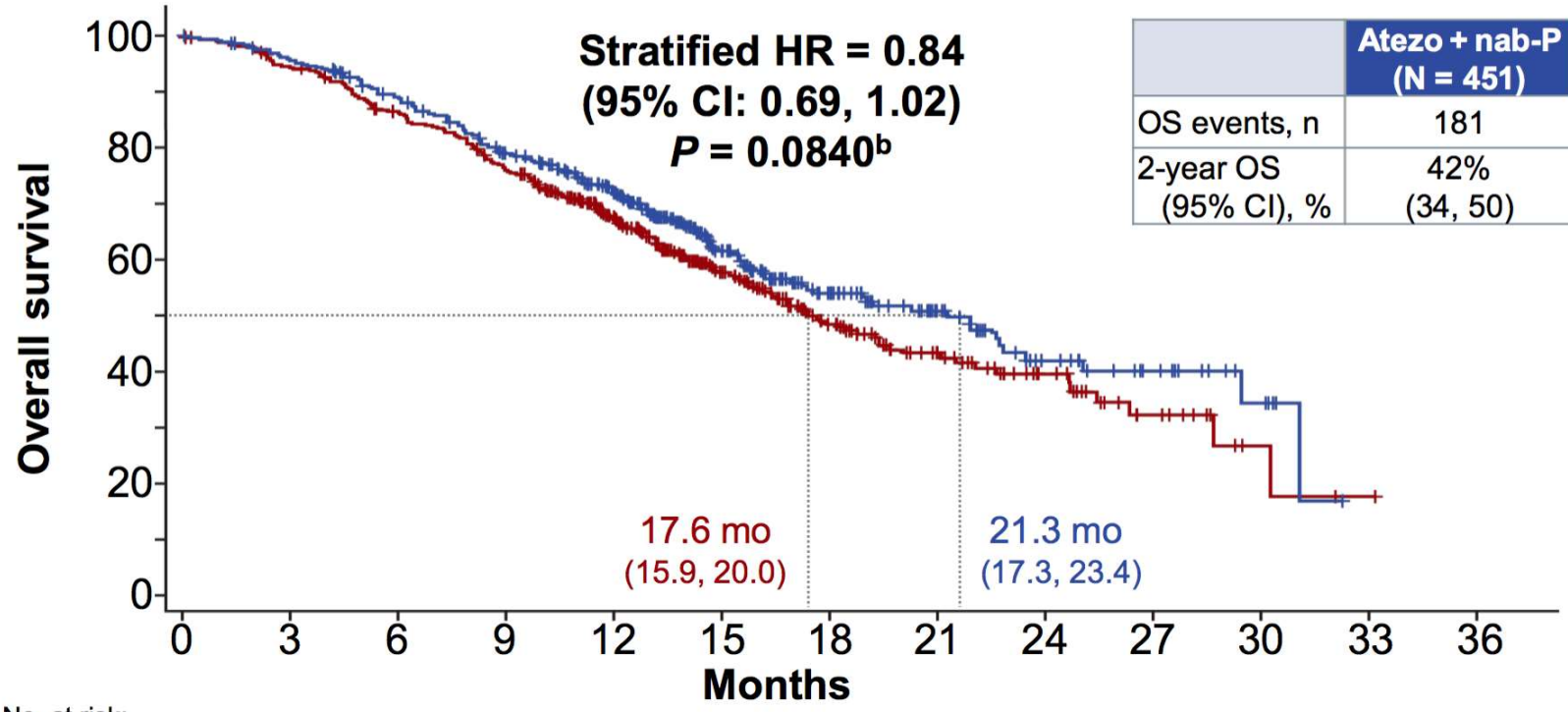
Interim OS analysis: ITT population[a]



	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
OS events, n	181	208
2-year OS (95% CI), %	42% (34, 50)	40% (33, 46)

No. at risk:

Atezo + nab-P	451	426	389	337	271	146	82	48	26	15	6	NE	NE
Plac + nab-P	451	419	375	328	246	145	89	52	27	12	3	1	NE

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.
[a] For the interim OS analysis, 59% of death events had occurred. [b] Significance boundary was not crossed.

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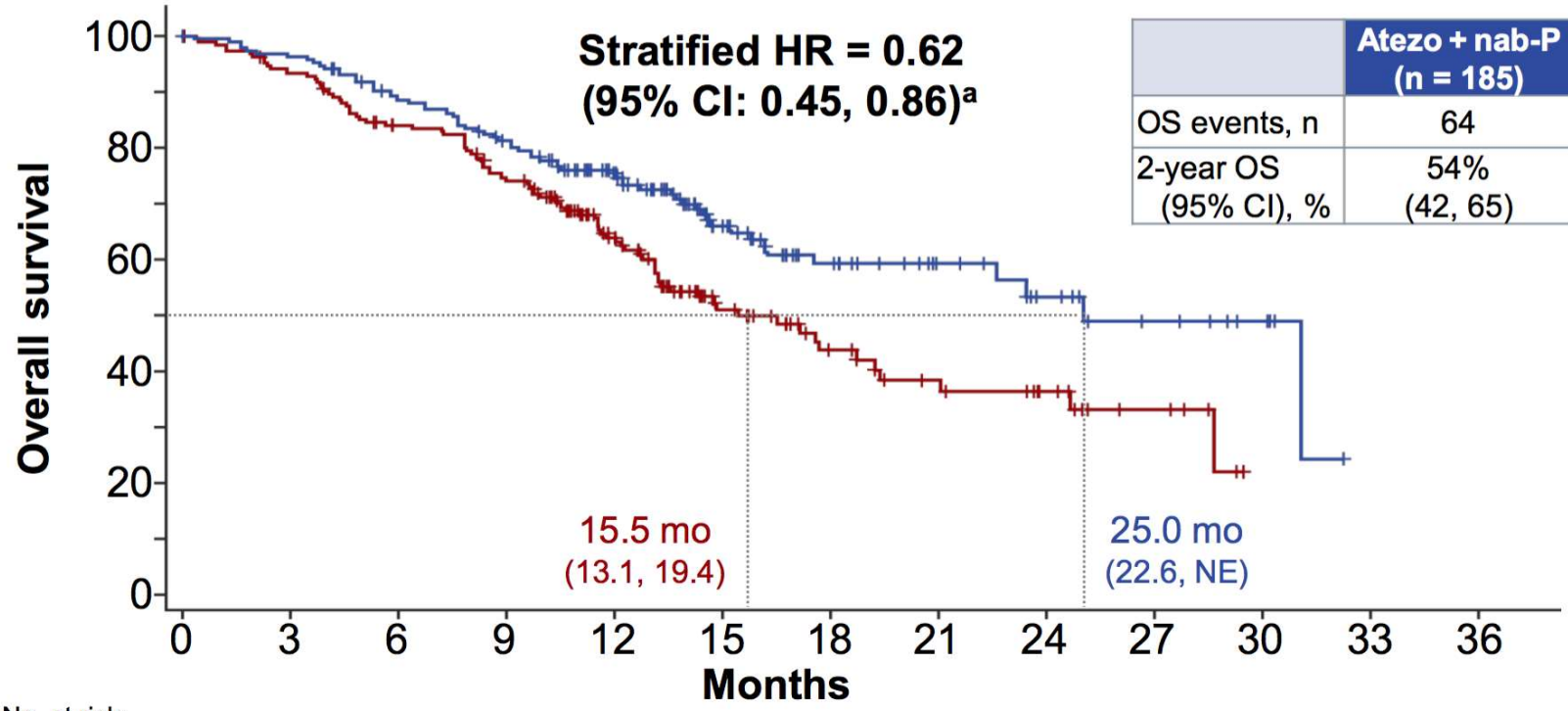
Interim OS analysis: PD-L1+ population



	Atezo + nab-P (n = 185)	Plac + nab-P (n = 184)
OS events, n	64	88
2-year OS (95% CI), %	54% (42, 65)	37% (26, 47)

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. [a] Not formally tested.

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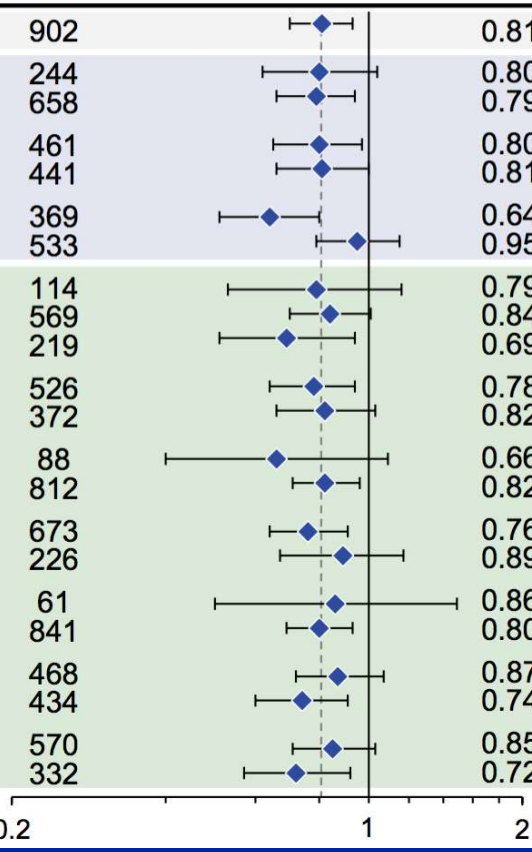
PFS subgroup analysis: ITT population

Characteristic		Patients	Hazard Ratio (95% CI)[a]
All		902	0.81 (0.70, 0.93)
Baseline liver metastases	Yes	244	0.80 (0.62, 1.04)
	No	658	0.79 (0.66, 0.94)
Prior taxane use	Yes	461	0.80 (0.65, 0.97)
	No	441	0.81 (0.66, 1.00)
PD-L1 status	PD-L1+ (IC1/2/3)	369	0.64 (0.51, 0.80)
	PD-L1– (IC0)	533	0.95 (0.79, 1.15)
Age group	18-40 y	114	0.79 (0.53, 1.16)
	41-64 y	569	0.84 (0.70, 1.01)
	≥ 65 y	219	0.69 (0.51, 0.94)
ECOG PS[b]	0	526	0.78 (0.64, 0.94)
	1	372	0.82 (0.66, 1.03)
Baseline disease status	Locally advanced	88	0.66 (0.40, 1.09)
	Metastatic[c]	812	0.82 (0.71, 0.96)
No. of metastatic sites	0-3[c]	673	0.76 (0.64, 0.91)
	> 3[c]	226	0.89 (0.67, 1.17)
Brain metastases	Yes	61	0.86 (0.50, 1.49)
	No	841	0.80 (0.69, 0.93)
Lung metastases	Yes	468	0.87 (0.72, 1.07)
	No	434	0.74 (0.60, 0.91)
Prior (neo)adjuvant chemo	Yes	570	0.85 (0.71, 1.03)
	No	332	0.72 (0.57, 0.92)



A + nab-P better ← → P + nab-P better

Stratification factors

Data cutoff: 17 April 2018.

[a] Unstratified HRs are shown; 95% CIs are plotted as error bars. Dashed vertical line represents value in ITT population.

[b] Patients with ECOG PS 2 not plotted.

[c] Excludes patients with unknown/other values.

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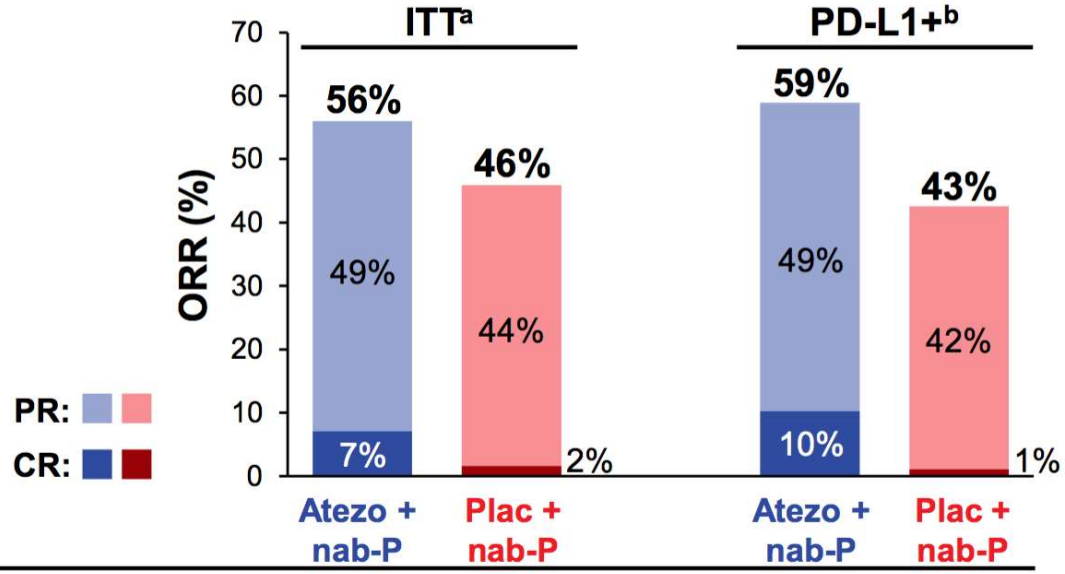
Secondary efficacy endpoints



	ITT[a]		PD-L1+[b]	
	Atezo + nab-P	Plac + nab-P	Atezo + nab-P	Plac + nab-P
DOR, median (95% CI), mo	7.4 (6.9, 9.0)	5.6 (5.5, 6.9)	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)
No. of ongoing responses, n (%)[c]	78 (31%)	52 (25%)	39 (36%)	19 (24%)

- Numerically higher and more durable responses were seen in the Atezo + nab-P arm
  - Differences were not significant based on α level = 0.1% (ITT: $P = 0.0021$; PD-L1+: $P = 0.0016$)
- The CR rate was higher in the Atezo + nab-P arm vs the Plac + nab-P arm
  - ITT population: 7% vs 2%
  - PD-L1+ patients: 10% vs 1%

Data cutoff: 17 April 2018. Objective response–evaluable patients: [a] 450 in Atezo + nab-P arm and 449 in Plac + nab-P arm. [b] 185 in Atezo + nab-P arm and 183 in Plac + nab-P arm. [c] No death or PD.

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Safety summary

AE, n (%)	Atezo + nab-P (n = 452)	Plac + nab-P (n = 438)
All-cause AEs		
Any grade	449 (99%)	429 (98%)
Grade 3-4	220 (49%)	185 (42%)
Grade 5	6 (1%)	3 (1%)
Treatment-related AEs		
Any grade	436 (96%)	410 (94%)
Grade 3-4	179 (40%)	132 (30%)
Grade 5[a]	3 (1%)[a]	1 (< 1%)[a]
Any grade serious AEs		
Serious AEs regardless of attribution	103 (23%)	80 (18%)
Treatment-related serious AEs	56 (12%)	32 (7%)
Any-grade AEs leading to any treatment discontinuation	72 (16%)	36 (8%)
Leading to atezo or plac discontinuation	29 (6%)	6 (1%)
Leading to *nab*-P discontinuation	72 (16%)	36 (8%)
Any-grade AEs leading to any dose reduction or interruption	212 (47%)	177 (40%)
Leading to atezo or plac dose interruption	139 (31%)	103 (24%)
Leading to *nab*-P dose reduction or interruption	195 (43%)	172 (39%)

AE, adverse event. Safety-evaluable population. Data cutoff: 17 April 2018. [a] Treatment-related deaths: autoimmune hepatitis, mucosal inflammation/death, septic shock (n = 1 each, Atezo + nab-P arm); hepatic failure (n = 1, Plac + nab-P arm).

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Most common serious AEs

SAEs occurring in ≥ 1% of patients in either arm (regardless of attribution)

SAE, n (%)	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	103 (23%)	78 (17%)[a]	80 (18%)	56 (13%)[b]
Pneumonia	10 (2%)	8 (2%)[c]	5 (1%)	0
Urinary tract infection	5 (1%)	2 (< 1%)	0	0
Dyspnoea	5 (1%)	3 (1%)	2 (< 1%)	2 (< 1%)
Pyrexia	5 (1%)	3 (1%)	3 (1%)	0

- A higher proportion of patients in the Atezo + nab-P arm than in the Plac + nab-P arm reported SAEs (23% vs 18%)
- No SAE was reported with a ≥ 2% difference between treatment arms

SAE, serious adverse event. Data cutoff: 17 April 2018. [a] Six Grade 5 events occurred. [b] Three Grade 5 events occurred. [c] One Grade 5 event occurred.

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AESIs suggestive of potential immune-related aetiology

AESI, n (%)[a]	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs				
Hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Hypothyroidism	78 (17%)	0	19 (4%)	0
Hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Meningoencephalitis[b]	5 (1%)	0	2 (< 1%)	0
Colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Nephritis	1 (< 1%)	0	0	0
Other AESIs[c]				
Rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

- 1 grade 5 AESI per arm (both treatment related):
  - Atezo + nab-P: autoimmune hepatitis
  - Plac + nab-P: hepatic failure
- All hypothyroidism AESIs were grade 1-2; none led to discontinuation
  - Atezo + nab-P: 17%
  - Plac + nab-P: 4%
- Pneumonitis was infrequent with only 1 grade 3-4 event in the Atezo + nab-P arm
  - Atezo + nab-P: 3%
  - Plac + nab-P: < 1%
- Hepatitis rates were balanced

AESI, adverse event of special interest. Data cutoff: 17 April 2018. [a] Baskets of preferred terms according to medical concepts. [b] All events of photophobia.
[c] Includes all AESIs occurring in ≥ 1% of patients in either arm.

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IMpassion130 conclusions

- IMpassion130 is the first Phase III study to demonstrate a benefit with first-line immunotherapy in mTNBC
  - Atezolizumab + *nab*-paclitaxel resulted in statistically significant PFS benefit in the ITT and PD-L1+ populations (ITT HR = 0.80 [95% CI: 0.69, 0.92] and PD-L1+ HR = 0.62 [95% CI: 0.49, 0.78]), which was clinically meaningful in the PD-L1+ population
  - At this first interim OS analysis, clinically meaningful improvement in OS with atezolizumab + *nab*-paclitaxel (vs placebo + *nab*-paclitaxel) was observed in the PD-L1+ population, with a HR of 0.62 and a median OS improvement from 15.5 months to 25.0 months (formal OS testing in PD-L1+ patients not performed per hierarchical study design)
  - No detriment observed for the PD-L1– subgroup
- Atezolizumab + *nab*-paclitaxel was well tolerated, with a safety profile consistent with each agent
- For patients with PD-L1+ tumours,[a] these data establish atezolizumab + *nab*-paclitaxel as a new standard of care

[a] PD-L1 expression on ≥1% of tumour-infiltrating immune cells.

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G.S. Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Investigators*

San Antonio Breast Cancer Symposium®
December 4-8, 2018

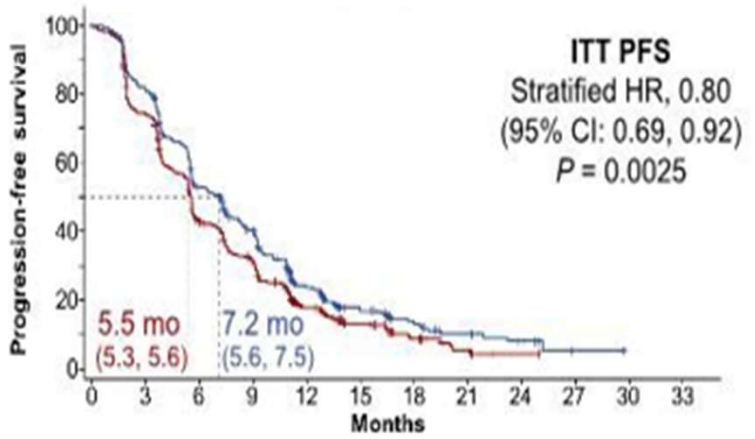
IMpassion130: Efficacy in immune biomarker subgroups from the global, randomized, double-blind, placebo-controlled, Phase III study of atezolizumab + *nab*-paclitaxel in patients with treatment-naive, locally advanced or metastatic triple-negative breast cancer

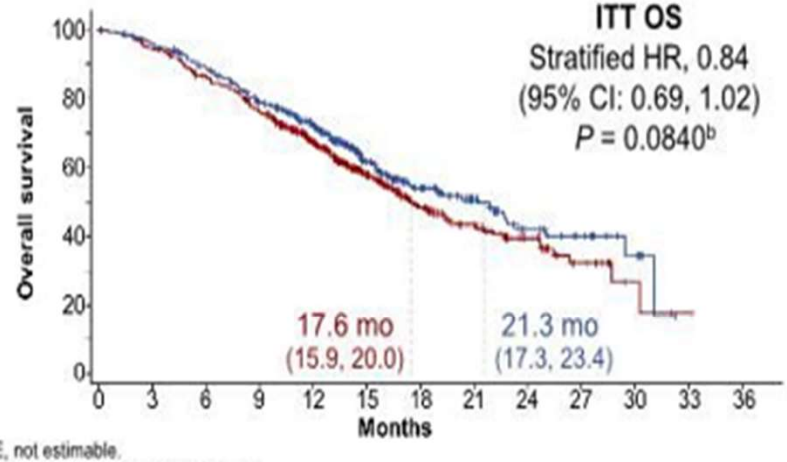
Leisha A. Emens,[1] Sherene Loi,[2] Hope S. Rugo,[3] Andreas Schneeweiss,[4] Véronique Diéras,[5] Hiroji Iwata,[6] Carlos H. Barrios,[7] Marina Nechaeva,[8] Luciana Molinero,[9] Anh Nguyen Duc,[10] Roel Funke,[9] Stephen Y Chui,[9] Amreen Husain,[10] Eric P. Winer,[11] Sylvia Adams,[12] Peter Schmid[13]

[1]UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA; [2]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA; [4]University Hospital Heidelberg, Heidelberg, Germany; [5]Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; [6]Aichi Cancer Center Hospital, Aichi, Japan; [7]Department of Medicine, PUCRS School of Medicine, Porto Alegre, Brazil; [8]Arkhangelsk Regional Clinical Oncology Dispensary, Arkhangelsk, Russia; [9]Genentech, Inc., South San Francisco, CA; [10]F. Hoffmann-La Roche AG, Basel, Switzerland; [11]Dana-Farber Cancer Institute, Boston, MA; [12]New York University Langone Medical Center, New York, NY; [13]Barts Cancer Institute, Queen Mary University of London, London, UK

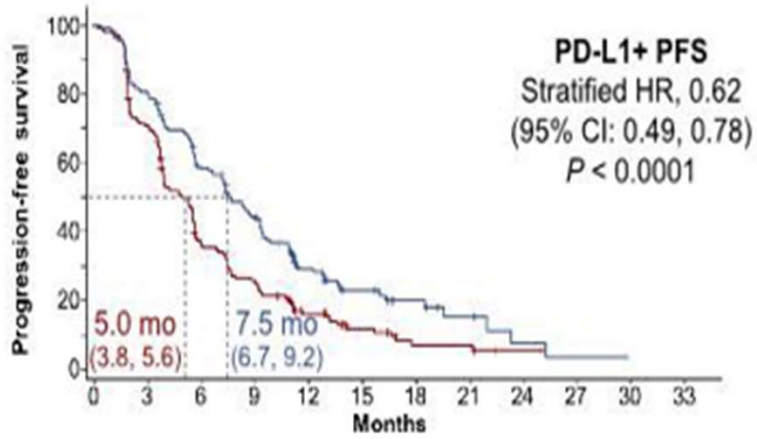
IMpassion130 primary analysis[1,2]: Clinically meaningful PFS and OS benefit in the PD-L1+ population

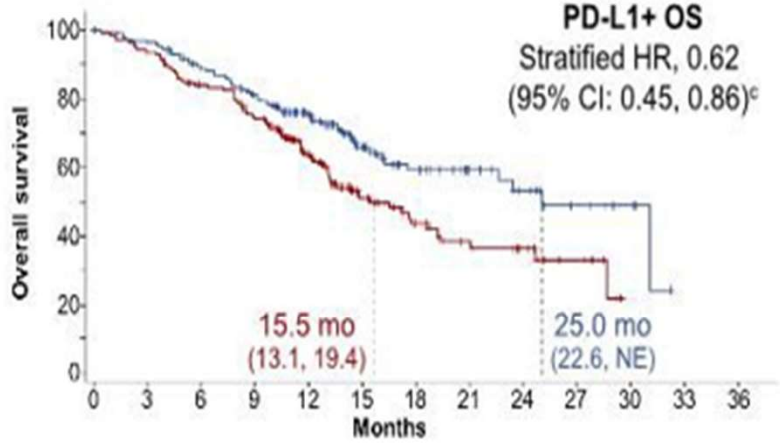
ITT population





PD-L1+ population[a]



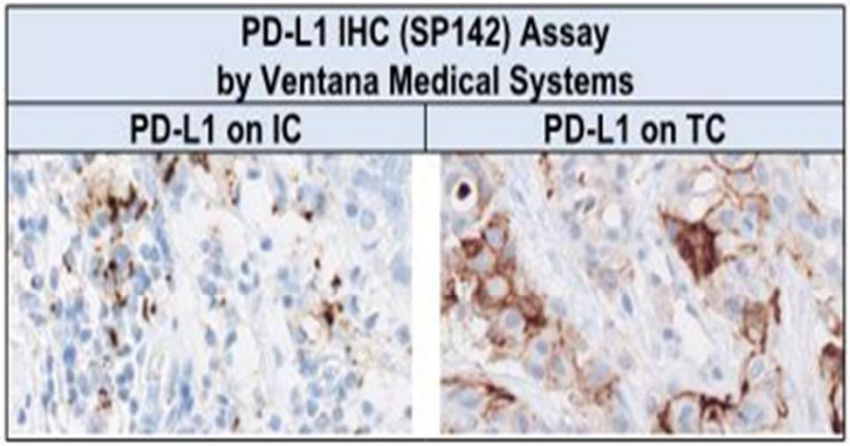


NE, not estimable.
Median follow-up (ITT): 12.9 months.
[a] PD-L1+; PD-L1 in ≥ 1% of IC. [b] Not significant. [c] Not formally tested per hierarchical study design.
1. Schmid *N Engl J Med* 2018. 2. Schmid ESMO 2018 [LBA1_PR].

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

IMpassion130 biomarker analyses

- Pre-existing immune biology, including PD-L1 expression on TC, CD8+ T cells and stromal TILs, has also been associated with clinical benefit from anti–PD-L1/PD-1[1,2]
- In this exploratory analysis, we sought to evaluate whether this immune biology and *BRCA1/2* mutation status were associated with clinical benefit from atezolizumab + *nab*-paclitaxel
- Biomarkers were centrally analyzed in pre-treatment biopsies
  - PD-L1 on IC and TC by VENTANA SP142 IHC assay[a]
  - Intratumoral CD8+ T cells by IHC (Dako clone C8/144B) and stromal TILs by H&E[b]
  - *BRCA1/2* mutation status by FoundationOne assay



H&E, hematoxylin and eosin staining; IHC, immunohistochemistry.
[a] PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.
[b] Pre-specified cutoffs for CD8 IHC and stromal TILs are based on references 1 and 2.
1. Adams *JAMA Oncol* 2018. 2. Denkert *Lancet Oncol* 2018.

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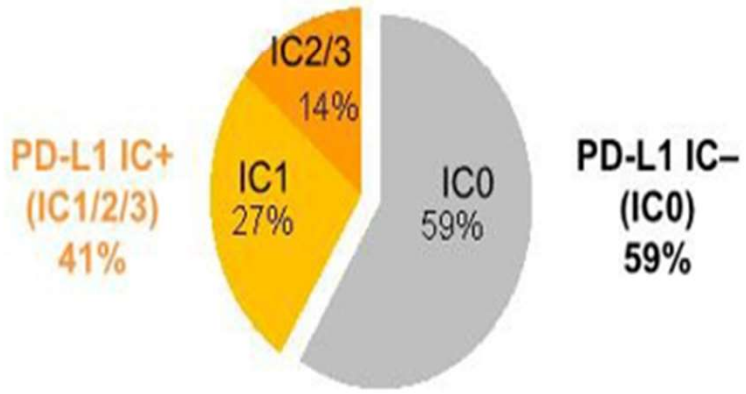
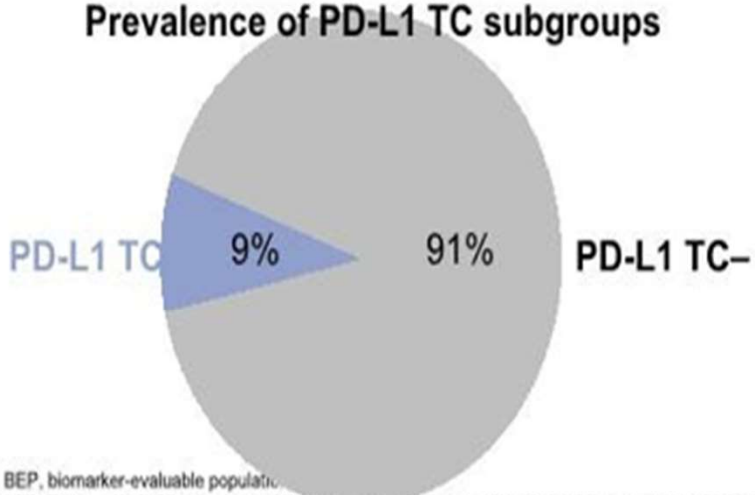
In IMpassion130, PD-L1 in TNBC is expressed mainly on tumor-infiltrating immune cells

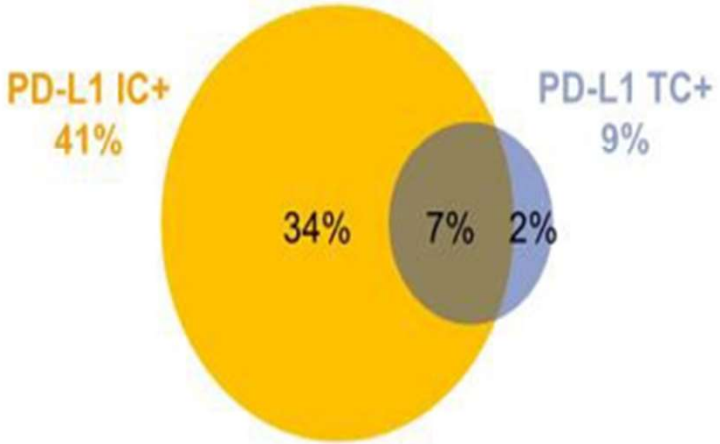
Prevalence of PD-L1 IC subgroups



Prevalence of PD-L1 TC subgroups



The majority of patients with expression of PD-L1 on TC are included within the PD-L1 IC+ population



BEP, biomarker-evaluable popula
BEP (TC): n = 900. PD-L1 scoring: IC0: < 1%, IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

Consistent clinical benefit with atezolizumab + *nab*-paclitaxel was observed across all PD-L1 IC+ subgroups

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	PD-L1 IC Status	n	PFS Median, mo A + nP	PFS Median, mo P + nP	PFS HR[a] (95% CI)	PFS *P* value	OS Median, mo A + nP	OS Median, mo P + nP	OS HR[a] (95% CI)	OS *P* value
Neg	IC0	532	5.6	5.6	0.93 (0.77, 1.12)	0.47	18.9	18.4	1.02 (0.79, 1.31)	0.90
Pos	IC1	243	7.4	3.9	0.59 (0.44, 0.78)	≤ 0.005	23.4	14.4	0.56 (0.38, 0.82)	≤ 0.005
Pos	IC2/3	125	9.3	5.7	0.64 (0.42, 0.97)	0.03	25.0	21.1	0.71 (0.39, 1.30)	0.26
	All	900	7.2	5.5	0.79 (0.68, 0.92)	≤ 0.005	21.3	17.6	0.83 (0.68, 1.02)	0.07

[a] Adjusted for prior taxane treatment and liver metastases.
A multivariate analysis was performed to account for imbalances in baseline characteristics between PD-L1 IC–expressing subgroups (IC1, IC2 and IC3).
IC0: < 1% PD-L1; IC1: ≥ 1% and < 5% PD-L1; IC2/3: ≥ 5% PD-L1. All *P* values are nominal. Data cutoff: April 17, 2018.

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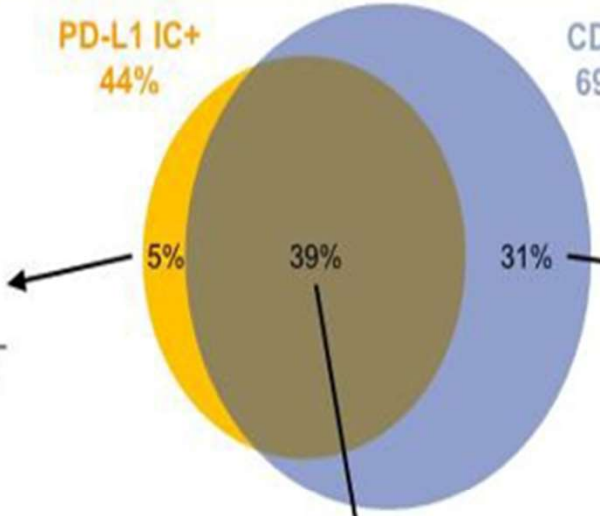
CD8+ IHC has clinical benefit if co-occurring with PD-L1 IC+



CD8–/PD-L1 IC+ (n = 37)

	HR (95% CI)	*P* Value
PFS	0.33 (0.13, 0.87)	0.03
OS	0.25 (0.06, 1.02)	0.05

CD8+/PD-L1 IC– (n = 220)

	HR (95% CI)	*P* Value
PFS	0.89 (0.66, 1.20)	0.45
OS	0.77 (0.50, 1.17)	0.21

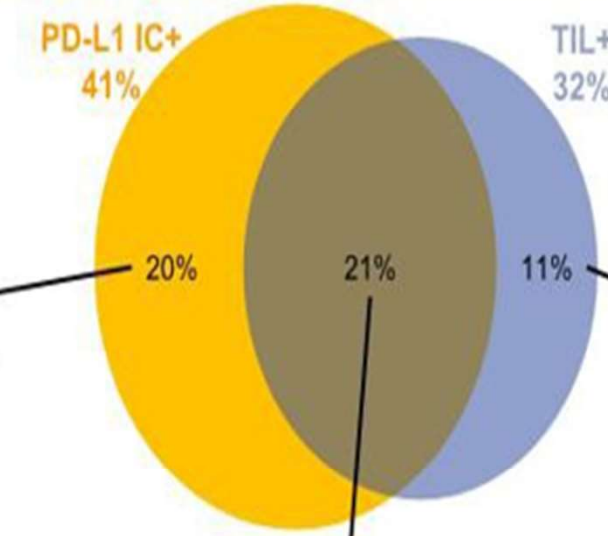
CD8+/PD-L1 IC+ (n = 280)

	HR (95% CI)	*P* Value
PFS	0.61 (0.46, 0.80)	≤ 0.005
OS	0.55 (0.38, 0.80)	≤ 0.005

- PD-L1 IC+ are enriched in CD8+ ($P < 0.0001$) and CD8+ are enriched in PD-L1 IC+ ($P < 0.0001$)[a]
- ***Patients with CD8+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

BEP (CD8): n = 720. A CD8+ cutoff of 0.5% was selected based on Phase Ib study in TNBC (Adams *JAMA Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

Stromal TILs has clinical benefit if co-occurring with PD-L1 IC+



TIL–/PD-L1 IC+ (n = 176)

	HR (95% CI)	*P* Value
PFS	0.74 (0.54, 1.03)	0.07
OS	0.65 (0.41, 1.02)	0.06

TIL+/PD-L1 IC+ (n = 190)

	HR (95% CI)	*P* Value
PFS	0.53 (0.38, 0.74)	≤ 0.005
OS	0.57 (0.35, 0.92)	0.02

TIL+/PD-L1 IC– (n = 94)

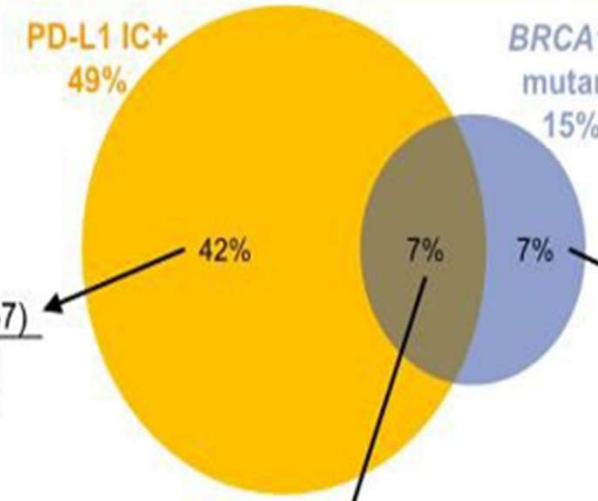
	HR (95% CI)	*P* Value
PFS	0.99 (0.62, 1.57)	0.97
OS	1.53 (0.76, 3.08)	0.24

- TIL+ were enriched for PD-L1 IC+ ($P < 0.0001$) but PD-L1 IC+ were not enriched for TIL+ (P = ns)[a]
- ***Patients with TIL+ tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+***

BEP (TILs): n = 893. Cutoff of 10% was used to distinguish low vs intermediate/high levels of TILs (Denkert *Lancet Oncol* 2018). All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

The clinical benefit derived by PD-L1 IC+ patients was independent of their *BRCA1/2* mutation status



***BRCA1/2* non-mut/PD-L1 IC+** (n = 257)

	HR (95% CI)	*P* Value
PFS	0.63 (0.48, 0.83)	≤ 0.005
OS	0.62 (0.43, 0.91)	0.01

***BRCA1/2* mut/PD-L1 IC+** (n = 45)

	HR (95% CI)	*P* Value
PFS	0.45 (0.21, 0.96)	0.04
OS	0.87 (0.26, 2.85)	0.82

***BRCA1/2* mut/PD-L1 IC–** (n = 44)

	HR (95% CI)	*P* Value
PFS	0.77 (0.37, 1.61)	0.49
OS	0.85 (0.29, 2.43)	0.76

- *BRCA1/2* mutants and PD-L1 IC+ are independent from each other (*P* = ns)[a]
- ***Patients with BRCA1/2-mutant tumors derived clinical benefit (PFS/OS) only if their tumors were also PD-L1 IC+[b]***

BEP (BRCA1/2): n = 612. Per FoundationOne *BRCA1/2* testing, *BRCA1/2* mutant: known and likely mutations. All *P* values are nominal.
[a] Data derived from contingency table with Fisher exact tests. [b] Data interpretation limited by small number of *BRCA1/2*-mutant patients.

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

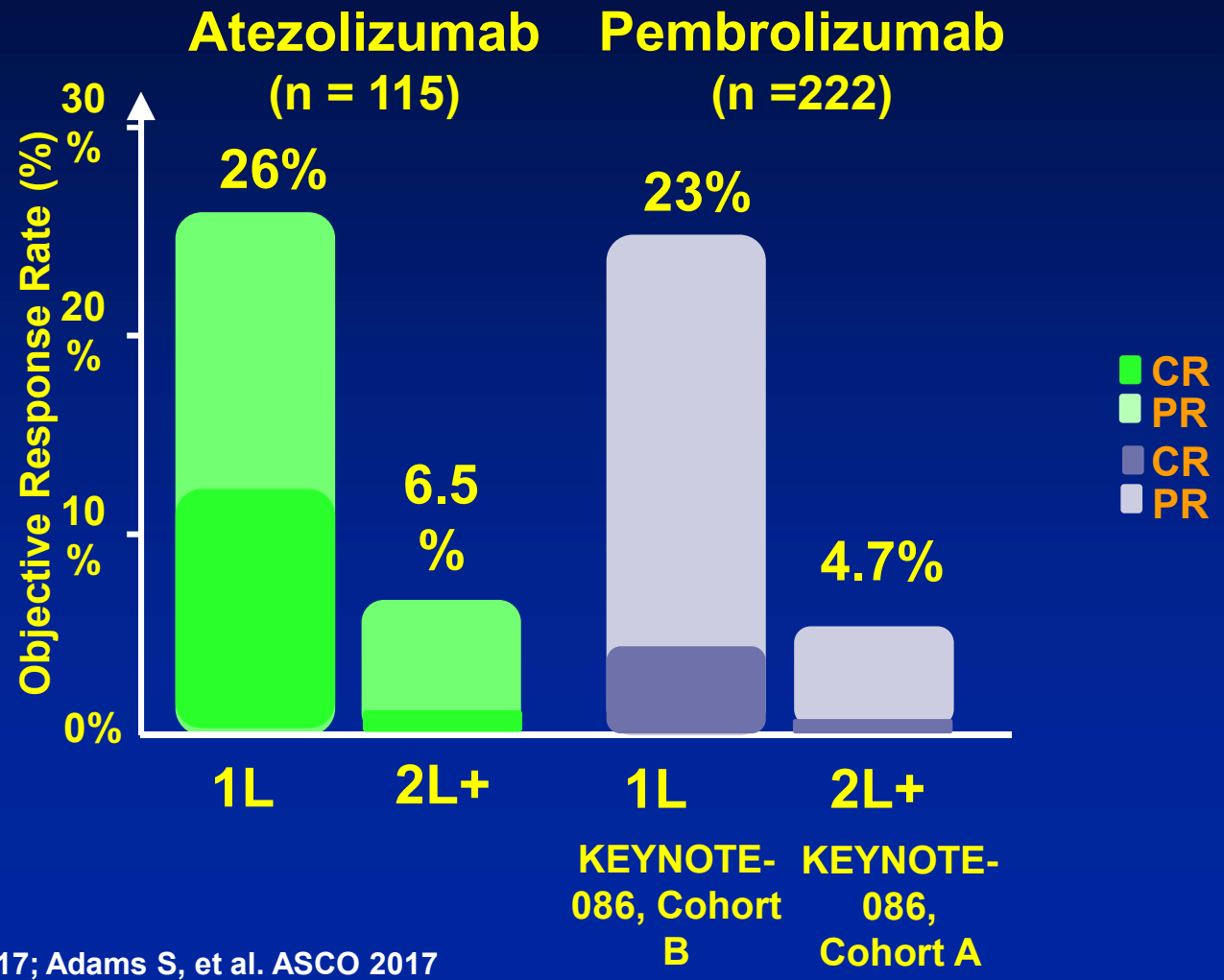
Conclusions

- In the Phase III IMpassion130 study, PD-L1 expression on IC is a predictive biomarker for selecting patients who clinically benefit from first-line atezolizumab + *nab*-paclitaxel treatment for mTNBC
  - PFS and OS benefit was observed in patients with a PD-L1 IC of ≥ 1% (by VENTANA SP142 IHC assay)
  - A treatment effect was not seen for adding atezolizumab to chemotherapy in the PD-L1–negative subgroup
- PD-L1 expression on TC did not provide additional information beyond PD-L1 IC status
  - Prevalence of tumor-cell PD-L1 expression was low, and the majority of these tumors were also PD-L1 IC+
- PD-L1 IC expression was the best predictor of clinical benefit as the patient subgroups with tumor-infiltrating immune cells (stromal TILs+) or cytotoxic T cells (CD8+) derived clinical benefit with atezolizumab + *nab*-paclitaxel if their tumors were also PD-L1 IC+
- PFS and OS results were consistent regardless of *BRCA1/2* mutation status
- Patients with newly diagnosed metastatic and unresectable locally advanced TNBC should be routinely tested for PD-L1 IC status to determine whether they might benefit from atezolizumab + *nab*-paclitaxel

Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04)

Response to single agent anti-PD-L1/PD-1

Anti-PD-L1/PD-1 single agent in mTNBC ≥1L, PD-L1+/-



Schmid P, et al. AACR 2017; Adams S, et al. ASCO 2017

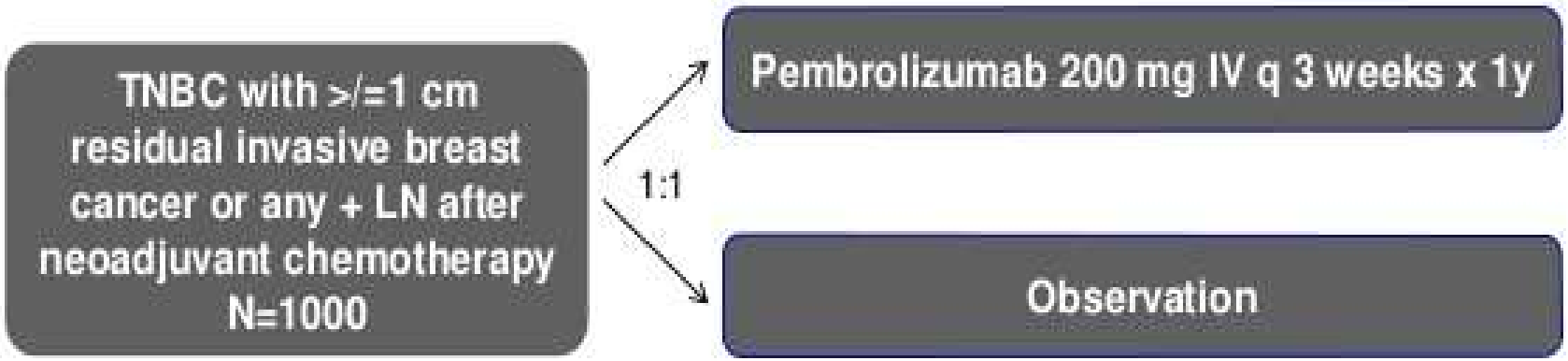
Small group of TNBC with transformative benefit but unable to define subgroup

Strategies going forward concentrating on combinations

Synergistic effect of chemotherapy and anti-PD-L1 treatment in vivo

1. Reduce T-regulatory cell activity
2. Enhance cross-presentation of tumour antigens
3. Chemo to increase tumour PD-L1 expression/infiltration of CD8+ T cells

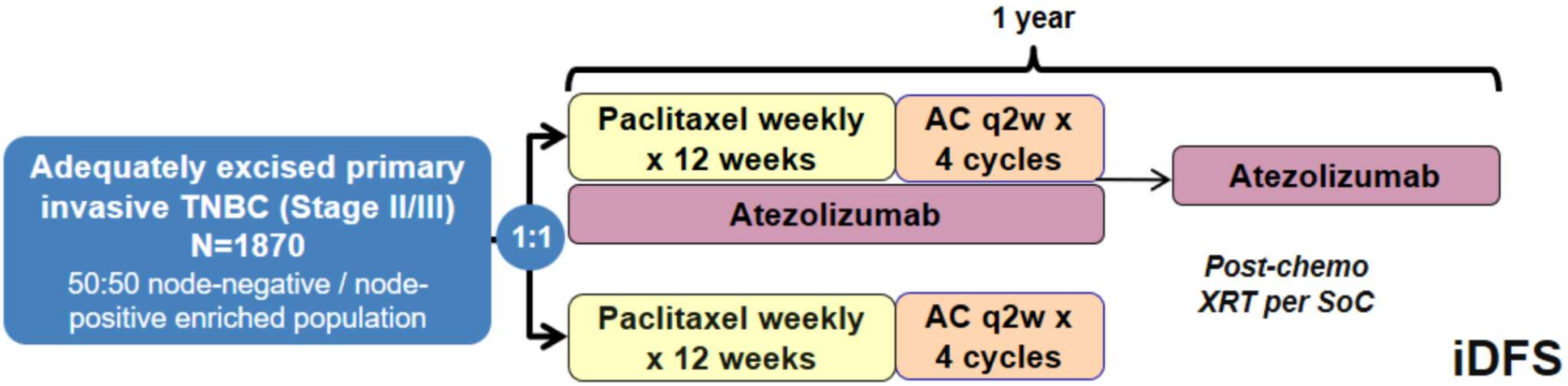
Post NAC residual disease: SWOG 1418



- **Registration:**
  - Central PD-L1 testing
- **Stratification:**
  - Nodal stage ypNo vs ypN+
  - Residual tumor ≥2 vs < 2cm
  - PD-L1 pos vs neg
  - Prior adjuvant chemo yes vs no

- **Hypothesis:**
  - Pembrolizumab reduces IDFS by 33% c/w observation alone
- **Primary Endpoint:**
  - Invasive DFS in PD-L1-positive and overall cohort
- **Secondary Endpoints:**
  - Toxicity
  - OS
  - DRFS
  - QOL (PROMIS, PRO-CTCAE forms, inflammatory markers)
  - Tissue banking

IMpassion030: Phase III randomized, open label adjuvant TNBC trial (Alliance/BIG)



Stratification factors:

- Axillary nodal status (0 vs. 1-3 vs. ≥4 positive lymph nodes)
- Surgery (breast conserving vs mastectomy)
- PD-L1 IC0 vs IC1/2/3

- **Primary endpoint:**
  - iDFS in ITT
- **Assumptions:**
  - iDFS HR=0.75
  - 3-yr iDFS +4.4% *(81% ➔ 85.4%)*
  - 80% power, alpha =5% (two sided)

- **Secondary endpoints:**
  - iDFS PD-L1 IC1/2/3
  - OS
  - Recurrence-free interval (RFI)
  - Distant RFI
  - Safety
  - Health-related QoL

Candidate Biomarkers for Immunotherapy

Tumor antigens

- Biomarkers indicative of hypermutation & neoantigens may predict response to immuno-oncology therapies

Examples:

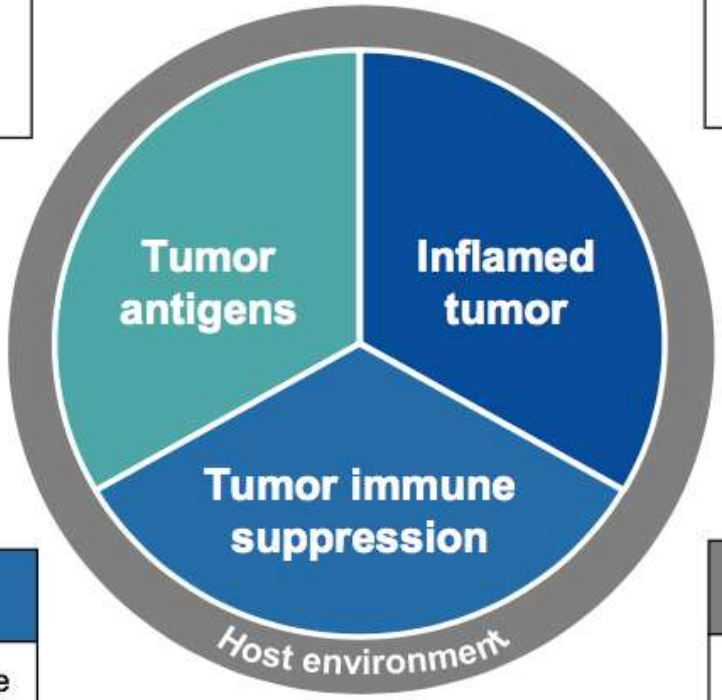
– ***TMB, MSI-high, neoantigens***

Inflamed tumor microenvironment

- Biomarkers (intra- or peri-tumoral) indicative of an inflamed phenotype may predict response to immuno-oncology therapies

Examples:

– ***PD-L1, inflammatory signatures***



Tumor immune suppression/evasion

- Biomarkers that identify tumor immune system evasion beyond PD-1/CTLA-4 to inform new immuno-oncology targets and rational combinations

Examples:

– ***Tregs, MDSCs, IDO, LAG-3***

Host environment

- Biomarkers that characterize the host environment, beyond tumor microenvironment, may predict response to immuno-oncology therapies

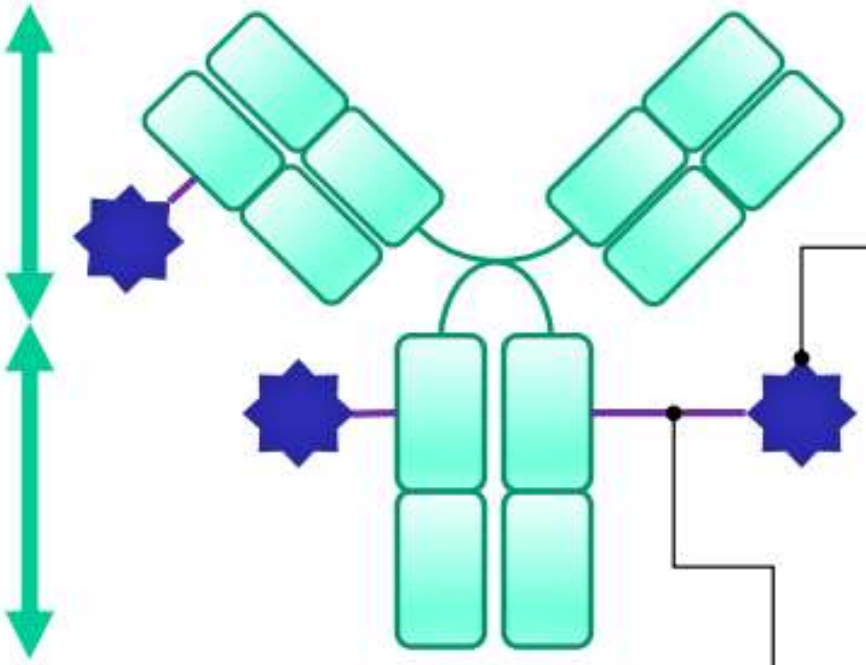
Examples:

– ***Microbiome, germline genetics***

Adapted from Blank CU, et al. Science 2016;352:658-660; Presented by Peters S. et al. AACR 2017

Antibody-Drug Conjugates (ADCs)

Components of ADC



Antibody

- High affinity and specificity to tumor antigen
- Efficient internalization
- Reduced immunogenicity

Payload

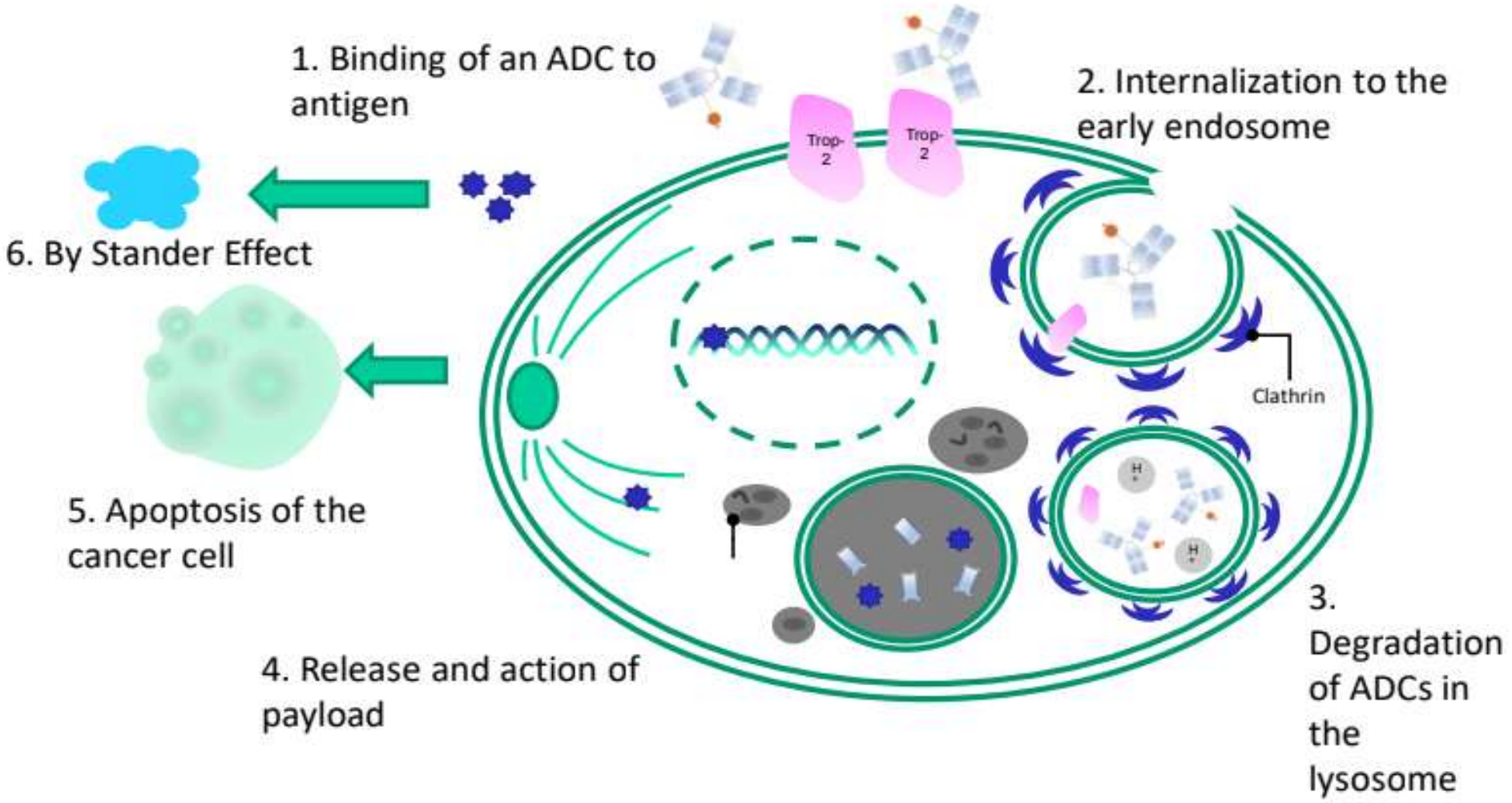
- Highly potent
- Microtubule inhibitors
  - Auristatins
  - Maytansines
- DNA damaging agents
  - Calicheamicin
  - Duocarmycins
  - SN-38

Linker

- Stable in the blood stream
- Capable of releasing payload once internalized
- Cleavable linker
- Non-cleavable linker

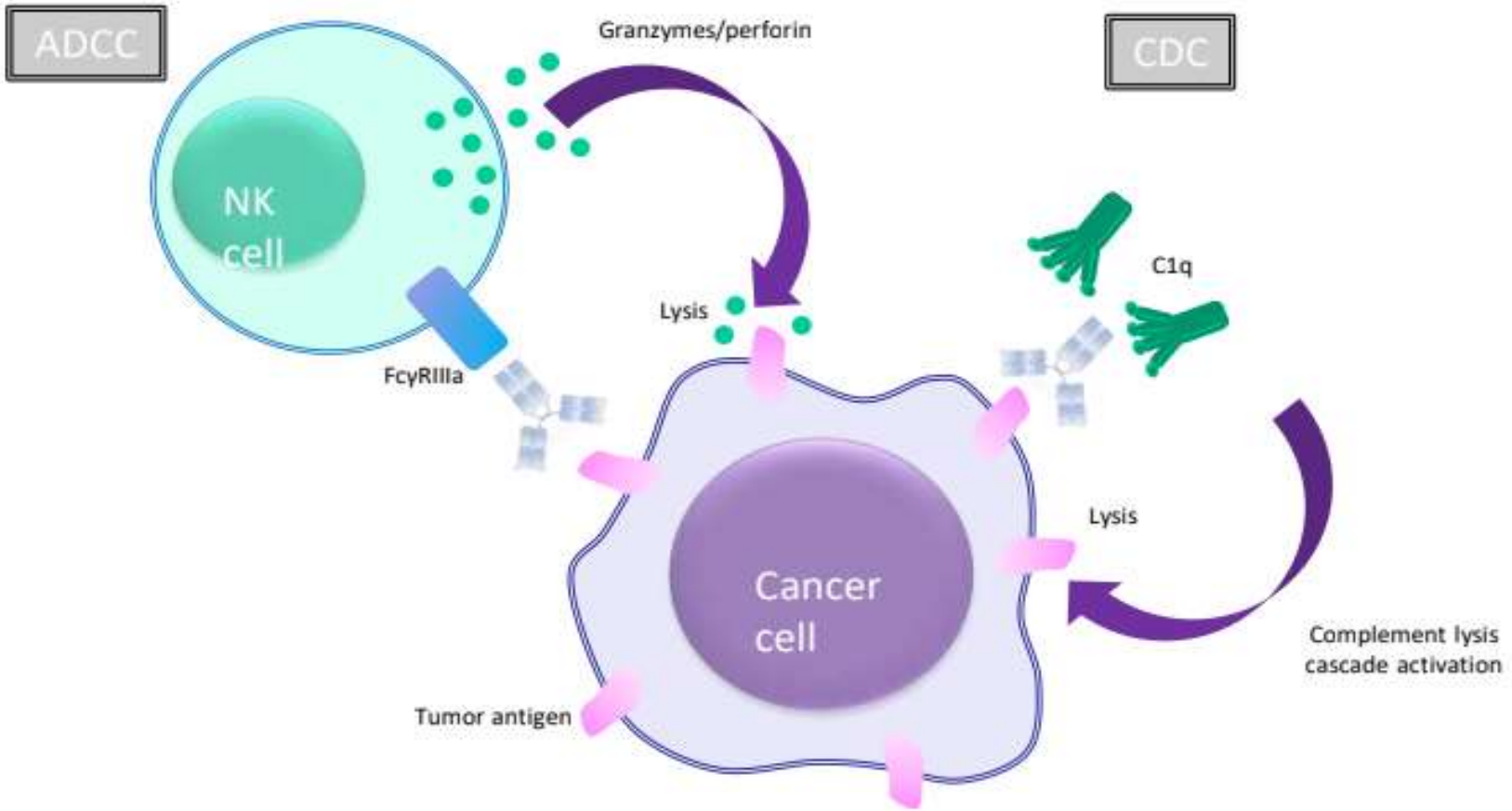
Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

Selective Delivery of Toxic Payload



Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

Another Mechanism of Action: Activation of ADCC?



Nagayama, A, Ellisen L, Chabner B, Bardia A. Target Oncol. 2017

Sacituzumab Govitecan (IMMU132): ADC Targeting *trop-2* in TNBC

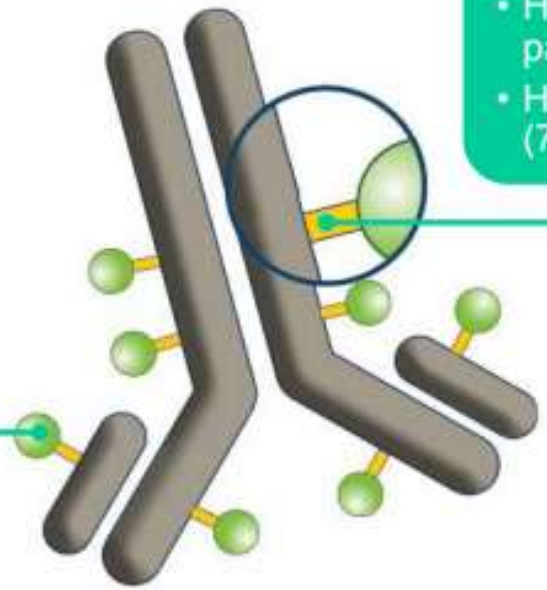
Sacituzumab Govitecan: ADC

Humanized anti-Trop-2 antibody

- Targets Trop-2, an epithelial antigen expressed on many solid cancers, including mTNBC

Linker for SN-38

- Hydrolysable linker for payload release
- High drug-to-antibody ratio (7.5:1)



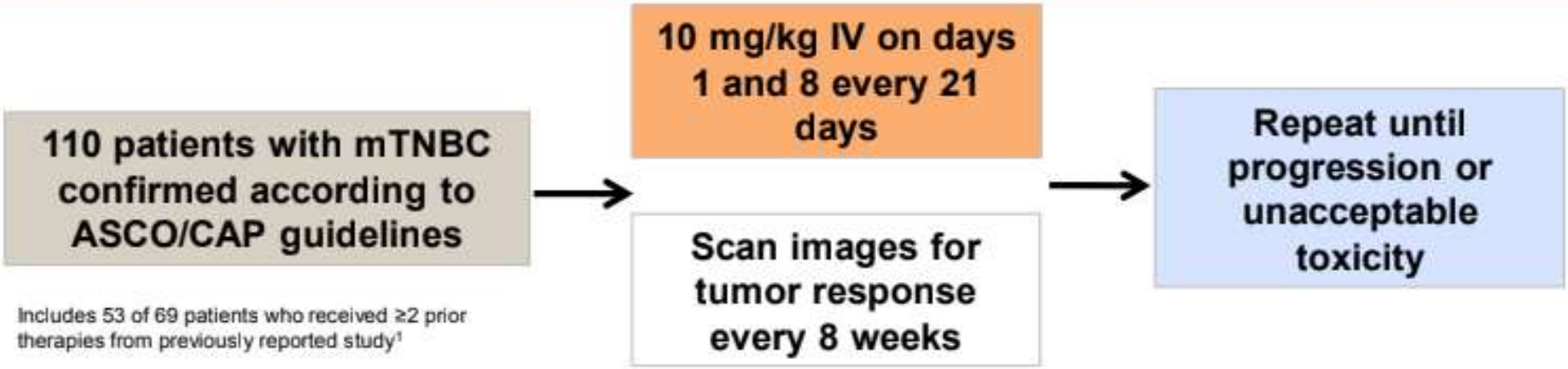
SN-38 payload

- SN-38 more potent than parent compound, irinotecan
- ADC delivers up to 136-fold more SN-38 than irinotecan *in vivo*

Bardia et al. 2017 SABCS. Abstract GS1-07.

Clinical Results in mTNBC

Single-Arm, Open-Label Study Design



Jul 2013 and Feb 2017. Data cutoff date of June 30, 2017.

Key eligibility criteria

- Female or male, ≥18 years of age, ECOG PS 0-1
- ≥2 prior therapies or >1 therapy for patients who progressed within 12 months of adjuvant therapy
- Prior taxane therapy
- Measurable disease

Evaluations

- Response evaluation by investigators
- Blinded independent central review of all CRs, PRs and ≥20% tumor reductions
- Other evaluations: safety, immunogenicity, Trop-2 expression

Bardia et al. *J Clin Oncol.* 2017.

Sacituzumab Govitecan: Demographics and Patient Characteristics

Characteristic	Patients (N=108)
Sex — no. (%)	
Female	107 (99.1)
Male	1 (0.9)
Median age (range) — yr	55 (31–80)
Race or ethnic group — no. (%)*	
White	82 (75.9)
Black	8 (7.4)
Asian	3 (2.8)
Other or not specified†	15 (13.9)
ECOG performance-status score — no. (%)‡	
0	31 (28.7)
1	77 (71.3)
Previous anticancer regimens — median no. (range)	3 (2–10)
Previous use of taxanes or anthracyclines for metastatic or nonmetastatic disease — no. (%)	
Taxanes	106 (98.1)
Anthracyclines	93 (86.1)
Previous use of chemotherapy drugs for metastatic disease — no. (%)	
Cyclophosphamide	20 (18.5)
Platinum agents	74 (68.5)
Gemcitabine	59 (54.6)
Fluoropyrimidine agents	56 (51.9)
Eribulin	49 (45.4)
Vinorelbine	17 (15.7)
Previous use of checkpoint inhibitors — no. (%)	18 (16.7)

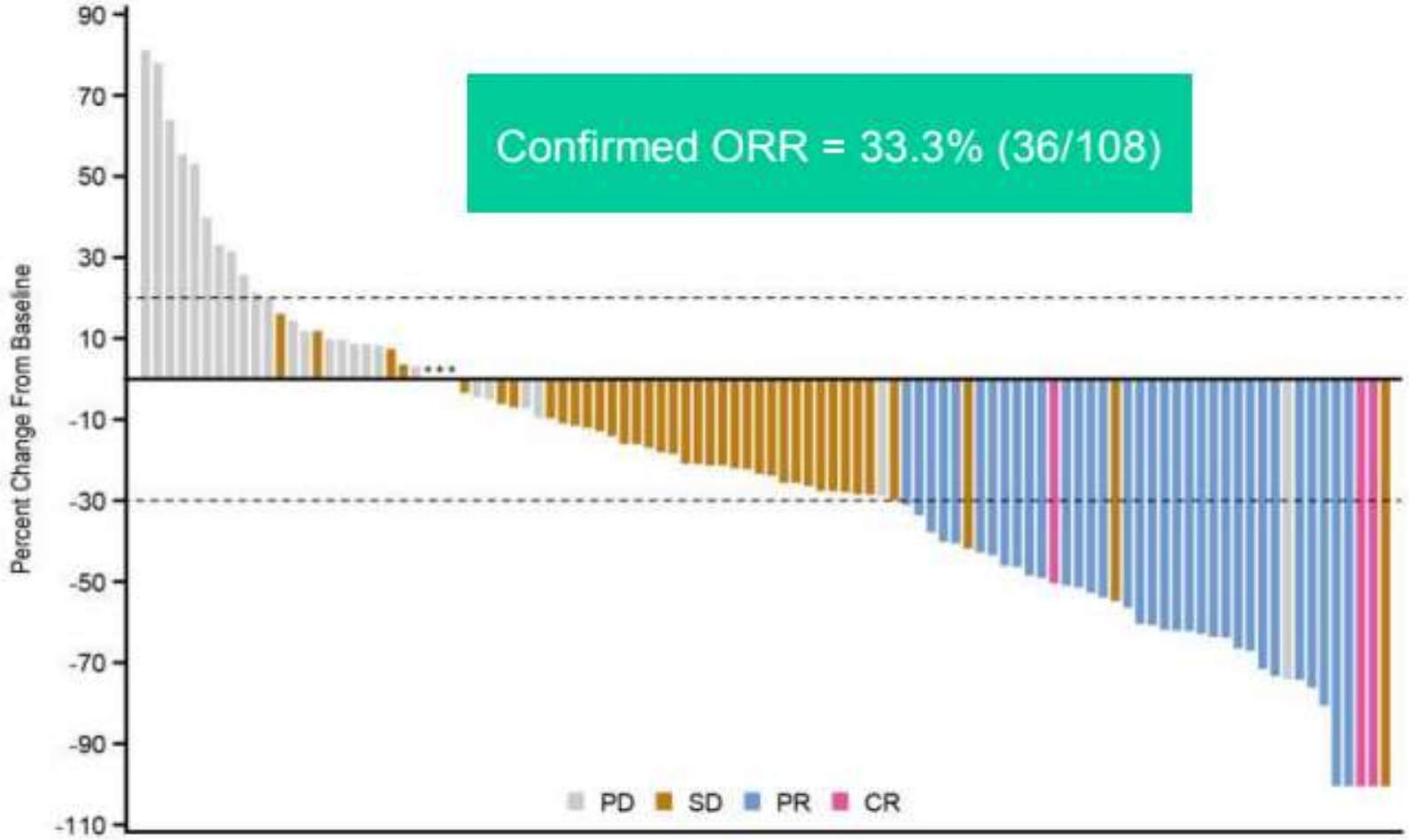
Bardia et al. *NEJM*. 2019.

Sacituzumab Govitecan: AEs in ≥10% of Patients by Worst CTCAE Grade

Adverse Event	mTNBC Population (N=108) All Grades no. (%)	Grade 3 no. (%)	Grade 4 no. (%)
Any adverse event	108 (100)	71 (66)	21 (19)
Gastrointestinal disorders	102 (94)	21 (19)	0
Nausea	**72 (67)**	**7 (6)**	**0**
Diarrhea	**67 (62)**	**9 (8)**	**0**
Vomiting	53 (49)	7 (6)	0
Constipation	37 (34)	1 (1)	0
Abdominal pain*	27 (25)	1 (1)	0
Mucositis†	15 (14)	0	0
General disorders and administration-site conditions	82 (76)	10 (9)	0
Fatigue and asthenia	**59 (55)**	**9 (8)**	**0**
Peripheral edema	17 (16)	0	0
Pyrexia	13 (12)	0	0
Blood and lymphatic system disorders	80 (74)	25 (23)	15 (14)
Neutropenia‡	**69 (64)**	**28 (26)**	**17 (16)**
Anemia	**54 (50)**	**12 (11)**	**0**

Bardia et al. *NEJM*. 2019.

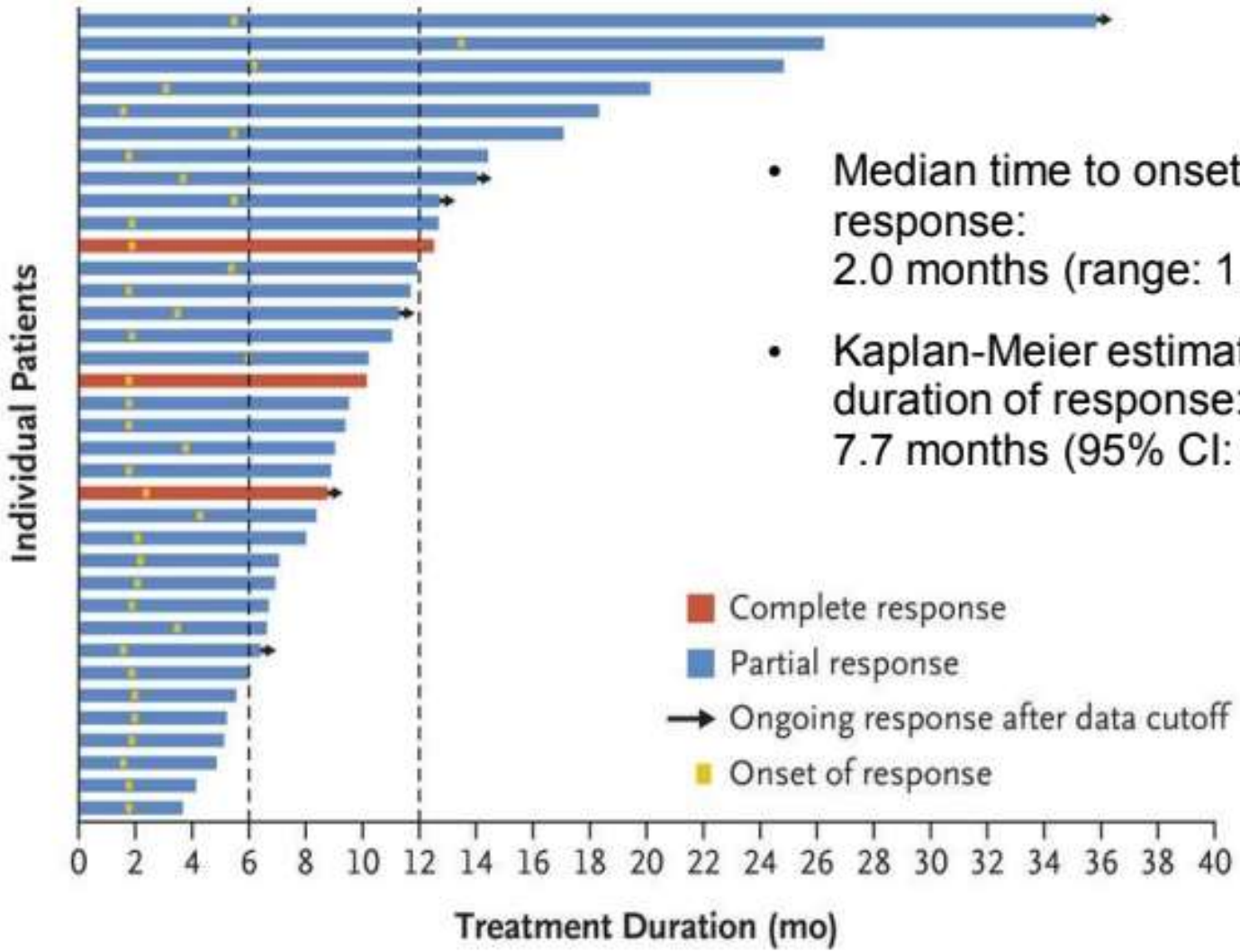
Sacituzumab Govitecan: Tumor Response to Treatment



Clinical benefit rate (CR+PR+SD≥6 mo) = 45.4% (49/108)

Bardia et al. *NEJM*. 2019.

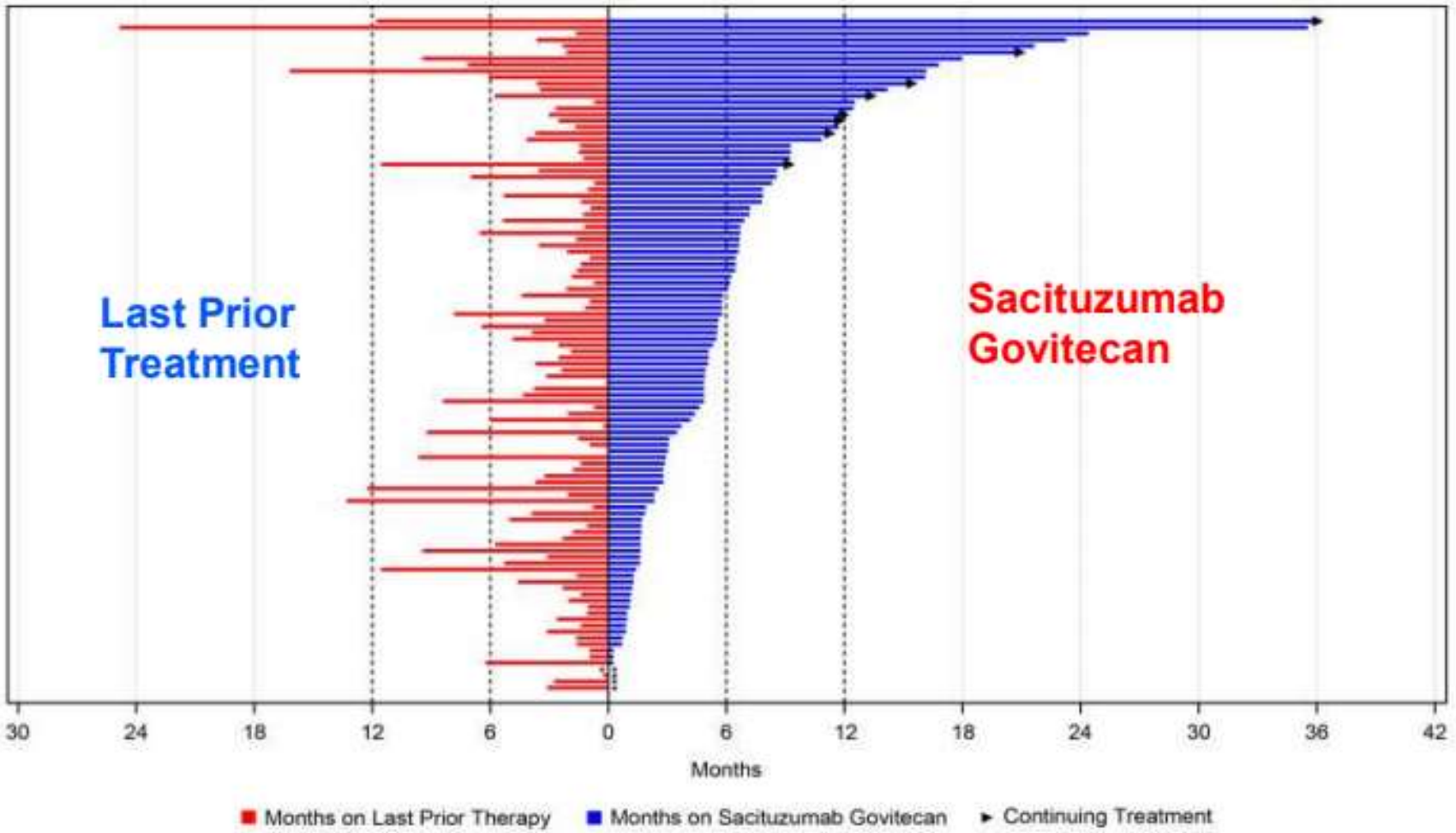
Sacituzumab Govitecan: Response Onset and Durability (n = 36)



- Median time to onset of response:
  2.0 months (range: 1.6-13.5)
- Kaplan-Meier estimated median duration of response:
  7.7 months (95% CI: 4.9, 10.8)

Bardia et al. *NEJM*. 2019.

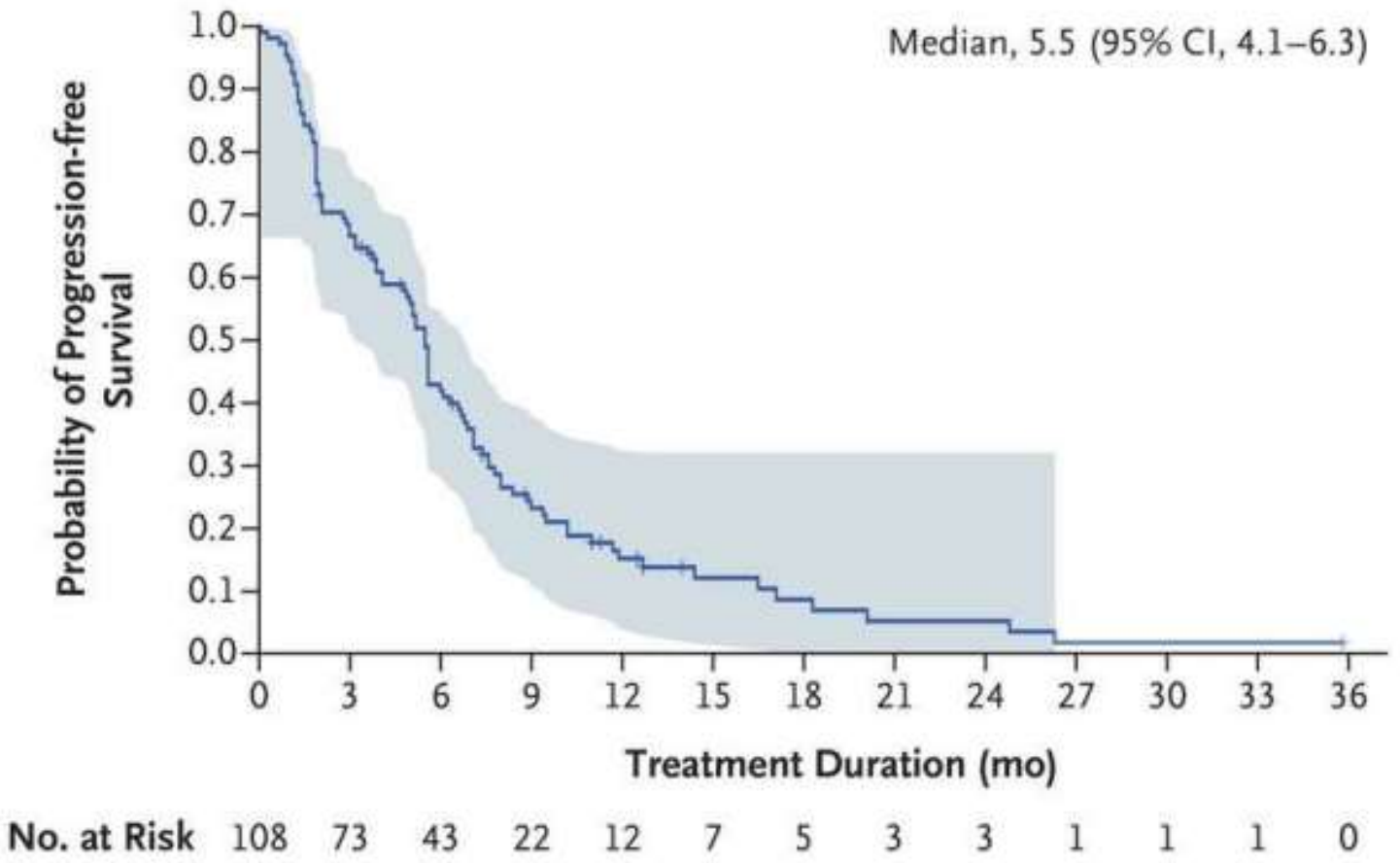
Sacituzumab Govitecan: Time on Treatment for All Patients (N = 110)



Last prior treatment time calculated as last dose date – first dose date. Sacituzumab govitecan time on treatment calculated as (date off study or data cut off date) – first dose date. If more than 1 agent is given in the regimen, the time of the regimen treatment is taken as the longest time for any one of the agents used

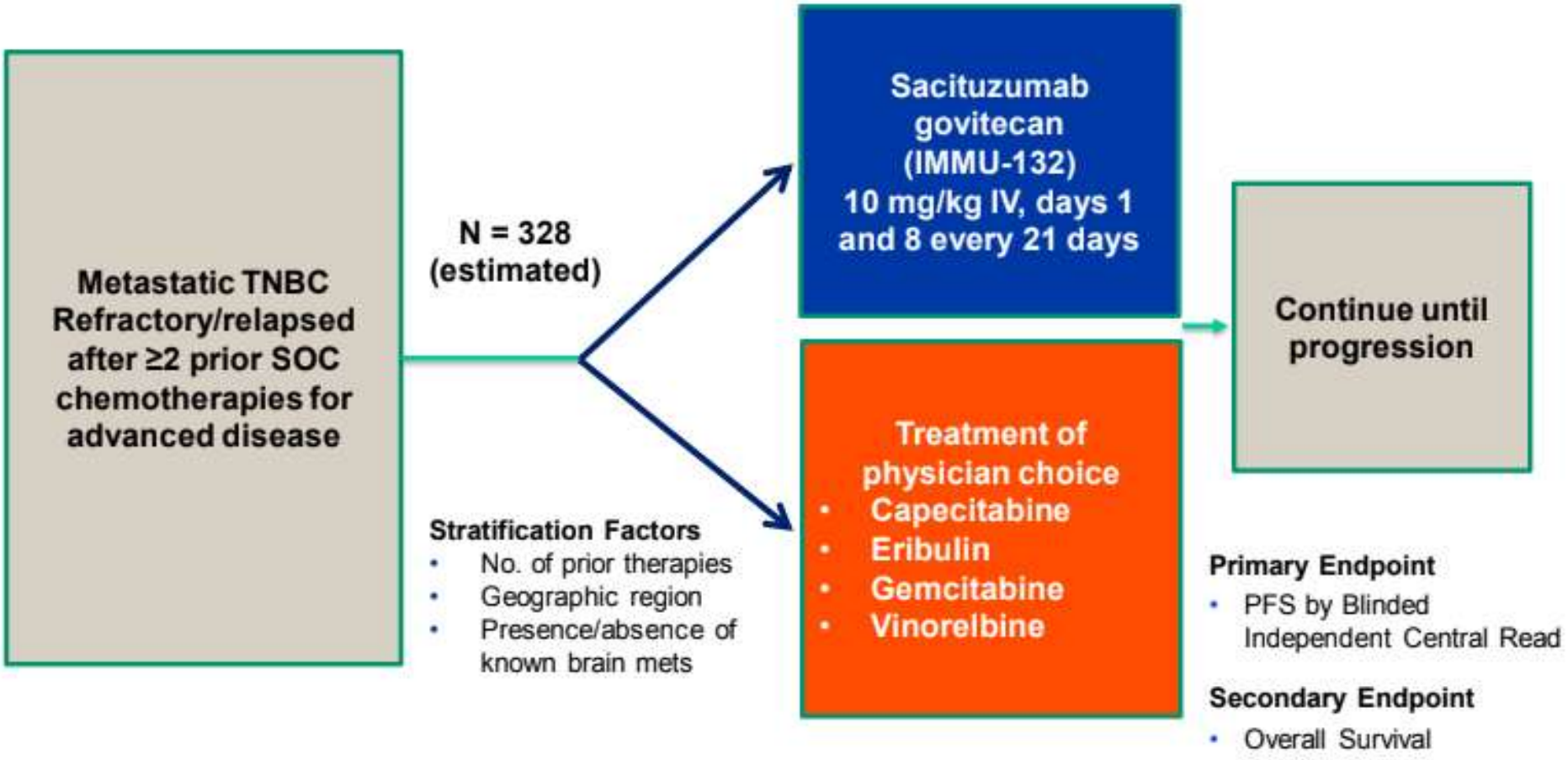
Bardia et al. *NEJM*. 2019.

Sacituzumab Govitecan: Progression-Free Survival



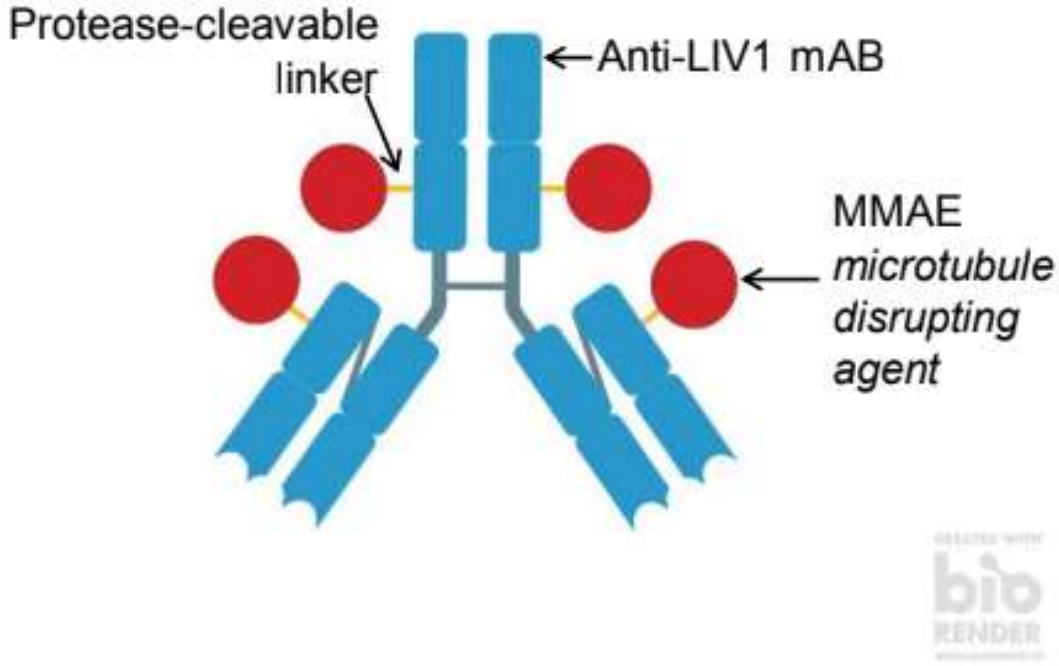
Bardia et al. *NEJM*. 2019.

ASCENT Phase III Study of Sacituzumab Govitecan: Overview



- Clinical trials number: NCT02574455
- Presented at: New Agents and Strategies; December 7, 2017(abstract# 733)

Ladiratuzumab Vedotin: ADC Targeting LIV1



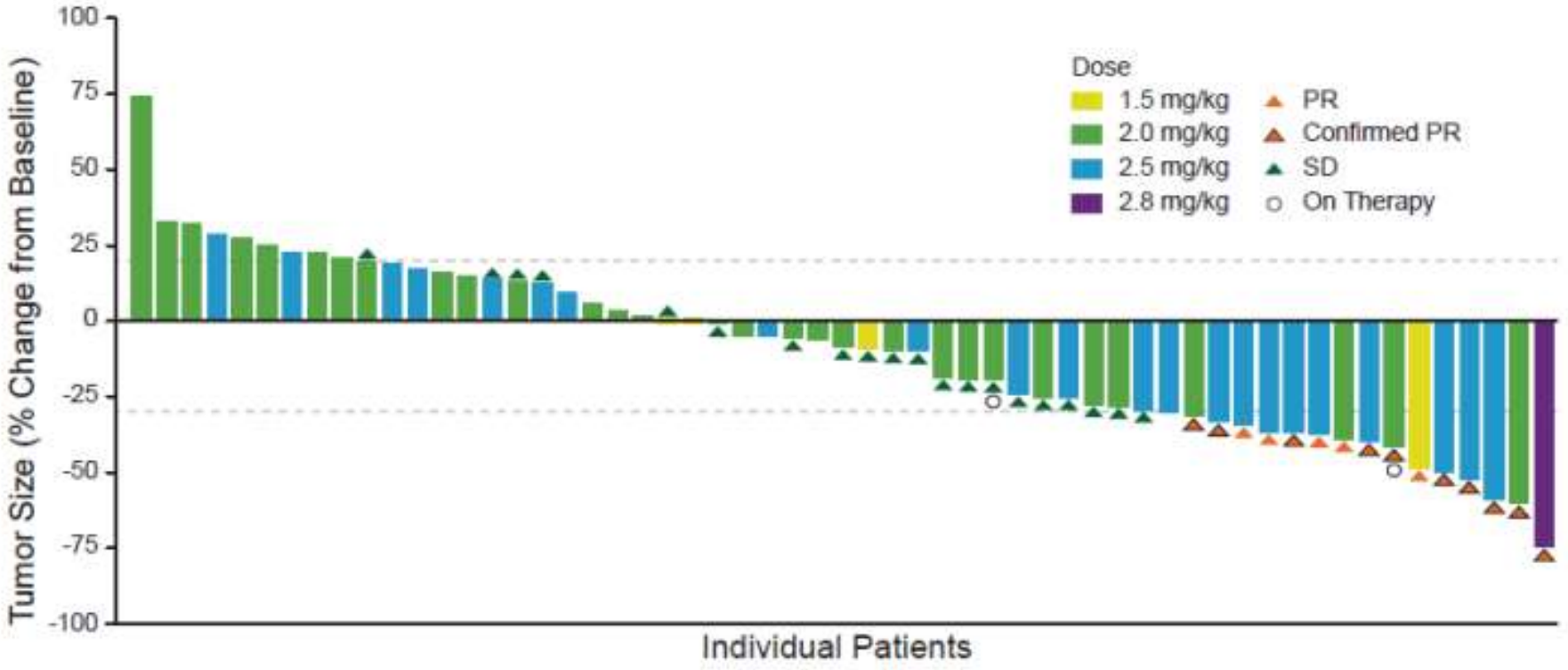
LIV1 is a transmembrane cell adhesion molecule highly expressed in metastatic breast cancer

Mech. of Action:

1. Binds to antigen
2. Complex internalized and trafficked to lysosome
3. Release of MMAE payload
4. Microtubule disruption
5. Cell cycle arrest/disruption

Ladiratuzumab Vedotin: ADC Targeting LIV1

Confirmed ORR = 25% (15/60)



Shanu et al. *SABCS*. 2017

SUMMARY

- Treatment of triple-negative MBC is finally becoming individualized with atezolezomab gaining approval
- PDL-1 testing should become part of the workup for such patients
- ADCs have shown promise and may be the next approval
- It is becoming increasingly clear that PDL-1 is an imperfect biomarker and there are other markers to select patients; perhaps a combination of biomarkers will emerge to better define optimal candidates
- Incorporation in curative settings is eagerly awaited