NOSCM
NEW ORLEANS SUMMER CANCER MEETING

Immunotherapy for Triple Negative Breast Cancer (TNBC)

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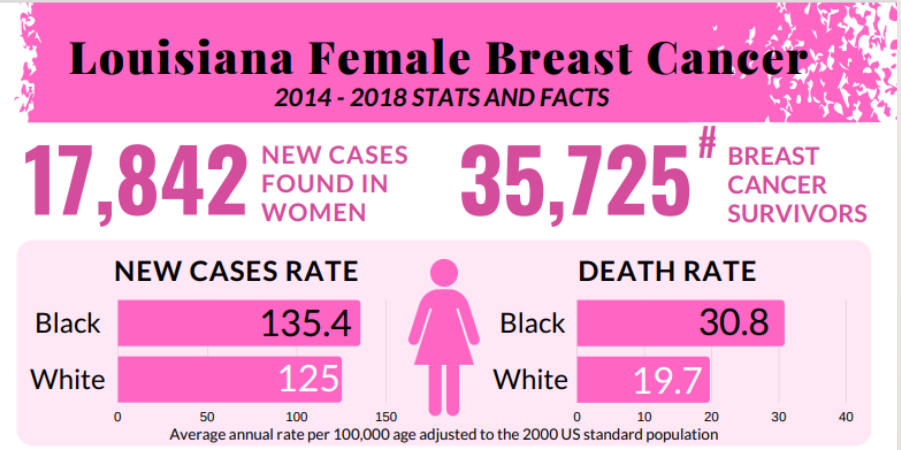
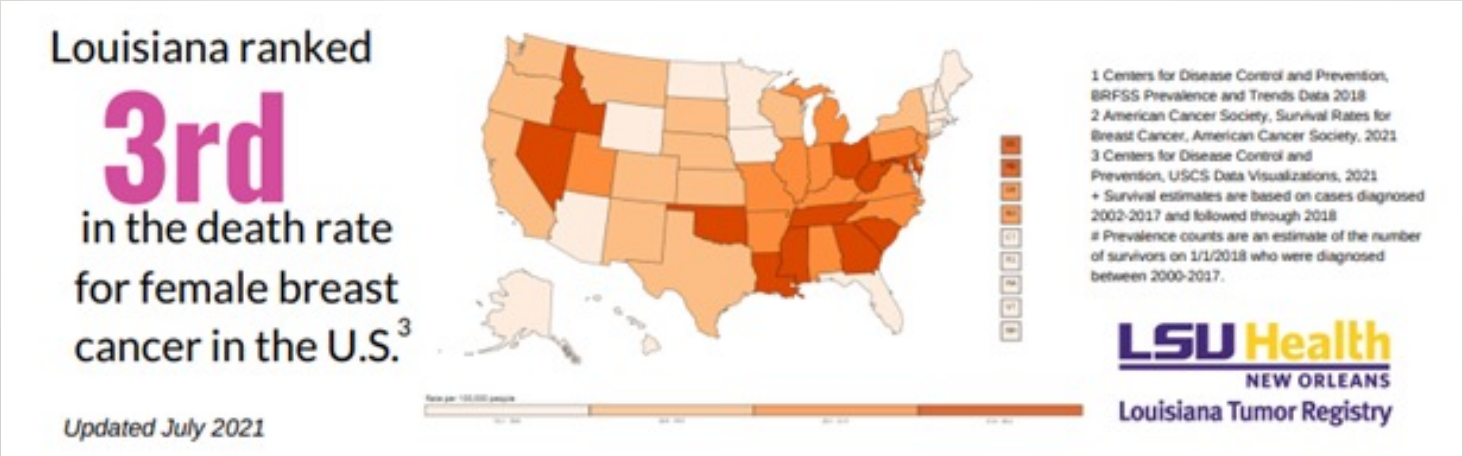
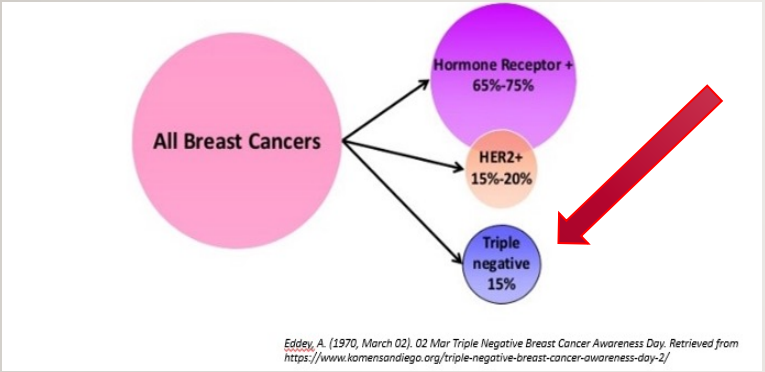
BREAST CANCER DISPARITIES IN LOUISIANA

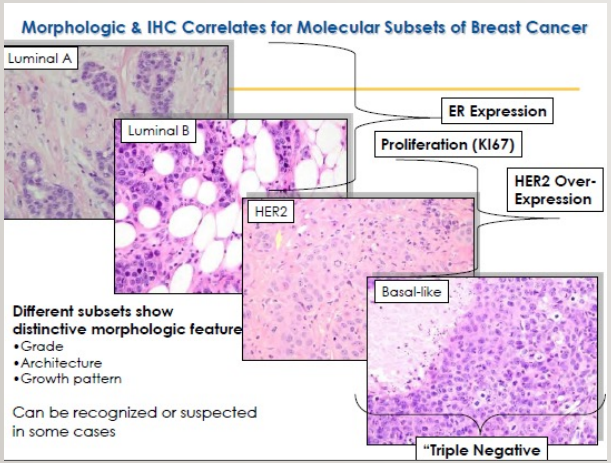


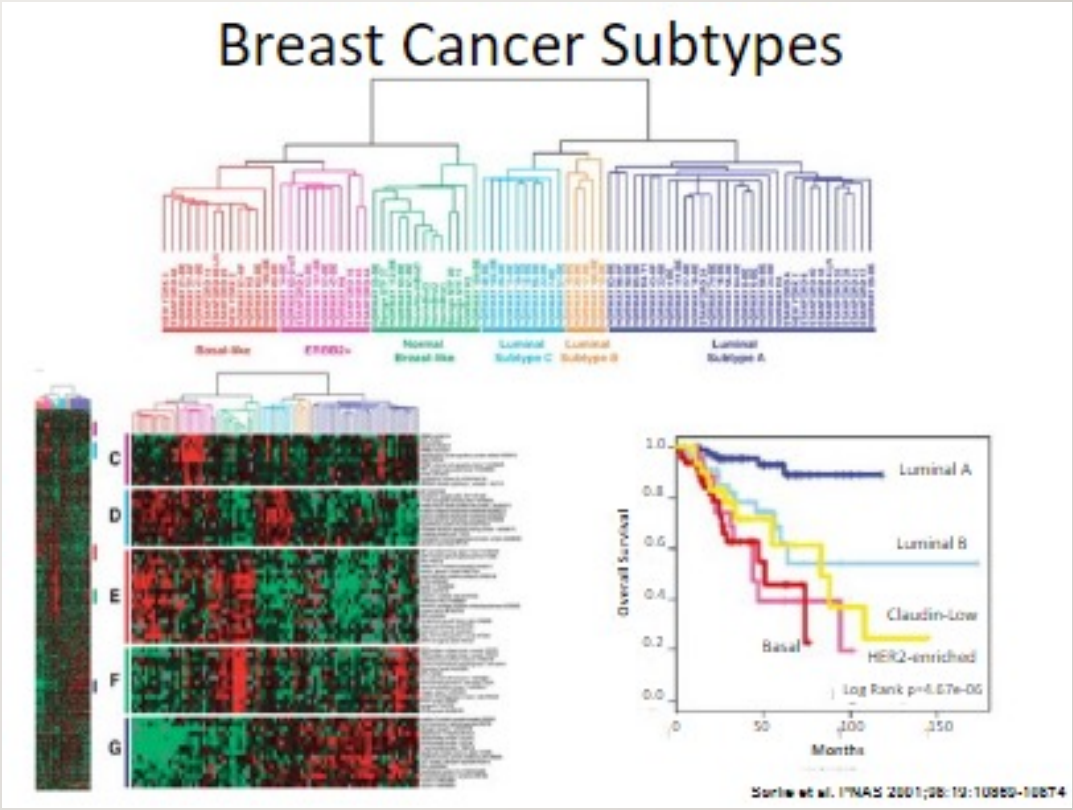


BREAST CANCER SUBTYPES



Eddey, A. (1970, March 02). 02 Mar Triple Negative Breast Cancer Awareness Day. Retrieved from https://www.komensandiego.org/triple-negative-breast-cancer-awareness-day-2/





TRIPLE NEGATIVE BREAST CANCER (TNBC): IMMUNOGENIC TUMOR

- Breast cancer has traditionally been considered a non-immunogenic tumor
- However, multiple studies have shown that TNBC can stimulate the immune system
- Compared with luminal breast cancer, TNBC has:
  - higher tumor mutational burden (TMB)
    - leads to synthesis of "neoantigens" which are recognized by APC
  - elevated levels of PD-L1 expression
  - increased levels of tumor infiltrating lymphocytes (TILs) in the tumor microenvironment—TIL infiltrate have high expression of PD-1
    - TILs are associated with higher rates of pCR to neoadjuvant chemotherapy and efficacy to immunotherapy

IMMUNOTHERAPY USE IN TREATMENT OF TNBC

- The use of targeted therapy in TNBC has been limited
- However, the higher immune response noted in TNBC makes immunotherapy a rational option to address this unmet need
- Promising immunotherapy options for treatment of TNBC include
  - Immune checkpoint (IC) inhibitors
    - PD-1/PDL1 and cytotoxic T-lymphocyte-associated antigen (CTLA-4) are the primary immune checkpoint blockades
  - Adoptive T-cell immunotherapy
  - Tumor vaccine immunotherapy
- The combination of immunotherapy with other treatments such as chemotherapy

EVOLUTION OF IMMUNOTHERAPY IN TREATMENT OF TNBC

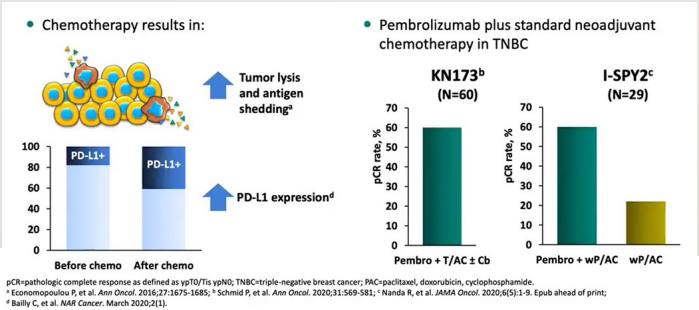
- 1st wave: immunotherapy monotherapy
  - Showed antitumor activity with modest results in advanced disease
- 2nd wave: immunotherapy in combination with chemotherapy
  - Chemotherapy can increase release of tumor antigens, alter tumor microenvironment, upregulate PD-L1 expression—increase immunotherapy effectiveness
- 3rd wave: immunotherapy with targeted therapies
  - Keylynk-009: olaparib+pembrolizumab vs chemotherapy (carboplatin/gemcitabine) + pembrolizumab after initial treatment with chemo+pembro
  - ASCENT trial which lead to approval of the antibody-drug conjugate sacituzumab govitecan as 3rd line or greater in mTNBC

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: PEMBROLIZUMAB

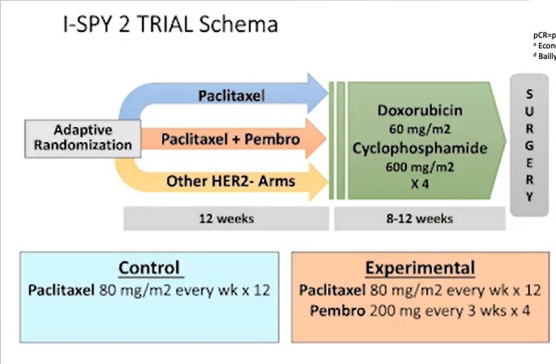
- Pembrolizumab monotherapy in mTNBC (KEYNOTE-012, June 2017)-Phase IB
  - Showed similar antitumor activity and manageable toxicity profile
    - ORR 18.5%, SDR 25.9%, PR 14.8% and CR 3.7%
- Pembrolizumab as ≥2nd line in mTNBC (KEYNOTE-086, March 2019)-Phase II
  - After anthracyclines & taxanes for up to 2 years
  - ORR in PD-L1+ 4.7%, SDR 20.6%, PR 4.1% and CR 0.6% with DOR 6.3 mo
- Pembrolizumab monotherapy in mTNBC (KEYNOTE-119, September 2019)-Phase III
  - Compared to single agent chemotherapy in previously treated mTNBC (1-2 prior systemic treatments) stratified by PD-L1 status: all pts vs CPS≥10 vs CPS≥20
    - No OS with CPS≥10 but with CPS≥20, OS 14. 9 mo vs 12.5 (HR 0.58) with chemotherapy
    - No PFS was observed
    - Grade 3-5 AEs were 14% vs 36% with chemotherapy

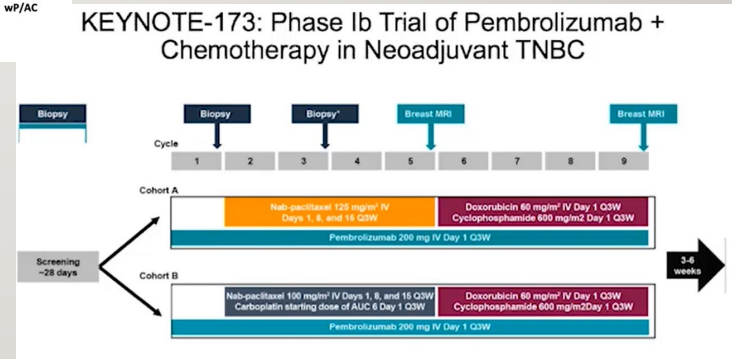
IMMUNOTHERAPY AGENTS APPROVED IN TNBC: PEMBROLIZUMAB

- Pembrolizumab + neoadjuvant chemotherapy in early stage II-III TNBC (KEYNOTE-173 & I-SPY2 studies
- Combined results from I-SPY2 and KEYNOTE-173 studies
  - Neoadjuvant paclitaxel ± pembro followed by AC
  - In TNBC subgroup, the combination increased pCR up to 3X more (62.4% vs 22.3%)



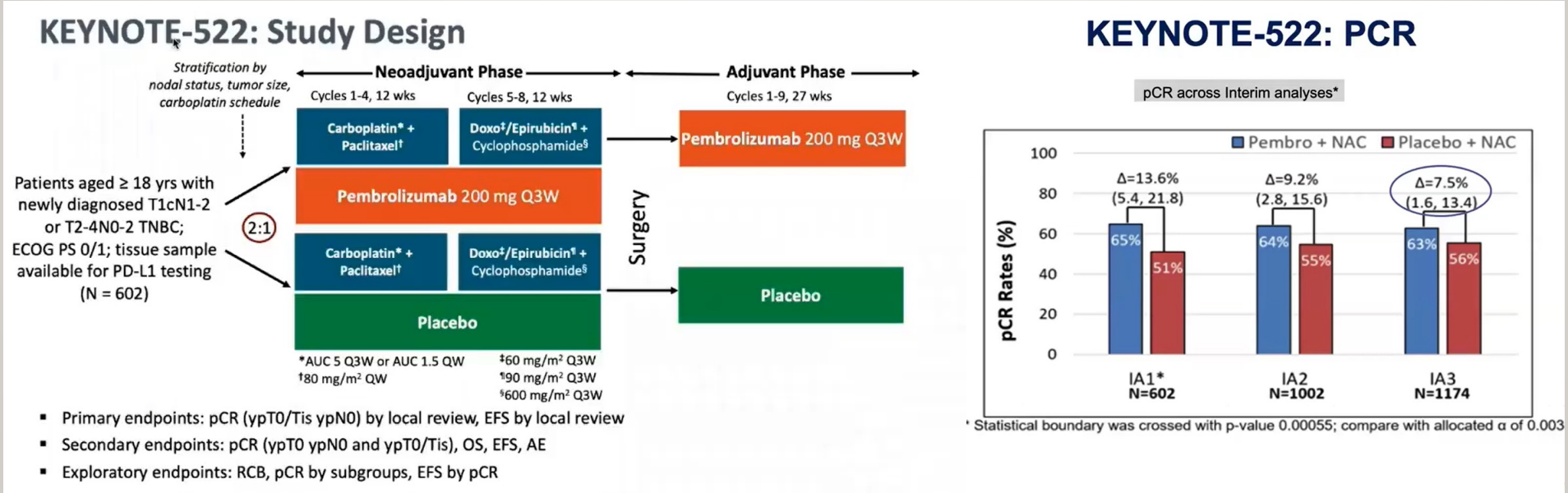
pCR=pathologic complete response as defined as ypT0/Tis ypN0; TNBC=triple-negative breast cancer; PAC=paclitaxel, doxorubicin, cyclophosphamide.
[a] Economopoulou P, et al. *Ann Oncol*. 2016;27:1675-1685; [b] Schmid P, et al. *Ann Oncol*. 2020;31:569-581; [c] Nanda R, et al. *JAMA Oncol*. 2020;6(5):1-9. Epub ahead of print;
[d] Bailly C, et al. *NAR Cancer*. March 2020;2(1).





IMMUNOTHERAPY AGENTS APPROVED IN TNBC: PEMBROLIZUMAB

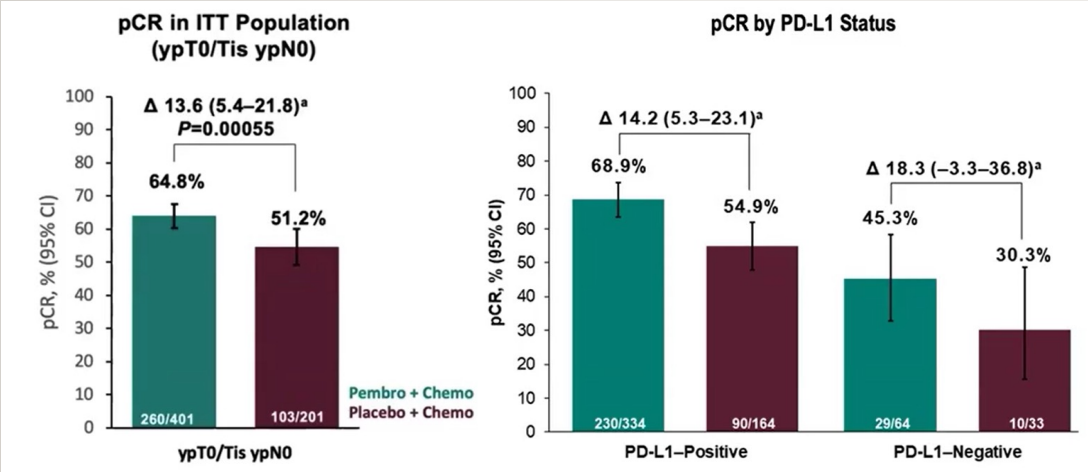
- Pembrolizumab + neoadjuvant chemotherapy in early stage TNBC (KEYNOTE-522, September 2017)-Ph2 Phase II

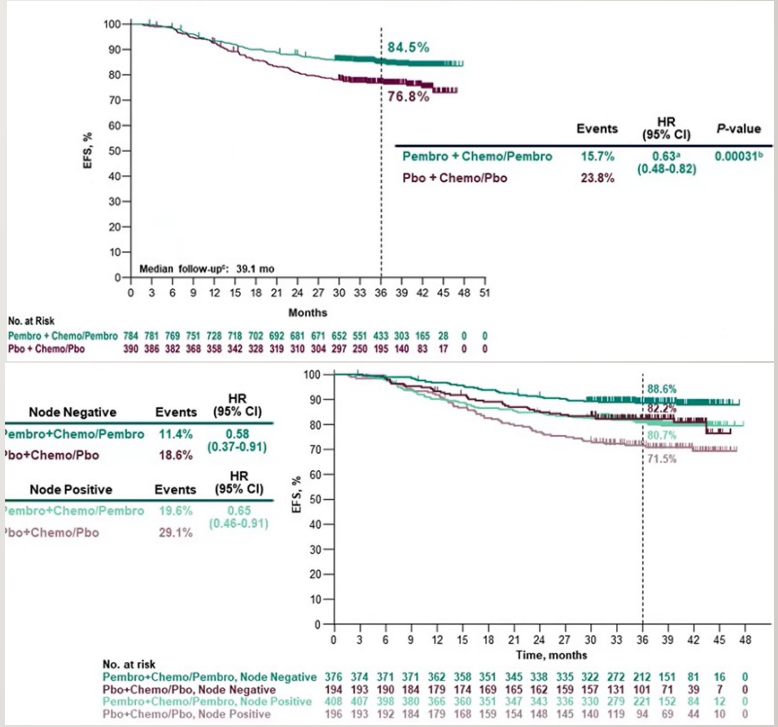


- Pembro improved pCR across all subgroups (64.8% vs 51.2%; p<0.001)
  - Stage IIIA (66.7% *vs* 42.1%, Δ 24.6) and IIIB (48.6% *vs* 23.1%, Δ 25.6)
  - N+ (64.8% *vs* 44.1%, Δ 20.6) *vs* N0 (64.9% *vs* 58.5%, Δ 6.3)

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: PEMBROLIZUMAB

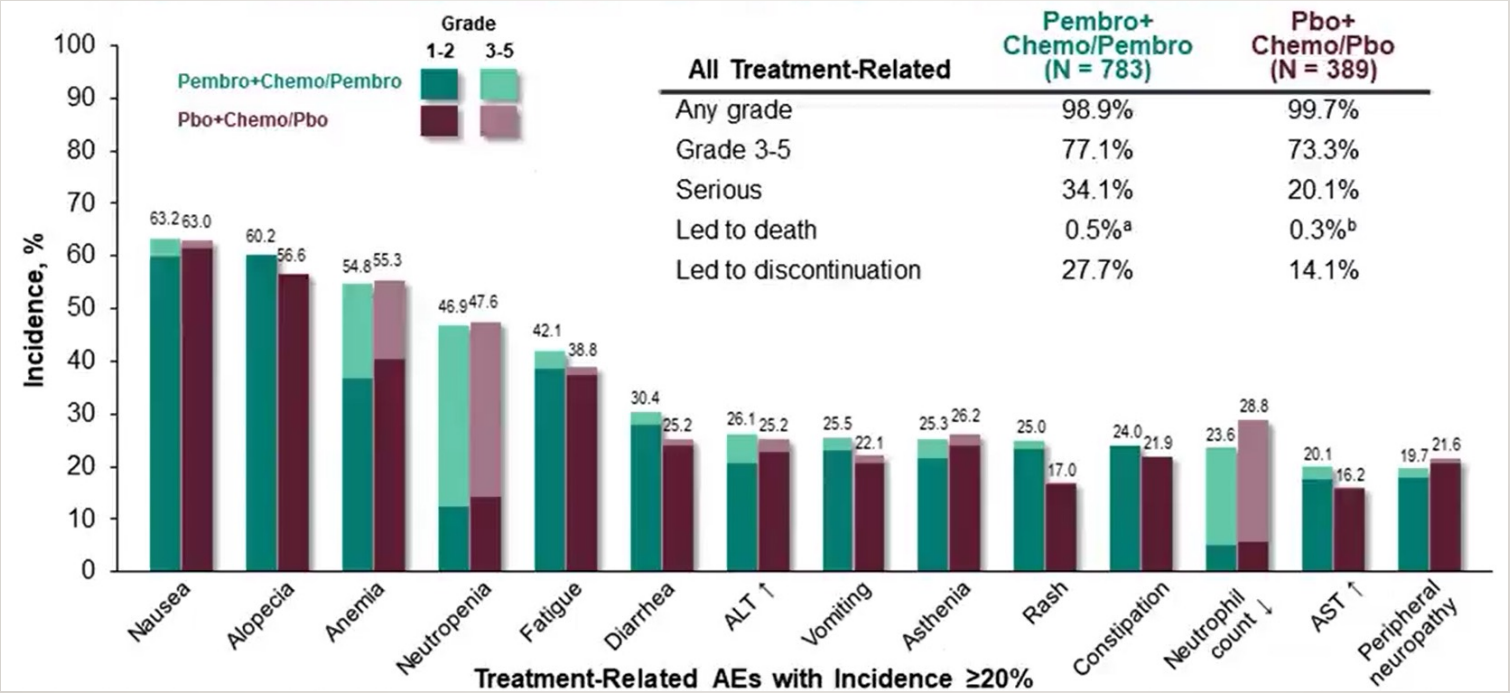
- Pembrolizumab + neoadjuvant chemotherapy (CT) in early stage TNBC





- Found PDL1 did not predict benefit to therapy
- Updates at SABC 2020 showed pembro + CT improved PFS, ORR, durable CR and duration of response in tumor with CPS≥10 regardless of CT partner

TREATMENT-RELATED ADVERSE EVENTS WITH PEMBROLIZUMAB



All Treatment-Related	Pembro+ Chemo/Pembro (N = 783)	Pbo+ Chemo/Pbo (N = 389)
Any grade	98.9%	99.7%
Grade 3-5	77.1%	73.3%
Serious	34.1%	20.1%
Led to death	0.5%[a]	0.3%[b]
Led to discontinuation	27.7%	14.1%

- Updates at SABC 2020 showed pembro + CT improved PFS, ORR, durable CR and duration of response in tumor with CPS≥10 regardless of CT partner

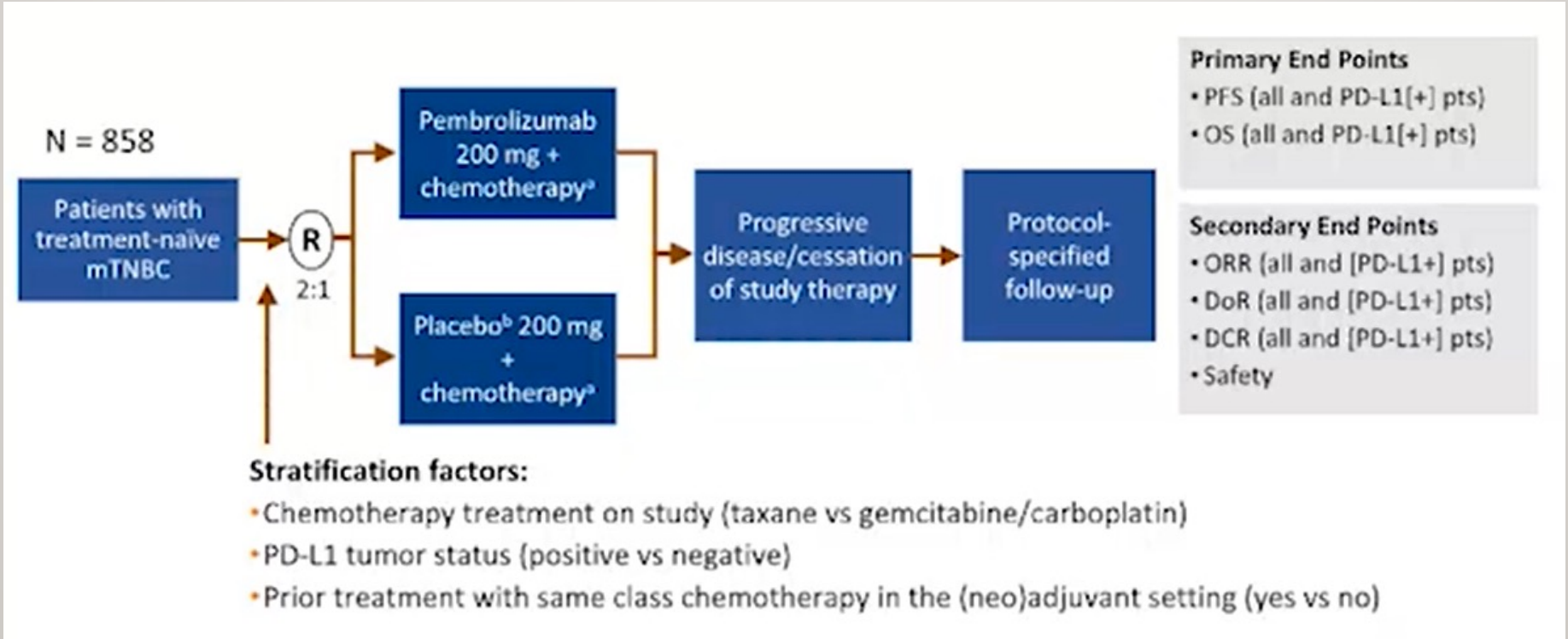
KEYNOTE-522 INVESTIGATOR CONCLUSIONS

- In patients with early-stage TNBC, neoadjuvant pembrolizumab + chemotherapy associated with a larger pCR benefit vs chemo alone
  - Particularly for patients with stage III or node-positive disease
  - Benefit seen in patients who received less than planned full chemotherapy
  - Similar benefit observed regardless of PD-L1 expression level
- Neoadjuvant pembrolizumab added to chemotherapy associated with higher rate of lower residual cancer burden
- Rate of immune-mediated adverse events in study consistent with that reported previously and no new safety signal observed
- Additional follow-up needed to confirm EFS benefit and long-term safety profile

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: PEMBROLIZUMAB

- Pembrolizumab + chemotherapy in mTNBC (KEYNOTE-355, December 2020)-Ph III

KEYNOTE-355 STUDY DESIGN



IMMUNOTHERAPY AGENTS APPROVED IN TNBC: PEMBROLIZUMAB

- Pembrolizumab + chemotherapy in mTNBC (KEYNOTE-355, December 2020)-Ph III
  - Untreated pts with inoperable disease or mTNBC
    - nab-paclcitaxel, paclitaxel or gemcitabine with carboplatin vs placebo/chemotherapy
    - Stratified by PD-L1 status: ITT vs CPS≥1 vs CPS≥10
      - PFS statistically significant (9.7 vs 5.6, p=0.0012, HR 0.65) in those with CPS≥10
        - Pembro effect increased in PD-L1 enriched population especially with paclitaxel (asymmetry of chemotherapy)
        - No difference in grade 3-5 AEs (68% with pembro vs 67% placebo)
        - Lead to pembrolizumab with chemotherapy as 1st line treatment option in mTNBC
    - Updates at SABC 2020 showed pembro+CT improved PFS, ORR, durable CR and duration of response in tumor with CPS≥10 regardless of CT partner
      - FDA granted accelerated approval of pembro+chemo in this setting in November 2020
    - Updates at SABC 2021 final results demonstrated improved OS over placebo with CPS≥10 reasonable cutoff to determine expected treatment benefit
      - Note: Different assays used to assess PD-L1

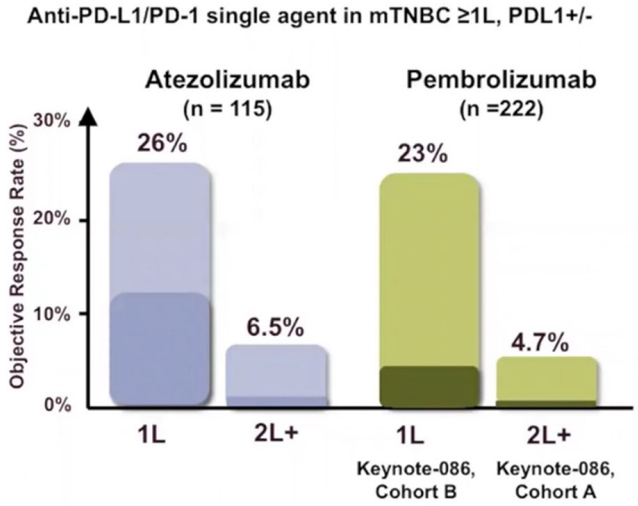
IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

- Have 3 phase III atezolizumab TNBC trials with similar designs, with the primary difference being the chemotherapy component:
- IMpassion130: Subjects receive either atezo + nab-paclitaxel or placebo + nab-paclitaxel.
  - The four primary endpoints include PFS in PD-L1+ subjects, where the drug was most successful and the patient population for which the drug combo was ultimately approved.
- IMpassion131: Subjects receive atezo +paclitaxel or placebo + paclitaxel.
  - The study failed to hit PFS in the PD-L1+ population, the primary outcome and low-hanging fruit of this trial (PFS in the intent-to-treat population follows). Unlike -130 and -132, OS is not included as a primary endpoint.
- IMpassion132: This one is a bit of a free-for-all: as with -130 and -131, they're enrolling previously untreated patients, but the primary endpoint is OS in the PD-

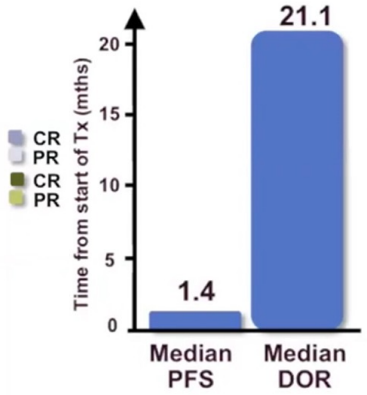
IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

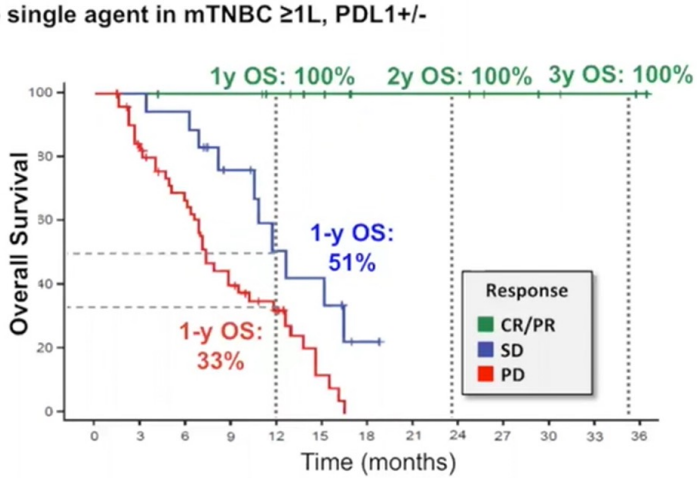
- Atezolizumab monotherapy in mTNBC (Schmid et al, 2017)-Phase I

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



PFS & Duration of Response to anti-PD-L1/anti-PD1

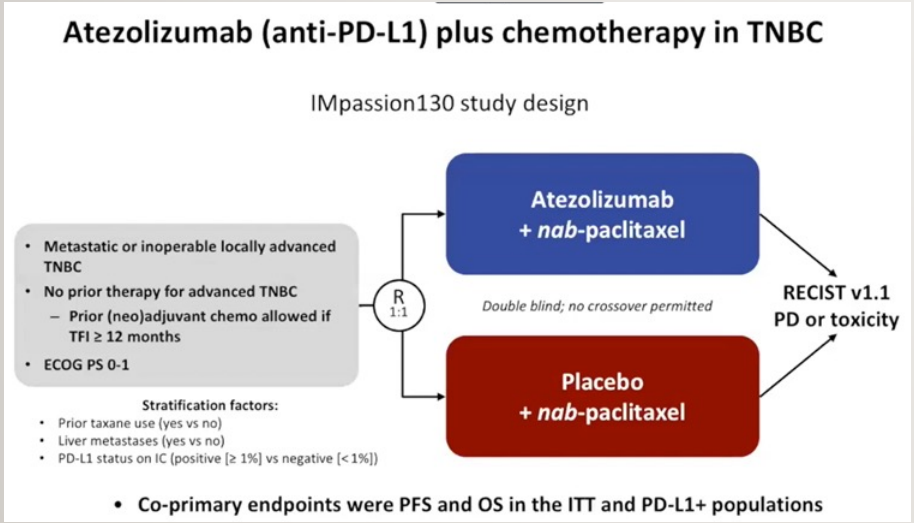


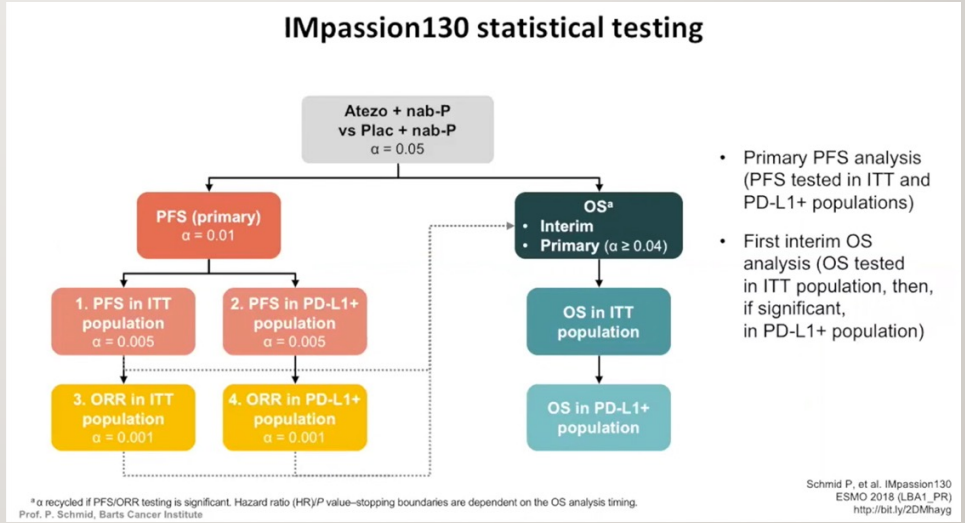


- Safe and tolerable with antitumor activity in mTNBC especially as 1st line
  - OS 41% at 1 yr, 19% at 2 yrs and 16% at 3 yrs—10% of responders alive in 1 year
  - PD-L1+ had higher ORR (12% vs 0%) and higher OS (10.1 mo vs 6 mo)
  - Grade 3-5 AEs were 14% vs 36% with chemotherapy

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

- Atezolizumab + nab-paclitaxel in mTNBC (Impassion130, November 2018)-Phase III
  - 1st line in mTNBC or unresectable locally advanced vs placebo+nab-paclitaxel





Schmid, P. et al, NEJM 2018

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

- Atezolizumab + nab-paclitaxel in mTNBC (Impassion130, November 2018)-Phase III
  - 1st line in mTNBC or unresectable locally advanced vs placebo+nab-paclitaxel

IMpassion130 baseline characteristics

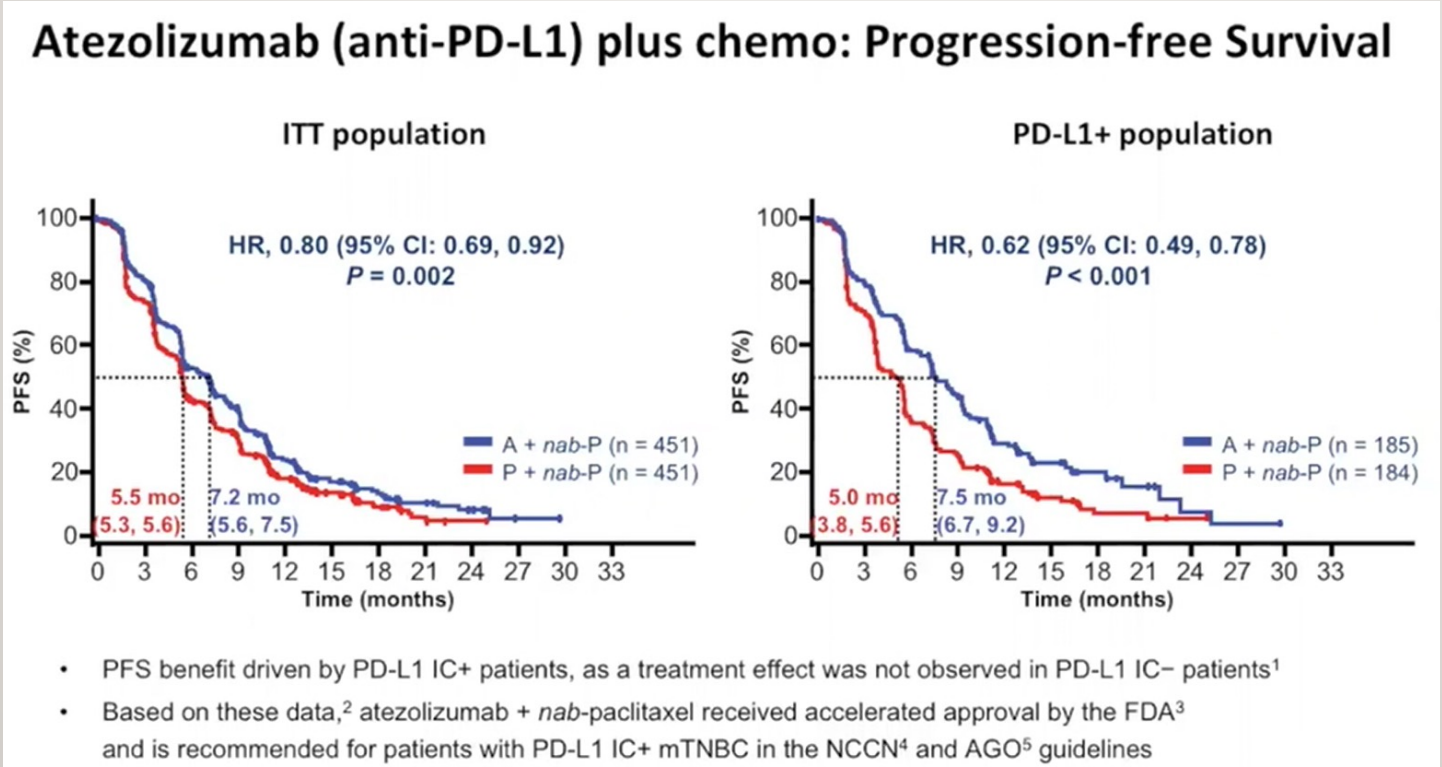
	Atezo + nab-P (N = 451)	Plac + nab-P (N = 451)
Median age (range), y	55 (20-82)	56 (26-86)
Race, n (%)[a]		
White	308 (68%)	301 (67%)
Asian	85 (19%)	76 (17%)
Black/African American	26 (6%)	33 (7%)
ECOG PS, n (%)[b,c]		
0	256 (57%)	270 (60%)
1	193 (43%)	179 (40%)
Prior (neo)adjuvant treatment, n (%)	284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

	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%)

Schmid, P. et al, NEJM 2018

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

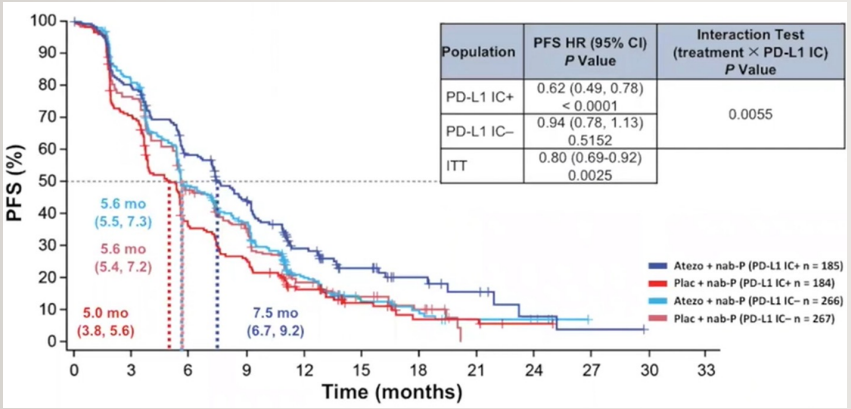
- Atezolizumab + nab-paclitaxel in mTNBC (Impassion130, November 2018)-Phase III
  - 1st line in mTNBC or unresectable locally advanced vs placebo+nab-paclitaxel



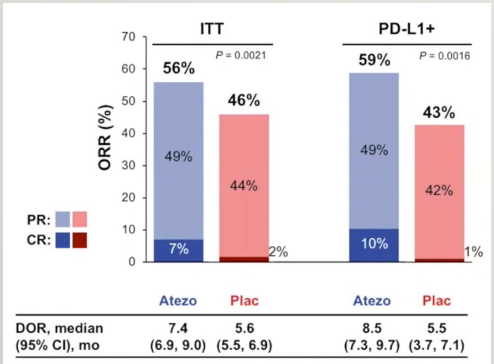
Schmid, P. et al, NEJM 2018

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

- PDL1 positivity predicts benefit of immunochemotherapy
- 1st line in mTNBC or unresectable locally advanced vs placebo+nab-paclitaxel



Population	PFS HR (95% CI) *P* Value	Interaction Test (treatment × PD-L1 IC) *P* Value
PD-L1 IC+	0.62 (0.49, 0.78) < 0.0001	0.0055
PD-L1 IC–	0.94 (0.78, 1.13) 0.5152	
ITT	0.80 (0.69-0.92) 0.0025	

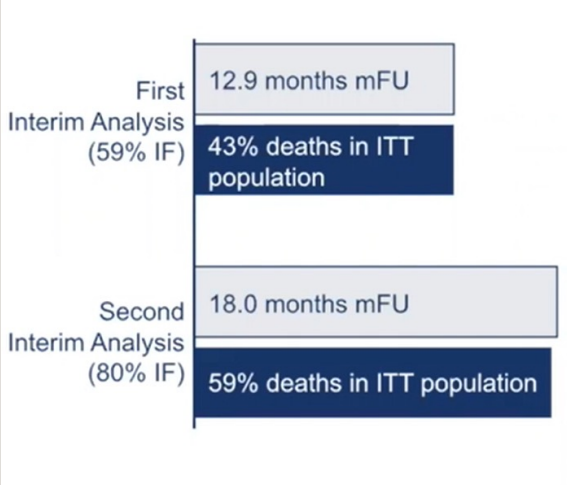


	ITT		PD-L1+	
DOR, median (95% CI), mo	7.4 (6.9, 9.0)	5.6 (5.5, 6.9)	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)

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)

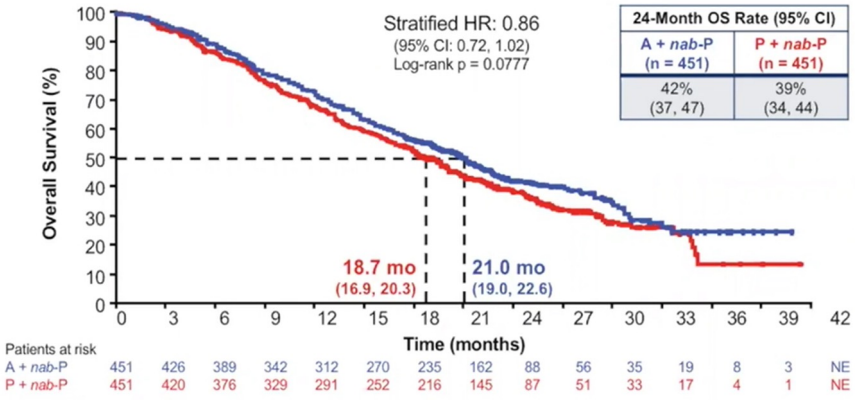
Schmid, P. et al, NEJM 2018

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB



Second Interim OS Analysis		
Patient Disposition	**Atezolizumab + *nab*-paclitaxel (n = 451)**	**Placebo + *nab*-paclitaxel (n = 451)**
Patients on study, n (%)		
Alive on treatment	39 (9%)	13 (3%)
Alive in survival follow-up	133 (30%)	135 (30%)
Patients who discontinued study, n (%)		
Dead	255 (57%)	279 (62%)
Lost to follow-up	24 (5%)	24 (5%)

Overall survival: 2nd Interim Analysis



Most common AEs regardless of attribution

AEs in ≥ 20% (all grade) or ≥ 3% (grade 3-4) of patients in either arm, n (%)	Atezo + nab-P (n = 452)		Plac + nab-P (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Alopecia	255 (56%)	3 (1%)	252 (58%)	1 (< 1%)
Fatigue	211 (47%)	18 (4%)	196 (45%)	15 (3%)
Nausea[a]	**208 (46%)**	**5 (1%)**	**167 (38%)**	**8 (2%)**
Diarrhoea	147 (33%)	6 (1%)	150 (34%)	9 (2%)
Anaemia	125 (28%)	13 (3%)	115 (26%)	13 (3%)
Constipation	113 (25%)	3 (1%)	108 (25%)	1 (< 1%)
Cough[a]	**112 (25%)**	**0**	**83 (19%)**	**0**
Headache	105 (23%)	2 (< 1%)	96 (22%)	4 (1%)
Neuropathy peripheral	98 (22%)	**25 (6%)**	97 (22%)	**12 (3%)**
Neutropaenia[a]	**94 (21%)**	**37 (8%)**	**67 (15%)**	**36 (8%)**
Decreased appetite	91 (20%)	3 (1%)	79 (18%)	3 (1%)
Neutrophil count decreased	57 (13%)	21 (5%)	48 (11%)	15 (3%)
Hypertension	22 (5%)	4 (1%)	24 (5%)	11 (3%)

Schmid, P. et al, NEJM 2018; ASCO 2019

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

- Atezolizumab + nab-paclitaxel in mTNBC (Impassion130, November 2018)-Phase III
  - After 12.9 mo followup:
    - In ITT, immunochemotherapy increased PFS (7.2 mo vs 5.5 mo, HR 0.80, p=0.002), although no increase in OS (21.3 mo vs 17.6 mo, HR 0.84; p=0.08)
    - PD-L1+ (IC≥1%), had improved PFS (7.5 mo vs 5.0 mo, HR 0.62, p<0.001) and OS (25 mo vs 15.5 mo, HR 0.62).
  - At 18. month followup, OS 21.0 mo vs 18.7 mo in ITT (p=0.0777) and PD-L1+ group with OS 25.0 mo vs 18.0 mo (HR 0.71)
    - Increased AEs leading to discontinuation in immunochemotherapy group (15.9% vs 8.2%)
  - Final analysis agreed with interim findings of prolongation of PFS (21.0 mo vs 15.5 mo) and OS in mTNBC subgroup with PD-L1+ but not in the ITT population
    - Achieved FDA accelerated approval in March 2019 but company voluntarily withdrew

IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

- Atezolizumab + paclitaxel vs placebo in mTNBC (IMpassion131; July 2021)-Phase III
  - 1st line in unresectable locally advanced or mTNBC or ≥12 mo since neoadjuvant chemotherapy

Trial Design

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R 2:1

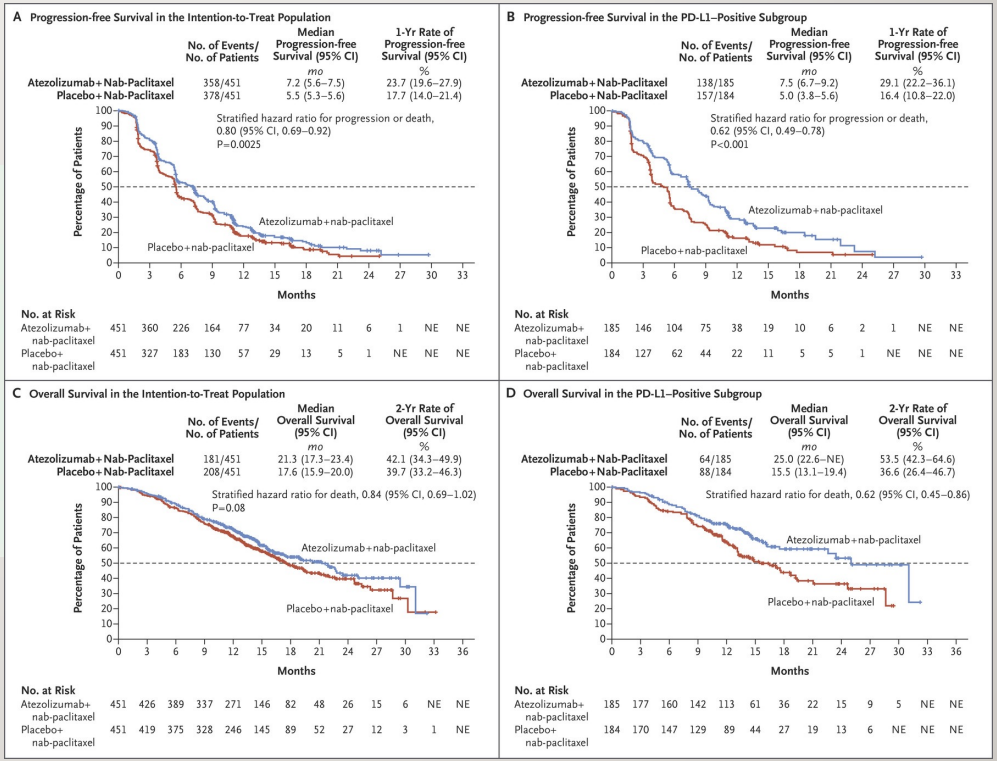
Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

Stratification:
- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)[a]
- Liver metastases (yes vs no)
- Geographical region (N America vs W Europe/Australia vs E Europe/Asia Pacific vs S America)

Primary endpoint: PFS (investigator assessed)
Secondary endpoints include:
- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research



Schmid, P. ESMO 2020

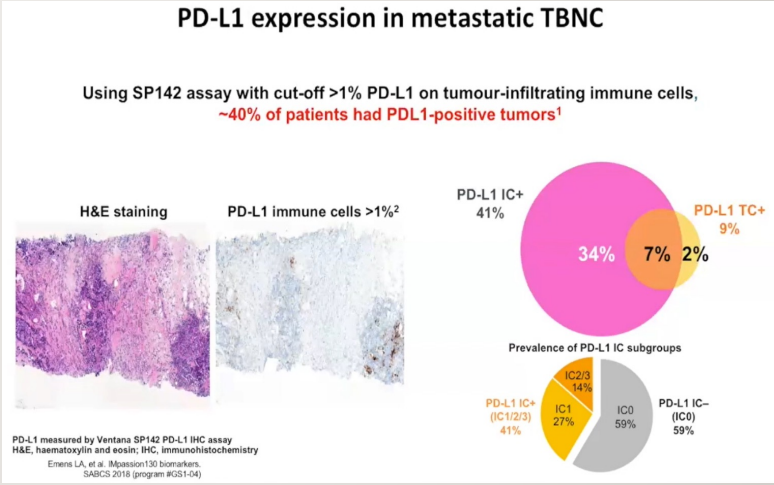
IMMUNOTHERAPY AGENTS APPROVED IN TNBC: ATEZOLIZUMAB

- Atezolizumab + paclitaxel vs placebo in mTNBC (IMpassion131; July 2021)-Phase III
  - Patient characteristics:
    - 45% PD-L1-positive, 48% treated with taxanes, 31% with mTNBC, 27% with liver metastases
  - Primary endpoint was PFS: NO difference in PFS in PD-L1+ group (5.7 mo vs 6 mo, HR 0.82; p=0.20) or ITT population (5.6 mo vs 5.7, HR 0.86)
    - NO benefit demonstrated in OS in either group
- Results divergent from what was seen in the IMpassion130 study
  - 130 showed benefit with immunochemotherapy combination in PD-L1 positive group
  - Divergence under investigation--?steroids with paclitaxel; tumor heterogeneity; BRCA status

DIFFERENCES IN IMPASSION 130 AND KEYNOTE-355 TRIALS

- Finding from these the IMpassion130 are similar to the KEYNOTE-355 results, which evaluated pembrolizumab and more chemotherapy backbones
  - Both had similar designs and results are consistent
- However, PD-L1 biomarker assessment differed
  - Need to identify most appropriate biomarker
  - IMpassion130 used IC using SP142 assay

  while KEYNOTE-355 used different antibody that looked at combined staining on ICs and the tumor cells.



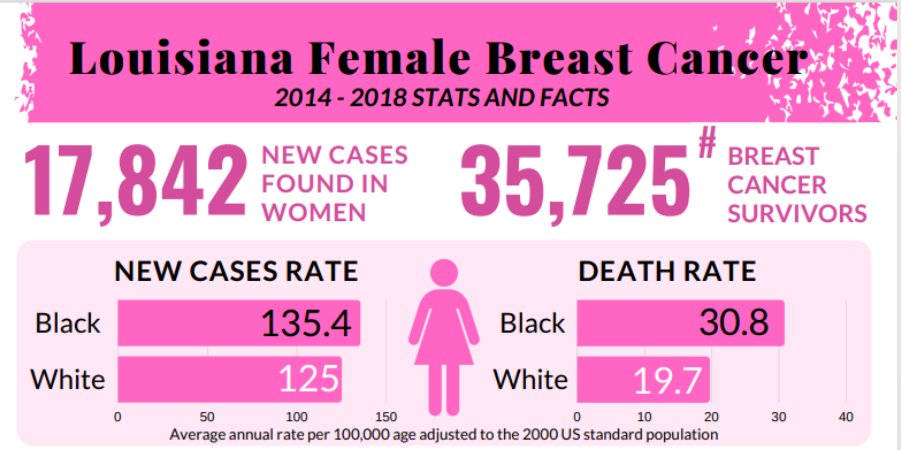
- KEYNOTE-355 also used several standard chemotherapy regimens whereas IMpassion130 used only nab-paclitaxel
  - KEYNOTE-355 not designed to compare chemotherapy but last update showed trend of benefit with taxanes instead of gemcitabine/carboplatin with pembrolizumab

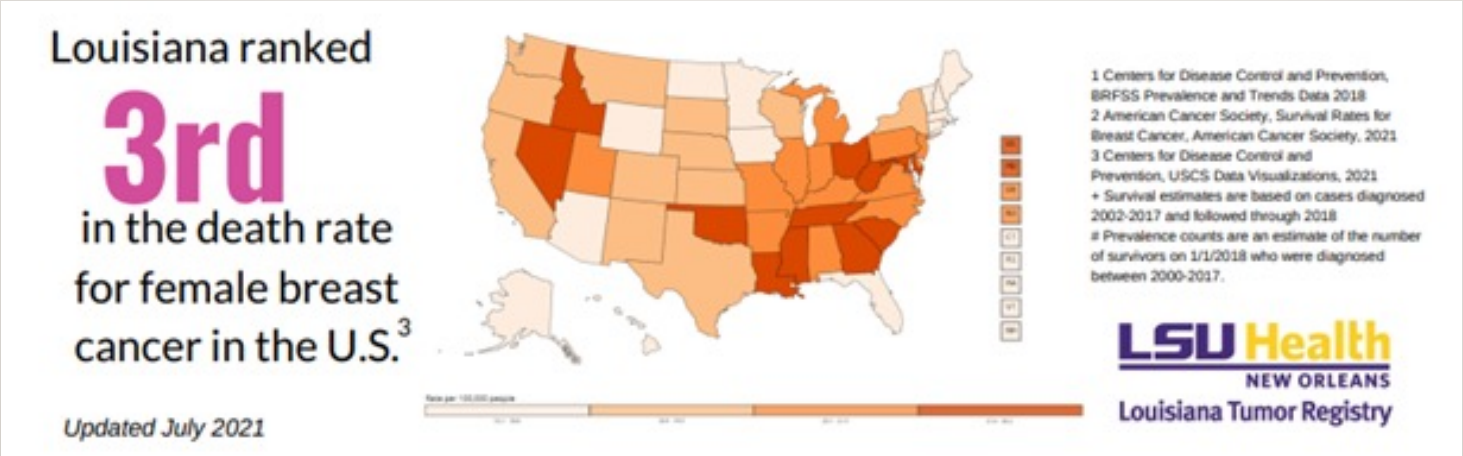
FUTURE DIRECTIONS IN USE OF IMMUNOTHERAPY IN TNBC

- The benefit of immunotherapy in mTNBC was shown in the PD-L1-positive subgroup of the IMpassion130 trial and several KEYNOTE trials
  - However, PD-L1 is not ideal biomarker for patient selection in TNBC as has been shown in other cancers
    - So urgent need to identify novel biomarkers that can predict response to immunotherapy
- Possible biomarkers
  - Stromal TILs
  - Genetic signatures
  - TMB
  - MSI-H/dMMR
  - MHC class

PD-L1 antibody	Immunotherapy	IHC assay	Cut-off	Line
22C3	Pembrolizumab	DAKO	TPS ≥ 1%	1L
			TC ≥ 1%	2L
28-8	Nivolumab	DAKO	TC ≥ 1%	2L
SP142	Atezolizumab	Ventana	TC ≥ 50% and/or IC ≥ 10%	1L
			TC ≥ 1% and/or IC ≥ 1%	2L
SP263	Durvalumab	Ventana	TC ≥ 1%	1L maintenance, in unresectable stage III after chemoradiation therapy
	Nivolumab		TC ≥ 1%	2L
	Pembrolizumab		TC ≥ 50%	1L
73-10	Avelumab	DAKO	TC ≥ 1%	2L (not approved)

BREAST CANCER DISPARITIES IN LOUISIANA





OUR SAVIOR: PRECISION MEDICINE??

- In cancer care today, genomics is the predominant factor influencing precision medicine

- However, our limited knowledge of cancer biology in racial and ethnic minorities diminishes the potential of precision medicine in these populations.
    - Genomic data without the right context, can be very misleading and can be life-threatening

- ***THUS PRECISION MEDICINE DIDN'T SOLVE OUR DISPARITY PROBLEM AND IN MANY INSTANCES CAUSED IT TO WIDEN!!!***
    - As with many new medical treatments, there is inequity in access to care based upon socioeconomic status but also race
        - even people of color with higher SES, still experience disparity in cancer care and thus outcomes

The Role Ancestry in Addressing Cancer Disparities


www.nature.com/scientificreports

scientific reports

OPEN

Investigation of triple-negative breast cancer risk alleles in an International African-enriched cohort

Rachel Martini[1,2], Yalei Chen[3,4], Brittany D. Jenkins[1,2], Isra A. Elhussin[5], Esther Cheng[6], Syed A. Hoda[6], Paula S. Ginter[6], Jeffrey Hanover[7], Rozina B. Zeidan[1], Joseph K. Oppong[8], Ernest K. Adjei[8], Aisha Jibril[10], Dhananjay Chitale[11], Jessica M. Bensenhaver[12], Baffour Awuah[13], Mahteme Bekele[14], Engida Abebe[14], Ishmael Kyei[15], Frances S. Aitpillah[8,15], Michael O. Adinku[15], Kwasi Ankomah[16], Ernest B. Osei-Bonsu[13], Saul David Nathansan[12], LaToya Jackson[3], Evelyn Jiagge[3], Lindsay F. Petersen[12], Erica Proctor[12], Petros Nikolinakos[17], Kofi K. Gyan[1], Clayton Yates[5], Rick Kittles[18], Lisa A. Newman[1] & Melissa B. Davis[1]

"We use 'precision medicine' to apply the right dose, of the right treatment, to the right patient at the right time."


Translational Oncology

www.transonc.com

Volume 12 Number 3 March 2019 pp. 493–501 49

Quadruple Negative Breast Cancers (QNBC) Demonstrate Subtype Consistency among Primary and Recurrent or Metastatic Breast Cancer

Anusha Angajala[2,1], Essynce Mothershed[*,1], Melissa B. Davis[1], Shweta Tripathi[1], Qinghua He[3], Deepa Bedi[4], Windy Dean-Colomb[1] and Clayton Yates[1]

[1]Department of Biology and Center for Cancer Research, Tuskegee University, Tuskegee, AL, 36088; [2]Department of Surgery, Weill Cornell Medicine, New York, NY, USA 10065; [3]Department of Chemical Engineering, Auburn University, AL 36849; [4]Department of Biological Sciences, College of Veterinary Medicine, Tuskegee University, AL; [5]Department of Hematology/Oncology, Our Lady of Lourdes Regional Medical Center, Lafayette, LA, USA

THIS IS NOT THE REALITY FOR MANY PEOPLE OF COLOR, BOTH IN DEVELOPED AND DEVELOPING COUNTRIES


CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COV

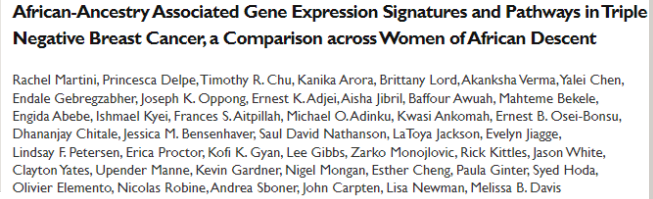
POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JUNE 01 2020

Abstract B052: Identification of differentially expressed micro-RNAs in African American women with Quadruple Negative Breast Cancer FREE

medRxiv

THE PREPRINT SERVER FOR HEALTH SCIENCES

CSH Cold Spring Harbor Laboratory BMJ Yale


African-Ancestry Associated Gene Expression Signatures and Pathways in Triple Negative Breast Cancer, a Comparison across Women of African Descent

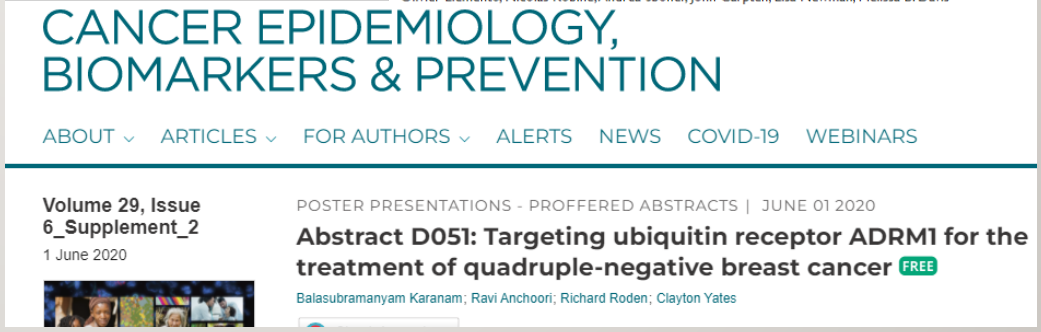
Rachel Martini, Princesca Delpe, Timothy R. Chu, Kanika Arora, Brittany Lord, Akanksha Verma, Yalei Chen, Endale Gebregzabher, Joseph K. Oppong, Ernest K. Adjei, Aisha Jibril, Baffour Awuah, Mahteme Bekele, Engida Abebe, Ishmael Kyei, Frances S. Aitpillah, Michael O. Adinku, Kwasi Ankomah, Ernest B. Osei-Bonsu, Dhananjay Chitale, Jessica M. Bensenhaver, Saul David Nathanson, LaToya Jackson, Evelyn Jiagge, Lindsay F. Petersen, Erica Proctor, Kofi K. Gyan, Lee Gibbs, Zarko Monojlovic, Rick Kittles, Jason White, Clayton Yates, Upender Manne, Kevin Gardner, Nigel Mongan, Esther Cheng, Paula Ginter, Syed Hoda, Olivier Elemento, Nicolas Robine, Andrea Sboner, John Carpten, Lisa Newman, Melissa B. Davis


PLOS ONE

RESEARCH ARTICLE

AR negative triple negative or "quadruple negative" breast cancers in African American women have an enriched basal and immune signature

Melissa Davis[1*], Shweta Tripathi[2*], Raymond Hughley[2], Qinghua He[3], Sejong Bae[4], Balasubramanyam Karanam[2], Rachel Martini[1], Lisa Newman[5], Windy Colomb[6], William Grizzle[7], Clayton Yates[2*]


CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION

ABOUT ARTICLES FOR AUTHORS ALERTS NEWS COVID-19 WEBINARS

Volume 29, Issue 6_Supplement_2

1 June 2020

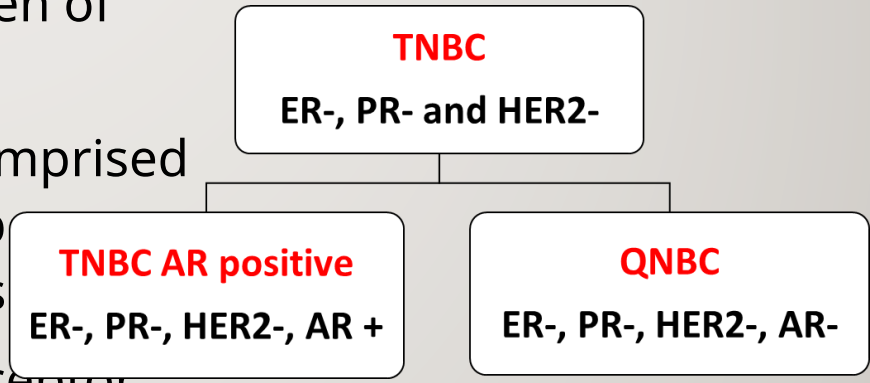
POSTER PRESENTATIONS - PROFFERED ABSTRACTS | JUNE 01 2020

Abstract D051: Targeting ubiquitin receptor ADRM1 for the treatment of quadruple-negative breast cancer FREE

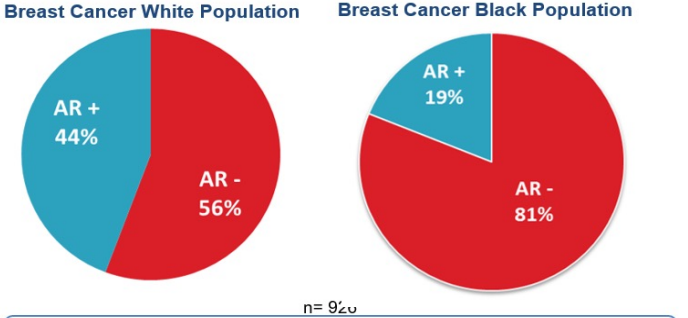
Balasubramanyam Karanam; Ravi Anchoori; Richard Roden; Clayton Yates

AR- TRIPLE NEGATIVE BREAST CANCER: QUADRIPLE NEGATIVE BREAST CANCER (QNBC)

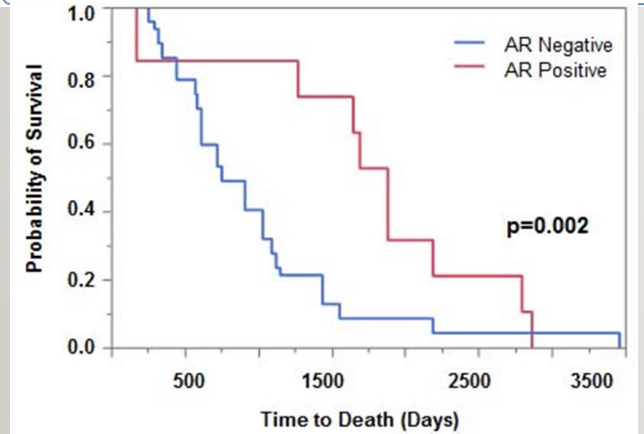
- TNBC represents ~15%-20% of breast cancers and is an aggressive subtype characterized by a poorer prognosis.
  - Disproportionately affects young women of African descent
- TNBC is a highly heterogeneous group comprised of multiple independent molecular subtyp underpinned by unique biologic pathways
- 15-30% of TNBC express the androgen receptor (AR)
  - associated with a more favorable prognosis



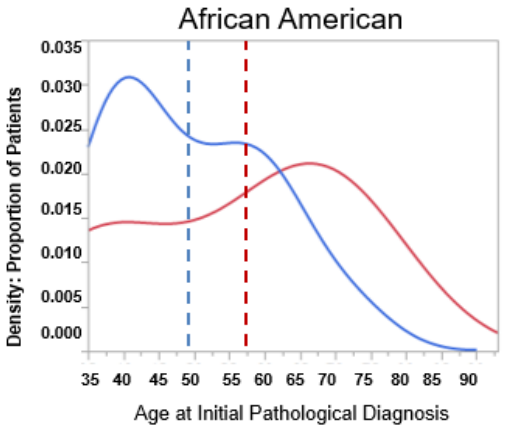
AR NEGATIVE TNBC: EMERGENCE OF QUADRIPLE NEGATIVE BREAST CANCER (QNBC)

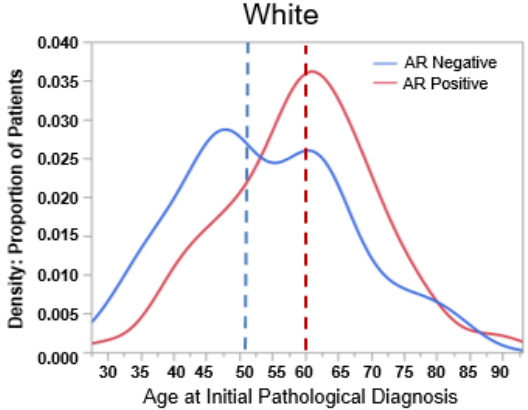


81% OF ALL Black Population are AR negative as compared to 56% in Whites



Androgen Receptor Negative Patients are diagnosed at younger age

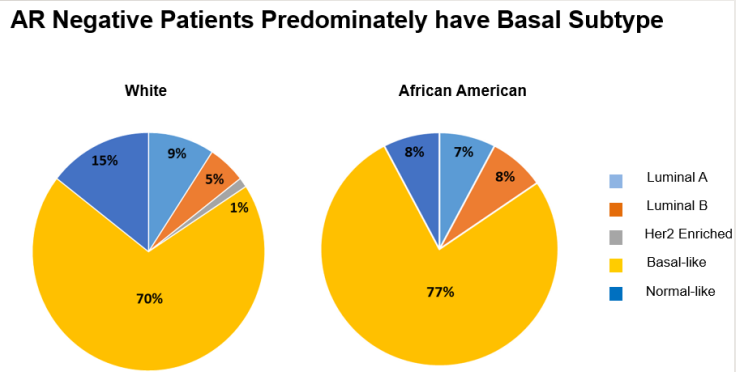


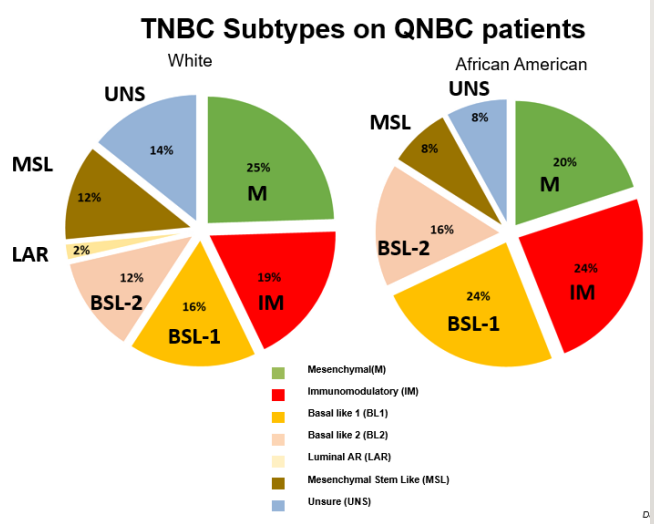


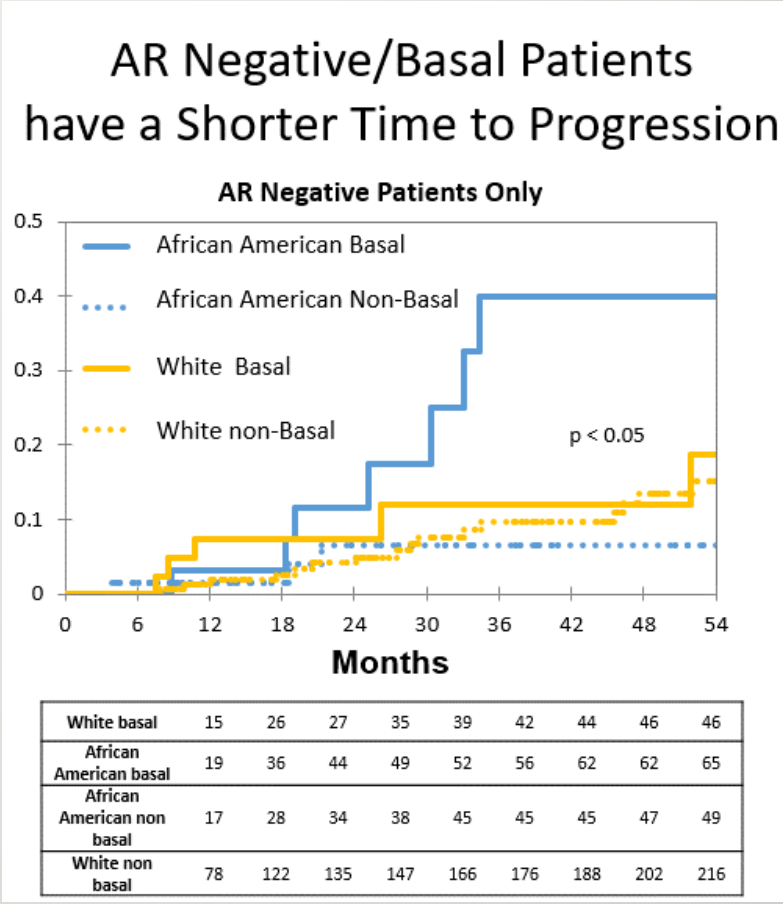
Average Age of Diagnosis
AR positive 56
AR negative 49

Average Age of Diagnosis
AR positive 59
AR negative 53

QNBC ASSOCIATED WITH BASAL-LIKE SUBTYPE



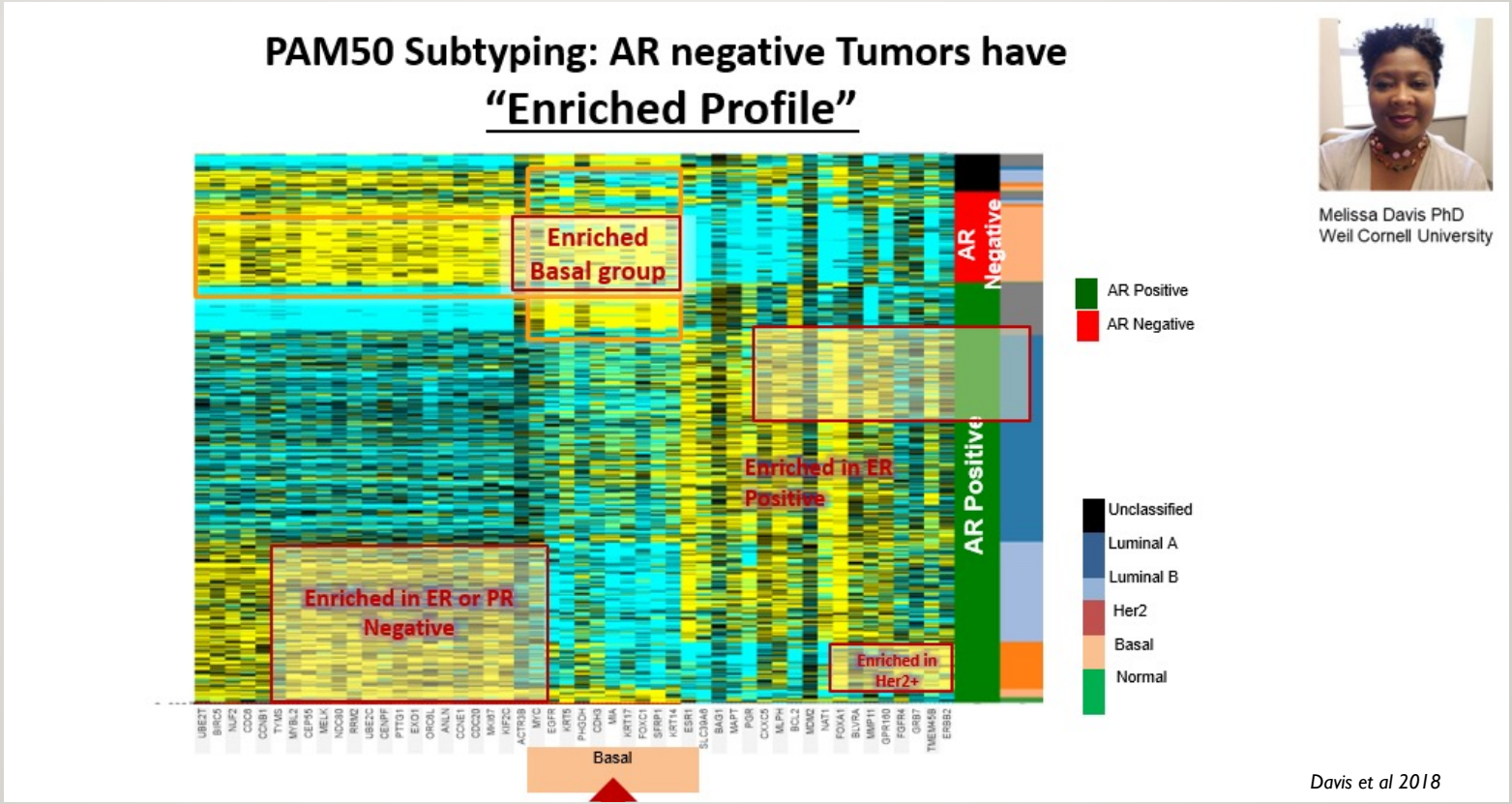




White basal	15	26	27	35	39	42	44	46	46
African American basal	19	36	44	49	52	56	62	62	65
African American non basal	17	28	34	38	45	45	45	47	49
White non basal	78	122	135	147	166	176	188	202	216

QNBC EXHIBIT BASAL-LIKE GENE SIGNATURE

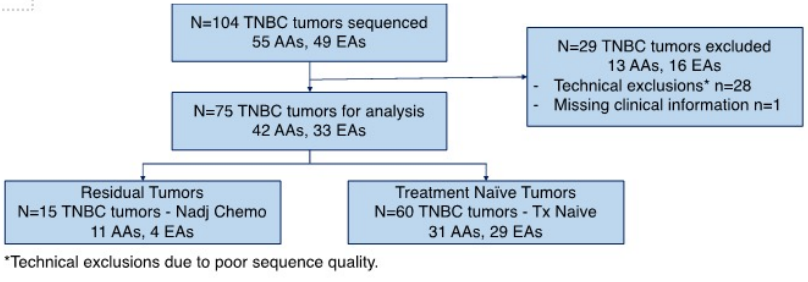
Clayton Yates PhD
Tuskegee University



Melissa Davis PhD
Weil Cornell University

THE ROLE ANCESTRY IN ADDRESSING CANCER DISPARITIES—SRR VS QUANTIFIED ANCESTRY

A



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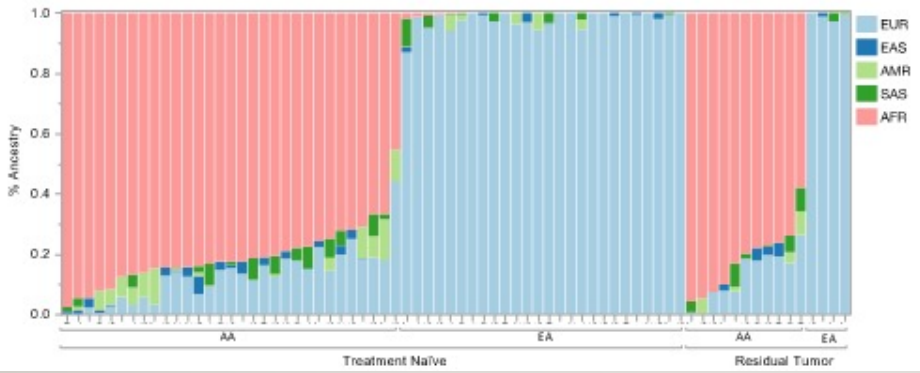

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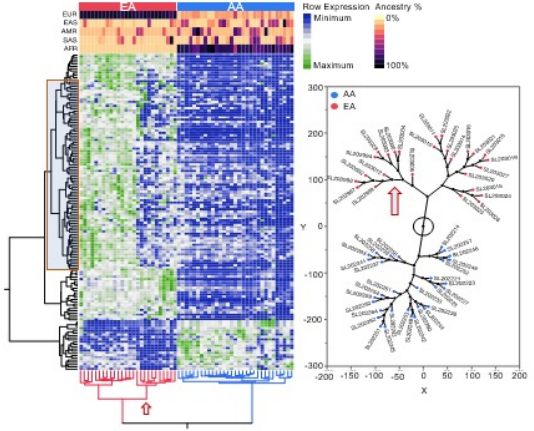


D

Treatment Naïve
Self-reported Race DEGs

Increased Gene	Fold Change	P-value
OVOS2	↑ 2.223	2.71E-05
GFRA1	↑ 1.876	4.84E-04
LOC105371893	↑ 1.781	1.91E-03
SOWAHA	↑ 1.765	1.65E-03
RN7SL471P	↑ 1.756	2.18E-03

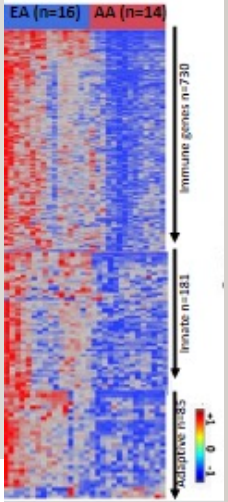
Decreased Gene	Fold Change	P-value
MTRNR2L10	↓ -4.944	7.07E-32
MTRNR2L6	↓ -4.731	1.14E-36
RNU6-7	↓ -4.486	1.94E-38
RP11_161H235	↓ -4.414	1.67E-30
RN7SKP48	↓ -4.236	1.58E-67

Residual Tumor
Self-reported Race DEGs

Ensembl ID	Gene	LogFold Change	P-value
ENSG00000130810	PPAN	↑ 2.65	1.58E-03
ENSG00000117016	RIMS3	↑ 3.00	6.15E-03
ENSG00000117650	NEK2	↑ 3.03	1.13E-02
ENSG00000170075	GPR37L1	↑ 3.04	6.88E-03
ENSG00000105877	DNAH11	↑ 3.45	6.15E-03
ENSG00000204771		↑ 3.78	8.52E-03

Ensembl ID	Gene	LogFold Change	P-value
ENSG00000196754	S100A2	↓ -4.31	7.37E-03
ENSG00000227227	AC017101.1	↓ -3.61	6.88E-03
ENSG00000169604	ANTXR1	↓ -2.09	2.69E-03
ENSG00000204262	COL5A2	↓ -2.01	6.15E-03
ENSG00000072952	MRVI1	↓ -2.01	4.88E-03
ENSG00000269958	AL049840.4	↓ -1.36	0.047254914
ENSG00000196663	TECPR2	↓ -1.17	0.012084124

E



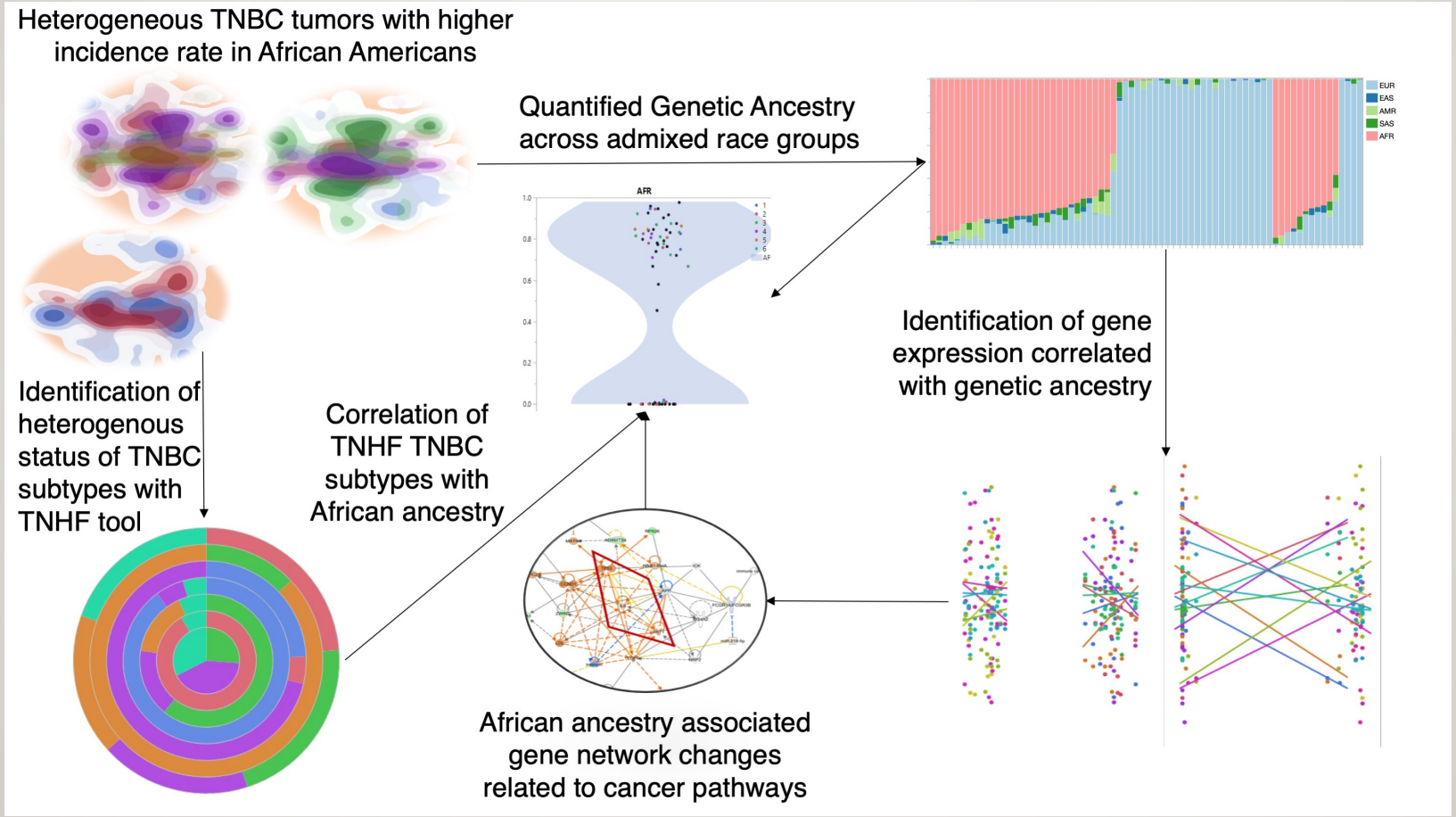
TNBC/QNBC AND ANCESTRY

Table. 1 Druggable Gene Targets that are associated with African Ancestry

Gene	Name	Drugs Tested in Cancer	Disease (Cancer or Other)	Organism (Human or Other)	Evidence Type (Trial, non-humn, gene-gene interactions)
AKT1	AKT Serine/Threonine Kinase 1	***Arsenic Trioxide***, Carboplatin, *Everolimus*, Cisplatin, Nelfinavir	Various Cancers	Human	Trial
CCND1	Cyclin D1	***Arsenic Trioxide***, Cetuximab, Aspirin, Trametinib, Palbociclib	Various Cancers and other diseases	Human	Trial
ZBTB22	Zinc Finger And BTB Domain Containing 22	Aspirin	Various Cancers	Human	Trial
SLC12A2	Solute Carrier Family 12 Member 2	Bumetanide and Furosemide	Neonatal Seizures, Autism, Heart Failure	Human	Trial
PPP2R4	Protein Phosphatase 2 Phosphatase Activator	Ceramide	Breast Cancer, Diabetes, Obesity	Human	Trial
RELA	RELA Proto-Oncogene, NF-KB Subunit	Dimethyl fumarate	Multiple Sclerosis	Human	Trial
CITED4	Cbp/P300 Interacting Transactivator With Glu/Asp Rich Carboxy-Terminal Domain 4	Fluorouracil	Cardiac ischaemia/reperfusion (I/R) injury	Mouse	Gene-Gene Interactions
PIM3	Pim-3 Proto-Oncogene, Serine/Threonine Kinase	Fostamatinib, Gefitinib, Sunitinib, Ruboxistaurin	Cancer and others	Human	Trial
EGFR	Epidermal Growth Factor Receptor	Gefitinib, Erlotinib, Lapatinib and Cetuximab	NSCLC	Human	Trial
RAB1B	RAB1B, Member RAS Oncogene Family	Guanosine triphosphate			Not Sure
LPL	Lipoprotein Lipase	Orlistat, Fenofibrate	Obesity and Diabetes	Human	Trial
NUDC	Nuclear Distribution C, Dynein Complex Regulator	Phenethyl Isothiocyanate	Various Cancers and Cardiovascular Disease	Human	Trial
MEPCE	Methylphosphate Capping Enzyme	S-Adenosyl methionine	Not Sure	Not Sure	Not Sure
IL6	Interleukin 6	Siltuximab, Vitamin C and E, Adalimumab	Various	Human	Trial
NFKB1	Nuclear Factor Kappa B Subunit 1	Thalidomide, Donepezil, Glycyrrhizin, Triflusal	Various	Human	Trial
ADAMTS4	ADAM Metallopeptidase With Thrombospondin Type 1 Motif 4	Tinzaparin	Brain Tumors, Thromboembolism, Thrombosis	Human	Trial
TP53	Tumor Protein P53	Venetoclax, Cyclophosphamide, Fluorouracil, Cisplatin	Various	Human	Trial

Dean-Colomb et al, JCO 38:18, 2020

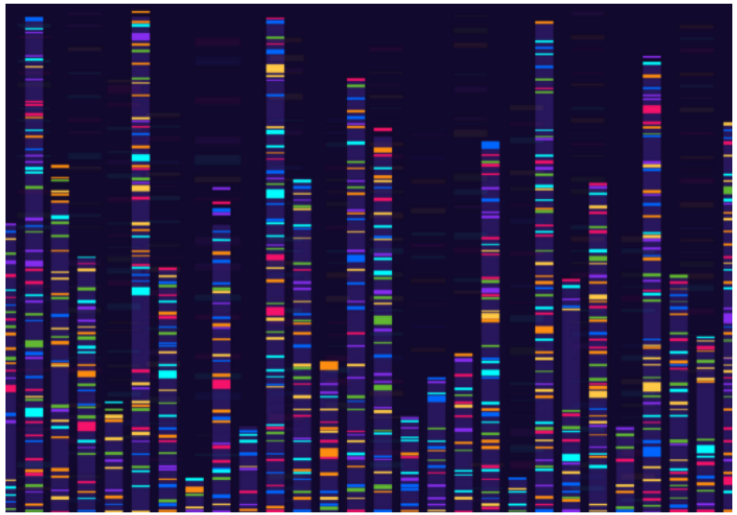
OUR SAVIOR: ANCESTRY-DRIVEN PRECISION MEDICINE



OUR SAVIOR: PRECISION MEDICINE??

Racial Differences in Genomic Profiles May Help Explain Breast Cancer Outcomes

By - March 30, 2022 12 0



- 6652 patients with breast cancer who were treated from 2014-2020 who had complete clinical and next-generation sequencing data in the AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE).
  - Black patients with metastatic breast cancer were less likely than their White counterparts to have actionable genetic variations.
    - Underrepresentation of Black patients in CTs has made it more difficult to discover mutations that can be successfully targeted in Black patients
      - This contributes to the poor outcomes observed in Black patients with breast cancer.

"As long as genome-wide association study populations are skewed toward predominately White and European patients, Dr Goel and colleagues argue, fewer actionable genomic variations will be discovered in minority populations, and treatment inequalities will persist.

- "We need to increase minority enrollment in precision oncology by increasing next-generation sequencing of both primary and metastatic breast cancer to potentially identify actionable mutations in diverse populations since studies have historically underrepresented Black and non-White breast cancer patients".
  - Although individual physicians cannot overhaul the majority of clinical trials alone, they can push for more sequencing of tumors in their minority patients.

THANK YOU!