Advances in Cancer Immunotherapy: Case Studies

A Focus on Breast Cancer

#LearnACI

Case Study 1:
Margaret E. Gatti-Mays, MD, MPH

Case Study 1: High TMB

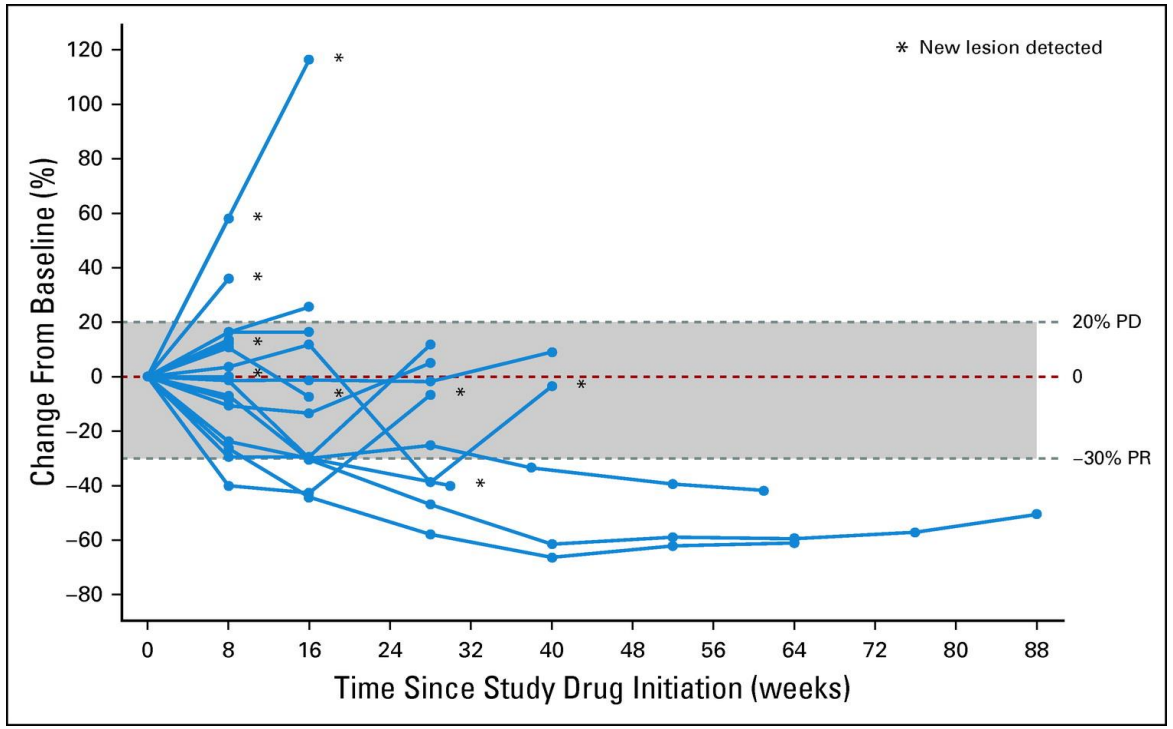
A 65 year old female with a history of ER+/PR-/HER2- ILC, developed a metastatic recurrence to bones and lymph nodes 5 years after completing her adjuvant endocrine therapy.

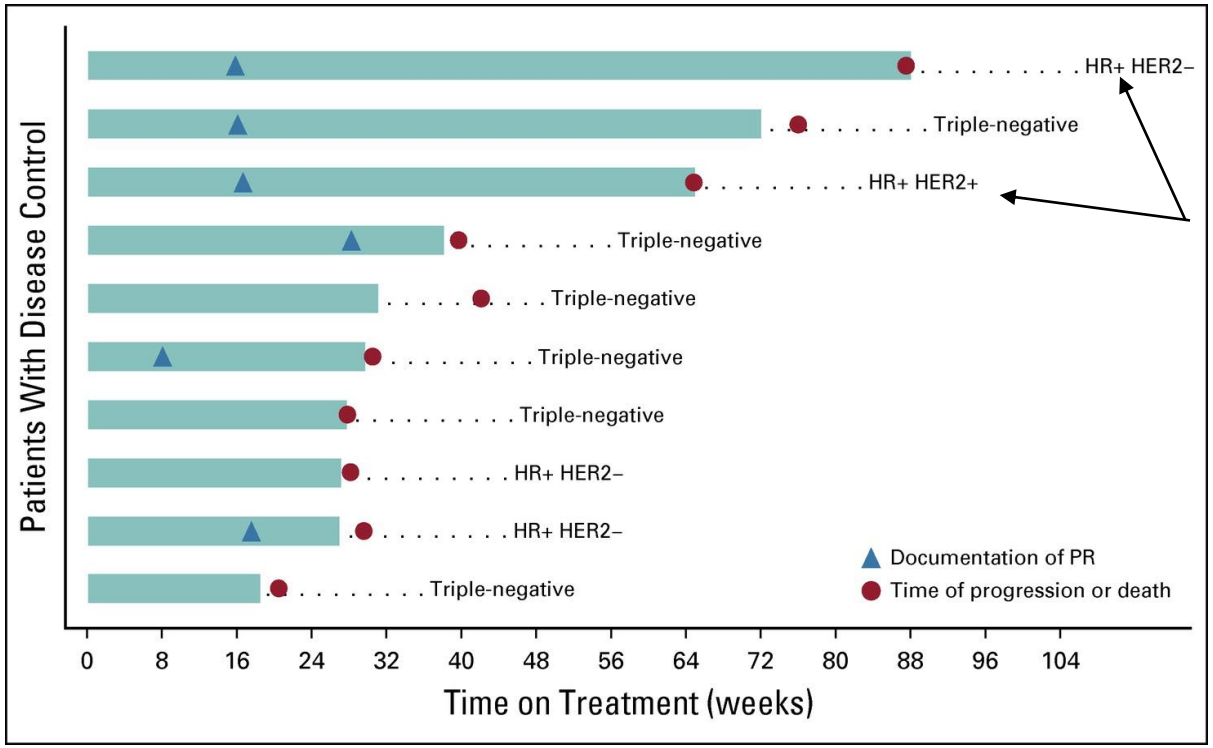
- A biopsy of a supraclavicular node confirmed ER+/HER2- ILC. She received first line therapy with Palbociclib/Letrozole and did well for almost 2 years.
- At progression, the previously biopsied lymph node was sent for genomic testing. Results included a tumor mutational burden (TMB) of 19 mutations/megabase but no actionable mutations (negative for PIK3CA).
- She received second line therapy with everolimus/fulvestrant and did well for another year but eventually progressed.

What is a reasonable next treatment option?

Pembrolizumab in TMB-H Breast Cancer

- **TAPUR Study (Ph2 basket study)**
  - 28 patients with metastatic breast cancer [TNBC = 13 (46%), HR+/HER2- = 12 (43%)]
  - **TMB: median 13 mut/Mb** (range 9 to 37 mut/Mb); PD-L1 status unknown
  - **Disease Control Rate 37%, ORR 21%** with median PFS = 10.6 weeks





Alva et al. JCO. 2021.

Case 2: Special Populations

- Your colleague asks you about a new patient she saw in clinic last week. The patient is a 34 year old female with a history of rheumatoid arthritis is found to have a 4cm triple negative breast cancer with local invasion into the pectoralis muscle. Scans were negative for distant disease.

- Your colleague asks if she can safety use the KEYNOTE-522 regimen for this patient with non-medicated RA. What do you advise?

irAEs in Special Patient Populations

- Early trials excluded patients with autoimmune diseases, HIV, or history of organ transplant
  - Developing area of immunotherapy
  - Real world data is forthcoming. Current trials now including these populations.

- **Autoimmune Disease:** Increased risk for worsening of baseline autoimmune-related symptoms while on ICB, often mild and rare to have extension of disease. No increased risk of high grade irAEs.

- **HIV:** No increased risk of high grade irAEs. HIV viral load remains suppressed in most patients. Improvement in CD4 counts.

- **Organ Transplant:** Increased risk of organ rejection with PD-1 (≥ 70%). No rejections with ipilimumab. May be an option if has alternative therapy should graft reject (eg, kidney).
  - Continue on maintenance immunosuppressive therapy

Jacobson et al. 1997. Clin Immunol Immunopath;
Gutzmer et al. 2017. Eur J Cancer.; Menzies et al. 2017. Ann Oncol;
Cortellini et al. 2018. The Oncologist.; Cook and Kim. 2019. JAMA Oncol;
Aguirre et al. 2019. The Oncologist.; Kittai et al. 2017. JITC.

Autoimmune Disease (AD) and ICB

- Approximately 3 to 8% of US population has an autoimmune disease
- Patients with AD (history or active) are at risk for worsening of AD while on ICB

Incidence	25 to 50% (rheumatologic > dermatologic > endocrine) No flare for GI, neurologic or respiratory ADs
Onset	Median 38 days (range 8 to 161)
Severity	Mild (grade 1 or 2) Recurrent or increased grade of prior symptoms Rare to have extension of the AD
Treatment	Few require discontinuation of ICB Immunosuppressives and symptomatic therapy

- Patients with AD (history or active) are at risk of increased all grade irAEs but no increased risk of high grade irAEs

Jacobson et al. 1997. Clin Immunol Immunopath.
Gutzmer et al. 2017. Eur J Cancer.
Menzies et al. 2017. Ann Oncol.
Cortellini et al. 2018. The Oncologist.

Breast Cancer Immunotherapy Cases

Leisha A. Emens, MD, PhD

Case #3

- 38 y/o premenopausal woman diagnosed with a right-sided T1cN0 TNBC with a Ki67 of 65%, gene panel testing was negative
- Treated with neoadjuvant AC x 4 cycles f/b weekly taxol x 12 weeks
- Bilateral mastectomy with residual disease ypT1aN0
- Adjuvant Xeloda for 24 weeks
- Observation

Case #3

- 2 years later she presents with enlarged right cervical lymph nodes 1-1.5 cm in size
- Staging scans ordered, and concurrent biopsy of cervical lymph nodes negative for cancer
- Staging scans reveal 2 lesions in the liver 2 cm and 1 cm suspicious for metastases
- Ultrasound guided core needle biopsy of the liver confirms triple negative breast cancer
- What is the next step to determine best management?

Case #3

- PD-L1 testing using the PDL1 IHC 22C3 PharmDx assay to determine the CPS score
  - Liver biopsy is PD-L1negative
  - Primary tumor is PD-L1-positive with CPS score of 12
- BRCA status
  - NGS analysis of liver tumor shows mutation in BRCA1 (somatic)
- What is the next best step in management?

Case #3

- You decide to treat her with pembrolizumab and taxol
- Re-staging scans at 4 months show that the liver lesions have resolved, but there are three new axillary lymph nodes measuring 1.0, 1.2, and 1.5 cm in size. She is clinically well except for grade 1 neuropathy.
- What to do next? Switch to second line therapy, or continue pembrolizumab and taxol?
- You decide to continue pembrolizumab and taxol
- Re-staging scans 6 weeks later show a CR

Case 4

45 year old woman with no significant PMH presents with a palpable mass in her right axilla. Subsequent evaluation with breast imaging and a PET scan reveals Stage IIIC breast cancer (cT2N3bM0, grade 3, ER-/PR-/HER2-). Genetic testing is negative for BRCA1/2 mutations. She receives treatment with the Keynote-522 neoadjuvant chemotherapy regimen. During the last 4 weeks of chemotherapy, she complains of profound fatigue and muscle weakness. Subsequent evaluation reveals a TSH = 20 and a free T4 = 0.02. Random AM cortisol is 8. She is started on levothyroxine prior to surgery.

Final surgical pathology reveals no residual tumor in the breast, 2/15 nodes with 1 macrometastasis and 1 micrometasis. What adjuvant therapy would you offer?

Case Study 5: Brain Mets

- 45 year old healthy female presented to the emergency room with a new onset seizure. Head CT shows three brain metastases with surrounding vasogenic edema.
  - During the clinical exam, she is found to have a 3cm right breast mass and multiple palpable axillary nodes. Staging scans shows several lymph nodes in the right supraclavicular and mediastinal chains.
  - A biopsy of the breast mass confirms PD-L1 positive, triple negative breast cancer.

What is the appropriate treatment?

Breast Cancer Brain Metastasis Basics

- TNBC accounts for 15% of all breast cancers and the incidence of brain metastases is between 22 and 46%. The overall survival of patients with TNBC brain metastases is 4-5 months.

- Metastases of the Central Nervous System (CNS)
  - Intraparenchymal
  - Leptomeningeal (*incidence 5 to 14%; median survival 3.5 to 4 months*)

- ***Dual Treatment Recommended ***
  - Local treatment with radiation (stereotactic radiosurgery or whole brain radiation) and/or surgery
  - Systemic therapy has historically had limited effect

Aversa et al. Breast. 2014; Niikura et al. Breast Cancer Res Treat. 2014; Brufsky et al, Clin Cancer Res. 2011; Kaider-Person et al. Breast Cancer Res Treat. 2018; Zimmer et al. Cancer Reports. 2020.

- Most clinical trials have excluded patients with brain metastases or leptomeningeal disease
  - Of the main Breast IO clinical trials, only 91 of the 2,692 (3.3%) patients included in these trials had brain metastases

- CNS and systemic responses have generally been similar and are more common among tumor subtypes that typically respond to ICIs such as melanoma and lung cancer.

Schlam and Gatti-Mays, unpublished. Under Review.

Case Studies

Darcy L. Ploucha, PA-C, MPAS

Case 6

- 59 y/o female with hx metastatic breast CA, currently receiving pembrolizumab 200 mg IV q 3 weeks, s/p 6 cycles. She was evaluated at an outside hospital for c/o upper abdominal pain, dry heaves, and chills without fever.
- PMHx also notable for HTN and depression
- Medications include lisinopril/HCTZ 10/12.5 daily and quetiapine 200 mg at bedtime

Workup

- Workup in the ED included CMP, CBC, and lipase. Amylase was not ordered. Results are remarkable for Lipase elevated at 2.76 x ULN (grade 3), and Na 123 (grade 3). Otherwise, results are unremarkable.
- CT scan of the abdomen was completed, notable for very mild strandy abnormal opacity in the anterior peripancreatic fat, possibly due to very mild acute pancreatitis.
- What would your treatment management include?

Management

- She was admitted to the hospital and started on prednisone 1 mg/kg/day. The following day her lipase had dropped to 1.67 x ULN, grade 2. Na improved to 130 and was attributed to hypovolemic hypometria in the setting of fasting at home due to abdominal pain.
- She was discharged hospital day 2 on prednisone 0.5 mg/kg/day with taper instructions over 4 weeks. Symptoms of pancreatitis resolved prior to discharge. Lipase returned to normal 1 week post D/C.
- Treatment was held while she completed the prednisone taper.

Follow up

- Two weeks after completing her prednisone taper, she presented for treatment. At that time, she again noted N/V with early satiety. She reported that these symptoms were not the same as prior to the pancreatitis diagnosis. She notes that now her nausea occurs only after eating and that she is vomiting small amounts. She is not taking any anti-emetics.
- Vitals WNL, BP 126/78. Labs notable for Na 125, Phos 2.2. TSH 4.594. Amylase/lipase WNL. CBC WNL.
- Treated with 1L IVF for presumed hypovolemic hyponatremia and Phos-Nak po x 1 for hypophosphatemia. Rx for po ondansetron 8 mg TID given. Pembrolizumab was held.

Follow up

- Pt presented for a two week follow up visit. She continues to c/o nausea and notes no significant improvement with ondansetron. Appetite is poor. She is also c/o increased fatigue, generalized weakness, LE edema, and cold intolerance. Vitals remain stable, with BP slightly elevated at 141/88.
- Na remains low at 127. Remaining CMP, amylase, lipase, and CBC unremarkable. Random cortisol 0.4 ug/dL. TSH 10.165, FT4 0.77
- What is your differential diagnosis?
- What is the next step in workup?

Follow up

- A cortisol stim test was completed the following morning.
  - Baseline AM cortisol 0.4 ug/dL
  - 30-minute cortisol 3.7 ug/dL
  - 60-minute cortisol 4.5 ug/dL
- Consistent with adrenal insufficiency
- Started on hydrocortisone 20 mg Q AM and 10 mg Q PM
- Other considerations: TSH was also newly elevated. Started on Synthroid 100 mcg daily
- MRI pituitary also ordered to rule out hypophysitis. Results were unremarkable

Case Presentations

Laura Kennedy, MD PhD

Assistant Professor of Medicine, Vanderbilt University Medical Center

Case 7

58 year old surgically post-menopausal woman presents with a palpable mass in her right breast. Subsequent evaluation with breast imaging and biopsies confirms a diagnosis of a 2.5 cm breast mass, grade 3, ER-/PR-/HER2- breast cancer in the right breast. Genetic testing is negative. There is no nodal involvement or distant metastatic dz on imaging. She has a past medical history notable for severe COPD and hypertension. She has good performance status despite her COPD and cares for multiple disabled adults full-time.

What neoadjuvant regimen would you offer her?

Case #8

- 55 y/o woman Dx with a right-sided 3.8 cm triple negative breast cancer with biopsy-proven lymph node involvement and a Ki67 of 90%
- Is additional information needed to determine the best therapy?

Case #8

- Staging scans including PET/CT and MRI brain show no evidence of metastatic disease, her cardiac function shows a LVEF of 55-60%
- Your pathologist evaluates her tumor for PD-L1 expression given the approval of pembrolizumab for breast cancer immunotherapy, and it has a CPS score of 0.
- What is the best therapy for her in light of this information?

Case #8

- She is treated with taxol + carboplatin + pembrolizumab, followed by AC + pembrolizumab
- Her physical exam is consistent with a complete clinical response
- Her evaluation prior to cycle 4 of AC is significant for relative hypotension and fatigue, her random cortisol level is 3
- You check an 8am cortisol level and it is 1, her ACTH level is normal
- What do you do next?

Case #8

- She has pembrolizumab-induced primary adrenal insufficiency
- You consult endocrinology
- She is placed on hydrocortisone 10mg in the morning and 5 mg in the afternoon
- Recommendations are for stress dose steroids prior to breast surgery, with resumption of standard hormone replacement afterwards with endocrine guidance
- Pathology reveals a complete pathologic response
- What is the next management step? Observation or more pembrolizumab?
- Endocrinology continues to help with her adrenal function management and she continues pembrolizumab to complete a total of one year
- She is then followed expectantly on no cancer therapy

Case #9

- 39 y/o woman with newly diagnosed left-sided 1.0 cm TNBC with an enlarged lymph node on imaging that is negative for tumor on biopsy
- Her tumor biopsy is notable for a brisk infiltrate of stromal TILs by H&E
- Which of the following is true?
  - This identifies her as more likely to respond to standard neoadjuvant chemotherapy
  - The presence of stromal TILs identify her as a candidate for the addition of immunotherapy to neoadjuvant chemotherapy as she may gain additional benefit
  - The presence of stromal TILs is a favorable prognostic biomarker of favorable long-term outcome

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  - The presence of stromal TILs is a favorable prognostic biomarker of favorable long-term outcome

Case #9

- She is treated with neoadjuvant AC for 4 cycles followed by weekly taxol for 12 weeks
- She has a segmental mastectomy with sentinel lymph node biopsy
- Pathology reveals a complete pathologic response

Currently stromal TILs have no role as a predictive biomarker for selecting therapy, or de-escalating therapy.

Case Study #10

- Pt is 48 y/o female receiving pembrolizumab 200 mg IV q 3 weeks for metastatic breast CA. Upon consideration of C4 she is found to have an erythematous maculopapular rash covering anterior and posterior trunk, b/l UE, and anterior upper thighs. She notes that the rash is pruritus and started about 3 days ago. She has tried to use moisturizing cream daily with no improvement.
- PE is remarkable for maculopapular rash as above. Vitals are WNL. CBC, CMP, amylase/lipase are all WNL.
- How would you grade the rash?
- What is the first step in management?
- What additional recommendations can you make to improve the patient's QOL?

- After completion of a steroid taper (prednisone 1 mg/kg) over 4 weeks, the patient's rash has resolved completely
- She was rechallenged with Pembrolizumab 200 mg IV q 3 weeks and has tolerated well with no return of the rash