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# Updated efficacy of first or second-line pembrolizumab plus in metastatic triple negative breast cancer and correlations with baseline lymphocyte and naïve CD4+ T-cell count

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# Updated efficacy of first or second-line pembrolizumab (pembro) plus capecitabine (cape) in metastatic triple negative breast cancer (mTNBC) and correlations with baseline lymphocyte and naïve CD4+ T-cell count

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## Background:

- Anti-PD-1/L1 is associated with objective response rates (ORR) of 23-26% in first line mTNBC, and 5-6% in later lines[1,2]
- Oral capecitabine (cape) is associated with ORR of 15-36% in metastatic breast cancer (MBC)[3]
- Fixed-dose cape(1 week on, 1 week off) is active and well tolerated in MBC, and maximizes tolerability/efficacy in mathematical models[4,5]
- Chemotherapy may induce immunogenic cell death, antigen presentation, regulatory cell depletion, & PD-L1 upregulation[6]

## Hypothesis:

Pembrolizumab (pembro, anti-PD-1) plus fixed-dose capecitabine is safe, and may enhance activity when combined for the treatment of mTNBC

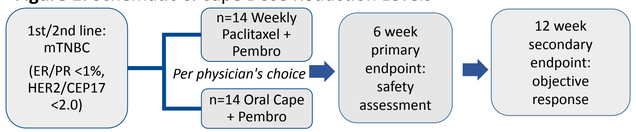
## Clinical Trial Objectives:

- Primary: To evaluate the tolerability of fixed-dose cape plus pembro
- Secondary: To evaluate the 3-month objective response rate (ORR) by RECIST1.1 and immune-related RECIST1.1

## Methods:

- Subjects with mTNBC with 0 or 1 prior systemic therapies were enrolled to receive pembro (n=14, 200mg IV q21d) plus physician's choice oral cape (2,000mg BID, weekly 1 on/1 off) or paclitaxel (n=14)
- Sample size is based upon stage 1 of a Simon Phase II design with null hypothesis of 25% ORR and alternative of 45% (80% power, 5% alpha)

**Figure 1:** Schematic & Cape Dose Reduction Levels




| Dose level | 0 | -1 | -2 | -3 | -4 |
|---|---|---|---|---|---|
| Dose | 2000mg BID | 1500mg BID | 1300mg BID | 1150mg BID | 1000mg BID |

## Results:

**Table 1:** Patient demographics

| Characteristic | No. (%) | Characteristic | No. (%) |
|---|---|---|---|
| Age, y | 62; range: 47-76 | Neo-/adjuvant chemo | |
| Ethnicity | | None | 2 (14) |
| White | 12 (86) | ACT (+ Carbo in n=3) | 9 (65) |
| Non-white | 2 (14) | TC | 3 (21) |
| ECOG | | Time from neo-/adjuvant chemo | |
| 0 | 7 (50) | ≤6mo from chemo | 5 (42) |
| 1 | 7 (50) | >6mo from chemo | 7 (58) |
| Line of therapy | | Liver involvement | |
| First | 12 (86) | Yes | 1 (7) |
| Second | 2 (14) | No | 13 (93) |

## Safety Results:

- 100% of patients (n=14/14) tolerated therapy (defined as >6 weeks without discontinuation related to toxicity)
- Hand foot syndrome rates (71%, grade III-IV: 0%) were similar to cape monotherapy (previous trials: 37-71%; grade III-IV: 8-26%)[7-11]
- Diarrhea rates (64%, grade III-IV: 14%) may be higher compared to cape monotherapy (previous trials: 21-48%, grade III-IV: 4-13%)[7-11] but was managed effectively with dose reduction

**Table 2.** Adverse events, all grades occurring in >15% study population

| Adverse Event | Patients, n (%) | Pembro attributed | Cape attributed |
|---|---|---|---|
| Fatigue | 10 (71%) | 4 (29%) | 9 (64%) |
| Hand Foot Syndrome | 10 (71%) | | 10 (71%) |
| Diarrhea | 9 (64%) | | 9 (64%) |
| Cough | 8 (57%) | 2 (14%) | |
| Dyspnea | 8 (57%) | 1 (7%) | |
| Pain | 8 (57%) | | 3 (21%) |
| Anemia | 6 (43%) | | 3 (21%) |
| Anorexia | 6 (43%) | | 2 (14%) |
| Hyponatremia | 6 (43%) | | 1 (7%) |
| Nausea | 6 (43%) | | 3 (21%) |
| Constipation | 5 (36%) | | 2 (14%) |
| Headache | 5 (36%) | | |
| Abdominal pain | 4 (29%) | | 3 (21%) |
| Dry skin | 4 (29%) | | 2 (14%) |
| Fever | 4 (29%) | | |
| Hypokalemia | 4 (29%) | | 3 (21%) |
| Lymphopenia | 4 (29%) | | 2 (14%) |
| Vomiting | 4 (29%) | | 2 (14%) |
| Wheezing | 4 (29%) | | |
| Depression | 3 (21%) | | |
| Dizziness | 3 (21%) | | |
| Dry mouth | 3 (21%) | 1 (7%) | 1 (7%) |
| Edema | 3 (21%) | | |
| GERD | 3 (21%) | | 2 (14%) |
| Hypothyroid | 3 (21%) | 3 (21%) | |
| Pleural Effusion | 3 (21%) | | |

**Table 3.** Grade III treatment-attributed adverse events (no grade IV)

| Adverse event | Patients, n (%) | Pembro attributed | Cape attributed |
|---|---|---|---|
| Lymphopenia | 3 (21) | | 2 (14) |
| Anemia | 2 (14) | | 1 (7) |
| Diarrhea | 2 (14) | | 2 (14) |
| Fatigue | 1 (7) | | 1 (7) |
| Sepsis | 1 (7) | | 1 (7) |
| Neutropenia | 1 (7) | | 1 (7) |
| Hyperglycemia | 1 (7) | 1 (7) | |

## Dose Reductions:

- Dose reductions were required in 3/14 patients at wk 8, and 6/9 at wk 12
- Reason for dose reduction was: H/F syndrome (57%), diarrhea (29%)

**Table 4.** Cape dose reductions (7d on/7d off)

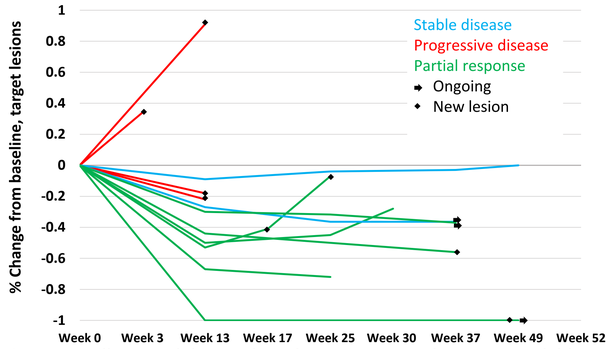
| Pt Study ID | Week 4 | Week 8 | Week 12 |
|---|---|---|---|
| 1 | 2000mg BID | 2000mg BID | 1500mg BID |
| 2 | 1500mg BID | 1150mg BID | |
| 3 | 2000mg BID | 2000mg BID | 2000mg BID |
| 4 | 2000mg BID | 2000mg BID | |
| 5 | 2000mg BID | 2000mg BID | 2000mg BID |
| 6 | 2000mg BID | 2000mg BID | 1500mg BID |
| 7 | 2000mg BID | 2000mg BID | |
| 8 | 2000mg BID | 2000mg BID | 1500mg BID |
| 9 | 2000mg BID | 2000mg BID | 1500mg BID |
| 10 | 2000mg BID | 2000mg BID | 1500mg BID |
| 11 | 2000mg BID | 2000mg BID | 2000mg BID |
| 12 | 2000mg BID | 1300mg BID | |
| 13 | 2000mg BID | 2000mg BID | 1500mg BID |
| 14 | 2000mg BID | 1500mg BID | |

Crosshatch: treatment discontinued

## Efficacy Results:

- Pembro/cape was associated with 43% ORR (6 PR, 0 CR, Clopper-Pearson 95% CI: 18-71%), with an additional subject with durable SD (49+ wk)
- Mixed responses and new lesions (with ongoing response of target lesions) were observed

**Figure 2: Tumor Response by RECIST 1.1**

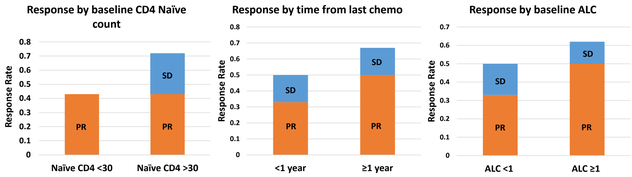



*2 pts not illustrated due to clinical progression and no scan available

## Preliminary Correlates of Response:

- In previous anti-PD-1/L1 mTNBC studies, response rates diminish with line of therapy, which could be related to chemotherapy-related lymphopenia[1,2]
- Curative-intent chemotherapy is associated with prolonged contraction of CD4 naïve cells
- In this dataset, we observe modest associations of response with CD4 naïve count, baseline ALC, and time from last chemo, suggesting that iatrogenic immunosuppression may contribute to non-response in the metastatic setting

**Figure 3.** Preliminary Correlates of Response




## Conclusion:

**Pembro plus cape is safe**

- Pembro plus fixed-dose cape was well tolerated, with no treatment discontinuations related to toxicity
- Cape dose reductions were common to 1500mg BID
- Diarrhea may be increased with combination but is managed effectively with dose reduction
- These data suggest that adjuvant cape can be safely co-administered with pembro in ongoing neo-/adjuvant registrational TNBC studies

**Pembrolizumab plus capecitabine is active**

- The estimated 43% ORR is favorable relative to cape or pembro monotherapy
- Sufficient responses were observed to warrant study expansion according to the trial's pre-specified Simon futility threshold
- Preceding cytotoxic chemotherapy may impair response to subsequent immunotherapy in mTNBC
- A comparative assessment of the clinical and pharmacodynamic activity of pembro/cape versus pembro/taxol is underway

## References:

**(1)** Adams S, ASCO 2017, Abstract 1008; **(2)** Schmid P, AACR 2017; Abstract 2986; **(3)** Leonard R, 2011 Clin Breast Cancer; **(4)** Gajria D, 2011 Cancer; **(5)** Traina T, 2010 Breast Dis; **(6)** Zitvogel L; 2007 Nat Rev Immunol; **(7)** Fumoleau P 2004 Eur J Cancer; **(8)** O'Shaughnessy J, 2001 Ann Oncol; **(9)** Kaufman P 2015, J Clin Oncol; **(10)** Harbeck N 2017, Breast Cancer Res Treat; **(11)** Kaufmann M 2010, Eur J Cancer; **(12)** Basho B 2017, JAMA Oncol; **(13)** Joneja U 2017, J Clin Pathol; **(14)** Adams S 2017, NPJ Breast Cancer

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