Identification of Symptoms Associated with irAEs in the I-SPY Trial

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On behalf of the I-SPY2 Investigators
**Immune checkpoint inhibitors**

- Introduced first in the metastatic breast cancer setting with improved outcome in PD-L1 positive disease

- The checkpoint inhibitor, pembrolizumab, is now approved as standard neoadjuvant therapy for high-risk early-stage triple negative breast cancer, with improvements in both response and event free survival

- Associated with immune-related adverse events, some of which are irreversible
  - Hypothyroidism
  - Adrenal insufficiency (often late onset)
  - Diabetes (late onset)

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Immune-related Adverse Events and Associated Symptoms

SYMPTOMS

- Diarrhea
- Fatigue
- Dizziness
- Shortness of breath
- Rash
- Vomiting
- Neuropathy
- Headache
- Nausea
- Palpitations
- Decreased appetite
- Acne
- Itching
- Insomnia
- Muscle pain
- Mouth/Throat sores
- Joint pain
- Abdominal pain
- Cough
- Constipation
- Taste changes
- Swelling
- Blurry vision
- Pain urination
- Dry eyes

Martins et al, 2019, Nature Reviews Clinical Oncology
Objectives

• Predict which patients are at risk for developing a serious irAE to enable early consideration of optimal treatment choices

• Understand which symptoms during treatment most contribute to impairment in overall quality of life
Balancing Toxicity and Efficacy: Developing a Standardized Method to Predict Immunotherapy Toxicities
The I-SPY 2 Trial Schema
Dataset Composition

ASSESSMENTS

Clinician-assessed adverse events (CTCAE v 5.0)
- Included all grade 1-4 AEs
- Collected weekly to every 2-3 weeks depending on chemotherapy schedule
- Follow-up: up to 1 year

Patient-reported Outcomes (PRO-CTCAE/PROMIS)
- Patients filled in at least 2 timepoints including baseline
- Surveys were collected weekly for symptoms, and monthly for QOL
- Surveys collected through 24 months
- Reported using the Likert scale 1-5 (from none/mild to severe)

STUDY POPULATION
- 482 patients prescribed at least 4 doses of immunotherapy in combination with chemotherapy (CTCAE)
- 346 patients (PRO-CTCAE/PROMIS), 72% completion rates, 20% overlap with CTCAE
irAEs Included in the Data Analysis

OUTCOMES VARIABLES – CTCAE Defined

• Hypothyroidism (12%)

• Adrenal insufficiency (AI) (8%)

• Pneumonitis (4%)

• Colitis (1%)
Demographic distribution of irAEs

<table>
<thead>
<tr>
<th></th>
<th>Overall (n=482)</th>
<th>Pneumonitis (n=20)</th>
<th>No Pneumonitis (n=462)</th>
<th>Colitis (n=6)</th>
<th>No Colitis (n=476)</th>
<th>Adrenal Insufficiency (n=38)</th>
<th>No Adrenal Insufficiency (n=444)</th>
<th>Hypothyroidism (n=61)</th>
<th>No Hypothyroidism (n=421)</th>
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<tbody>
<tr>
<td>Age (Mean (SD))</td>
<td>47.6 (11.6)</td>
<td>54.0 (9.2)</td>
<td>47.4 (11.6)</td>
<td>51.6 (12.2)</td>
<td>47.6 (11.6)</td>
<td>48.5 (11.7)</td>
<td>47.6 (11.6)</td>
<td>46.4 (10.3)</td>
<td>48.5 (11.7)</td>
</tr>
<tr>
<td>Age (Median (Min-Max))</td>
<td>47.3 (20-79)</td>
<td>55.3 (35-69)</td>
<td>47 (20 – 79)</td>
<td>54.5 (32 – 66.2)</td>
<td>47(20 – 79)</td>
<td>49.5 (31 – 79)</td>
<td>47 (20 – 76)</td>
<td>45.5 (28.8 – 71)</td>
<td>47.9 (20 – 79)</td>
</tr>
<tr>
<td>Race American Indian Alaska Native</td>
<td>3 (.6%)</td>
<td>1 (5 %)</td>
<td>2 (.4%)</td>
<td>0 (0%)</td>
<td>3 (0.63%)</td>
<td>0 (0%)</td>
<td>3 (0.7%)</td>
<td>1 (1.6%)</td>
<td>2 (0.5%)</td>
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<tr>
<td>Black</td>
<td>60 (12.4%)</td>
<td>2 (10%)</td>
<td>58 (12.6%)</td>
<td>1 (16.7%)</td>
<td>31 (6.5%)</td>
<td>5 (13.2%)</td>
<td>55 (12.4%)</td>
<td>2 (3.3%)</td>
<td>58 (13.5%)</td>
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<tr>
<td>White</td>
<td>382 (79.3%)</td>
<td>16 (80%)</td>
<td>366 (79.2%)</td>
<td>4 (66.7%)</td>
<td>378 (79.4%)</td>
<td>32 (84.2%)</td>
<td>350 (78.8%)</td>
<td>53 (86.9%)</td>
<td>329 (78.1%)</td>
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<td>Asian</td>
<td>32 (6.6%)</td>
<td>0 (0%)</td>
<td>32 (6.9%)</td>
<td>1 (16.7%)</td>
<td>31 (6.5%)</td>
<td>1 (2.6%)</td>
<td>31 (7.0%)</td>
<td>2 (3.3%)</td>
<td>30 (7.1%)</td>
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- Pneumonitis rates were higher in patients over 50 than under 50 (P<.01)
- No other significant associations were observed
Cumulative incidence of irAEs over time
Goal: Predict which patients were at risk for developing an irAE using symptom trajectory

- Symptoms leading up to an AE may be interconnected- “symptomics”
- Knowledge about which individual or constellation of symptoms (mild or severe) leading up to an AE are more predictive or sentinel
- Important implications for individualizing therapy to minimize toxicity
Methods: Predicting who is at risk for developing an irAE

Cohort and data
- All patients on immunotherapy
- Created separate model for each irAE

Method
- Elastic net regression
  - Input: Area under curve for each symptom
  - Output: Grade of irAE

Evaluation of Results
- Error estimates for each model
Methods: Calculation of Symptom Burden

AUC(sympont) = \sum_{n=1}^{n} Grade \times Duration

- Incorporated duration of symptom (days)
- Symptoms only up to the diagnosis of the irAE
- 4-12 weeks after treatment initiation

Grade

Days

Fatigue    Rash    Dry eyes

0     84

42     84

irAE
Results: Early Symptoms Associated with Hypothyroidism

Early onset of symptoms by 6 weeks was associated with subsequent development of hypothyroidism.

Error Estimate: 30%

- Grade 2 or higher fatigue
- Grade 2 or higher headache
- Grade 1 or higher shortness of breath

Developed hypothyroidism
No hypothyroidism

X axis – weeks
Y axis – proportion of patients

(Wks)

(Wks)
Results: Early Symptoms Associated with Adrenal Insufficiency

- Grade 2 or higher fatigue
- Grade 1 or higher shortness of breath
- Grade 2 or higher decreased appetite
- Grade 1 or higher diarrhea

Early onset of symptoms by 6 weeks was associated with subsequent development of adrenal insufficiency.

Error Estimate: 25%
Results: Co-occurring Symptoms up until 6 week timepoint

HYPOTHYROIDISM

ADRENAL INSUFFICIENCY

- Headache
- Vomiting
- Itching
- Palpitations
- Decreased Appetite
- Mouth Throat Sores
- Nausea
- Acne
- Heartburn
- Insomnia
- Blurry Vision
- Joint Pain
- Cough
- Hot Flashes
- Neuropathy
- Muscle Pain
- Diarrhea
- Rash
- Mouth Throat

- Swelling
- Acne
- Decreased Appetite
- Nasal Congestion
- Nausea
- Vomiting
- Mouth Throat
- Joint Pain
- Muscle Pain

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Results: Removal of specific symptoms significantly decreases model performance

HYPOTHYROIDISM

- Headache
- Vomiting
- Itching
- Palpitations
- Decreased Appetite
- Mouth Throat Sores
- Nausea
- Acne
- Heartburn
- Insomnia
- Blurry Vision
- Joint Pain
- Cough
- Hot Flashes
- Neuropathy
- Muscle Pain

ADRENAL INSUFFICIENCY

- Swelling
- Acne
- Decreased Appetite
- Hot Flashes
- Insomnia
- Tense Silences
- Constipation
- Nausea
- Vomiting
- Mouth Throat Sores
- Headache
- Diarrhea
- Muscle Pain
Methods: Patient Reported Outcomes in I-SPY

ePRO launched in 2021 across 28 sites
Results: PRO enables us to evaluate symptoms and their impact on quality of life longitudinally

Joint and muscle pain starting at week 4 is most predictive of reduced QOL at week 12

Poster ID: P5-07-03
Poster Title: The Association Between Symptom Severity and Physical Function among Participants in I-SPY2

Thursday, 5 pm CT
Conclusions and Next Steps

• Early onset of symptoms may predict subsequent risk for irAEs
  ➢ Understanding the risk factors for developing an irAE will help to optimize intensity of surveillance and potential treatment modification to minimize the impact of toxicity

• Further confirmation of this model is required
  ➢ Analysis of PRO is ongoing
  ➢ Analysis of genetic predictors to identify who is at risk of developing a severe irAE
Acknowledgements

WORKING GROUP CHAIRS

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PROJECT OVERSIGHT

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Biomarkers/Specimens:

Imaging Lab:

Data Analysis, Data Management & IT:

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## Participating Organizations

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