Modeling of Tumor Kinetics and Overall Survival to Identify Prognostic and Predictive Biomarkers of Efficacy for Durvalumab

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Durvalumab is an anti-PD-L1 mAb that blocks the interaction between PD-L1 and its receptors (PD-1 and CD80).

Blocking PD-L1 and PD-1/CD80 interaction by anti-PD-L1 results in enhanced T cell activity and T cell mediated tumor cell killing.

Durvalumab is approved for patients with locally advanced or metastatic urothelial carcinoma (UC) who have progressed following platinum containing chemotherapy.
Durvalumab Demonstrated Favorable Efficacy in UC Patients

Study 1108: a Phase 1/2 dose escalation/expansion study to evaluate the safety, tolerability, and PK of durvalumab in patients with advanced solid tumors (UC expansion cohort: 10 mg/kg Q2W)

Best Percentage Change from Baseline in Tumor Size by BICR
(Patients with Target Lesions at Baseline and ≥1 Post-baseline Scan)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>PD-L1 high</th>
<th>PD-L1 low/negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=191</td>
<td></td>
<td>N=98</td>
<td>N=79</td>
</tr>
<tr>
<td>Confirmed ORR, n (%) (95% CI)</td>
<td></td>
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<tr>
<td>34 (17.8)</td>
<td>27 (27.6)</td>
<td>4 (5.1)</td>
<td></td>
</tr>
<tr>
<td>(12.7, 24.0)</td>
<td>(19.0, 37.5)</td>
<td>(1.4, 12.5)</td>
<td></td>
</tr>
</tbody>
</table>

Powles et al., JAMA Oncol. 2017 Sep 14;3(9):e172411
Durvalumab Demonstrated Favorable Efficacy in UC Patients

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Overall Survival

Powles et al., JAMA Oncol. 2017 Sep 14;3(9):e172411
Question

How can we best identify patients who are likely to respond to durvalumab treatment?
A Tumor Kinetic-OS Modeling Framework for IO Therapy

Tumor kinetic model $(K_g, K_{kill})$

Multi-variate covariate analysis

 Dropout model

Predicted tumor dynamics

OS model
The Population Tumor Kinetic Model for Durvalumab

Observed individual tumor profiles* in UC cohort from Study 1108

*Sum of longest diameter
#159 with post-bsln data

The Population Tumor Kinetic Model for Durvalumab

Model-Based Covariate Analysis Identified Potential Prognostic and Predictive Factors

Potential prognostic factors:
Impact tumor growth rate ($K_g$)

Potential predictive factors:
Impact tumor killing rate ($K_{kill}$)

Model Simulations Predicted Tumor Response Rate in Various Patient Subgroups and Biomarker Cutoffs

Tumor response rate by covariate subgroups

- Simulated
- Observed

% Patients with >30% Tumor Shrinkage

- All subjects
- TC ≥ 25%
- TC ≥ 50%
- TC ≥ 75%
- IC ≥ 25%
- IC ≥ 50%
- IC ≥ 75%
- BDI tumor ≤ 60
- BDI tumor > 60
- N/L Ratio ≤ 4
- N/L Ratio > 4
- LDH < 230
- LDH ≥ 230
- Albumin < 4
- Albumin ≥ 4
- Hemoglobin < 10
- Hemoglobin ≥ 10
- ECOG = 0
- ECOG = 1
- No liver metastasis
- Liver metastasis
- Not LN only
- LN only
- Prior chemo < 3M
- Prior chemo ≥ 3M
- LOT = 1 or 2
- LOT ≥ 3
A Tumor Kinetic-OS Modeling Framework for IO Therapy

- Tumor kinetic model ($K_g, K_{kill}$)
- Dropout model
- Multi-variate covariate analysis
- Predicted tumor dynamics
- OS model
The Final OS Model Predicted the Observed Survival Curves from Study 1108 UC Cohort

K-M curve of OS (overall)

- Observed
- Predicted 95% CI

K-M curve of OS (by response type)

- Responders (no delay)
- Responders (delay)
- Non-responder-and-non-progressors
- Progressors

Covariate Analysis Using the OS Model Identified Significant Factors for Survival

Simulated OS curves by covariates

- **Immune cell PD-L1**
  - IC Score
    - High (100%)
    - Low (0%)
  - Other covariates:
    - Smoking History (Never)
    - Prior Chemo <= 3M
    - N/L Ratio (21)
    - N/L Ratio (1.5)
    - LN Only disease
    - Line of Therapy >= 3
    - LDH (700 U/L)
    - LDH (140 U/L)
  - IC Score (100%)
  - IC Score (0%)
  - Hemoglobin (9 g/dL)
  - Hemoglobin (14 g/dL)
  - ECOG = 0
  - Albumin (4.5 g/dL)
  - Albumin (2.7 g/dL)
  - Age (81 yrs)
  - Age (49 yrs)

- **Tumor cell PD-L1**
  - TC Score
    - High (100%)
    - Low (0%)
  - Other covariates:
    - Smoking History (Never)
    - Prior Chemo <= 3M
    - N/L Ratio (21)
    - N/L Ratio (1.5)
    - LN Only disease
    - Line of Therapy >= 3
    - LDH (700 U/L)
    - LDH (140 U/L)
  - IC Score (100%)
  - IC Score (0%)
  - Hemoglobin (9 g/dL)
  - Hemoglobin (14 g/dL)
  - ECOG = 0
  - Albumin (4.5 g/dL)
  - Albumin (2.7 g/dL)
  - Age (81 yrs)
  - Age (49 yrs)

- **Albumin**
  - Level (Q1, Q2, Q3, Q4)
  - Liver metastasis
  - LM: No, Yes

Summary

A population tumor kinetic – OS – dropout modeling framework is developed to describe the longitudinal change in tumor size and survival in cancer patients treated with durvalumab.

This modeling framework is a useful tool to study tumor response and its correlation with OS, in which the effect of multiple prognostic and predictive biomarkers can be evaluated in a multivariate analysis.

This modeling approach can be used to guide patient selection and enrichment strategies and to optimize clinical trial designs for IO therapies across various cancer indications.
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