Clonal Neoantigen Load and Tertiary Lymphoid Structure Formation are Associated with Exceptional Response to Immune Checkpoint Inhibition in Clear Cell Renal Cell Carcinoma

Tejas Jammihal¹, Renee Maria Saliby², Chris Labaki², Bradley McGregor², Ziad El Bakouny², Talal El Zarif², David A Braun³*, Toni K Choueiri²*, Sachet A Shukla¹*

1. Department of Hematopoietic Biology and Malignancy, The University of Texas MD Anderson Cancer Center, Texas, Houston, TX, USA 2. Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA 3. Center of Molecular and Cellular Oncology (CMCO), Yale University, New Haven, CT, USA.
Exceptional response (ER) to immune checkpoint inhibition (ICI) in clear cell renal cell carcinoma (ccRCC)

• Only a minority of ccRCC patients have “exceptional” response to ICI
  • Deep tumor regressions
  • Prolonged survival benefit

What are the genomic and transcriptomic correlates of exceptional response to ICI in ccRCC?
Defining Exceptional Response in ccRCC

- **Intermediate Response (IR)** – CR/PR but not ER
- **Progressive Disease (PD)**

- **Complete Response**
  - PFS ≥ 12 months

- **Partial Response, Tumor Shrinkage ≥ 50%**
  - PFS ≥ 24 months

- **Partial Response**
  - PFS ≥ 36 months
Baseline samples from treatment-naïve, advanced ccRCC

**IO+IO (PD-1i + CTLA-4i)**
- WES (n=224)
  - Exceptional Response (ER): 24.94%
  - Intermediate Response (IR): 36.96%
  - Intermediate Response: 18.36%
  - Progressive Disease (PD): 19.72%

**IO+VEGF (PD-(L)1i + VEGFi)**
- WES (n=285)
  - RNA (n=357)
  - Exceptional Response (ER): 6.34%
  - Intermediate Response: 30%
  - Intermediate Response: 13.41%
  - Progressive Disease (PD): 50.24%
  - Stable Disease (SD): 50.24%
Identifying genomic correlates of ER to IO+IO therapy

IO+IO (PD-1i + CTLA-4i)
- WES (n=224) - 24.94%
- RNA (n=357) - 18.36%
- PD (n=357) - 19.72%
- IR (n=357) - 36.96%

IO+VEGF (PD-(L)1i + VEGFi)
- WES (n=285) - 50.24%
- RNA (n=357) - 30%
- PD (n=357) - 13.41%
- IR (n=357) - 6.34%

ER Exceptional Response (ER)
IR Intermediate Response
nonER CR/PR (IR)
PD Progressive Disease (PD)
SD Stable Disease (SD)
Clonal neoantigen load is associated with ER in IO+IO

- Clonal neoantigen load = # predicted neoantigens from clonal mutations

Clonal neoantigen load is associated with exceptional, but not overall, response
Higher clonal neoantigen load is correlated with improved progression free survival outcomes in IO+IO.
Identifying correlates of ER to IO+VEGF therapy

IO+IO (PD-1i + CTLA-4i)
- WES (n=224)

IO+VEGF (PD-(L)1i + VEGFi)
- WES (n=285)
- RNA (n=357)

- Exceptional Response (ER) 6.34%
- Intermediate Response 13.41%
- nonER CR/PR (IR) 30%
- Progressive Disease (PD) 50.24%
- Stable Disease (SD) 18.36%
IO+VEGF ERs are marked by increased intratumoral humoral responses

Is the observed B-cell/plasma cell signature driven by TLS formation in ccRCC?
Tertiary lymphoid structures are associated with IO+VEGF ER

TLS score is preferably associated with exceptional response as compared to intermediate response
TLS signature is an independent predictor of PFS in IO+VEGF
Exceptional Responders in IO+VEGF have two subgroups
Conclusions

**IO+IO**

- Clonal neoantigen load is
  - associated with exceptional, but not overall, response
  - an independent predictor of PFS

**IO+VEGF**

- ER are marked by signatures of intratumoral humoral responses and TLS formation, as compared to intermediate response
  - TLS signature is an independent predictor of PFS in IO+VEGF
- TLS-low exceptional responders have high clonal neoantigen load
Acknowledgements

- Bradley McGregor
- Ziad El Bakouny
- Talal El Zarif

Sachet Shukla  Toni Choueiri  David Braun

Renée Maria Saliby  Chris Labaki

- Patients and their families

Shukla Lab @MDAnderson