Memorial Sloan Kettering Cancer Center

(PD47-02) “Actionable” genomic alterations in chemotherapy resistant muscle-invasive bladder cancer

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Conflicts of Interest

- Nothing to disclose

Background/Rationale

- Patients with residual MIBC after neo-adjuvant chemotherapy have a poor prognosis

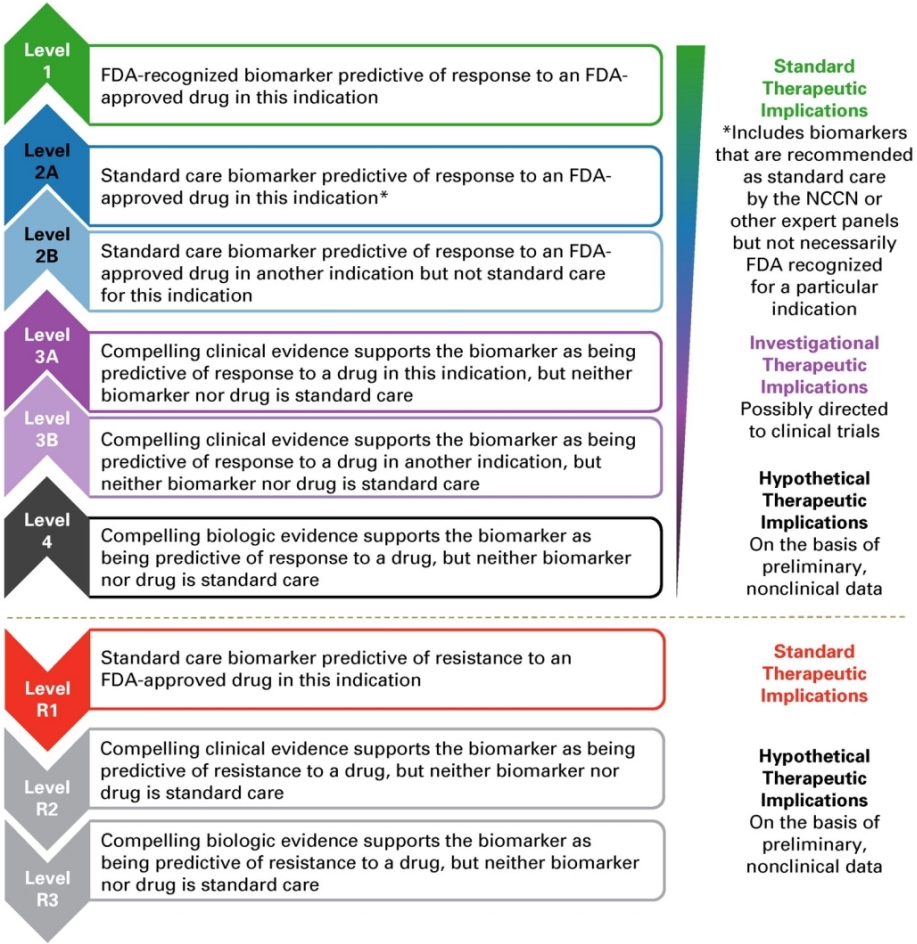
- Currently several large adjuvant clinical trials ongoing for immune checkpoint inhibitors, however <25% of patients have a durable response to immunotherapy

- Goal: analyze the genomic landscape of actionable alterations in chemotherapy resistant tumors that may aid in patient selection for adjuvant treatments and guide the rationale for development of targeted therapy

Materials and Methods

- Patients who completed four cycles of planned Gemcitabine and Cisplatin NAC followed by RC at MSKCC were identified
- These patients were enrolled on a prospective IRB-approved protocol for which IMPACT testing was performed on post-chemotherapy tumor DNA
- Of those patients, we identified those with >/=T2 disease or any LN positive disease on RC pathology, which we defined as chemo-refractory
- Actionable genomic alterations including somatic mutations and structural alterations that predict response to targeted drug therapy were identified and stratified by level of evidence using OncoKB

OncoKB Therapeutic Levels of Evidence



Chakravarty et al., JCO PO 2017

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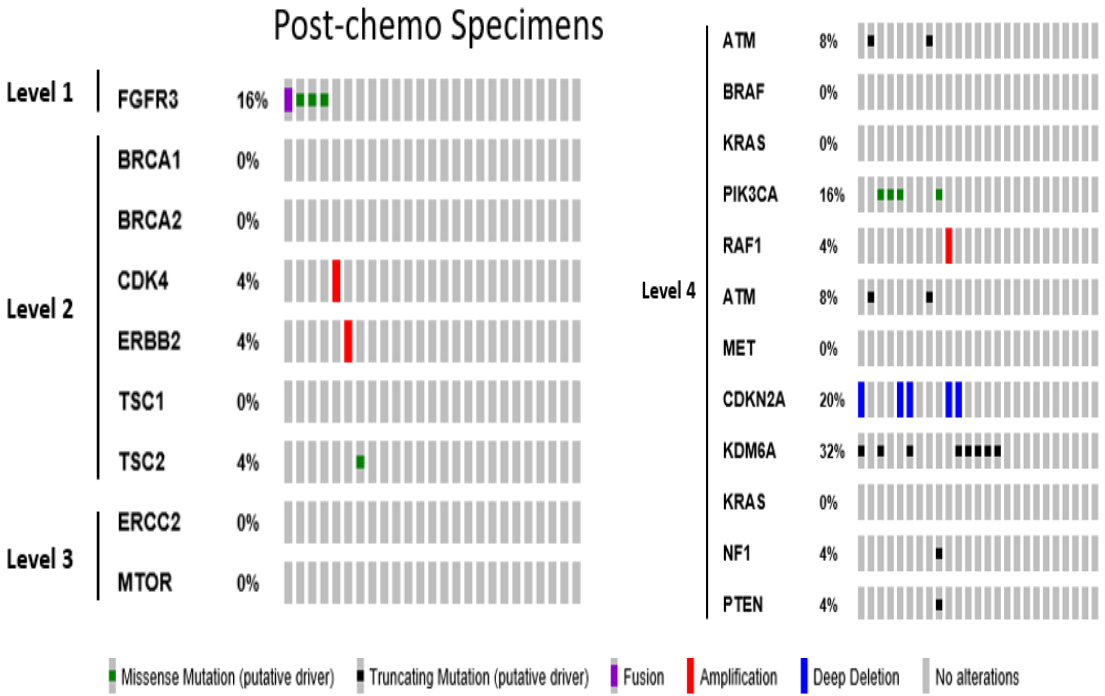
Actionable genomic alterations identified



-201 patients with chemorefractory MIBC were identified

-25 of these underwent sequencing of a post-chemotherapy specimen

-IMPACT sequencing revealed one or more actionable alterations in 15 specimens (60%)

-31 actionable alterations identified

-4 (16%) with FGFR3 alteration (level one)

-3 (12%) with alterations in *CDK4*, *ERBB2* and *TSC2* (level 2)

-No level 3 alterations

-24 (77%) level 4 alterations

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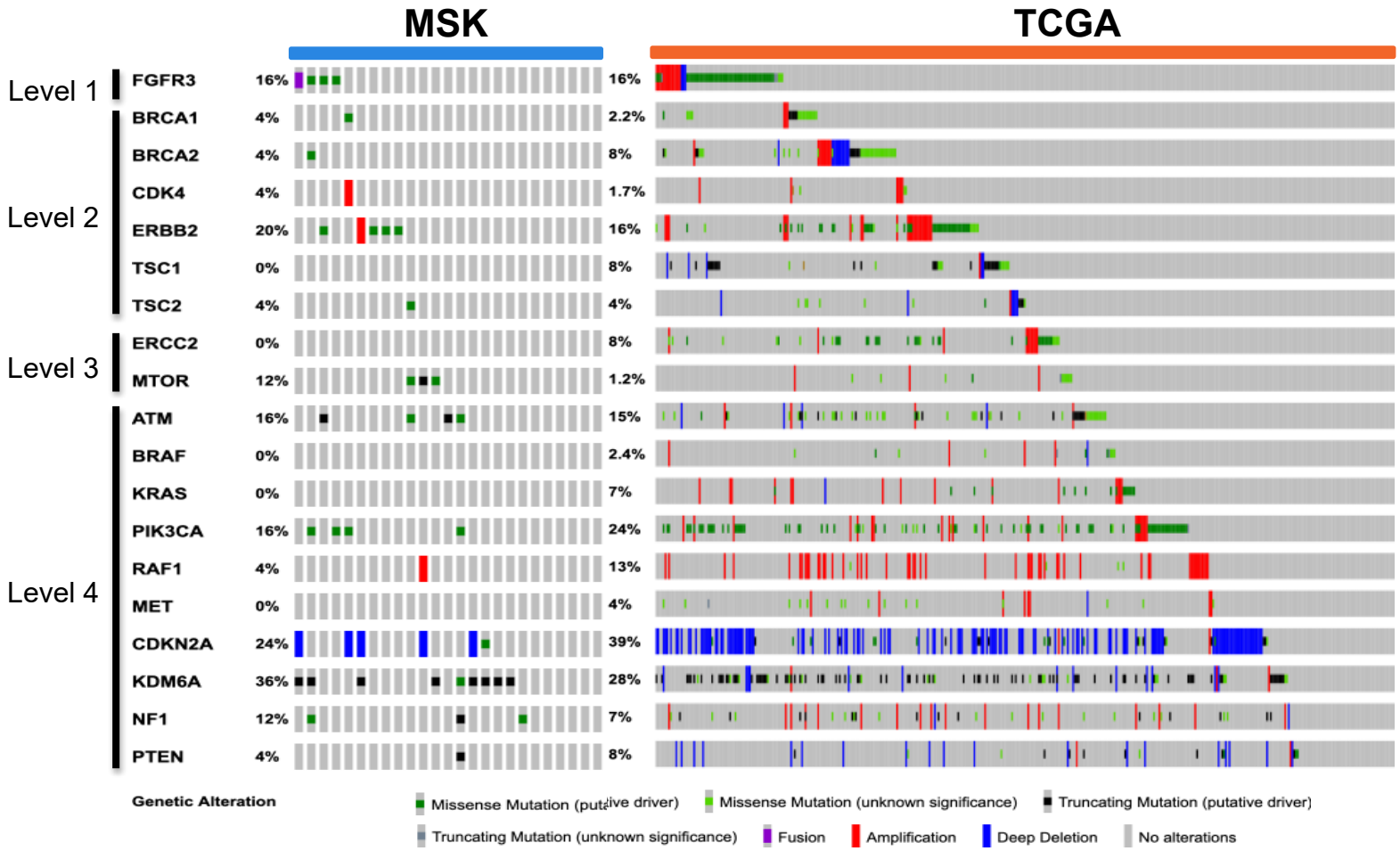
Level 1 Evidence

Erdafitinib

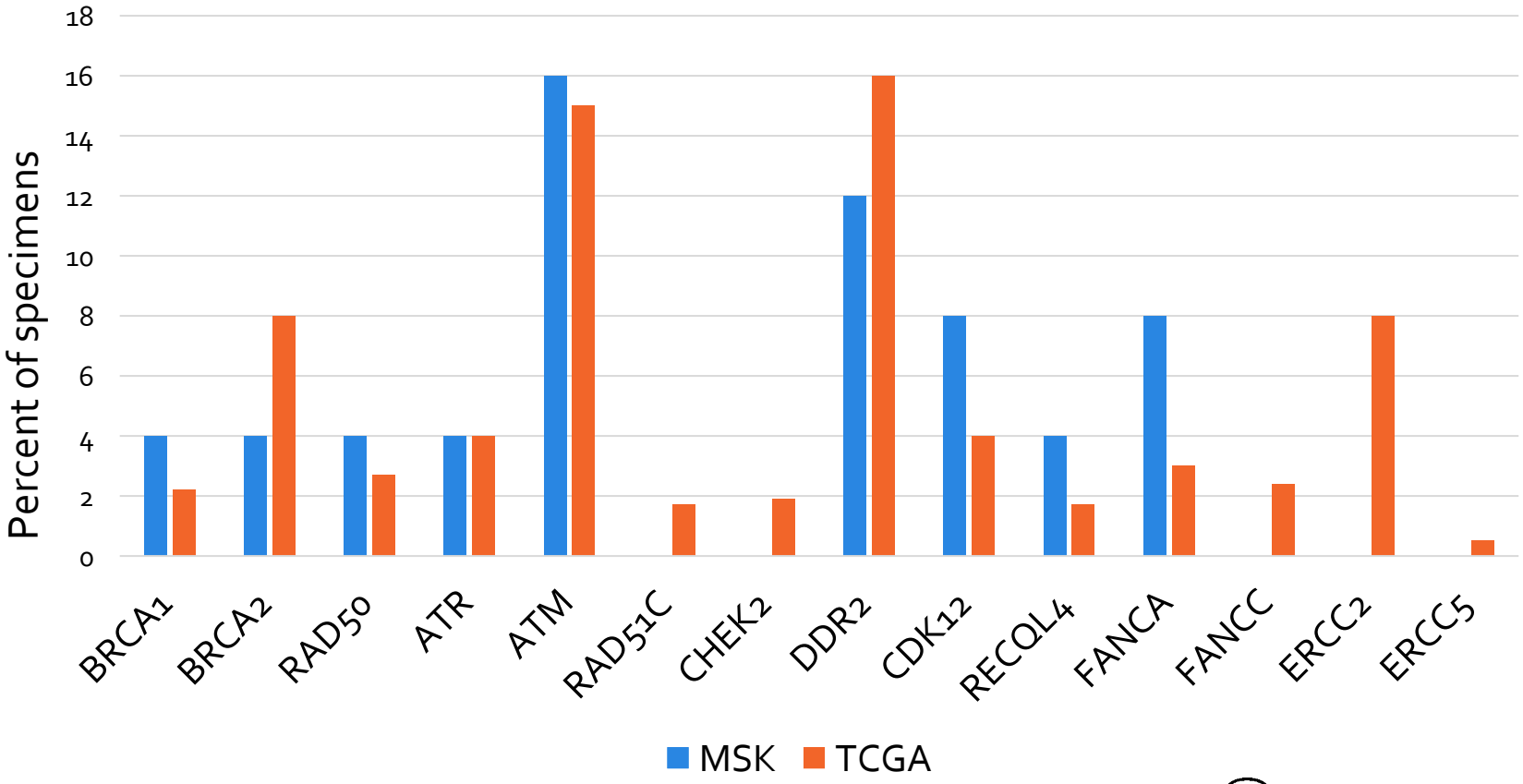
- Erdatifinib recently received FDA approval for treatment of urothelial tumors harboring fusions in FGFR2/3, and oncogenic mutations in FGFR3 (Y373C, G370C, S249C, R248C)

  (*Loriot et al, NEJM 2019*)

Chemorefractory specimens compared to TCGA



Frequency of Alterations in DNA Damage Repair Genes



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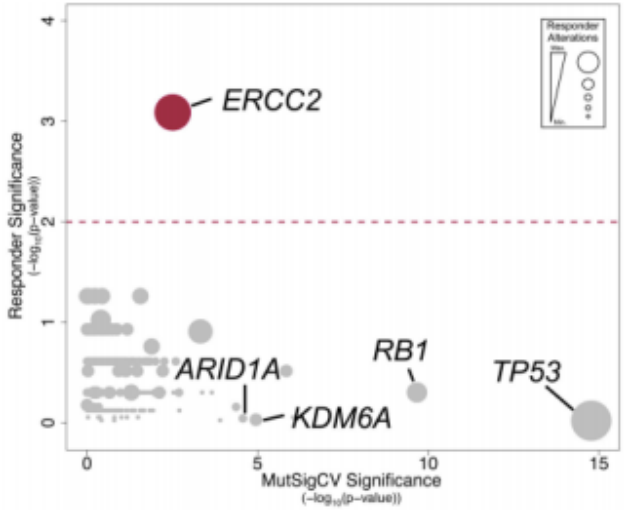
DNA Damage Response/Repair

- *ERCC2* mutations found to be significantly associated with cisplatin responders compared with non-responders in MIBC
- whole exome sequencing performed on *pre-treatment* tumor and germline DNA

(Van Allen et al, Cancer Discov 2015)



- Somatic alterations in genes associated with DNA damage response and repair are associated with enhanced platinum responsiveness, which leads to a higher likelihood of pathologic downstaging in neoadjuvantly treated bladder cancers.
- Also associated with increased tumor-infiltrating lymphocytes.

(Teo et al, CCR 2017)

Conclusions

- With the recent approval of FGFR3 inhibitors, there now exists OncoKB level 1 evidence for those with FGFR2/3 alterations, which are highly prevalent in urothelial carcinoma

- There are multiple other potentially actionable alterations in chemotherapy-resistant MIBC that may provide rationale for future studies utilizing novel targeted therapies

Acknowledgements

Source of Funding: This work was supported by the Sidney Kimmel Center for Prostate and Urologic Cancers, the Michael and Zena Wiener for Therapeutics Program in Bladder Cancer, Pin Down Bladder Cancer, Cycle for Survival, the Marie-Josee and Henry R. Kravis Center for Molecular Oncology, NIH/NCATS Grant Number UL1-TR002384, the National Cancer Institute Cancer Center Core Grant Number P30-CA008748, MSKCC SPORE in Bladder Cancer P50-CA221745, NIH/NCI K12 Paul Calabresi Career Development Award for Clinical Oncology (K12 CA184746)

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