Effect of concomitant medications on overall survival in patients with cancer undergoing immunotherapy

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Taking antibiotics near the start of immunotherapy is correlated with reduced overall survival

Background

- Response to Immunotherapy (IO) is affected by concomitant medications including:
  - Antibiotics [1]
  - Corticosteroids [2]
- We explored these relationships across a variety of cancers, as well as other medications and estimated the relative impact of each medication when given in combination.

Methods

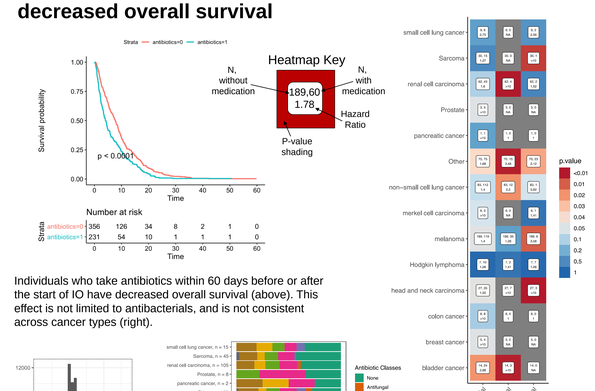
- Retrospective review
- Advanced cancer who received ICIs from 2011 to 2017 at the Ohio State University
- Data from Information Warehouse requests and manual chart abstraction into a REDCap database [3].
- Overall Survival (OS) was calculated from the initiation of ICI to date of death or last follow-up.
- Significance of Cox Proportional-Hazards models were evaluated by log-rank test (α = 0.05).
- All calculations performed in R (packages reference [4].

Table 1. Cohort summary

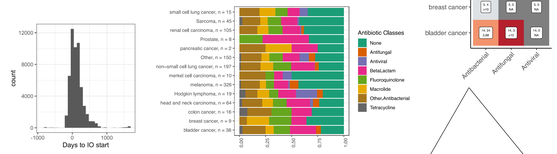
Overall n	1100
BMI (mean (sd))	28.33 (6.96)
staging (%)	
1	1 (0.1)
2	6 (0.5)
3	97 (8.8)
4	800 (72.7)
NA	196 (17.8)
age (mean (sd))	62.15 (13.26)
sex = Male (%)	645 (58.6)
Cancer (%)	
bladder cancer	38 (3.5)
breast cancer	9 (0.8)
colon cancer	16 (1.5)
head and neck carcinoma	64 (5.8)
Hodgkin lymphoma	19 (1.7)
melanoma	326 (29.6)
merkel cell carcinoma	10 (0.9)
non-small cell lung cancer	197 (17.9)
Other	150 (13.6)
pancreatic cancer	2 (0.2)
Prostate	8 (0.7)
renal cell carcinoma	105 (9.5)
Sarcoma	45 (4.1)
small cell lung cancer	15 (1.4)
NA	96 (8.7)
Immunotherapy (%)	
Atezolizumab	33 (3.0)
Ipilimumab	195 (17.7)
Medi4736 + Tremelimumab	6 (0.5)
MEDI4736, durvalumab	14 (1.3)
nivo + chemo	12 (1.1)
Nivo + Ipi	70 (6.4)
Nivolumab	530 (48.2)
Other	19 (1.7)
Pembrolizumab	216 (19.6)
Tremelimumab	5 (0.5)
ECOG (%)	
0	346 (31.5)
1	381 (34.6)
2	136 (12.4)
3	27 (2.5)
4	3 (0.3)
NA	207 (18.8)

Results

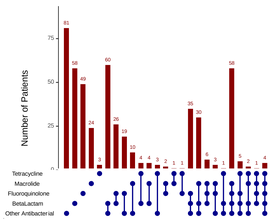
Correlation between antibiotics at time of IO start and decreased overall survival



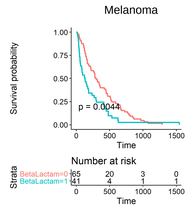
Individuals who take antibiotics within 60 days before or after the start of IO have decreased overall survival (above). This effect is not limited to antibacterials, and is not consistent across cancer types (right).

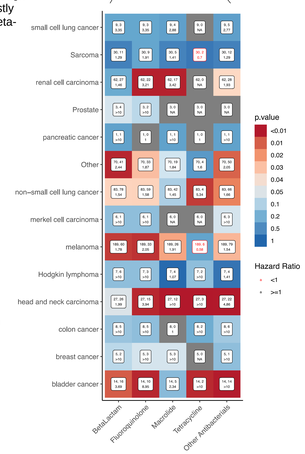


Most patient records list antibiotics after the start of IO, though some EMR incompleteness is expected (above, left). Mostly antibacterials are administered, with a large fraction as beta-lactams (above, right).



It is common for several antibiotics to be prescribed within 60 days of the start of IO.

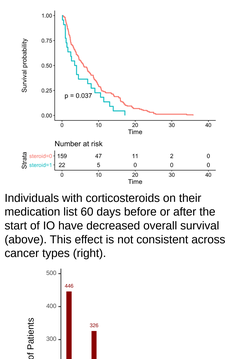




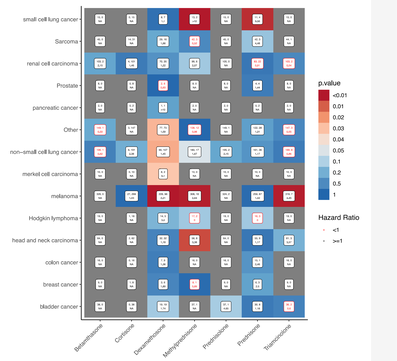
Antibiotics and antibacterials show varying effects across cancer types (above), and the majority show negative effects (hazard ratio > 1). Many comparisons derive from small, unbalanced sample sizes and more data are needed to parse the effects of each.

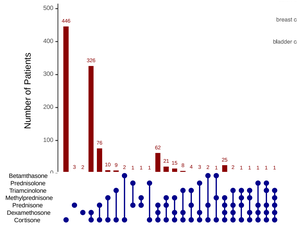
Results

Correlation between corticosteroids at time of IO start and decreased overall survival



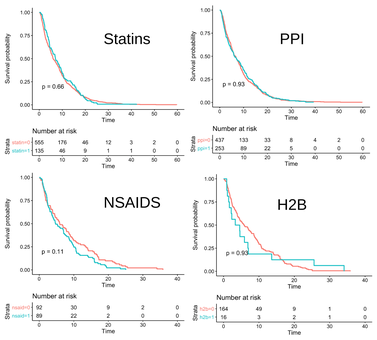
Individuals with corticosteroids on their medication list 60 days before or after the start of IO have decreased overall survival (above). This effect is not consistent across cancer types (right).



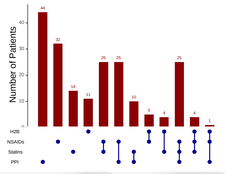


Corticosteroid effects are confounded by simultaneous use (e.g. cortisone and dexamethasone). Larger sample sizes are needed to separate the effects of each and in combination.

Correlation between other medications at time of IO start and overall survival

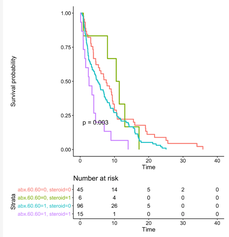


Other concomitant medications do not significantly associate with overall survival (above), though in some cases associations are observed within a cancer type (above, right).

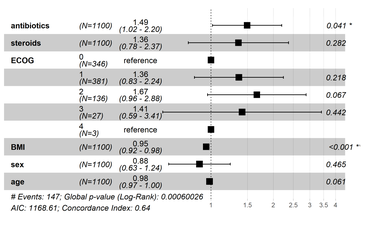


Results

Combined models



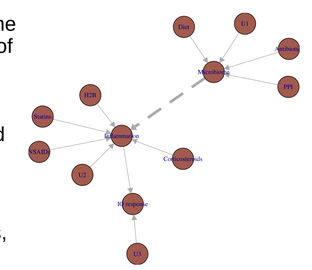
When both antibiotics and corticosteroids are on the medication list at the start of IO, the effect is additive..



In a combined model controlling for covariates including ECOG, BMI, sex and age, antibiotics, but not steroids, remain significant.

Conclusions

- Antibiotics or steroids on the medication list at the time of start of immunotherapy correlated with decreased overall survival -- Statins, NSAIDs, PPIs and H2B did not
- In a combined model, controlling for covariates, antibiotics, but not steroids, remained significant



Acknowledgements

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[2] Fucà, G. *et al.* Effect of Early Steroids use in Advanced NSCLC Patients Treated with Immunotherapy. *Journal of Thoracic Oncology* **13**, (2018).
[3] Harris, P. *et al*. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support, *J Biomed Inform*. 2009 Apr;42(2):377-81.
[4] survminer, survival, magrittr, tableone, officer, causaleffects, igraph, rgl