



Improved Survival: What Trade-offs Make Sense?

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Disclosure Information

- I have no financial relationships to disclose.
- I will not discuss off-label use and/or investigational use in my presentation.



Liver Injury in Oncology

- Several challenges specific to oncology
- Sick patients; multiple confounders
- Attribution is difficult
- Sub-optimal work-ups
- Bottom line: Efficacy trumps all



Case study



- 54 y.o. female from India with heavily pre-treated metastatic breast cancer
 - PMH: HTN, hypothyroid
 - liver metastases: 1.4, 3.3, 6.0 cm
 - Day -8: **screening** ALT 39, AST 42, TBIL 1.2
 - Cycle 1 Day 1: **baseline** ALT 68, AST 70, TBL 1.4 → received one dose of I.V. study drug on phase 3 trial*
 - Cycle 1 Day 5: Jaundice (Gr4 bilirubin), AMS
 - Cycle 1 Day 6 : ALT 159, AST 820, TBL 12.8, cre 2.3, NH3 78
 - Cycle 1 Day 7: Died. No autopsy. No testing for acute hepatitis.
 - Fatal fulminant liver failure related to study drug per investigator

* Unclear if investigator knew of rising liver tests prior to dosing, but still acceptable numbers as per protocol

Case study (continued)

	ALT (xULN)	AST (XULN)	TBILI (XULN)
Day -8	0.8	0.8	1.2
Day 1	1.4	1.5	1.4
Day 5	3.2	16.4	12.8

Would an unacceptable rate of ALT rise $(68-39)/8 = 3.6$ IU per day have been useful to screen out “bad actors”?



Threshold for Hepatotoxicity

- Need to consider risk/benefit
- High threshold in metastatic disease
- Lower threshold in non-invasive disease, chemoprevention, or neo-adjuvant/adjuvant therapy
 - Shorter allowable duration, lower allowable elevations



Biologics and Immunotherapies

Given differences in ADME, conventional approaches to evaluate DILI in small molecule drugs may not apply

- Liver injury may be due to on-target unintended toxicities rather than xenobiotic injury
- We have no data that Hy's Law in Mabs predicts hepatic failure/death
- Further evaluation needed prior to extrapolation
- Does adaptation/tolerance occur differently or at all compared to SMDs?
- What factors predict likelihood of liver failure? Need better understanding of pathophysiology and time-course of liver injury



Combination Immunotherapies

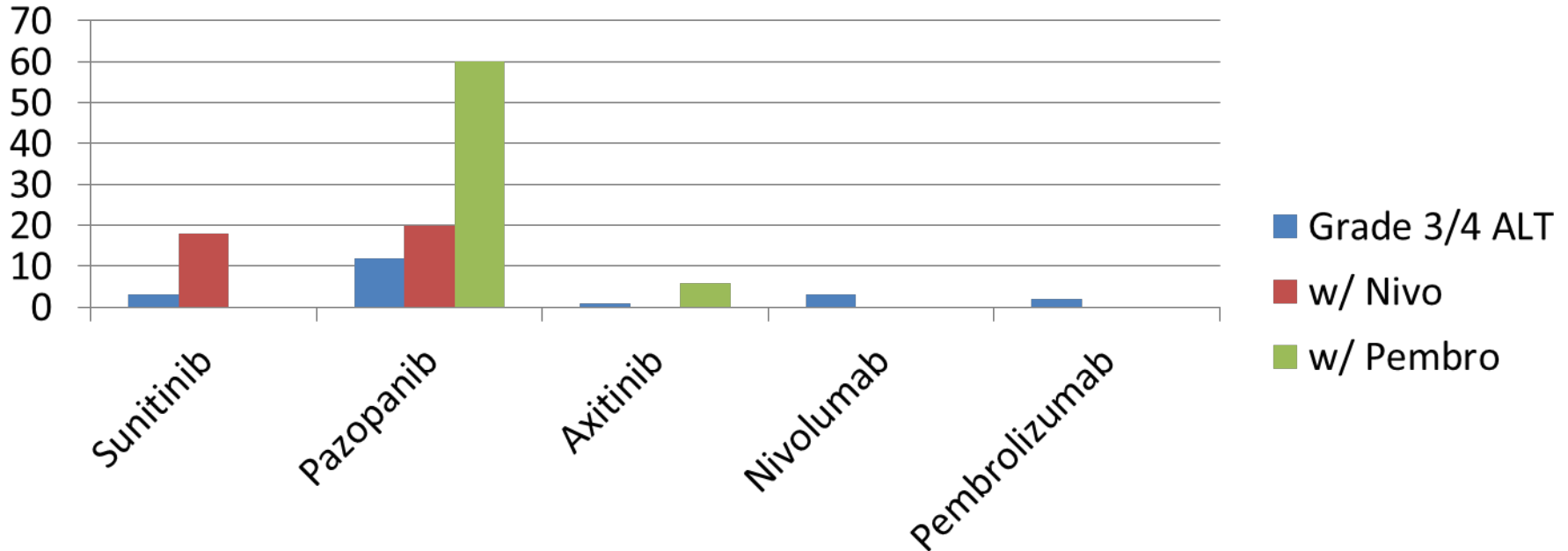


- Synergistic hepatotoxicity?
- Vemurafenib
 - Metabolized largely through CYP1A2
 - 3% AST/ALT >5x ULN
 - ?Toxic intermediate
- Ipilimumab
 - Immune-mediated hepatitis 3.8%
 - Both hepatocellular and bile duct injury reported
- Vemurafenib + Ipilimumab phase I in patients with BRAF-mutated metastatic melanoma
 - No theoretical DDI or overlapping toxicity
 - 1 month of vemurafenib run-in at full dose + 4 infusions of ipilimumab
 - DLT in 4/6 patients in 1st cohort (G3 AST/ALT 2-5 weeks post ipilimumab)
 - Aminotransferase elevations in 3/4 patients in lower-dose vemurafenib cohort
 - Two cases of Hy's Law



Immunotherapy + TKI

Choice of Partner





Clinical Trial vs “Real World”

- Small sample size
- Healthier patients
- Fewer concomitant medications
- Homogenous (ethnic, geographic, age)



Regulatory Considerations

- Identification of susceptible subpopulations
 - History of autoimmunity?
 - Hepatic reserve
 - Polymorphisms
 - HFE -> pazopanib
 - HLA-DRB1*07:01/DQA1*02:01 -> lapatinib



Wish List

- Organ dysfunction studies
- Long-term follow-up/post-marketing assessments
- Real world data
 - COTA (mostly academic), Flatiron (mostly community)
 - De-identified patient information



Concluding Remarks



- Efficacy is key, clinical context is important
 - Identification of susceptible subgroups
- We should strive for better diagnostic DILI workup
 - Exclude other causes
 - Liver biopsy
 - Autopsy
 - recommendations for eligibility, dose modification, dose discontinuation, diagnostic DILI workup (excluding other causes, liver biopsy, autopsy)
 - drug labeling
- Additional caution may be warranted with immunotherapy combinations
- Flexible criteria beyond Hy's Law may be needed depending on drug mechanism and benefit/risk ratio

