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A Different Approach to the Overall Survival Conversation: A Bayesian Analysis of Overall Survival Benefits Among Oncology Accelerated Approvals

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Background

- The Food & Drug Administration Accelerated Approval (AA) Program approves drugs based on surrogate endpoints[1]
- Some oncology drugs may not show statistically significant overall survival (OS) benefit when converted to Regular Approval (RA)
  - A lack of statistical significance is often considered to be a failure to demonstrate survival benefit
  - Recent studies have focused on failure to demonstrate OS within a set time-frame as proof that drugs in the AA pathway do not provide clinical benefit
  - However, there are many challenges associated with demonstrating OS in randomized controlled trials (RCTs)
  - Bayesian frameworks may guide clinical decision-making under uncertainty by providing the probability of an OS benefit
- The aim of this analysis was to identify the most-recent OS data for AA drug-indications converted to RA on a non-OS endpoint and apply a Bayesian framework to identify probability of clinical benefit and harm

Methods

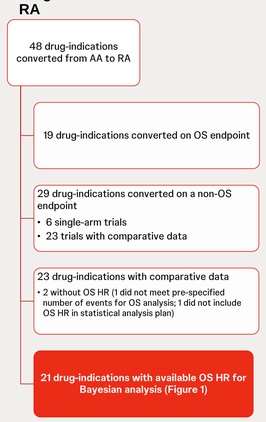
- This is a retrospective cohort study of AA drug-indication pairs from 2013 – 2023
  - Used a similar approach to the cohort study recently completed by Liu et al., 2024[2]
  - Drug-indications with available OS HR were included in the Bayesian analysis (Table 1)
  - OS data extracted through 12/1/2024 from publicly available sources: FDA communications, clinical trial protocols, and publications
- Bayesian Analysis: assumed normally distributed hazard ratios (HR), non-informative priors, and used HR thresholds of 0.8 and 1.0
  - A threshold of 0.8 was selected to evaluate probability of OS survival benefit of 20%[3], and a threshold of 1.0 was selected to evaluate probability of no harm
    - OS HR and 95% confidence intervals (CI) were used as inputs for the function; function adjusted for available CI if 95% was not reported
    - Output of the Bayesian analysis was the probability that OS would be less than the set thresholds (0.8 & 1.0) for each drug-indication pair

TABLE 1: INCLUSION / EXCLUSION CRITERIA

Inclusion criteria	Exclusion criteria
• AA drug-indications from 2013 - 2023 converted to a RA on a non-OS endpoint • Drug-indications with available OS data from longer-term follow up or confirmatory trial associated with RA	• Trials withdrawn from AA: evidence of AA program removing drug-indications not showing efficacy • Trials pending RA conversion: lacked confirmatory data to be included in Bayesian analysis • Trials converted to RA on OS endpoint

Results

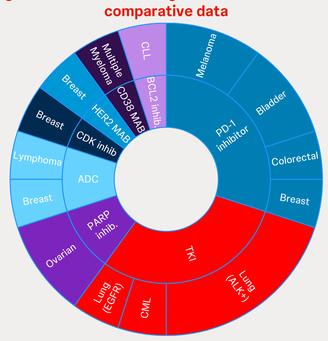
- **Between 2013 – 2023, there were 48 drug-indications converted from AA to RA**



Profiles of the non-OS AA drug-indications:

- Drug-indications spanned various disease areas (Figure 1)
- Majority of drug-types were PD-1 inhibitors or TKIs
- 5 of the drug-indications had statistically significant OS with additional follow-up of the confirmatory trial

Figure 1: Diagram of non-OS AA drug-indications converted to RA with comparative data



Results of Bayesian Analysis

Bayesian Probability of OS HR <0.8

- Range from 0.018 (1.8% probability of at least a 20% lower risk of death to 1.0 (100% probability of at least a 20% lower risk of death) (Figure 2A)
- Over half (52%) of drug-indications had a 65% or greater probability of at least a 20% lower risk of death (Figure 2B)

Bayesian Probability of OS HR < 1.0

- Range from 0.519 (51.9% probability of no harm) to 1.0 (100% probability of no harm from being in active arm) (Figure 2A)
- Majority of the drug-indications had a 65% or higher probability that true OS HR < 1
- All drug-indications had a 50% or higher probability that OS HR < 1 (Figure 2B)

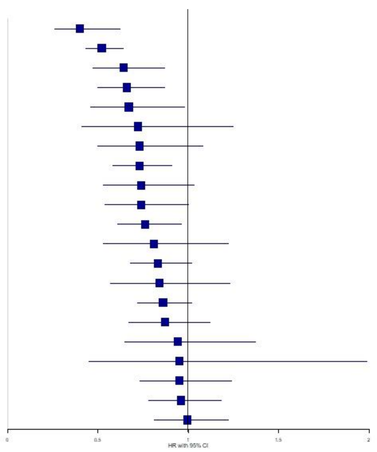
Figure 2B: Probability for 20% lower risk of death (OS HR <0.8) & no harm (OS HR <1.0)

Limitations

- Not all trials had fully mature OS data: some drug-indications may show significant OS with additional follow-up time
- Our analysis only focused on the confirmatory trials associated with AA to RA conversions: though, some indications, such as osimertinib for EGFR NSCLC[4] and nivolumab for metastatic melanoma[5] showed significant OS benefit in separate phase III trials in broader patient populations
- HR of 0.8 selected as offering potential clinical benefit, but precise clinical benefit is unique for each disease
- Drug-indications pending a conversion to RA were excluded due to lack of available confirmatory trial data. However, this cohort of drug-indications should be included in future analyses
- Note: rucaparib was voluntarily withdrawn by manufacturer after OS analyses. It is included in this data set as the drug-indication was converted from AA to RA

Figure 2A: Forest Plot of OS HR with Bayesian probabilities for non-OS drug-indications

Drug-Indication	OS HR	p-value	CI	Addn'l follow-up (mos)	Bayesian Prob <1.0 HR	Bayesian Prob <0.8 HR
**Venetoclax: r CLL with 17p deletion	0.4	<0.0001	[0.26, 0.62]	37	1	0.999
**Nivolumab: untreated metastatic melanoma	0.52	<0.0001	0.43, 0.66]	41	1	1
**Fam-trastuzumab deruxtecan-nxki: refr. metastatic ERBB2+ Breast ca	0.64	0.0037	[0.47, 0.87]	11	0.998	0.923
**Pembrolizumab: metastatic PD1 TNBC	0.66	0.0015	[0.51, 1.02]	59	0.998	0.914
*Alectinib: refr. metastatic ALK + NSCLC	0.67	NR	[0.46, 0.98]	42	0.98	0.82
*Loralatinib: refr. ALK+ metastatic NSCLC	0.72	NR	[0.41, 1.25]	0	0.878	0.646
*Ceritinib: refr. ALK+ metastatic NSCLC	0.73	0.056	[0.50, 1.08]	4	0.997	0.792
**Daratumumab: refr. MM	0.73	0.0044	[0.58, 0.91]	66	0.942	0.677
*Pembrolizumab: MSI-H or dMMR r colorectal ca	0.74	0.036	[0.53, 1.03]	13	0.963	0.678
Olaparib: refr. BRCA-mutated ovarian ca	0.74	0.054	[0.54, 1.00]	38	0.975	0.694
Nivolumab: r locally advanced or metastatic urothelial ca	0.76	NR	[0.61, 0.96]	15	0.989	0.667
*Brigatinib: refr. ALK+ metastatic NSCLC	0.81	NR	[0.53, 1.22]	15	0.843	0.476
Pertuzumab: ERBB2+locally advanced breast ca	0.83	0.078	[0.68, 1.02]	55	0.962	0.363
*Selinexor: r/r MM	0.84	0.185	[0.57, 1.23]	0	0.815	0.401
*Pembrolizumab: advanced urothelial ca	0.86	0.0407	[0.72, 1.02]	0	0.958	0.203
Osimertinib: refr. metastatic EGFR T790M+ NSCLC	0.87	0.277	[0.67, 1.12]	16	0.86	0.258
Polatuzumab vedotin-piiq: r/r DLBCL	0.94	0.75	[0.65, 1.37]	0	0.626	0.201
*Bosutinib: CML	0.95	NR	[0.45, 1.99]	0	0.554	0.324
Nivolumab: r/r metastatic melanoma†	0.95	NR	[0.73, 1.24]	0	0.651	0.098
Palbociclib: ER+ ERBB2- advanced breast ca	0.96	0.34	[0.78, 1.18]	67	0.651	0.042
Rucaparib: refr. advanced ovarian ca	0.995	0.960	[0.81, 1.22]	49	0.519	0.018



* Median OS not reached; ** statistically significant OS HR; †Increased proportion of pt in nivolumab group with poor prognostic factors & increased dropout rate before treatment; NR = Not Reported; p-value of NR not denoted as significant, Most recent or final analysis used for each drug-indication pair; Additional follow-up calculated from the difference between median follow-up time at time of RA conversion compared to median follow-up time associated with most recent or final data from confirmatory trial; r = relapsed, r/r = relapsed refractory, refr = refractory; CI = confidence interval; Addn'l = Additional; Mos = Months

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Abbreviations: ADC: Antibody Drug Conjugate; HER2: human epidermal growth factor receptor 2; MAB : Monoclonal antibody; CDK: cyclin-dependent kinase; PARP: poly(ADP-ribose) polymerase inhibitor; BCL-2: B-cell lymphoma 2 protein; ALK + NSCLC: Anaplastic Lymphoma Kinase-positive Non-Small Cell Lung Cancer; CLL: Chronic Lymphocytic Leukemia; DLBCL: Diffuse Large B-Cell Lymphoma; TNBC: Triple Negative Breast Cancer; CML: Chronic Myeloid Leukemia; EGFR T790M + NSCLC: Epidermal Growth Factor Receptor Threonine790Methionine Non-Small Cell Lung Cancer; ER+ ERBB2: Estrogen Receptor positive Erb-B2 receptor; TKI: tyrosine kinase inhibitor; MM: Multiple Myeloma; Ca: Cancer; PD-1: Programmed Death 1; MSI-H: Microsatellite Instability-High cancer; dMMr: Deficient DNA Mismatch Repair; RCTs: Randomized Controlled Trials

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Key takeaway

Most drug-indications approved through the AA pathway and converted to RA have a 65% or higher probability of the true hazard ratio indicating OS benefit, despite being converted to RA on a non-OS endpoint

Conclusions

- Bayesian analysis offers a different perspective and informative approach for evaluating the potential clinical benefit or harm compared to frequentist approaches relying on p-values
- All drug-indications had a greater than 50% probability that OS HR <1.0, or no harm to the active arm vs. the control arm
- Future work can include AA drug-indications pending regular approval and incorporate median survival differences to evaluate clinical benefit
- Findings should provide confidence in the AA system and may inform shared-decision making processes

Disclosures

JS, LA, SB, SC, SH, DB, and MS are employees of Johnson & Johnson. SB, SC, SH, DB, & MS have stock ownership in Johnson & Johnson.