ACCUMULATED INDUSTRY EXPERIENCE IN BRIDGING REGULATORY AND HTA RESEARCH METHODOLOGIES

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HTA STATISTICS

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Latest Trends in Health Technology Assessments

Regulatory and HTA submissions

- Regulatory and HTA submissions for new treatments are extensively using clinical trial data and results
  - Regulatory submissions demonstrate quality, safety and efficacy and benefit risk
  - HTA submissions demonstrate relative effectiveness and cost effectiveness
- Timelines for regulatory submissions and HTA submissions are different, with HTA approval following Market Authorization by several months [1]
- It is common that follow-up results become available after the HTA submission, before the HTA approval
  - Typical in clinical programs using time-to-event endpoints, specifically when submissions are based on interim results
  - Additional database locks
  - Frequent in oncology programs for potent new treatments
  - Strong emphasis on overall survival, an endpoint typically used for follow-up analyses and key endpoint for relative effectiveness evaluation
  - Results are presented in scientific meetings and/or published
- Follow-up results are very informative but require statistical approach specific to the objective (regulatory or HTA)

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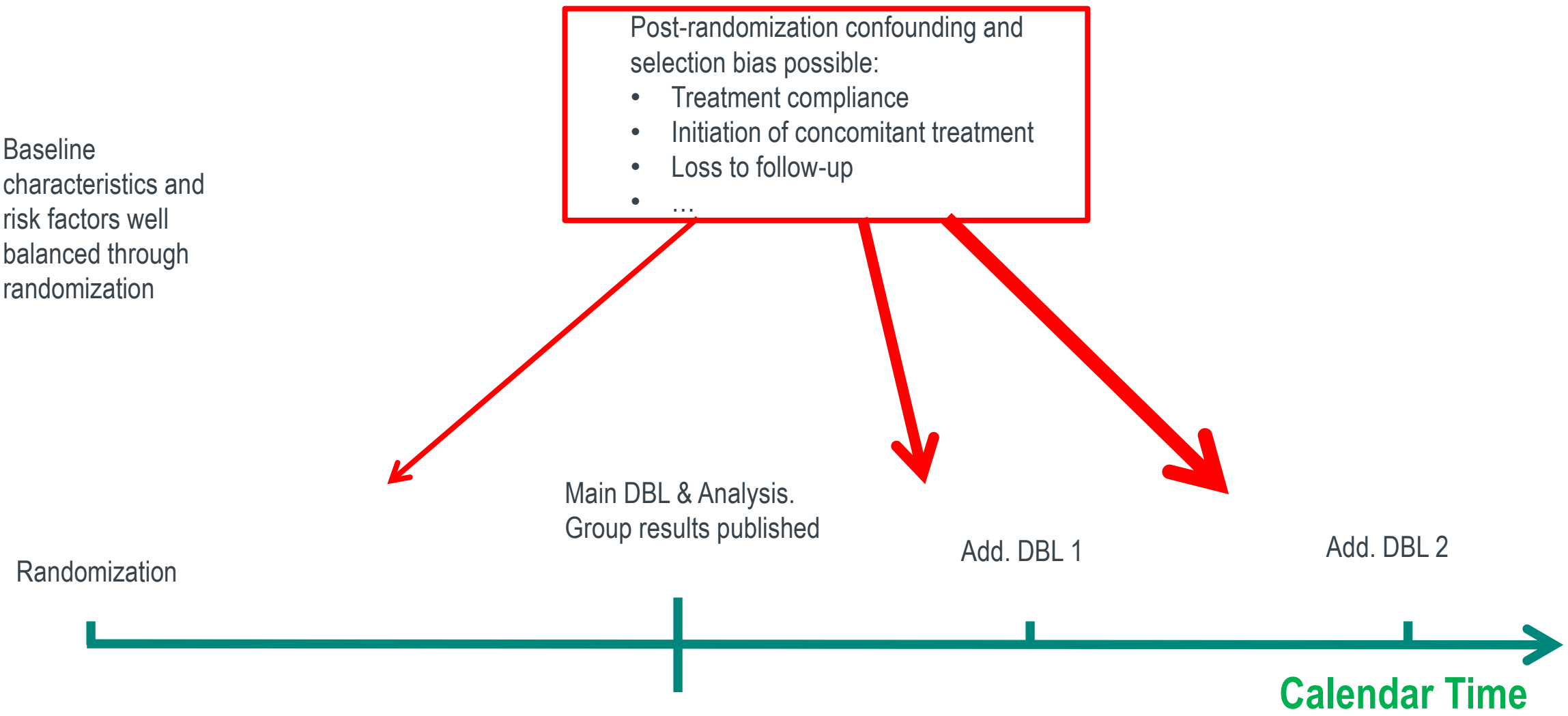
Potential Confounding and Selection Bias in Clinical Trial

Baseline characteristics and risk factors well balanced through randomization

Post-randomization confounding and selection bias possible:

- Treatment compliance
- Initiation of concomitant treatment
- Loss to follow-up
- …



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Interpretation of DBL results

	Regulatory perspective	HTA perspective
Estimation	• Focus on main DBL estimate • Focus on ITT estimate for all DBLs (may be conservative due to confounding and post-randomization selection bias)	• Focus on main DBL estimate and follow-up estimates • Attempt to be non-conservative (critical for health economic evaluation)
Statistical significance (p-value)	• Multiplicity (multiple endpoints, interim analyses, ..) strategy well-defined in protocol for efficacy and safety endpoints • Regulatory decision driven by multiplicity strategy	• Strategy for multiplicity is less strict (PROs less frequently included in strict multiplicity strategy) • Decision making less linked to multiplicity strategy
Analyses of follow-up period	• Typically ITT as primary approach • Primary importance of follow-up period up to main DBL • Post main DBL follow-up informative to assess treatment effect over longer follow-up	• ITT primary approach but room for sensitivity analyses accounting for post-randomization confounders and selection risks • Post main DBL follow-up important for decision making

HTA Approval

Strong interest for additional follow-up data capitalizing on randomization
Results with longer follow-up provide data driven estimates as opposed to modelling
(Important for IQWIG)

Strong need for statistical methodologies adjusting for post-randomization confounding [5]. Of special interest for post unblinding DBLs in the HTA framework

Increased risk of confounding as follow-up increases

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Motivating example

Pembrolizumab KEYNOTE-024 clinical trial

- Randomized, stratified, open-label clinical trial in advanced NSCL cancer
- Untreated patients (N=305) showing PD-L1 expression on at least 50% of tumor cells
- 1/1 randomization to Pembrolizumab 200 mg Q3W or Investigator's choice of platinum based therapy
- Primary endpoint: PFS, secondary efficacy endpoints: OS, ORR
- Possible crossover to pembrolizumab for patients randomized to platinum based therapy, after disease progression
- Plan for interim / final analyses
  - IA 1: 191 patients with minimum 6 months follow-up
  - IA 2: 175 patients with progression or death
  - Final analysis: 170 patients with death
- External DMC recommended to stop the trial at IA 2 because of PFS and OS superiority of Pembrolizumab.
- Follow-up continued after IA 2 until end of study
- Publication [2] and regulatory submissions based on IA 2 results obtained at IA 2 DBL (primary DBL)

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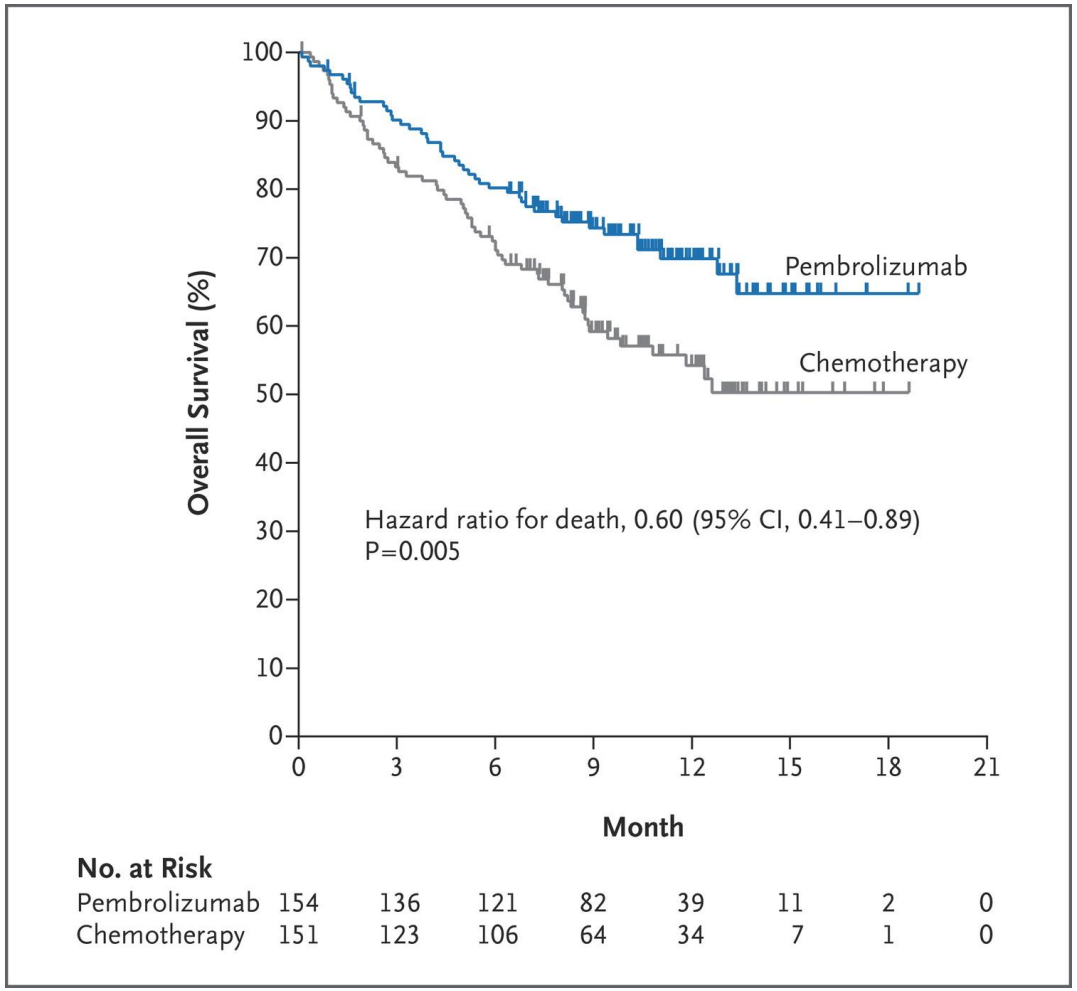
Motivating example

Pembrolizumab KEYNOTE-024 IA2 overall survival results



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Motivating example

Following the IA 2 publication, two follow-up data base locks (DBLs) took place and results were presented in scientific meetings

	Meeting	Cut-off Date	Median Follow-Up (Months)	# Crossover	HR (95% CI) OS
IA 2	ESMO 2016, Copenhagen	May 9, 2016	11.2	66 (44%)	0.60 (0.41-0.89)
Add. DBL 1	ASCO 2017, Chicago [3]	Jan. 5, 2017	19.1	79 (52%)	0.63 (0.46-0.88)
Last DBL	IASCL 2017, Yokohama [4]	Jul. 10, 2017	25.2	82 (54%)	0.63 (0.47-0.86)

- Additional DBL1 and last DBL were not part of the formal testing strategy of the protocol, after study was unblinded at IA 2
- Analyzing OS after IA2 was informative in providing follow-up information but essentially exploratory in nature, in light of the IA 2 results
- Hazard ratio was remarkably stable across analyses despite the high cross-over rate and the disclosure of IA 2 results

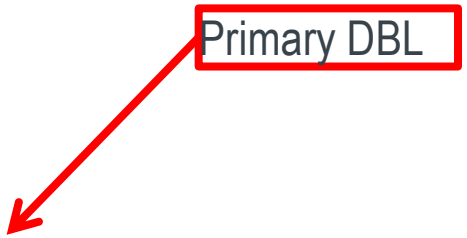
Application to motivating example

Analyses of OS adjusting for potential crossover to pembrolizumab in patients randomized to platinum based therapy

- OS is critical for the determination of added benefit. Sensitivity analyses (adjustment for crossover and additional DBLs) are justified for HTA decision making
- 3 approaches were used
  - Simplified 2-stage method [Latimer et al. 2014]
  - Rank preserving structural failure time method (RPSFT) [Robins et al. 1991]
  - Inverse probability of censoring weighting method (IPCW) [Robins et al. 2000]
- "Treatment group" based approach for simplified 2-stage and RPSFT
- Applied to unblinding DBL and two additional DBLs
- Results are of primary importance for HTA agencies interested in adjusted quantitative effect of new treatment over standard of care and use in economic modeling
  - Less important for IQWIG (Germany)
  - Important for NICE (UK)

Motivating example: OS adjusted for crossover [9]

	Median Follow-Up (Months)	# Crossover	OS ITT HR (95% CI)	Statistical approach for Adjusted OS analysis	OS Ajusted HR (95% CI)
IA 2	11.2	66 (44%)	0.60 (0.41-0.89)	Simplified 2 stage	0.50 (0.34-0.76)
				RPSFT	0.57 (0.32-0.86)
				IPCW	0.55 (0.34-0.87)
Add. DBL 1	19.1	79 (52%)	0.63 (0.46-0.88)	Simplified 2 stage	0.51 (0.35-0.73)
				RPSFT	0.51 (0.32-0.79)
				IPCW	0.55 (0.33-0.86)
Last DBL	25.2	82 (54%)	0.63 (0.47-0.86)	Simplified 2 stage	0.49 (0.34-0.69)
				RPSFT	0.52 (0.33-0.75)
				IPCW	0.52 (0.33-0.80)



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Motivating example: OS adjusted for crossover

- ITT OS results were quite stable across Data Base Locks (hazard ratio ranging from 0.60 to 0.63) despite increasing number of patients with crossover to prembrolizumab in the platinum based regimen treatment group and public availability of results
- Simplified 2-stage method provided adjusted hazard ratio estimates in a range of 0.49 to 0.51, with a value of 0.50 at the primary (unblinding) DBL
- RPSFT method is likely to be conservative as there is evidence of deviation from the assumption of common treatment effect
- For the regulatory submission, ITT OS result at main DBL analysis was primary
- For HTA submissions, the main DBL was primary but adjusted OS results were important at main and follow-up DBLs (economic modeling and relative effectiveness)

Conclusions / Recommendations

	Primary DBL	Follow-up DBLs	Adjusted OS
Regulatory process	Critical	Informative	Possibly informative
HTA process	Critical	Key importance * Longer follow-up	Key importance * Adjusting for follow-up confounders
		Important for assessment of longer time horizon for treatment difference (QWIG does not consider extrapolations) Important for quantification of added value of new treatment compared to standard of care Analyzing clinical trial data using observational methods is important for HTA submissions, specially after primary DBL	

- Regulatory and HTA submissions make use of information from clinical trials with different emphasis
  - Longer follow-up is key for HTA submission and can influence the decision
  - Because of the longer follow-up and this higher risk of bias in post main DBL, methodologies adjusting for confounders and selection risks are of primary importance and complement the ITT analyses
  - Methods adjusting for crossover mitigate one important risk of confounding in OS analyses

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