FDA-AACR-ASA Workshop

OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS

July 18, 2023 | 8 a.m.-5 p.m. | Bethesda, Maryland

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Welcome

Richard Pazdur, MD
U.S. Food & Drug Administration

INTRO:

Nicole Gormley, MD
U.S. Food & Drug Administration

WORKSHOP OVERVIEW:

Ken Anderson, MD, FAACR
Dana-Farber Cancer Institute

Ruixiao Lu, PhD
Alumis Inc./American Statistical Association

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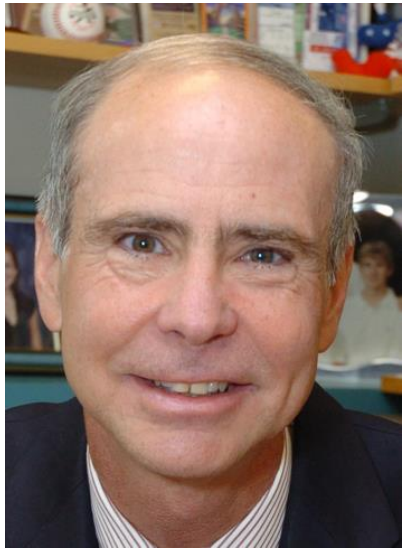
Workshop Co-Chairs



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OVERALL SURVIVAL IN ONCOLOGY CLINICAL TRIALS

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U.S. Food and Drug Administration
July 18, 2023

U.S. Regulatory Approval Pathways

- Regular Approval
  - Approval is based on demonstration of clinical benefit or an effect on an established surrogate

- Accelerated Approval
  - Treatment of serious or life-threatening illness
  - Taking into account the condition and availability of alternative treatments
  - Approval is based on an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint other than survival or irreversible morbidity
  - May require post-approval trials to verify and describe its clinical benefit

21 CFR 314.510
FDA Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics

Types of Endpoints

- Clinical Benefit
  - Direct measure of how a patient feels, functions, or survives
- Surrogate Endpoint
  - Predicts clinical benefit, but is not a measure of clinical benefit
  - Clinical validation that the marker predicts clinical benefit
- Surrogate endpoint reasonably likely to predict clinical benefit
- Intermediate clinical endpoint
  - Can be measured earlier than morbidity or mortality, but reasonably likely to predict clinical benefit

Cancer Endpoint Considerations

Endpoint	Advantages	Disadvantages
Overall Survival	• Easily and precisely measured • Objective measurement • Measures safety and efficacy	• Affected by crossover or subsequent therapy • May require long follow-up in some diseases • Includes non-cancer deaths • Cannot be accurately assessed in single arm trials
Progression-free survival or Event-free survival	• Can be assessed earlier than survival • Usually requires smaller sample size than trials with survival endpoint	• Potentially subject to assessment bias • Definitions may vary among trials • Balanced timing of assessments critical to minimize bias • Includes non-cancer deaths • May not always correlate with overall survival • Cannot be accurately assessed in single arm trials • May require frequent radiological or other assessments
Response Rate	• Can be assessed earlier than survival • Usually requires smaller sample size than trials with survival endpoint • Effect on tumor attributable to study drug and not natural history	• Definitions may vary among trials • May not always correlate with overall survival. • May require frequent radiological or other assessments • Does not incorporate safety
MRD, pCR, etc.	• Can be assessed earlier than survival • Usually requires smaller sample size than trials with survival endpoint • Effect on tumor attributable to study drug and not natural history	• Definitions may vary among trials • May not always correlate with overall survival. • Does not incorporate safety • May be differences in assays and their sensitivities

Adapted from FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics

Overall Survival

- Clinically meaningful, objective measure of both safety and efficacy
- Gold standard for oncology drug approvals
- Endpoints such as ORR, PFS, EFS have been used to expedite oncology drug approval because they can be assessed earlier than OS
- Even when earlier endpoints have been used to support approval, the FDA always evaluates OS if approval is based on a randomized trial

Interpreting OS Results

- OS hazard ratio, confidence interval, death rates, survival curves
- Take OS maturity into account
- Carefully consider important subgroups and interpret with caution due to small sample sizes
- Subsequent therapy or crossover may impact interpretation

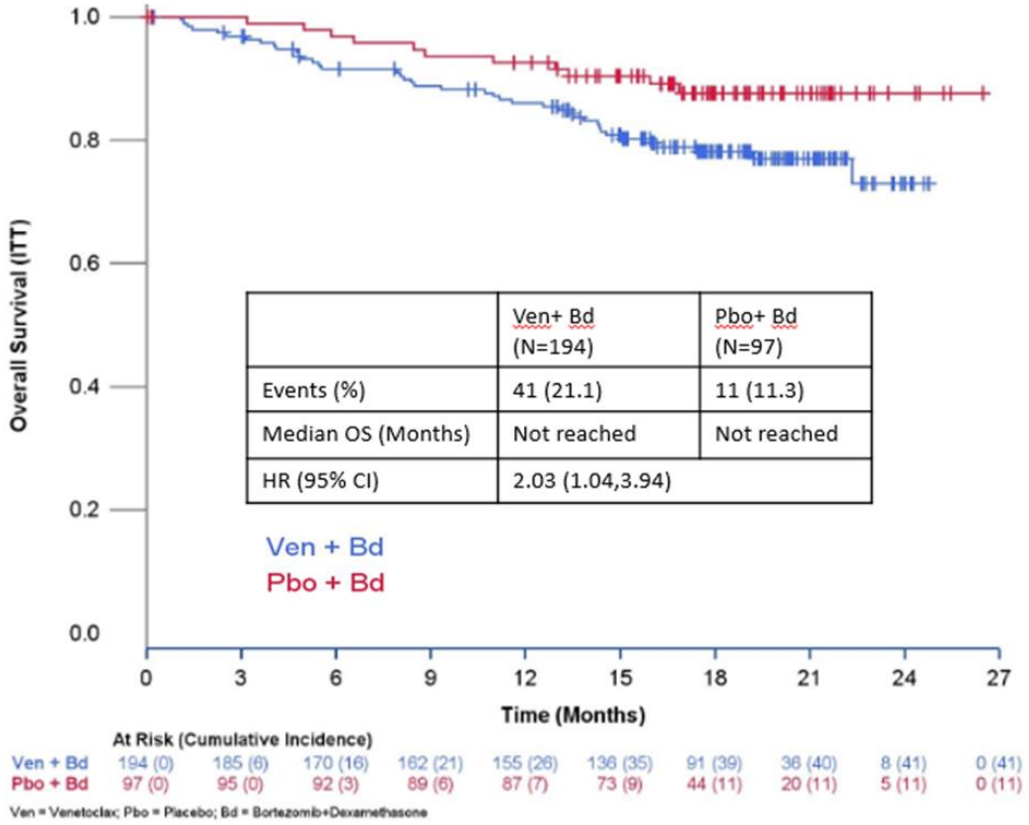
Challenges in OS Assessment

Challenge	Description
Not formally tested	• Trial cannot conclude statistical significance
Not formally powered	• Trial may not be able to detect OS difference
Based on very few events (eg, 20-50) or immature	• May provide inaccurate treatment effect estimate • Wide confidence intervals
Subgroups	• Subgroups with biologic plausibility may have different effectiveness in response to treatment • Interpret with caution due to small sample sizes
Confounding factors	• May distort interpretation of treatment effect
Not prospectively collected for follow-up	• Cannot accurately interpret OS results due to missing (or censored) data

BELLINI Trial: A Cautionary Tale

- Phase 3, double-blind, randomized, placebo-controlled trial of bortezomib and dexamethasone with or without venetoclax in patients with relapsed/refractory, multiple myeloma who had received 1-3 prior lines of therapy

	Venetoclax Arm	Placebo Arm
ORR	82.0% (75.8, 87.1)	68.0% (57.8, 77.1)
MRD negativity rate (10^{-5})	13.4% (8.9, 19.0)	1.0% (0.0, 5.6)
Median PFS (mos) (95% CI)	22.4 (15.3, NR)	11.5 (9.6, 15.0)
Hazard Ratio (95% CI)	0.63 (0.44, 0.90)	



https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-risks-associated-investigational-use-venclexta-multiple-myeloma

BELLINI Trial: A Cautionary Tale

Table. Progression-Free Survival, Overall Survival, and Clinical Response Rates.

	PFS HR (95% CI)	OS HR (95% CI)
All patients (N=291)	0.630 (0.443-0.897)	2.027 (1.042-3.945)
High-risk cytogenetics[a] (N=49)	1.206 (0.577-2.520)	NE
Standard-risk cytogenetics[b] (N=213)	0.544 (0.354-0.837)	1.505 (0.727-3.115)
t(11;14) (N=35)	0.110 (0.022-0.560)	0.343 (0.031-3.842)
BCL-2 high (N=140)	0.502 (0.294-0.856)	1.446 (0.568-3.678)
BCL-2 low (N=37)	1.387 (0.431-4.468)	NE

	All patients		t(11;14)		BCL-2 high	
	Ven (N=194)	**Pbo (N=97)**	**Ven (N=20)**	**Pbo (N=15)**	**Ven (N=93)**	**Pbo (N=47)**
ORR	82%	68%	90%	47%	86%	68%
≥CR	26%	5%	45%	7%	32%	4%
≥VGPR	59%	36%	70%	27%	68%	34%
uMRD	13%	1%	25%	0%	17%	2%

CI, confidence interval; CR, complete response; HR, hazard ratio; NE, not estimable due to no events in placebo; ORR, overall response rate; OS, overall survival; Pbo, placebo; PFS, progression-free survival; uMRD, undetectable minimal residual disease (10^{-5}); VGPR, very good or better partial response.

a. t(4;14), t(14;16), or del(17p)
b. No high-risk cytogenetics

Kumar. EHA Library. 2019 273254; LB2601

BELLINI Trial: A Cautionary Tale

- Concerning OS results
  - Need evaluation of endpoints that can be assessed at Early timepoints *and* Late timepoints that provide definitive evidence of clinical benefit
    - Bellini Trial showed divergent OS and ORR, PFS, MRD results

Potential OS Detriments Demonstrated Across the PI3K Inhibitor Class

Study	Population & Treatment	Deaths PI3Ki arm	Deaths Control arm	Hazard Ratio (95% CI)
DUO	• Previously treated CLL/SLL • **Duvelisib** vs ofatumumab	50% (80/160)	44% (70/159)	1.09 (0.79, 1.51)
312-0123	• Untreated CLL • Bendamustine and rituximab ± **idelalisib**	8% (12/157)	3% (4/154)	3.34 (1.08, 10.39)
313-0124	• Previously treated indolent NHL • Rituximab ± **idelalisib**	5% (10/191)	1% (1/95)	4.74 (0.6, 37.12)
313-0125	• Previously treated indolent NHL • Bendamustine and rituximab ± **idelalisib**	8% (27/320)	6% (9/155)	1.51 (0.71, 3.23)
CHRONOS-3	• Previously treated indolent NHL • Rituximab ± **copanlisib**[#]	18% (56/307)	21% (32/151)	0.87[#] (0.57, 1.35)
UNITY-CLL	• Untreated and previously treated CLL • **Umbralisib** + ublituximab vs GC	*	*	1.23

[#]In the CHRONOS-3 trial, decreased overall survival was demonstrated in the first 2 years in the copanlisib arm, followed by a crossing of KM curves
*Not publicly available

CI, confidence interval; CLL, chronic lymphocytic leukemia; GC, obinutuzumab plus chlorambucil; NHL, non-Hodgkin lymphoma, OS, overall survival; SLL, small lymphocytic lymphoma

PARP inhibitors for 2L+ Maintenance Treatment

Drug	Trial	Design	Progression- Free Survival			Overall Survival
			Cohort	HR (95% CI)	Median, months	
Niraparib	NOVA	Randomized, Separate Cohorts	gBRCA Non-gBRCA, HRD+ Non-gBRCA, All	**0.26** (0.17, 0.41) **0.37** (0.24, 0.58) **0.45** (0.34, 0.61)	21.0 vs. 5.5 12.9 vs. 3.8 9.3 vs. 3.9	Potential detriment in non-gBRCA
Rucaparib	ARIEL3	Randomized, Nested Cohorts	tBRCA HRD+ All	**0.23** (0.16, 0.34) **0.32** (0.24, 0.42) **0.36** (0.30, 0.45)	16.6 vs. 5.4 13.6 vs. 5.4 10.8 vs. 5.4	Potential detriment in non-tBRCA

HRD – homologous recombination deficient

NOVA - Final OS, 78% Maturity

	gBRCA (n=203)		Non-gBRCA, HRD+ (n=162)		Non-gBRCA (n=350)	
Treatment Arm	**Niraparib (N=138)**	**Placebo (N=65)**	**Niraparib (N=106)**	**Placebo (N=56)**	**Niraparib (N=234)**	**Placebo (N=116)**
Median OS, months (95% CI)	40.9 (34.9, 52.9)	38.1 (27.6, 47.3)	35.6 (28.3, 43.4)	41.4 (33.9, 57.6)	31.0 (27.8, 35.6)	34.8 (27.9, 41.4)
HR (95% CI)	**0.85** (0.61, 1.20)		**1.29** (0.85, 1.95)		**1.06** (0.81, 1.37)	

Missing survival status reduced from 17% to 2% of patients following data retrieval

ARIEL3 – Additional OS Analyses, 73% Maturity

ARIEL 3	tBRCA (n=196)		Non-tBRCA, HRD (n=158)		Non-tBRCA, All (n=368)	
Endpoint	**Rucaparib (N=130)**	**Placebo (N=66)**	**Rucaparib (N=106)**	**Placebo (N=52)**	**Rucaparib (N=245)**	**Placebo (N=123)**
Median OS, months (95% CI)	45.9 (37.7, 59.6)	47.8 (43.2, 55.8)	36.8 (31.4, 46.3)	44.7 (34.4, 58.2)	32.2 (29.5, 35.7)	38.3 (29.9, 43.6)
HR (95% CI)	**0.83** (0.58, 1.19)		**1.28** (0.84, 1.95)		**1.08** (0.84, 1.40)	

Interpreting Subgroup Analyses

- Must interpret with caution if subgroups were not formally powered and tested

- Factors that increase confidence in results
  - Biologic rationale
  - Larger sample size
  - Consistent findings in other trials
  - Subgroup included as a stratification factor

Regulatory Considerations

- When OS is not a prespecified efficacy endpoint, a rigorous plan for assessment of OS as a safety endpoint can provide additional information
- Plans for continued OS data collection minimize missing data
- Results of OS analysis and maturity of the data may affect the appropriate approval pathway in trials where approval is based on an early endpoint
  - If approval in a randomized trial is based on PFS, and there are concerning results or significant uncertainty regarding the OS results, accelerated approval may be most appropriate

Merino et al. JCO 2023

FDA-AACR-ASA Workshop: Overall Survival in Oncology Clinical Trials

- To discuss best practices of trial design, analyses, and interpretation of overall survival in oncology clinical trials
- Explore approaches to address the uncertainty of OS analyses based on early or limited data and incorporate this information into the benefit-risk assessment
- Advance methods to incorporate OS when it is not the primary or secondary endpoint to evaluate for the potential for harm

Workshop Sessions and Objectives

Session 1: Trial Design Considerations for Optimal Assessment of Overall Survival

- Discuss best practices in the clinical trial design to allow for adequate assessment of OS including randomization schemes, crossover, duration of OS follow-up, etc.

Session 2: Overall Survival as a Pre-Specified Endpoint

- Discuss pre-specified statistical OS analyses to assess the potential for harm

Session 3: Post-hoc Analyses of Overall Survival

- Discuss analysis methods to assess for harm when no pre-specified analyses for OS were planned.

Session 4: Subgroup Considerations

- Discuss the role of subgroups in relation to the primary ITT analyses and the interpretation of subgroup results

Session 5: Incorporation of Overall Survival into the Benefit-Risk Assessment

- Discuss best practices for incorporation of early or limited OS results into the benefit-risk assessment and discuss potential regulatory implications of OS analyses evaluating the potential for harm

Oncology Center of Excellence Initiatives

Project Optimus

- An Initiative to reform the dose optimization and dose selection paradigm in oncology drug development
- Goals
  - Communicating expectations for dose-finding and optimization
  - Provide opportunities for developers to meet with FDA to discuss dose optimization
  - Develop strategies for efficient dose finding

Project Endpoint

- Aims to enhance use of early endpoints and foster engagement with external stakeholders committed to the advancement of endpoints in oncology drug development
- Goals
  - Promote external engagement with stakeholders to advance early endpoint development
  - Standardize assessment of data using early endpoints

https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence

Acknowledgements

- Mirat Shah
- Mallorie Fiero
- Lisa Rodriguez
- Nicholas Richardson
- Marc Theoret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Chair, AACR Regulatory and Policy Subcommittee

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Kenneth C. Anderson, MD, PhD, FAACR

I have the following relevant financial relationships to disclose:

None

My additional financial relationship disclosures are:

Consultant for: Pfizer, Janssen, Astrazeneca, Daewoong

Founder/Stockholder: Oncopep, C4Therapeutics, Dynamic Cell Therapies, NextRNA, Window, Starton

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Introduction

Overall survival (OS) is both a safety and efficacy endpoint, represents clinical benefit, and has been used as a primary endpoint in oncology clinical trials.

However, in diseases with extended survival of many years, OS as primary endpoint is not possible and other endpoints, ie progression free survival or durable response rates, have been used to support regulatory approval decisions.

When other endpoints are used, FDA has required submission of OS data at the time of approval or as a post marketing requirement.

Introduction

When OS is not primary endpoint, it has been analyzed in a descriptive manner without formal statistical power calculations based on mature OS evaluations or without Type I error control for formal statistical testing.

In diseases with long natural histories, there may be few events at the time of analysis of OS, with substantial uncertainty regarding the estimates.

NB regardless of Type I error control for OS testing, interpretation of OS is challenging due to potential confounders:

heterogeneous results across subpopulations, non-proportional hazards, crossover, and subsequent therapies.

Introduction

In person workshop with on-line attendance (>3,000 registrants)

Attendees: FDA staff, statisticians from academia, clinicians from academia, industry representatives, patients

Structure:

Pre meetings: Working groups to develop recommendations, chaired by individuals with expertise in each topic

Day of meeting: Presentations by working group chairs, with panel discussions on each topic/set of recommendations.

Introduction

Workshop Sessions

1. **Trial design considerations:** unequal randomization, crossover, intercurrent events, duration of OS follow-up

2. **OS as a pre-specified endpoint:** intercurrent events, pre-specification for observation of non-proportional hazards, crossover, subsequent therapy

3. **OS when it is not a pre-specified endpoint:** methods to assess potential harm, interpretation of post hoc analyses, degree of uncertainty that is acceptable in post hoc OS analyses

Introduction

Workshop Sessions

4. **Subgroup considerations:** role of subgroups in relation to primary intent to treat analyses and interpretation of OS subgroup results, regardless of Type I error control.

5. **Incorporation of OS into the overall benefit-risk assessment:** best practices for incorporation of early or limited OS results and of safety data including deaths, adverse events, and drug tolerability.

   Regulatory implications of OS analyses for potential harm or early or limited OS results, ie accelerated approval for randomized trials without sufficient OS information, post marketing requirements to obtain OS information.

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FDA-AACR-ASA Workshop: Overall Survival in Clinical Trials

Ruixiao Lu, PhD

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Treasurer and Executive Committee Member of the Board, American Statistical Association (ASA)

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Ruixiao Lu, PhD

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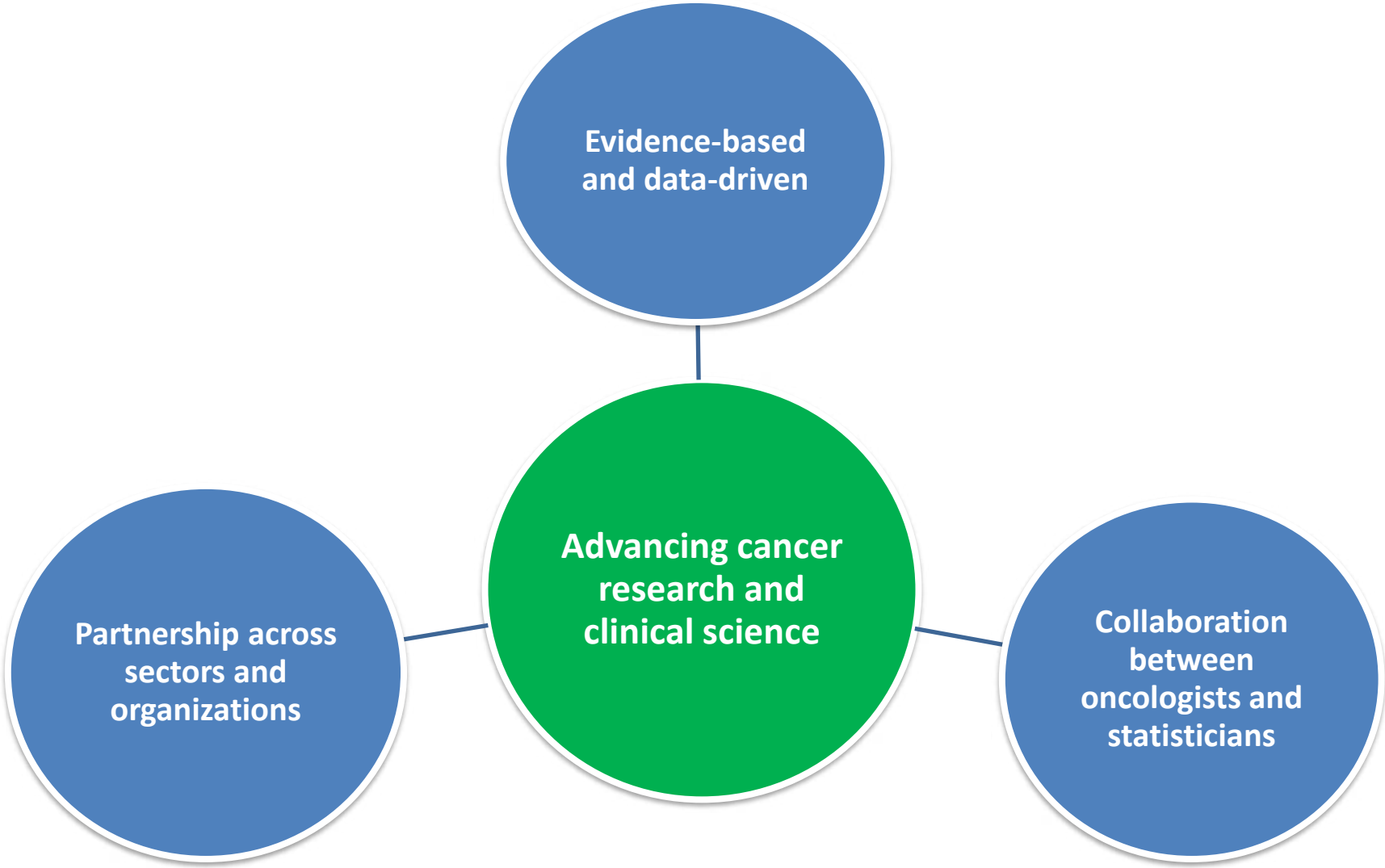
Employee of Alumis Inc.

My additional financial relationship disclosures are:

None

Workshop Overview



Workshop Overview

Get the answers with more certainty

- Ask right questions; ask questions right
- Better tools; trustworthy and reliable evidence
- Expect the unknowns

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