Current and Upcoming COG Renal Tumor Studies:

AREN 1721, AREN 1921, AREN 2231

Bilateral Wilms Working Group

Rhabdoid Tumor Working Group

Please promote the meeting on social media: #PAYAUroOncCourse @PedsUroOnc

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Disclosure

- No relevant disclosures
- I have no relevant financial relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity
- I do not intend to discuss an unapproved or investigative use of a commercial product/device in my presentation

Disclosure

- I do serve as the Surgical Discipline Lead for and am a Vice-Chair of the Children's Oncology Group (COG) Renal Tumor Committee

  BUT . . .

- I am not acting as an official representative of COG and the views expressed herein are my own and do not represent those of COG as a whole

Renal Tumor Committee

- What are we?
  - A group working on research for children, adolescents and young adults with renal tumors
  - Biology, Protocol Development, and Clinical Trial Conduct
  - Resource for community
- What are we ***not***?
  - Judicial panel
  - Clinical guidelines committee (NCCN Wilms Tumor Guidelines Panel)

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National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Wilms Tumor (Nephroblastoma)

Version 2.2021 — June 17, 2021

NCCN.org

Continue

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Renal Tumor Committee

- Who are we?
  - Disciplines: Oncology, Surgery, Pathology, Radiology, Radiation Oncology
  - Sub-committees: Biology, Developmental Therapeutics, Young Investigator
  - Family/Patient Advocate

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Renal Tumor Committee

- Structure
  - Chair: Jim Geller
  - Past Chairs: Jeff Dome, Conrad Fernandez
  - Vice-Chairs: Elizabeth Mullen, Nicholas Cost
- Discipline Leads:
  - Pathology – Elizabeth Perlman
  - Radiology – Geetika Khanna
  - Radiation Oncology – John Kalapurakal
  - Surgery – Nicholas Cost

Renal Tumor Committee Surgeons

- Jennifer Aldrink - Nationwide
- Nicholas Cost – Children's Colorado
- Andy Davidoff – St. Jude
- Peter Ehrlich – U of Michigan
- Elizabeth Fialkowski - OHSU
- Richard Glick – LIJ/Cohen Children's
- Ken Gow – Seattle Children's
- Kathleen Kieran – Seattle Children's
- Meera Kotagal - Cincinnati
- Marcus Malek – Children's Pittsburgh
- Andrew Murphy – St. Jude
- Rodrigo Romao - Halifax
- Robert Shamberger – Boston Children's
- Elisabeth (Lisa) Tracy - Duke

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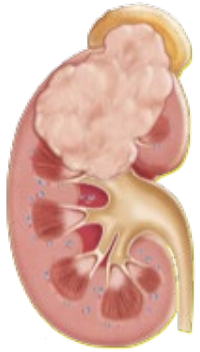
COG Studies Decoded

- AREN – Indicates it is a renal tumor study
- AREN 0321
  - First two numbers (03) – Year the study was activated
  - Third number (2) – Phase of study (i.e., 1, 2, 3 or B)
  - Last number (1) – Order study rolled out in that year
- Example: AREN 0532 – Activated in 2005, Phase 3 study, 2nd study that year
- AREN 03B2
  - B for Biology



Renal Tumor Committee Studies

AREN 1721
Translocation RCC - Does not flow through AREN 03B2

AREN 03B2 BIOLOGY and BANKING STUDY
(Central Review)

FH WT - AREN 2231

- Very Low Risk (I) Low Risk (I/II)
- Standard Risk (III)
- High risk (IV)

Anaplastic WT and FH WT Relapse AREN 1921

- Anaplastic WT
- Relapsed FHWT

Rhabdoid Working Group

Bilateral Working Group

Surgical Guidelines/Key Concepts/ Terminology

- Rupture = Preoperative Event
  - Important because of implications for Whole Abdominal Radiation
- Spill = Intraoperative Event
- These decisions made by surgeon (not path or radiology)

Importance of Sampling LNs

- To get on all current and future Renal Tumor Committee therapeutic studies, patients **MUST** have LNs surgically sampled and available for pathologic review

Importance of Sampling LNs

- To determine 4-yr EFS/OS and rate of LN positive disease based on number of LNs sampled (0, 1-5, and >5 LNs) and location of sampling
- To increase LN sampling at the time of nephrectomy by providing a pre-operative surgical checklist (decrease failure to sample LN rate from 14% to 7%)

AREN 1721

- *"A Randomized Phase 2 Trial of Axitinib/Nivolumab Combination Therapy vs Single Agent Axitinib or Nivolumab for the Treatment of TFE/Translocation Renal Cell Carcinoma Across <u>All Age Groups</u>"*

An Intergroup Study: Coordinated effort via NCTN with adult cooperative groups (ECOG, Alliance, SWOG, etc.)

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A few notes on RCC. . .

- AREN 0321 – Arm for RCC
  - 68 patients enrolled
  - Surgical resection alone, no adjuvant therapy

A Prospective Study of Pediatric and Adolescent Renal Cell Carcinoma: A Report From the Children's Oncology Group AREN0321 Study

James I. Geller, MD [1]; Nicholas G. Cost, MD [2]; Yueh-Yun Chi, PhD[3]; Brett Tornwall, PhD[3]; Mariana Cajaiba, MD[4]; Elizabeth J. Perlman, MD[5]; Yeonil Kim, PhD[6]; Elizabeth A. Mullen, MD[7]; Richard D. Glick, MD[8]; Geetika Khanna, MD[9]; Najat C. Daw, MD[10]; Peter Ehrlich, MD [11]; Conrad V. Fernandez, MD[12]; Jeffrey S. Dome, MD[13]; and On Behalf of the Children's Oncology Group (COG) Renal Tumor Committee

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AREN 0321 – RCC outcomes

T classification	
T1	32 (47.1)
T2	8 (11.8)
T3	23 (33.8)
T4	1 (1.5)
TX	4 (5.9)
N classification	
N0	21 (30.9)
N1	21 (30.9)
NX	26 (38.2)
M classification	
M0	60 (88.2)
M1	8 (11.8)
AJCC stage of disease[b]	
I	26 (38.8)
II	7 (10.4)
III	26 (38.8)
IV	8 (11.9)

No correlation between T-stage and N-stage

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AREN 0321 – RCC outcomes

Histology	
TFE3 or TFEB translocations	40 (58.8)
Papillary	9 (13.2)
Renal medullary carcinoma	6 (8.8)
Other[c]	13 (19.1)
Resection status	
Complete resection	60 (88.2)
Incomplete resection	8 (11.8)
Surgical type[d]	
Radical nephrectomy	53 (81.5)
Partial nephrectomy	12 (18.5)
Surgical approach[d]	
Open	50 (76.9)
Minimally invasive	15 (23.1)

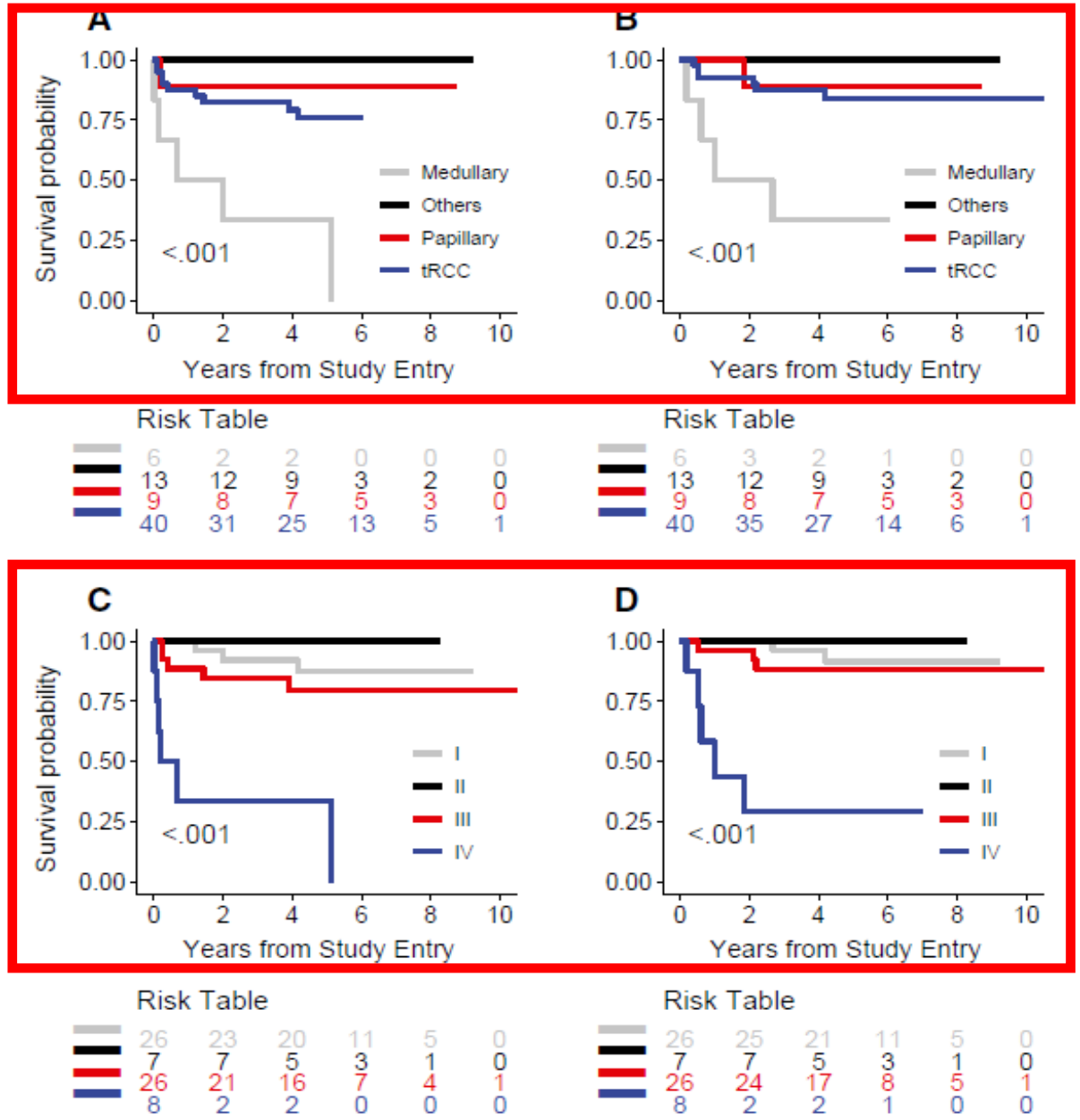

FIGURE 1. Survival outcomes shown by histology and American Joint Committee on Cancer TNM seventh edition stage of disease. (A) Event-free survival (EFS) by histology. (B) Overall survival (OS) by histology. (C) EFS by stage of disease. (D) OS by stage of disease. tRCC indicates translocation-type renal cell carcinoma.

AREN 0321 – RCC outcomes

TABLE 4. Survival Outcomes by Clinical Features

Feature	4-Year EFS (95% CI)	P^a	4-Year OS (95% CI)	P^a
Overall	80.2% (69.6%-90.9%)		84.8% (75.2%-94.5%)	
Age, y		.36		.67
≤13	75.7% (59.7%-91.7%)		82.4% (67.9%-96.8%)	
>13	84.8% (71.0%-98.6%)		87.4% (74.7%-100.0%)	
Resection status				
Complete resection (all)	86.1% (76.3%-95.9%)	<.001	91.4% (83.3%-99.4%)	<.001
Incomplete resection (all)	33.3% (0.0%-71.1%)		29.2% (0.0%-63.2%)	
Complete resection (AJCC stage III/IV)	76.5% (58.4%-94.7%)	.018	84.7% (69.0%-100.0%)	.001
Incomplete resection (AJCC stage III/IV)	38.1% (0.0%-79.6%)		34.3% (0.0%-72.8%)	
Histology		<.001		<.001
Papillary	88.9% (66.9%-100.0%)		88.9% (66.9%-100.0%)	
Renal medullary carcinoma	33.3% (0.0%-71.1%)		33.3% (0.0%-71.1%)	
TFE3 or TFEB translocations	79.2% (65.0%-93.3%)		87.2% (75.5%-99.0%)	
Other	100% (100.0%-100.0%)		100% (100.0%-100.0%)	
NM classification		.32		.45
N1M0	87.5% (68.3%-100.0%)		87.1% (67.6%-100.0%)	
NX	80.6% (64.6%-96.6%)		80.4% (64.4%-96.4%)	
AJCC stage (with complete resection)[b]		.001		.11
I	92.2% (80.8%-100.0%)		96% (87.8%-100.0%)	
II	100% (100.0%-100.0%)		100% (100.0%-100.0%)	
III	78.6% (60.2%-97.0%)		87.7% (72.6%-100.0%)	
IV	50% (0.0%-100.0%)		50% (0.0%-100.0%)	
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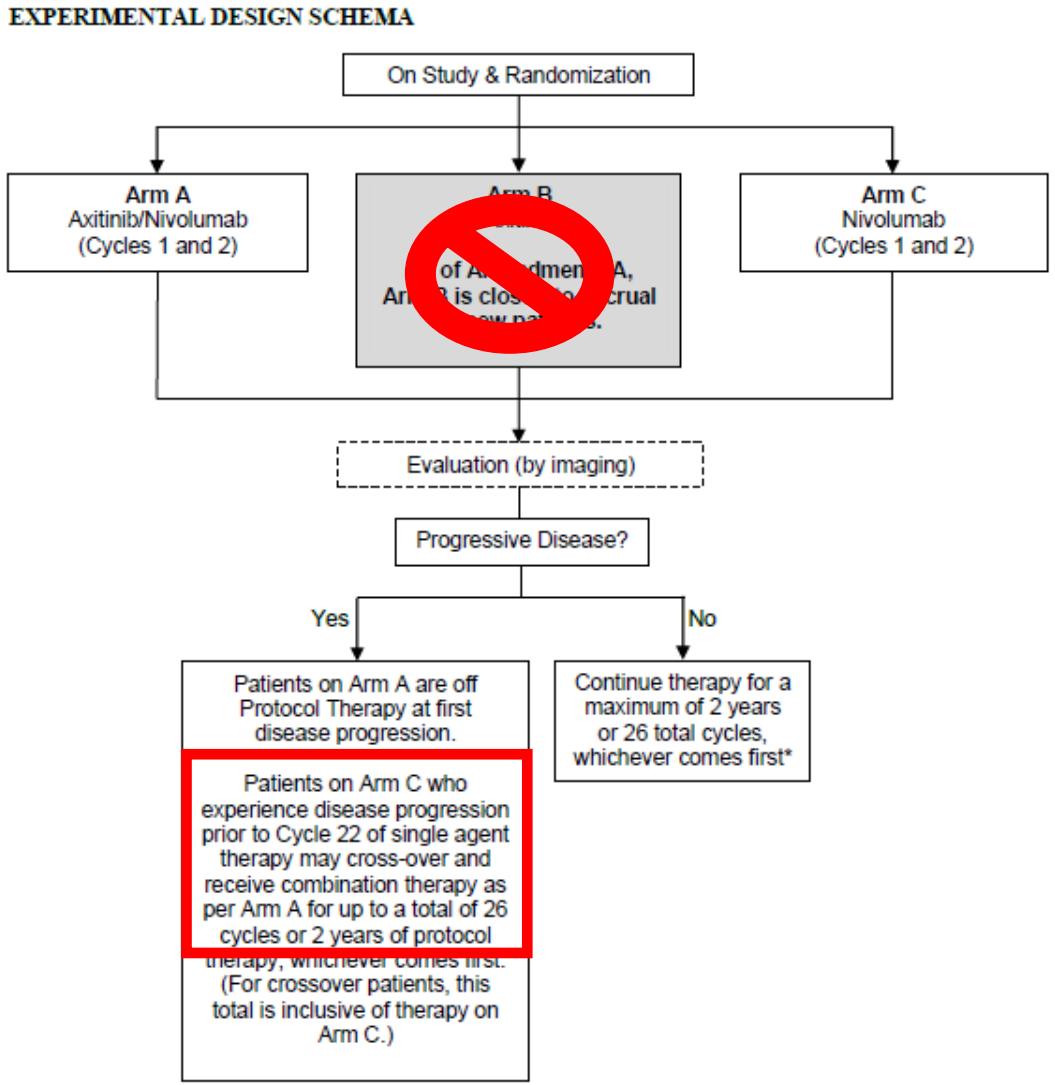
AREN 1721



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Plea for help with AREN 1721

- Please help us enroll . . . 25 more patients needed!
- Patients of all ages with metastatic TFE+ RCC
  - Collaborate with adult Urologic Oncology and GU Medical Oncology colleagues
- Call me with any questions

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AREN 1921

- Treatment of High-Risk Wilms tumor
    - Anaplastic WT (stages II-IV)
    - Relapsed FH WT
- Surgical Questions
    - To determine EFS/OS for patients with relapsed FHWT who undergo gross total resection during relapse treatment
    - To assess the timing of local control in Anaplastic WT
        - Goal is after week 6
        - If surgery not possible after week 6, they will get RT in week 7

AREN 2231

- Approved by COG Scientific Council
- FHWT by Risk
  - Very Low Risk (I), Low Risk (I/II), Standard Risk (III), High Risk (IV)
- Very Low Risk – Age <4y, Stage I, no adverse biology
  - Goal - To demonstrate that patients treated by nephrectomy and observation alone will have 4 year EFS >85% and 4 year OS >95%

AREN 2231

- Low Risk
  - Stage I patients ≥4 years of age or those with any negative prognostic biomarker (LOH of 1p and 16q, LOH 11p15, or 1q gain)
  - Stage II patients
  - Will trial novel regimen (VIVA = EE4A + VI) in Stage II with negative prognostic biomarker

AREN 2231

- Standard Risk – Stage III
  - Will include pathways for upfront and delayed nephrectomy
  - Will de-intensify treatment for some patients
    - DD4A to EE4A (no Doxo) for some selected patients
    - Avoid RT for some selected patients
  - Use Gain 1q to stratify treatment
  - Will look at novel Regimen MVI
    - Less gonadotoxic Cyclophosphamide dose (4.4gm) than Reg M and added VI

AREN 2231

- High Risk – Stage IV
  - Further assess avoiding WLI in those with CR at week 6 (DD4A)
  - Use Gain 1q to stratify treatment
  - Assess Regimen MVI
- Important Surgical Questions
  - To describe the outcome of patients with hepatic metastases
  - To assess feasibility of resection of limited residual pulmonary metastases at week 6 to achieve a Complete Response and thus avoid WLI
    - WLI spared in patients if resected metastases show no viable tumor/necrosis

Bilateral Working Group

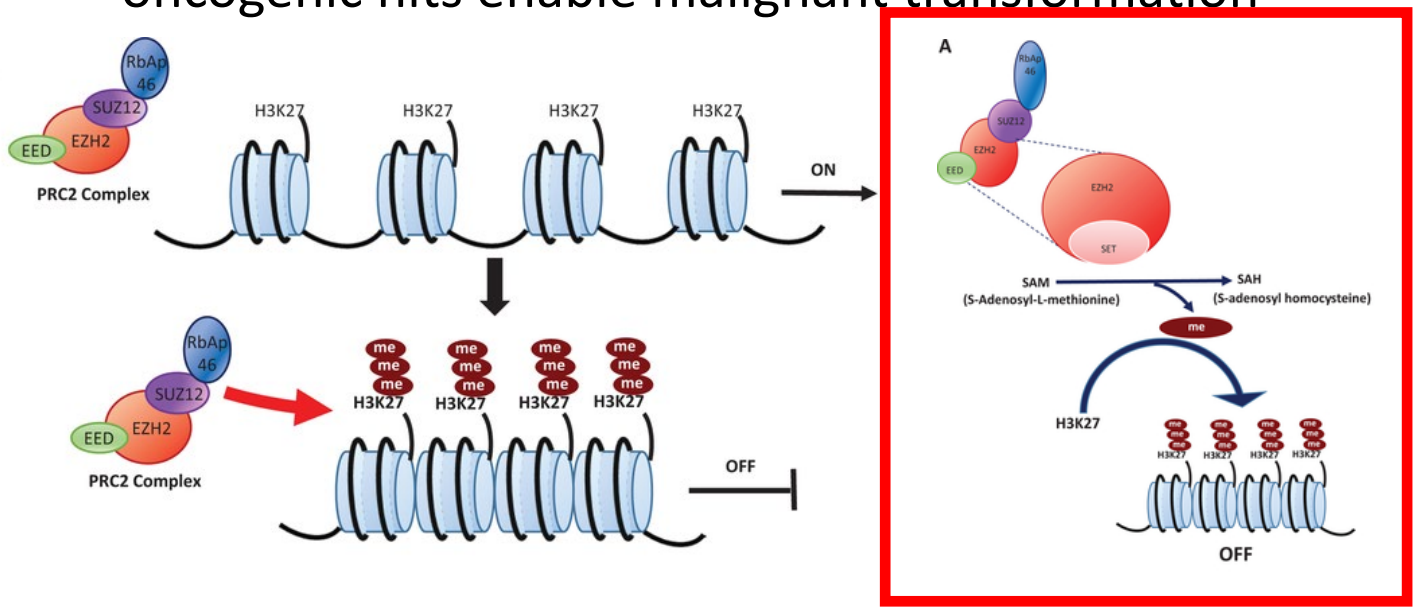
- Goals of increasing rate of bilateral NSS
  - Number of strategies being considered
    - Objective assessment of complexity – Nephrometry
    - Central review of feasibility of NSS
    - Potentially recommend referral to “centers of excellence”

Rhabdoid Working Group

- All Stage II-IV, non-CNS primary Rhabdoid Tumors
- Kathleen Kieran leading the surgical part of this group
  - Largely, the study is a question of adding a targeted therapy to treatment:
    - Tazemetostat
  - Surgical questions:
    - Questions about timing of resection
    - Emphasizing earlier resection

Tazemetostat- EZH2 inhibitor

- EZH2 forms the catalytic subunit of the Polycomb Repressive Complex 2 (PRC2)
- EZH2 is responsible for methylating lysine 27 of histone 3 to generate H3K27me3, associated with condensed chromatin and transcriptional repression.
- The occurrence of EZH2 mutations aberrantly sustains repression of important proliferation checkpoint and differentiation genes, resulting in oncogenesis. Additional oncogenic hits enable malignant transformation



Gulati et al., *Leukemia & Lymphoma* 2018

Tazemetostat- EZH2 inhibitor

- EZH2 forms the catalytic subunit of the Polycomb Repressive Complex 2 (PRC2)
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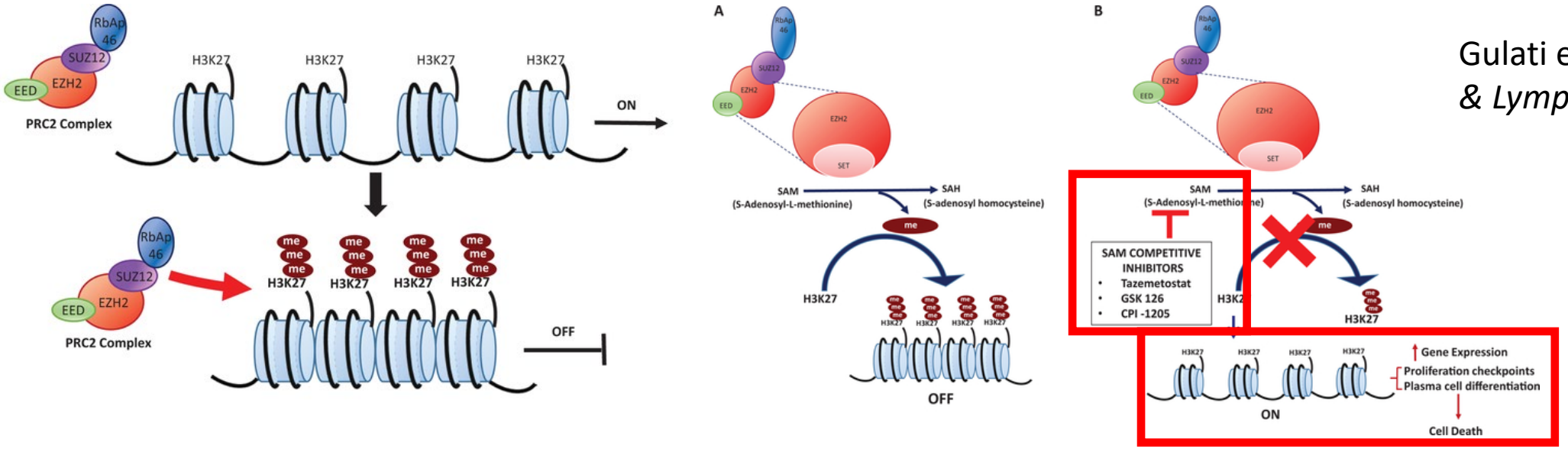

Gulati et al., *Leukemia & Lymphoma* 2018

Conclusions

- COG Renal Tumor Committee is:
  - Active with old, current and new studies
  - Here to help
  - Please contact us!

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Conclusions

- Thank you!
- Questions? Comments?
- Please reach out!
  - nicholas.cost@childrenscolorado.org
  - nicholas.cost@cuanschutz.edu
  - 214-883-3199
  - @cost_nicholas

Please be interactive!!! Ask questions!!!

Please promote the meeting on social media:
#PAYAUroOncCourse
@PedsUroOnc

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