Rhabdomyosarcoma Updates

January 2025

Dana L. Casey MD

CHILDREN'S ONCOLOGY GROUP

COG Trials by Risk Group

Low Risk	Intermediate Risk	High Risk
D9602 ARST0331 ARST2032 (ongoing)	D9803 ARST0531 ARST1431 ARST2531 (upcoming)	D9802 ARST0431 ARST2031 (ongoing)

*Cyclophosphamide dose lowered from D-series to ARST-series

LOW RISK RMS UPDATES

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Low risk: COG ARST0331

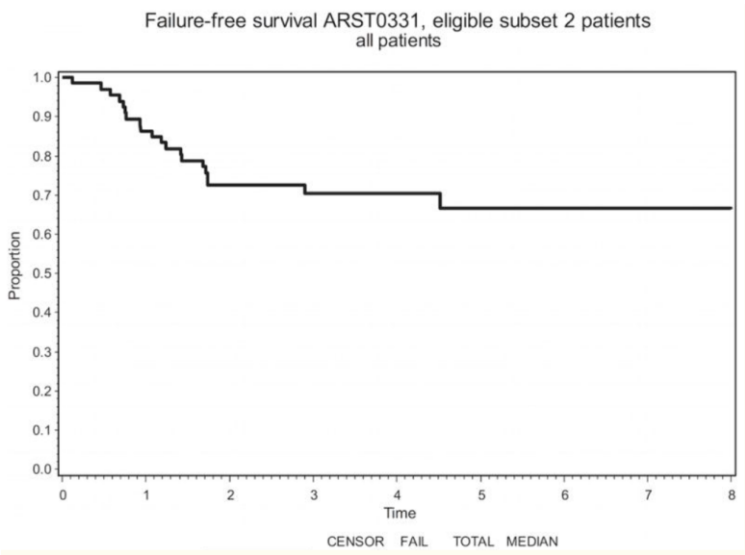
Question asked: Can we decrease length of systemic treatment for low risk patients and can we exclude RT for vaginal tumors?

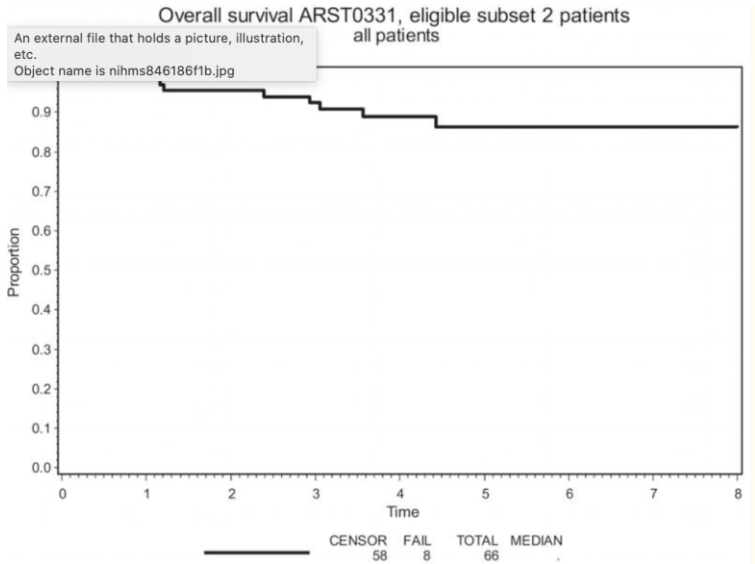
- VAC/VA (24 weeks if subset A, 48 weeks if subset B)
- *Reduced dose for orbital tumors (45 Gy) and also excluded RT for vaginal tumors in CR*

Walterhouse et al JCO 2014

Cancer. 2017 Jun 15;123(12):2368-2375. doi: 10.1002/cncr.30613. Epub 2017 Feb 17.

Reduction of cyclophosphamide dose for patients with subset 2 low-risk rhabdomyosarcoma is associated with an increased risk of recurrence: A report from the Soft Tissue Sarcoma Committee of the Children's Oncology Group

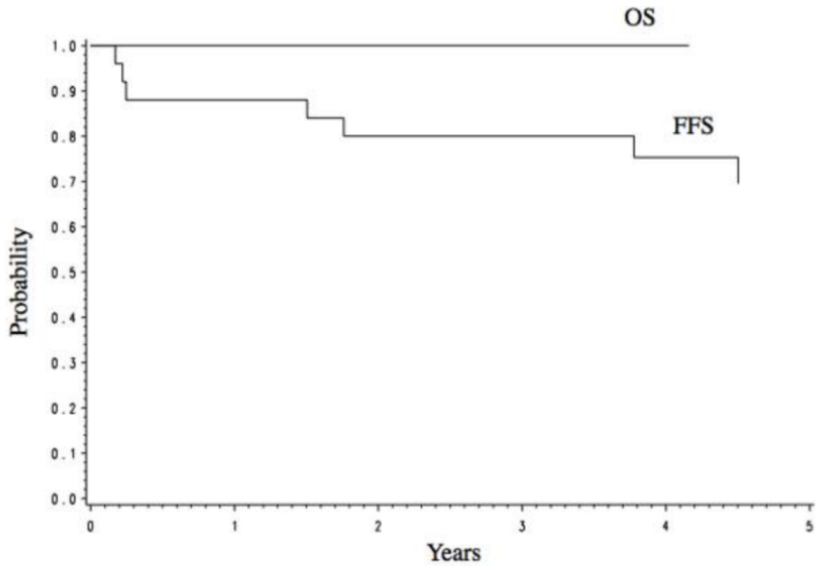




3 year FFS for subset 2: 70% on ARST0331 vs 83% on D9602

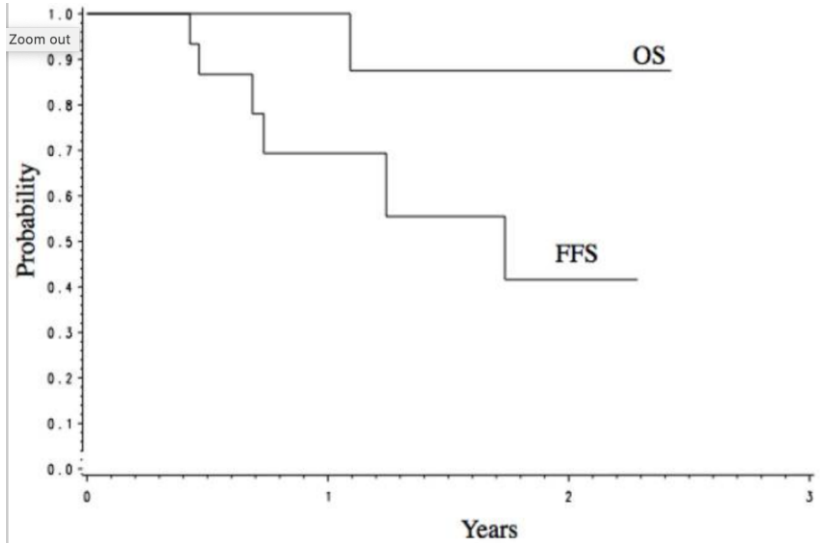
Cannot omit RT for vaginal RMS in setting of lower cyclophosphamide

D9602



5-year LR 26%

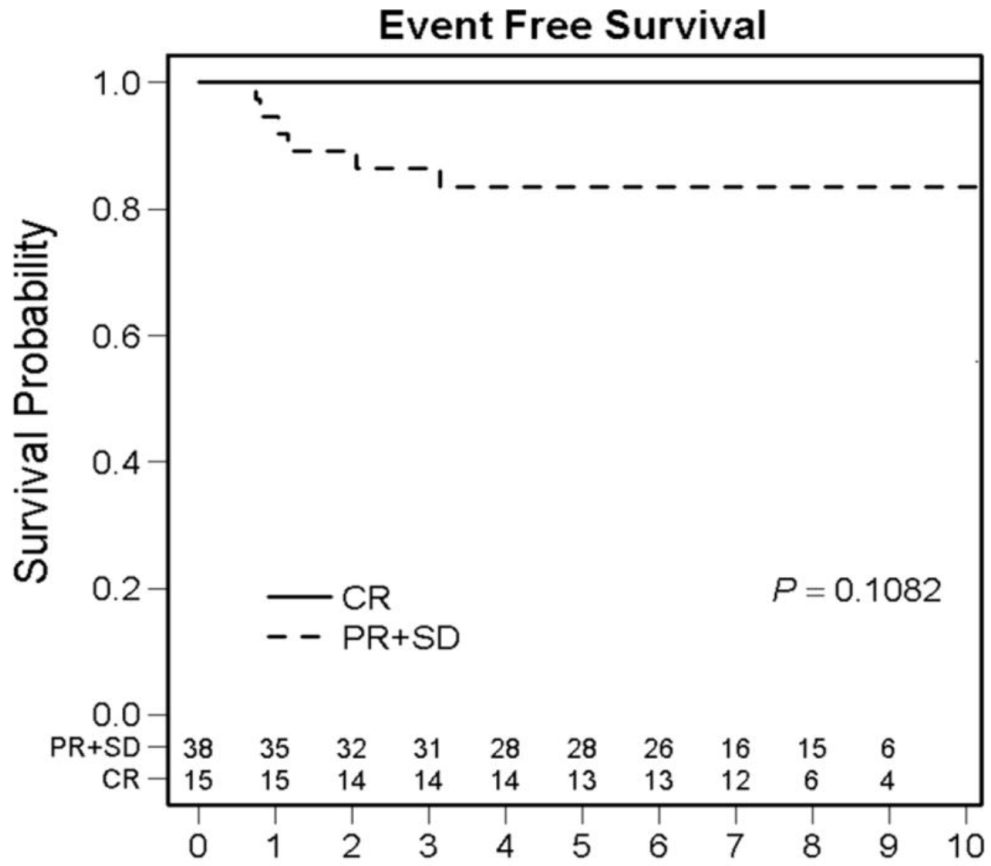
ARST0331



5-year LR 43%

Walterhouse et al PBC 2011

45 Gy not sufficient for orbital tumors that do not achieve CR

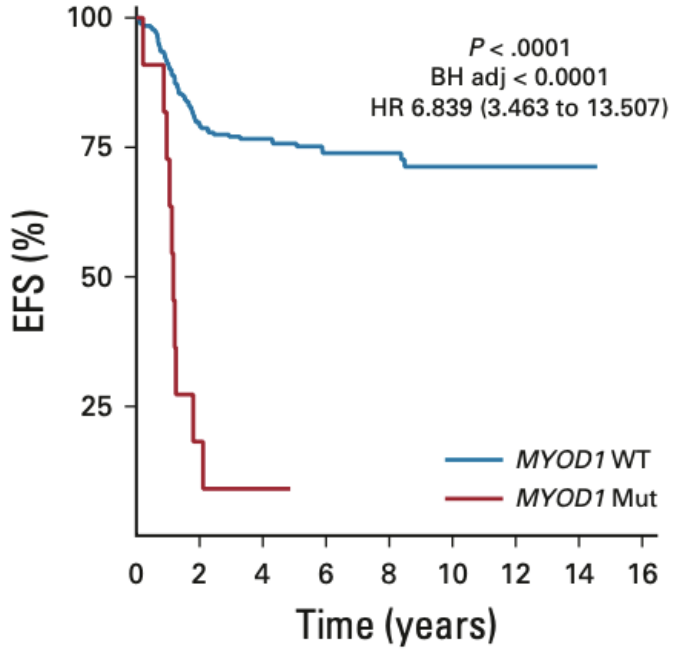


IRS-IV local control: 96%

ARST0331 local control: 83%

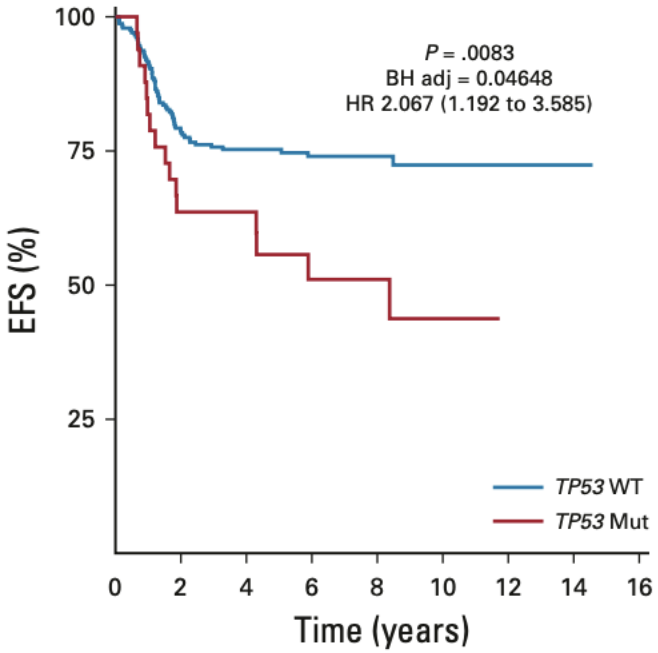
Ermorian et al PBC 2017

TP53 and *MYOD1* mutations are associated with worse outcomes



No. at risk:

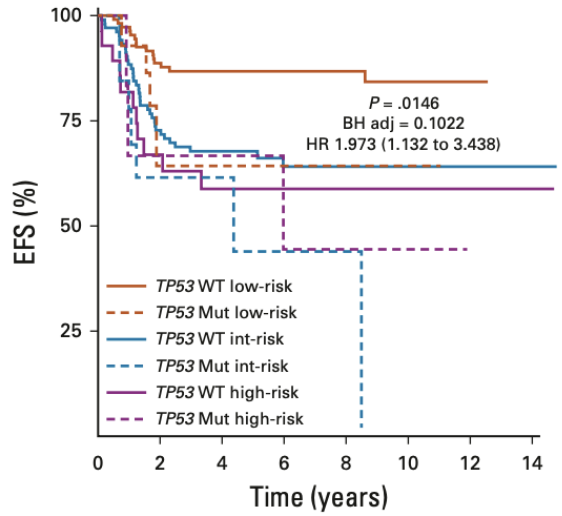
MYOD1 WT	264	199	172	111
MYOD1 Mut	11	2	1	0



No. at risk:

TP53 WT	241	180	154	100	56	25	3
TP53 Mut	34	21	19	11	7	5	0

B



No. at risk:

TP53 WT low-risk	110	90	78	60	43	16	1	1
TP53 Mut low-risk	14	9	7	5	4	3	0	0
TP53 WT int-risk	103	73	62	28	8	5	1	1
TP53 Mut int-risk	13	8	8	4	1	0	0	0
TP53 WT high-risk	28	17	14	12	5	4	1	1
TP53 Mut high-risk	7	4	4	2	2	2	0	0

Shern et al JCO 2021

Ongoing Low Risk Trial: ARST2032

A Prospective Phase 3 Study of Patients with Newly Diagnosed Low-risk Fusion Negative Rhabdomyosarcoma

- Primary objectives
  - To evaluate FFS in very low risk patients treated with 24 weeks of VA only (*must be *MYOD1* WT, *TP53* WT)
  - To evaluate FFS in low risk patients treated with 12 weeks of VAC, 12 weeks of VA (*must be *MYOD1* WT, *TP53* WT)

Now using genomic risk factors to identify clinically and molecularly defined low risk patients

Radiation recommendations on ARST2032

Target Volume	Clinical Scenario	Dose (Gy for photon therapy and Gy(RBE) for proton therapy)	Fraction Size (Gy for photon therapy and Gy(RBE) for proton therapy)	Treatments per Day
PTV1*	• Group IIa • Pre-chemo volume for orbital primary with R0 resection after DPE.	36	1.8	One
PTV1*, PTV1nodal*	• Group IIb • Group IIc • Involved nodal chain for N1 disease	41.4	1.8	One
PTV1*	• Pre-chemo volume for Group III orbital primary	45	1.8	One
PTV2*+ (post-induction chemotherapy volume)	• Boost dose for residual gross disease for Group III orbital primary	5.4	1.8	One
PTV2*nodal (post-induction chemotherapy volume)	• Boost dose to gross lymph nodes	9	1.8	One

Patients with orbital tumors and residual disease receive 50.4 Gy

INTERMEDIATE RISK RMS UPDATES

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COG ARST0531 (2006-2013)

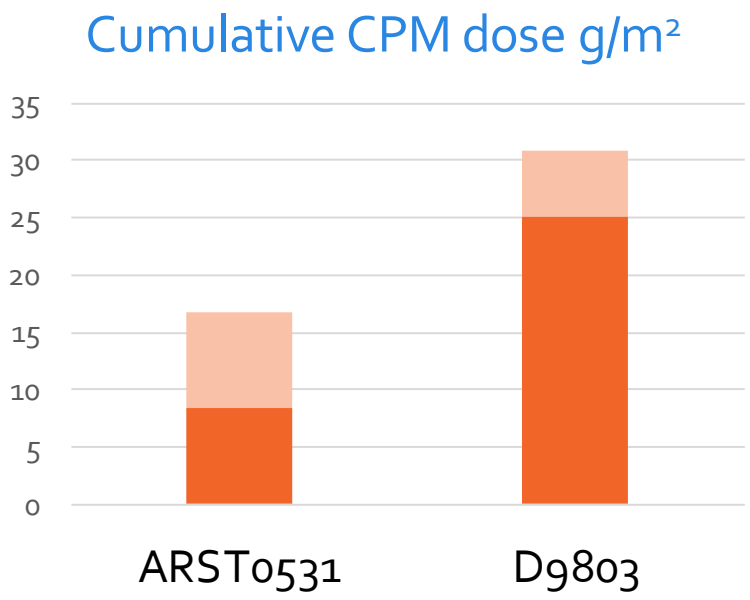
Question asked: VAC vs VAC / VI. Can irinotecan improve outcomes? Can we use lower cyclophosphamide dosing for intermediate risk?

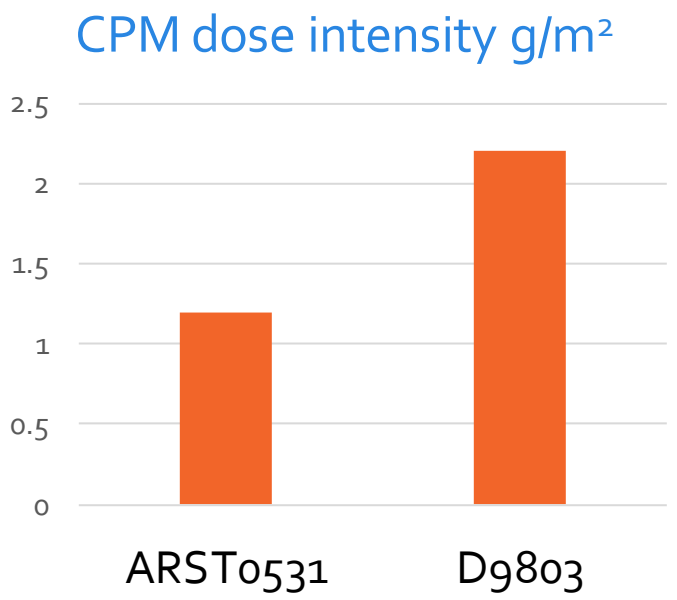
- Goal was to improve local control→EFS/OS
- Early radiotherapy for all patients at week 4
  -Attempt to improve local & possibly distant control
- Concurrent Irinotecan with radiotherapy
  -potential for radiosensitization
- DPE discouraged

Hawkins et al JCO 2018

COG ARST0531

Lower cyclophosphamide dose utilized with goal of reducing toxicity

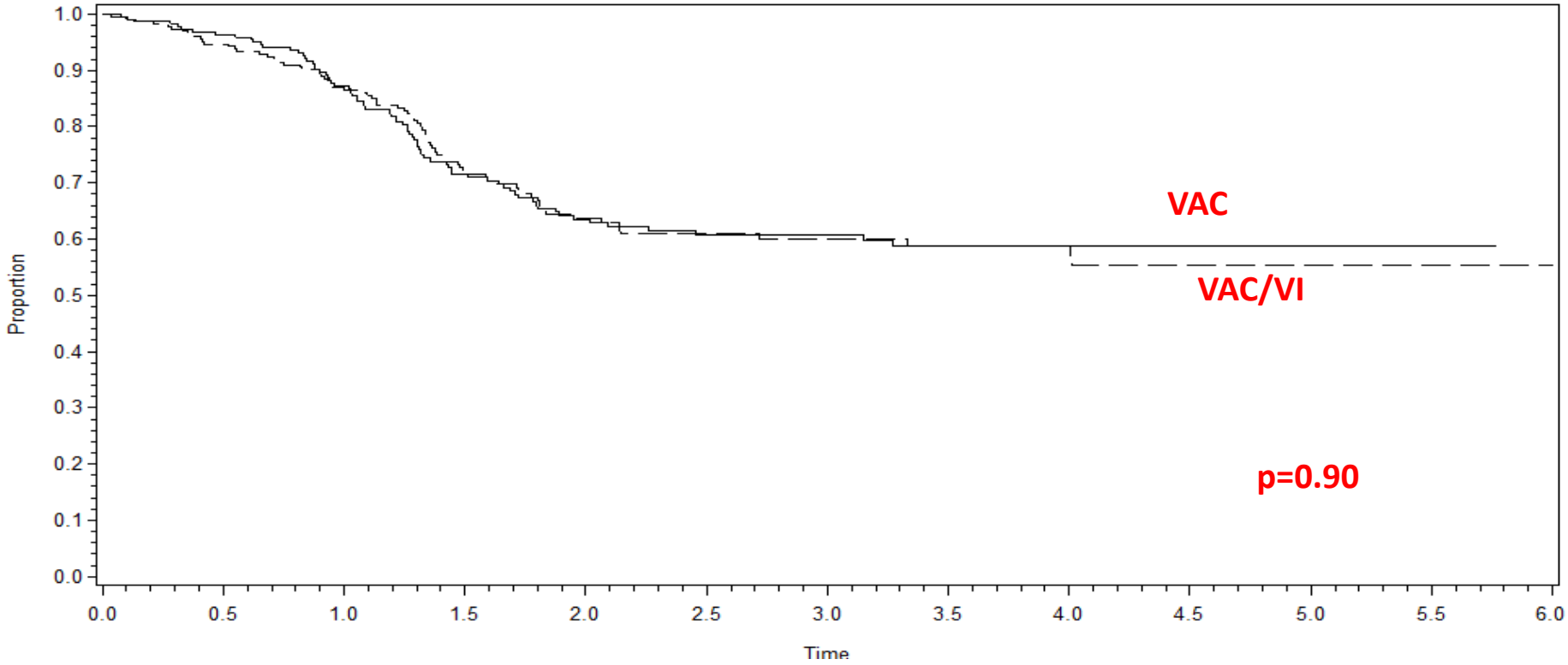




8.4-16.8 g/m² on ARST0531vs 25.1-30.8 g/m² on D9803

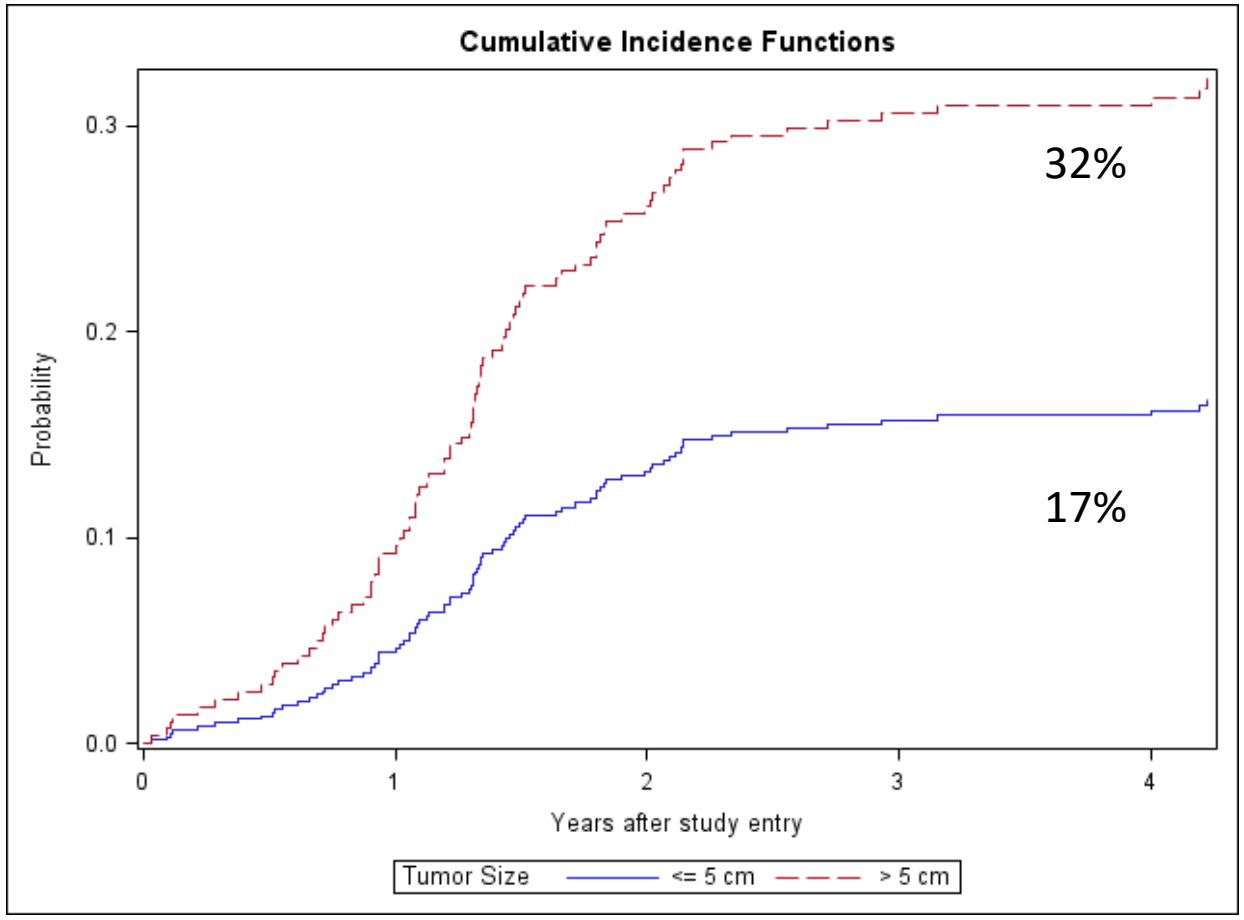
Hawkins et al JCO 2018

COG ARST0531: VAC vs VAC/VI
EFS Results



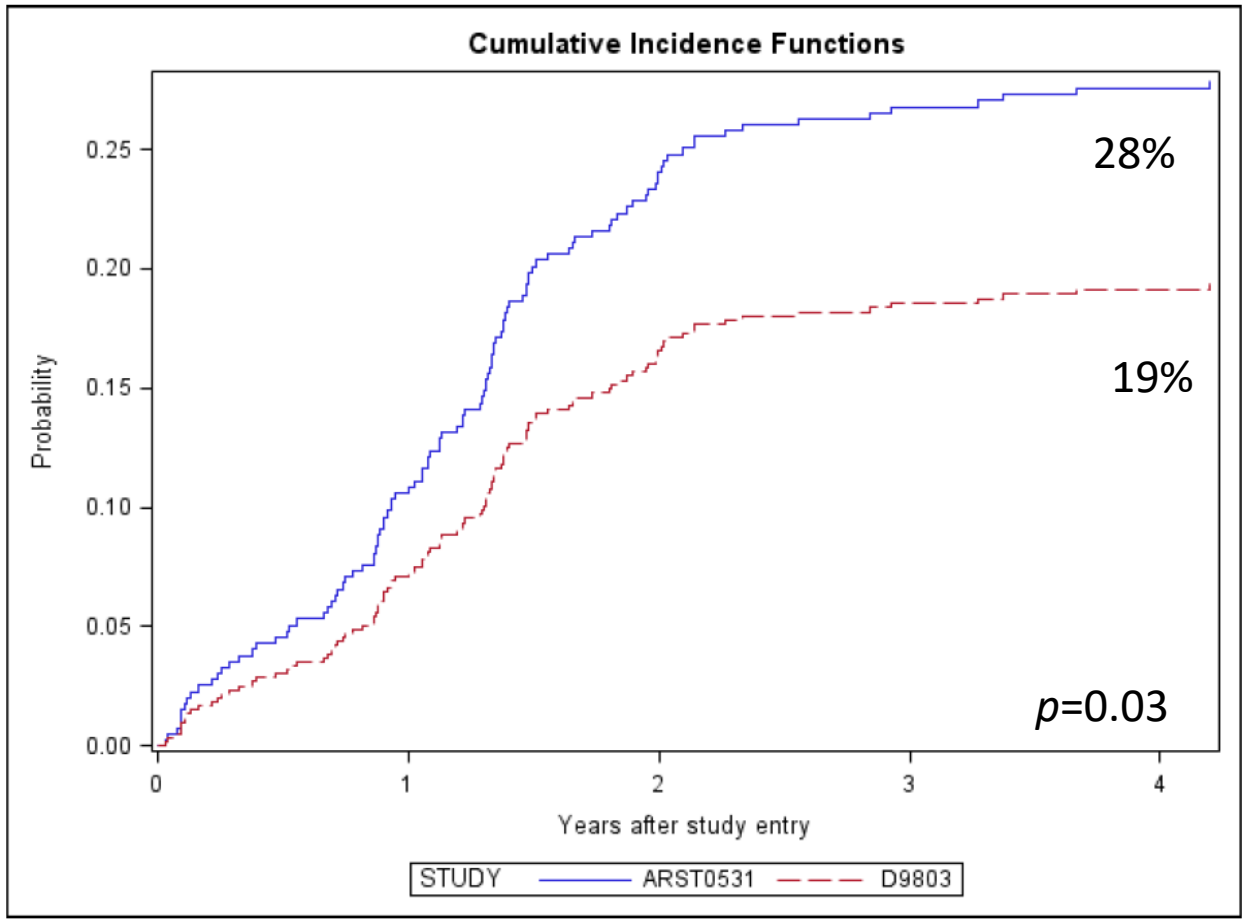
Hawkins et al JCO 2018

COG ARST0531: Local failure by Tumor Size



Casey et al. Cancer 2020

Local Failure by for Group III ERMS on ARST0531 vs D9803



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Casey et al. Cancer 2020

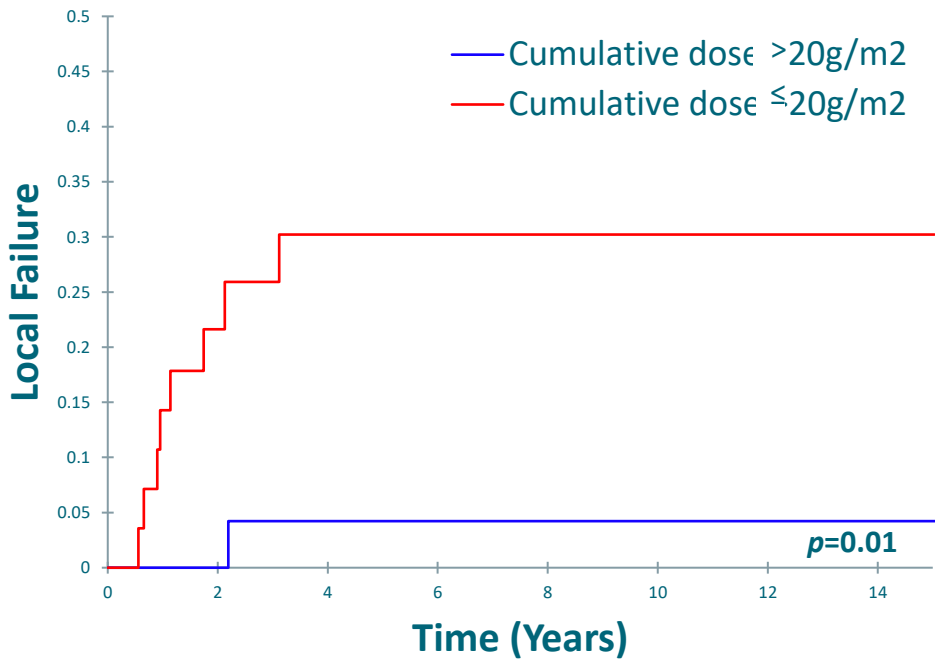
COG ARST0531 EFS MVA

Covariate	HR	95% CI	P value
Study (ARST0531 vs D9803)	1.4	1.11-1.73	0.004
Histology (alveolar vs embryonal)	1.4	1.10-1.84	0.007
Site (favorable vs unfavorable)	0.8	0.52-1.20	0.26
Size (≤ 5cm vs >5cm)	0.6	0.50-0.80	<0.001
Group (I vs II)	0.5	0.21-1.20	0.25
(I vs III)	0.5	0.22-1.13	
Age (1-10 vs <1 and ≥10 years)	0.6	0.49-0.78	<0.001

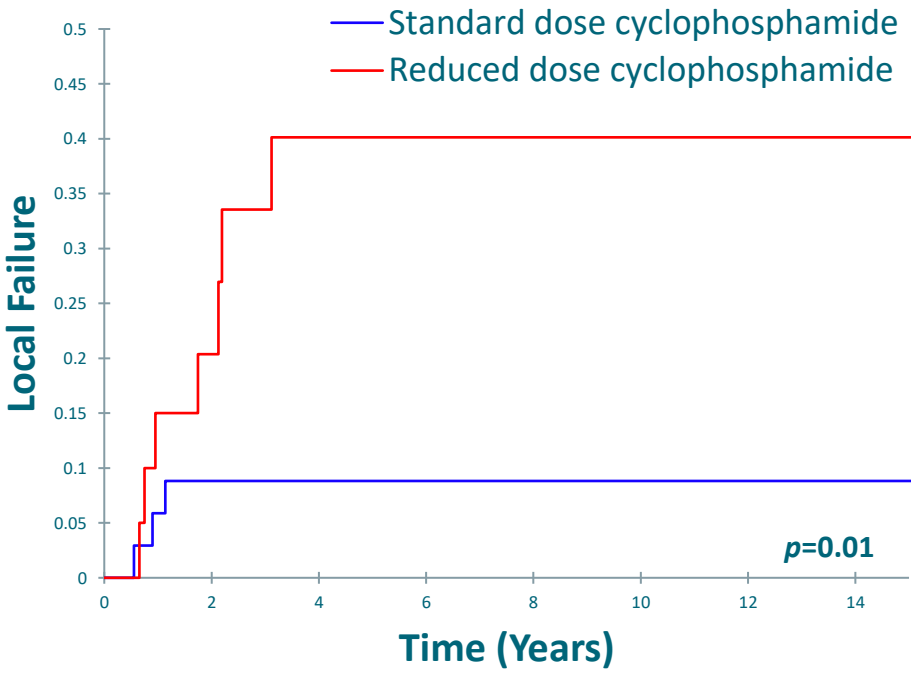
Casey et al. Cancer 2020

Cyclophosphamide dose may influence local failure after RT

Cumulative CPM dose



CPM Dose Intensity



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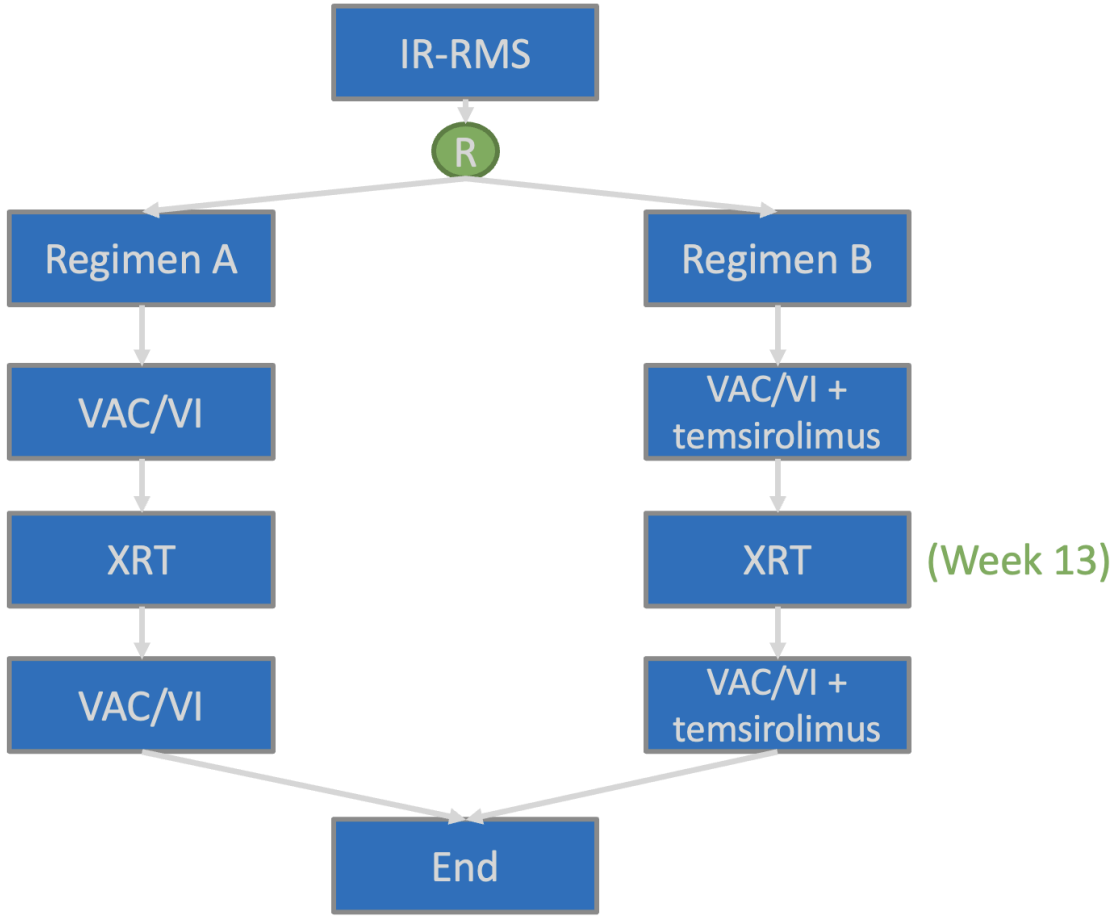
Casey, Wolden et al. IJROBP 2018

ARST1431 Schema



*amended in 2019 to include maintenance cyclophosphamide/vinorelbine in both arms

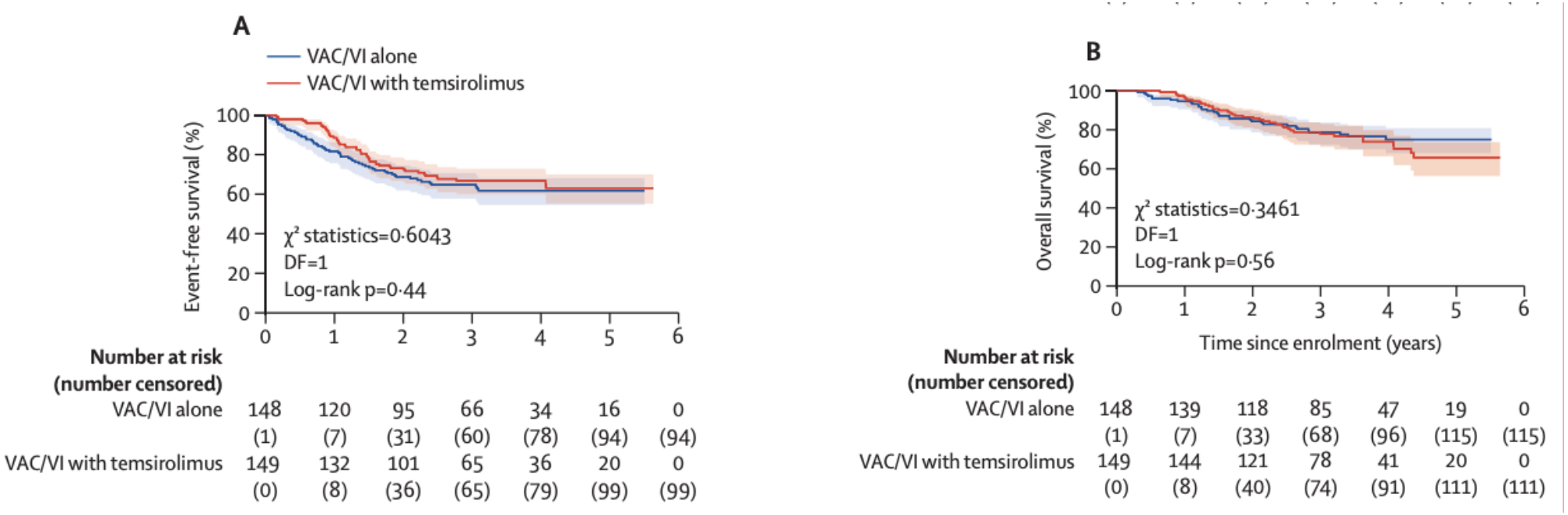
Gupta et al Lancet Onc 2024

ARST1431 RT Guidelines

	No DPE – Total Dose (Gy)		Post DPE – Dose (Gy)		
Clinical Group	No CR at week 9	CR at week 9	GTR, negative margin	GTR, microscopic margin	Gross residual disease
I, FP	36	36	None	None	None
II, FP	36	36	None	None	None
III*, ≤ 5cm	50.4	36	36	41.4	50.4
III*, > 5cm	59.4	36	36	41.4	59.4

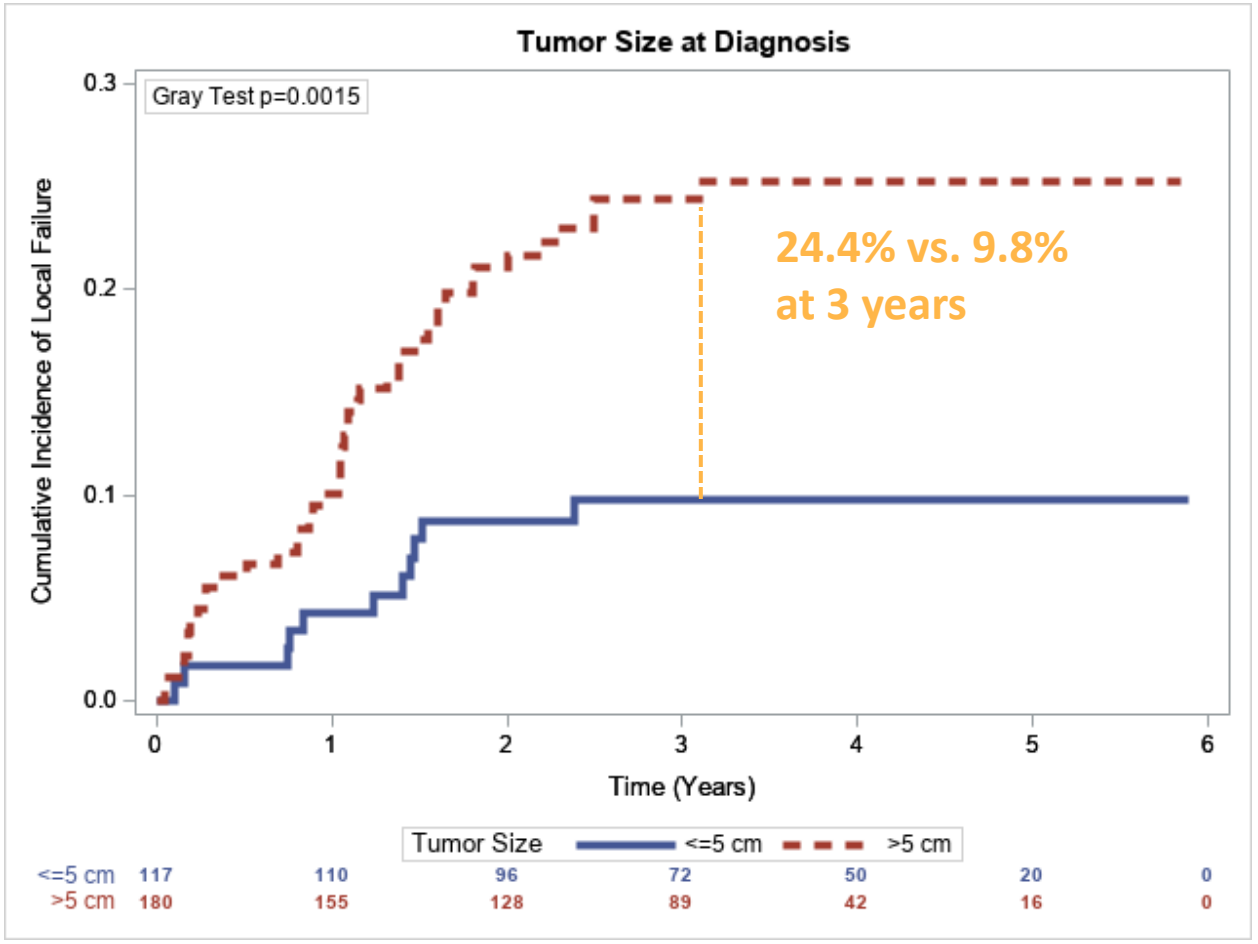
*Treatment of Group IV tumors is according to clinical group of primary site.
DPE = Delayed Primary Excision
FP = Fusion positive
CR = Complete Response
GTR = Gross Total Resection

ARST1431 results: No difference in EFS/OS with temsirolimus



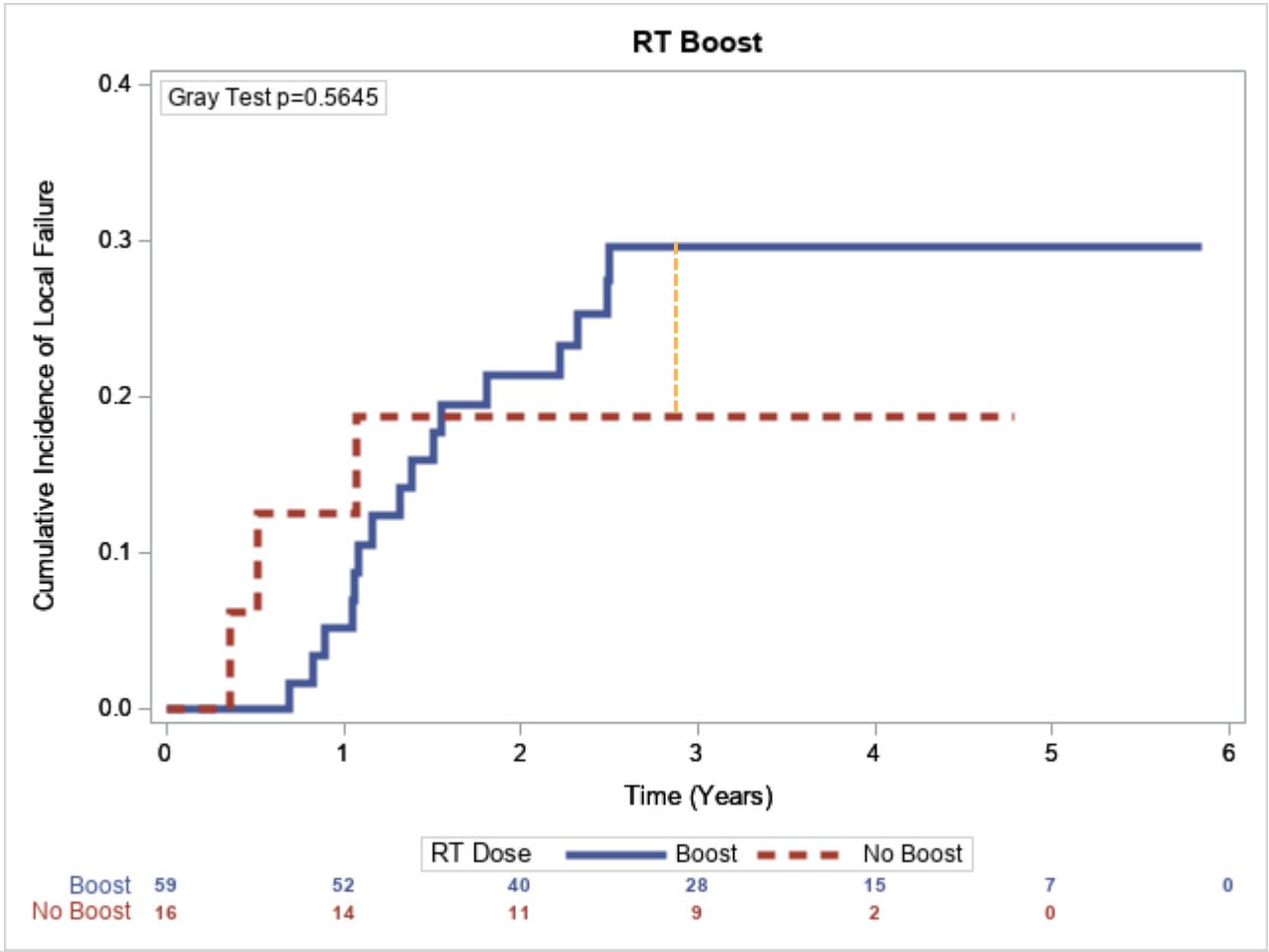
Gupta et al Lancent Onc 2024

ARST1431 Local failure by tumor size



Jackson et al ASCO 2024

ARST1431 Local failure with vs without boost to 59.4 Gy



29.7% vs. 16.1% at 3 years

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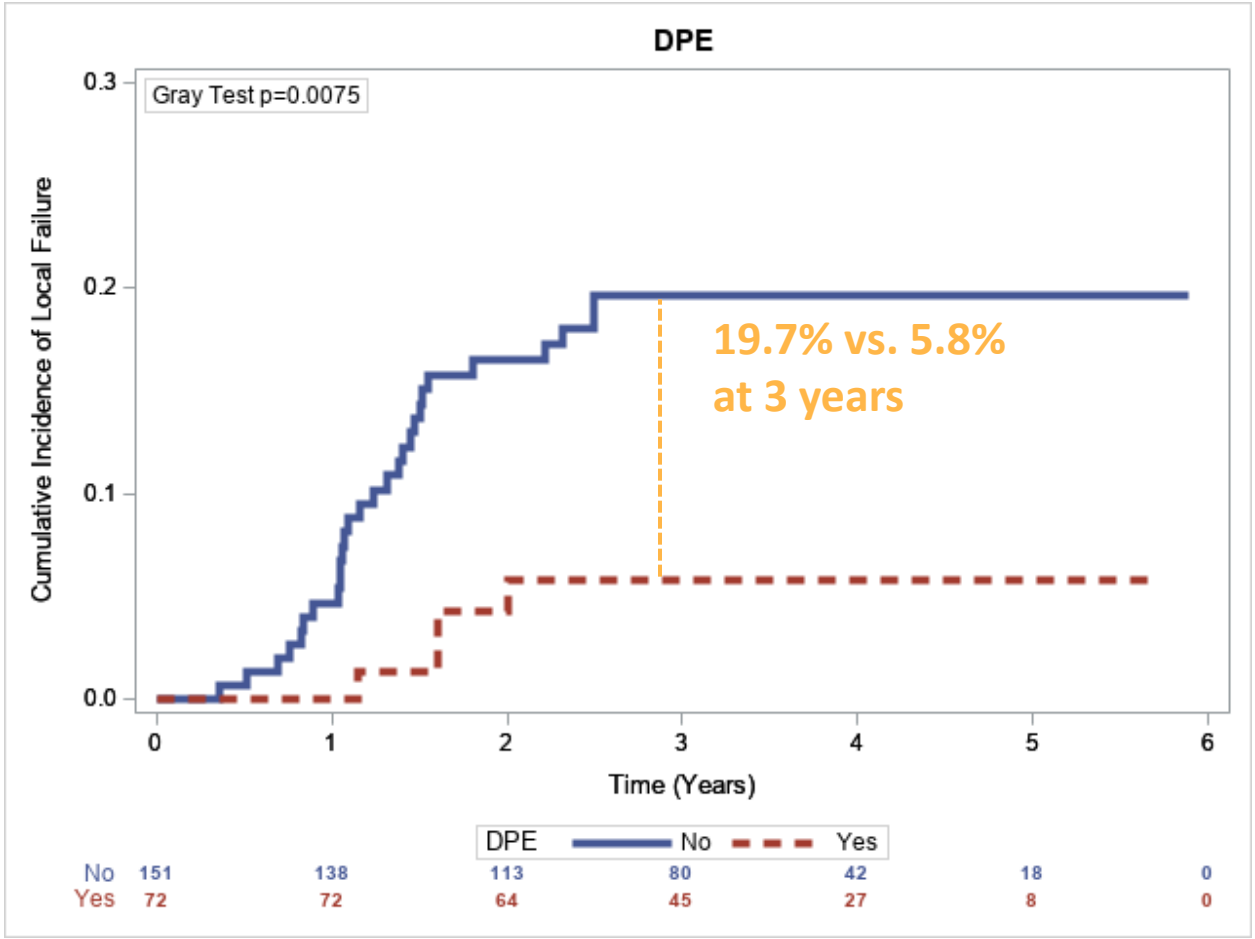
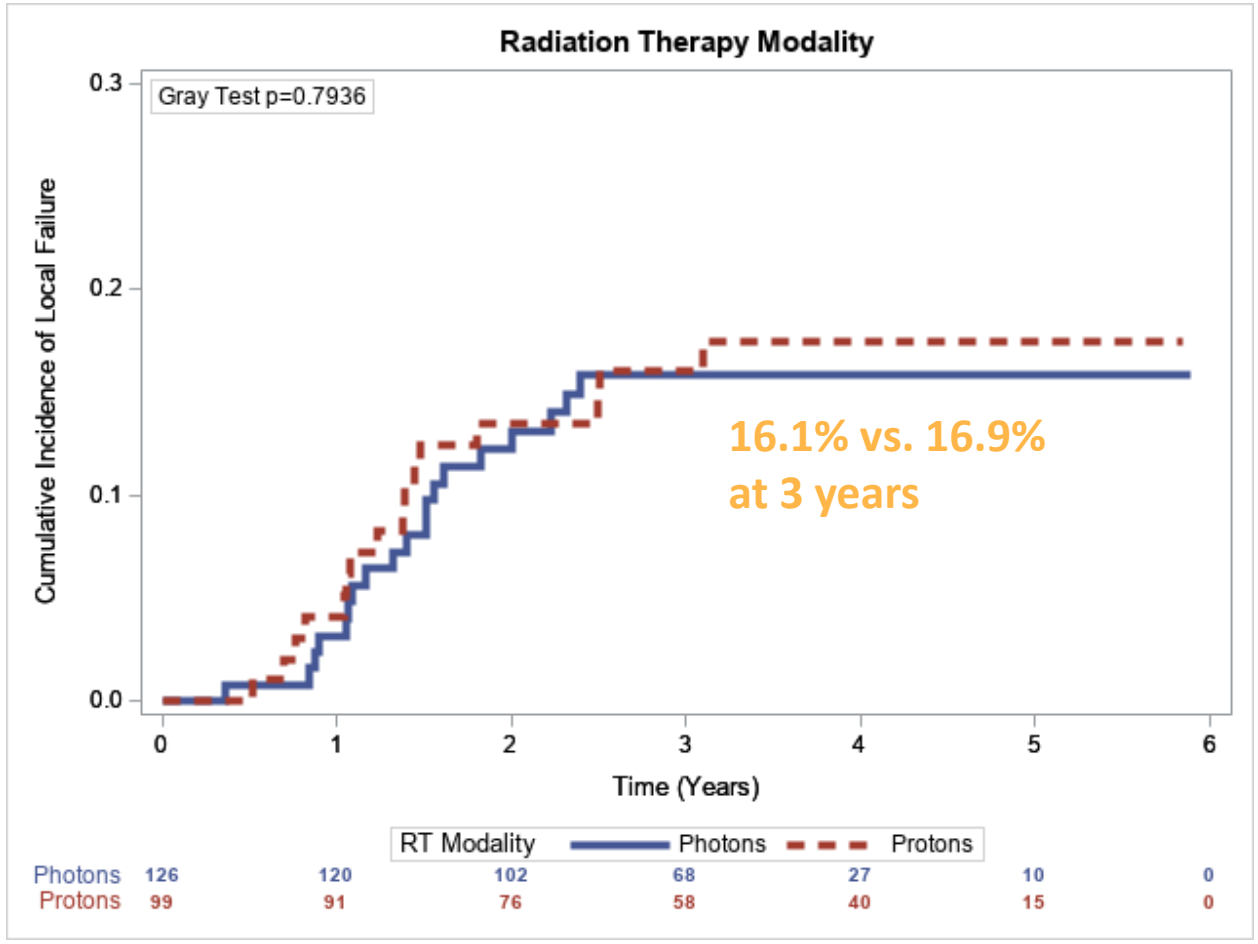
Jackson et al ASCO 2024

ARST1431 Local failure after DPE vs no DPE (group III/IV)



Jackson et al ASCO 2024

ARST1431 Local failure by RT modality

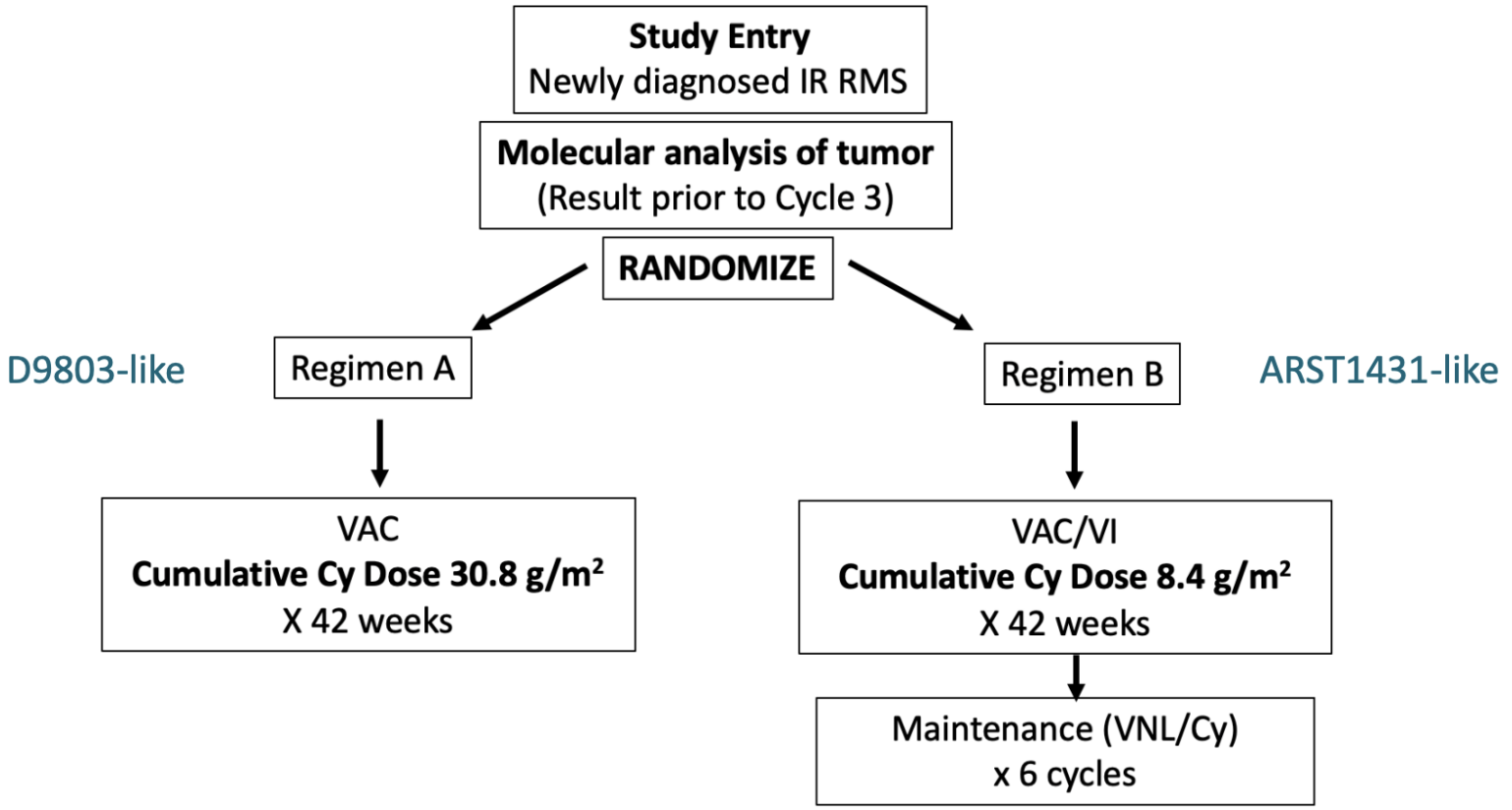


Jackson et al ASCO 2024

ARST1431 Local failure data conclusions

- No difference in local failure with proton vs photons
- Large tumors (>5cm) at diagnosis again a risk factor for local failure (like D9803, ARST0531)
- Radiotherapy dose-escalation to 59.4 Gy did not improve outcomes for patients with large tumors
- For select patients, DPE significantly improved local control

ARST2531 (upcoming intermediate risk trial)



- Radiation recommendations – stop at 50.4 Gy, no boost to 59.4 Gy for tumors >5cm
- After DPE for fusion negative tumors (node negative), considering omission of radiation (TBD)

HIGH RISK RMS UPDATES

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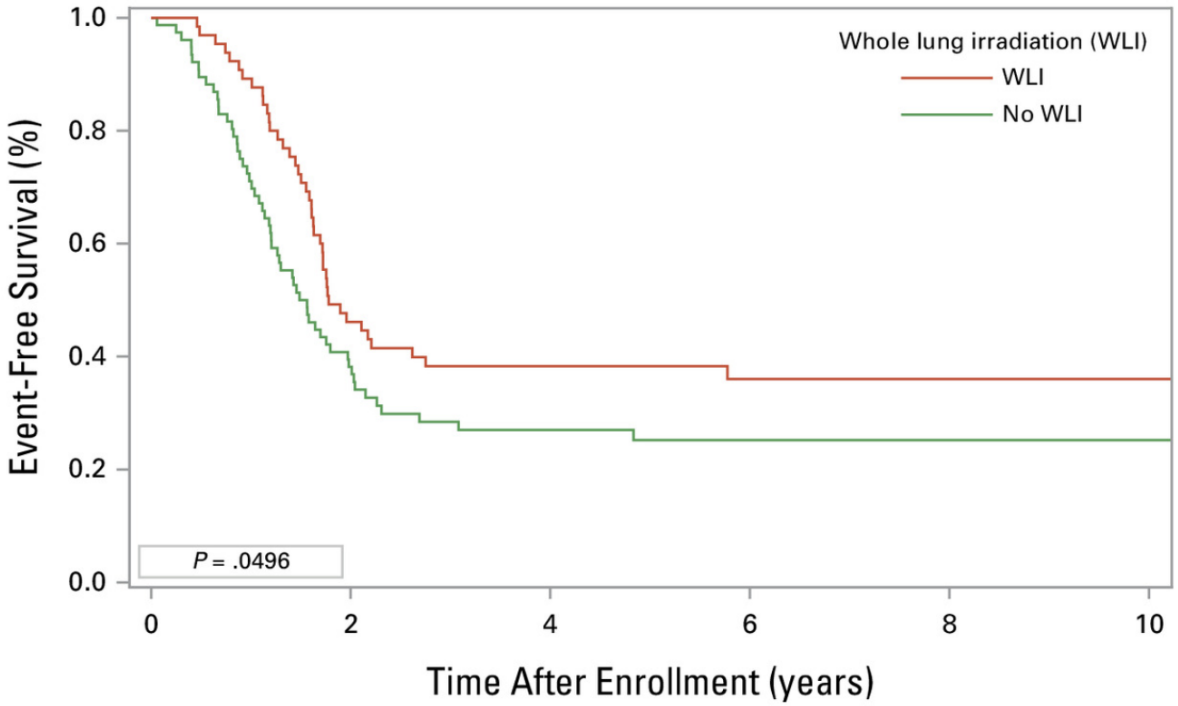
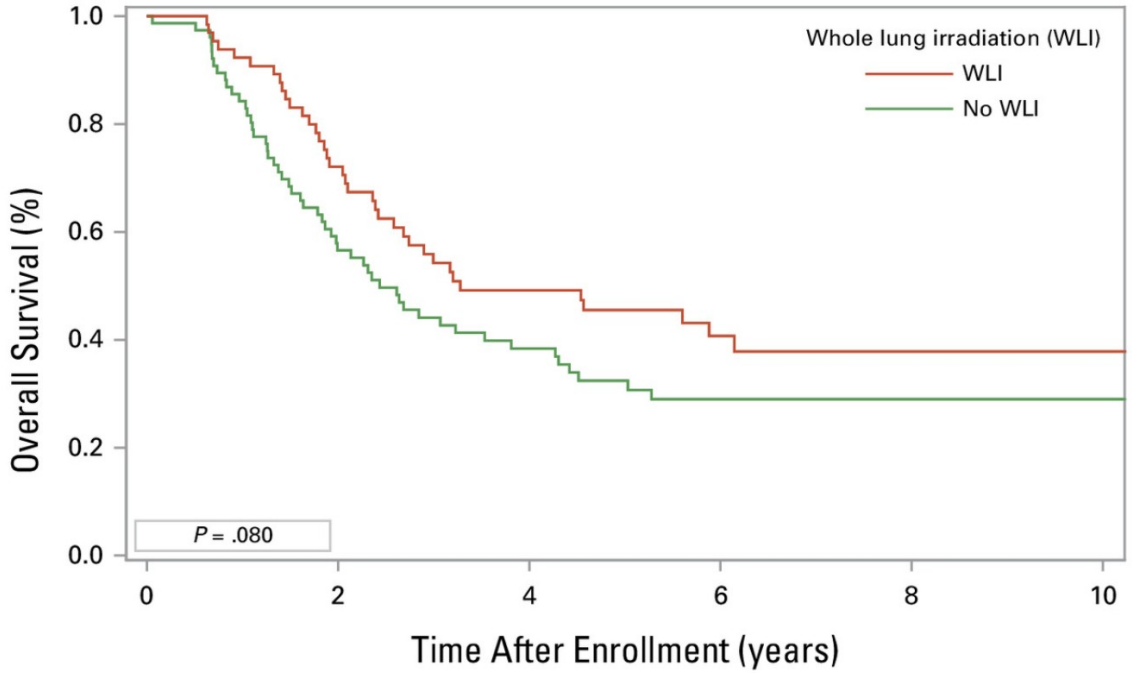
WLI improves EFS, OS on recent trials

Patients with lung metastases on D9802, D9803, ARST0431, ARST08P1



No. at Risk						
No WLI	78	29	18	8	6	5
WLI	65	30	22	14	7	4



No. at Risk						
No WLI	78	43	26	11	7	6
WLI	65	46	28	15	7	4

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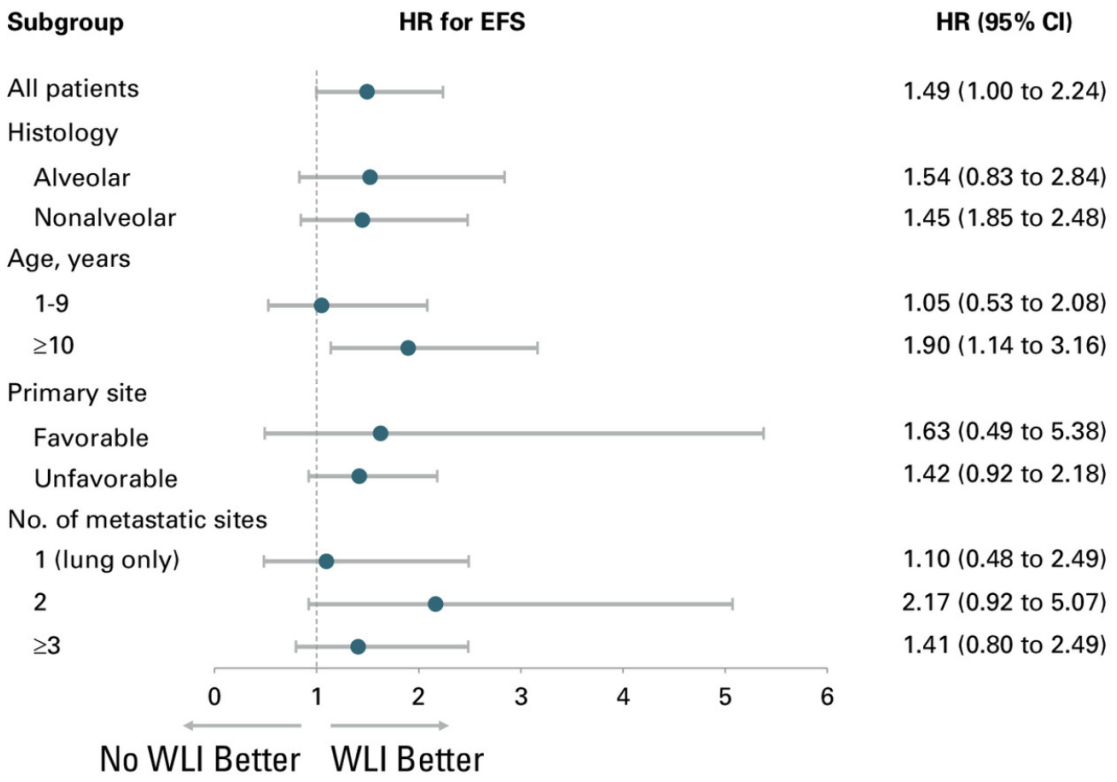
Luo et al JCO 2024

WLI improves EFS on recent trials



Luo et al JCO 2024

Metastatic-directed radiation improves outcomes: summary of studies

Study	Eligibility	Total No. of Patients	Radical vs. Partial vs. None RT	EFS Outcome	OS Outcome
BERNIE[1]	Age < 18, mRMS	97	28% vs. 47% vs. 25%	3Y: 61% vs. 41% vs. 9% (p=0.016)	3Y: 84% vs. 54% vs. 23% (p=0.00018)
Milan[2]	Age < 21, mRMS	80	21% vs. 49% vs. 4%	5Y: 71% vs. 5% vs. 0% (p<0.001)	5Y: 76% vs. 12% vs. 0% (p<0.001)
Texas Children[3]	Age 1-16, mRMS	35	46% vs. 54% vs. NA	5Y: 31% vs. 0% (p=0.002)	5Y: 37% vs. 0% (p<0.001)
Johns Hopkins[4]	Age < 39, mRMS or mES	34 (85 including ES)	40% vs. 60% vs. NA	3Y: 72% vs. 26% (p=0.002)	3Y: 74% vs. 43% (p=0.016)

1. Cameron, IJROBP 2021
2. Ferrari, PBC 2022
3. Mohan, PBC 2017
4. Chang, IJROBP 2024

Metastatic radiation timing, dose, # of sites

Study	Timing of RT	Number of Metastatic Sites Treated on the Radical arm	Radiation Dose and Fractionation
BERNIE[1]	After cycle 6, between cycle 7 and 9	1 site – 56% 2 sites – 26% 3 sites – 19%	30Gy to bone and brain metastases, 15Gy whole lung, 40-50Gy to limited sites
Milan[2]	After cycle 3-4, between week 18-20 (or week 20-24 for high dose chemo patients)	N/A	45-54.8Gy, 25-30Gy whole abdomen, 15-20Gy whole lung
Texas Children[3]	N/A	1-3 sites – 81% 4 or more sites – 19%	30-50.4Gy, 15Gy whole lung
Johns Hopkins[4]	After cycle 4 or cycle 6	1-2 sites – 43% >2 sites: 57%	Mean 53.7Gy EQD2, 15Gy whole lung

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1. Cameron, IJROBP 2021
2. Ferrari, PBC 2022
3. Mohan, PBC 2017
4. Chang, IJROBP 2024

COG ARST2031 (Ongoing high-risk trial)

- Timing of RT : Week 40, prior to maintenance
  Guidelines:
  - WLI recommended for anyone with lung metastases
  - Should treat any metastases close to primary during primary site RT
  - Definitive RT recommended to all other sites not in CR after consolidation chemotherapy
  - SBRT specifically recommended to all metastatic sites ≤5 cm
- Dosing:
  - SBRT: 30-35 Gy in 5 fractions
  - Conventional: 30-45 Gy in 10-15 fractions

Week	1	2	3	4	5	6	7	8	9	10	11	12
	V	V	V	V	V	V	V	V	V	V	V	V
	A			A			A			A		**Evaluation**
	C			C			C			C		

Week	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
	V			V	V		V	V		V	V	V	V	V		V		
	A						A			A		**Evaluation**	A			A		
	C			C			C			C			C			C		
	Primary Site Radiation Therapy																	

Week	31	32	33	34	35	36	37	38	39	40	41	42
	V	V	V	V			V	V		V		★
	A			A			A		**Evaluation**	A		
	C			C			C			C		
										Metastatic Site Radiation Therapy		

Week	43	44	45	46	47	48	49	50	51	52	53	54
	VRL	VRL	VRL		VRL	VRL	VRL		VRL	VRL	VRL	**Evaluation**
	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO

Week	55	56	57	58	59	60	61	62	63	64	65	66	67
	VRL	VRL	VRL		VRL	VRL	VRL		VRL	VRL	VRL		**End of Therapy Evaluation**
	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	CPO	