

# **The role of immunotherapy in anal cancer**

# Radioimmunotherapy in anal cancer: Rationale

- **3-year DFS of ~60%** in T2  $\geq$ 4cm, T3-4 and/or cN+ anal cancer
- **HPV positivity (80-90%)**  $\rightarrow$  higher tumor “**immunogenicity**”  $\rightarrow$  better response to CRT and PD-1/PD-L1 immune checkpoint inhibitors (**ICI**)
- **PD-L1+ in 30%-60%** of patients with anal cancer
- Immunomodulating effect of **chemoradiotherapy (CRT)**  $\rightarrow$  potentially **complementary role with ICI**
- PD-1/PD-L1 ICI showed **encouraging responses** in pretreated recurrent/metastatic anal cancer

# Recent immunotherapy trials in recurrent and metastatic anal cancer

Trial registration (phase)	Treatment setting (N)	Drug/Schedule	Clinical outcome and toxicity
NCT02054806 (Ib)	Refractory (n=24)	Nivolumab	ORR: 24%; CR: 8% Median OS: 11.5 months Median PFS: 4.1 months Good toxicity profile, no SAEs
NCT02314169 (I/II)	Refractory (n=37)	Pembrolizumab	ORR: 17% Median OS: 9.3 months Median PFS: 3 months Grade 3-4 colitis: 2%
NCT02628067 (II)	Refractory (n=112)	Pembrolizumab	ORR: 10.7% Median OS: 11.9 months Median PFS: 2 months Grade 3-4 colitis: 1%

Morris et al, Lancet Oncology 2017

Marabelle J Clin Oncol. 2020;38(suppl 4)

Ott et al, Annals Oncology 2017

# Ongoing immunotherapy trials in recurrent and metastatic anal cancer

Trial registration (phase)	Treatment setting (N)	Drug/Schedule	Primary endpoint
NCT03519295 (II)	Untreated (n=99)	DCF +/- Atezolizumab	PFS
EA2176 (II)	Untreated (n=205)	Carboplatin/paclitaxel +/- Nivolumab	PFS
NCI9673 (II)	Refractory (n=100)	Nivolumab +/- Ipilimumab	PFS
NCT03074513 (II)	Refractory (n=20)	Atezolizumab + Bevacizumab	ORR (12 weeks)
NCT03439085 (II)	Refractory (n=77)	Durvalumab+HPV DNA vaccine	ORR

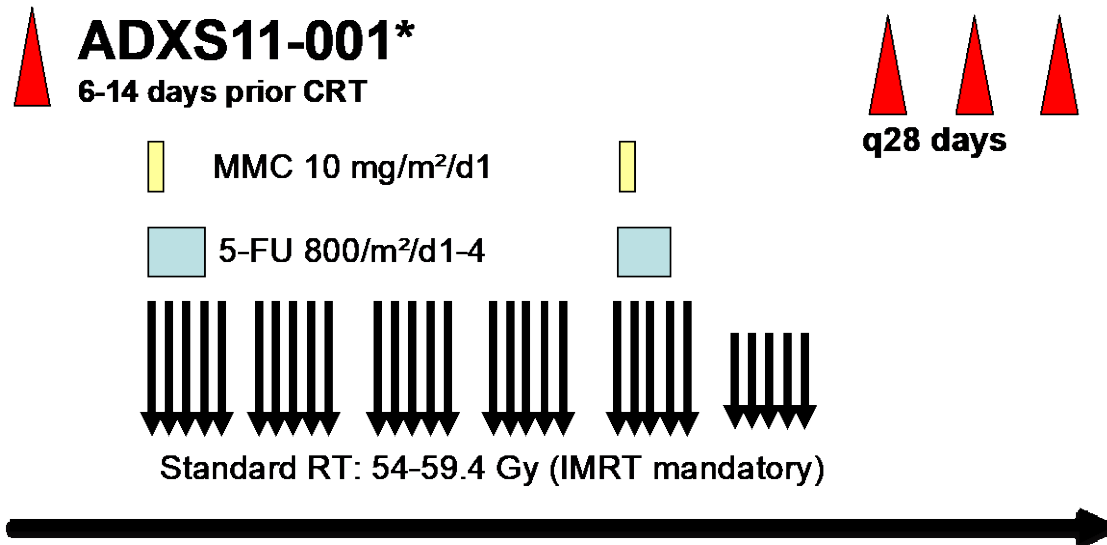
# ADXS11-001 with CRT in anal cancer

## Phase I trial (NCT01671488)

- Primary Endpoint: SAE, CR at 6 months

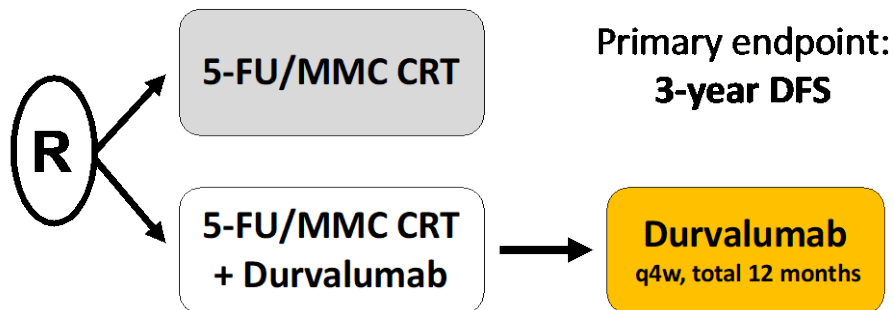
## Results (N=10):

- ADXS11 G3: 20% (chills/rigors, hyponatremia)
- Median follow up: 42 months; cCR: 100%; PFS: 90%



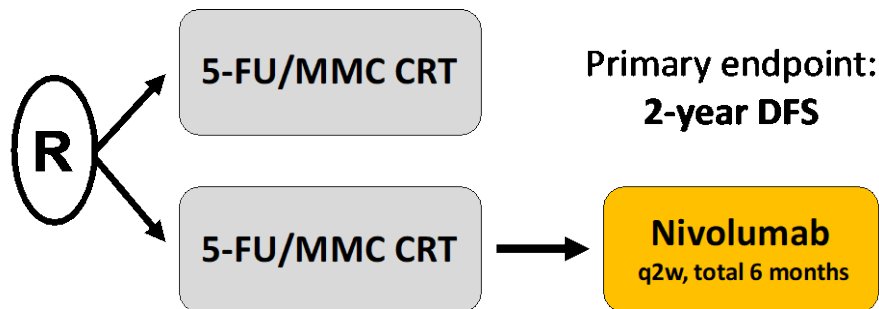
\*Attenuated *Listeria monocytogenes*: fused to HPV E7 inducing an immune response against HPV+ tumor cells

# Does the combination sequence of CRT with immunotherapy matter in anal cancer?



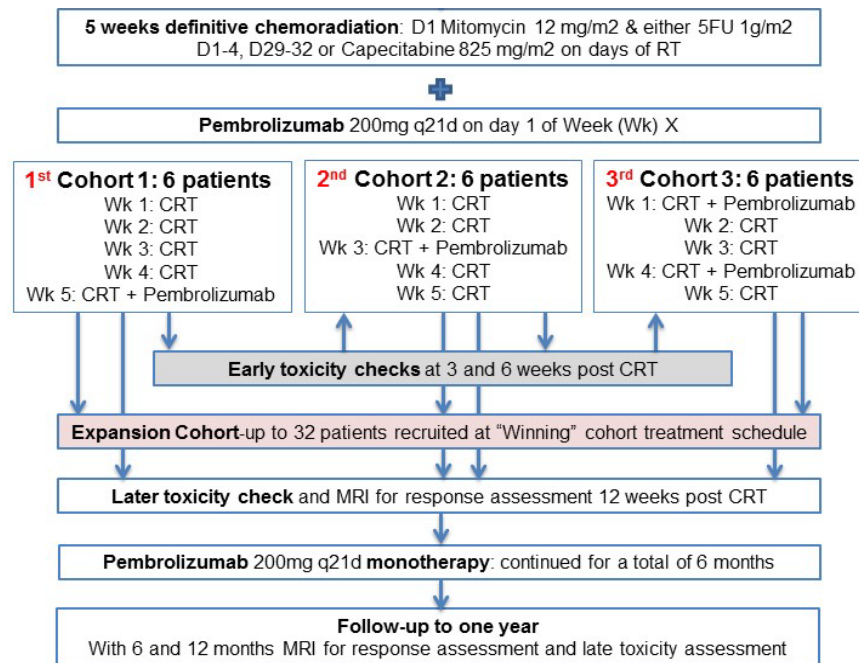
## RADIANCE phase 2, NT04230759

Durvalumab: before, during and after CRT



## NCI/ECOG/ACRIN phase 2/3, NCT03233711

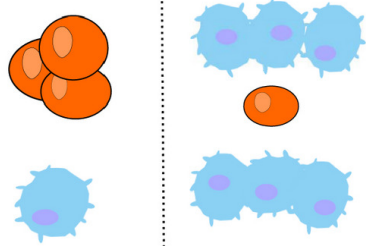
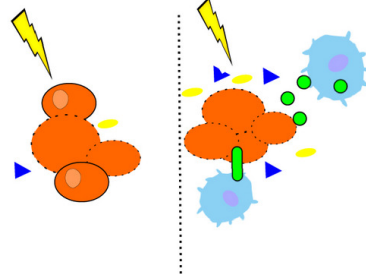
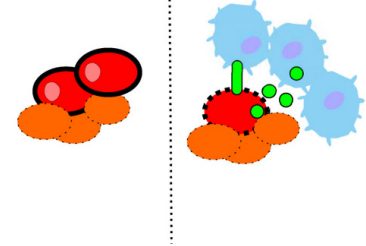
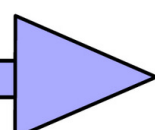
Nivolumab: only after CRT



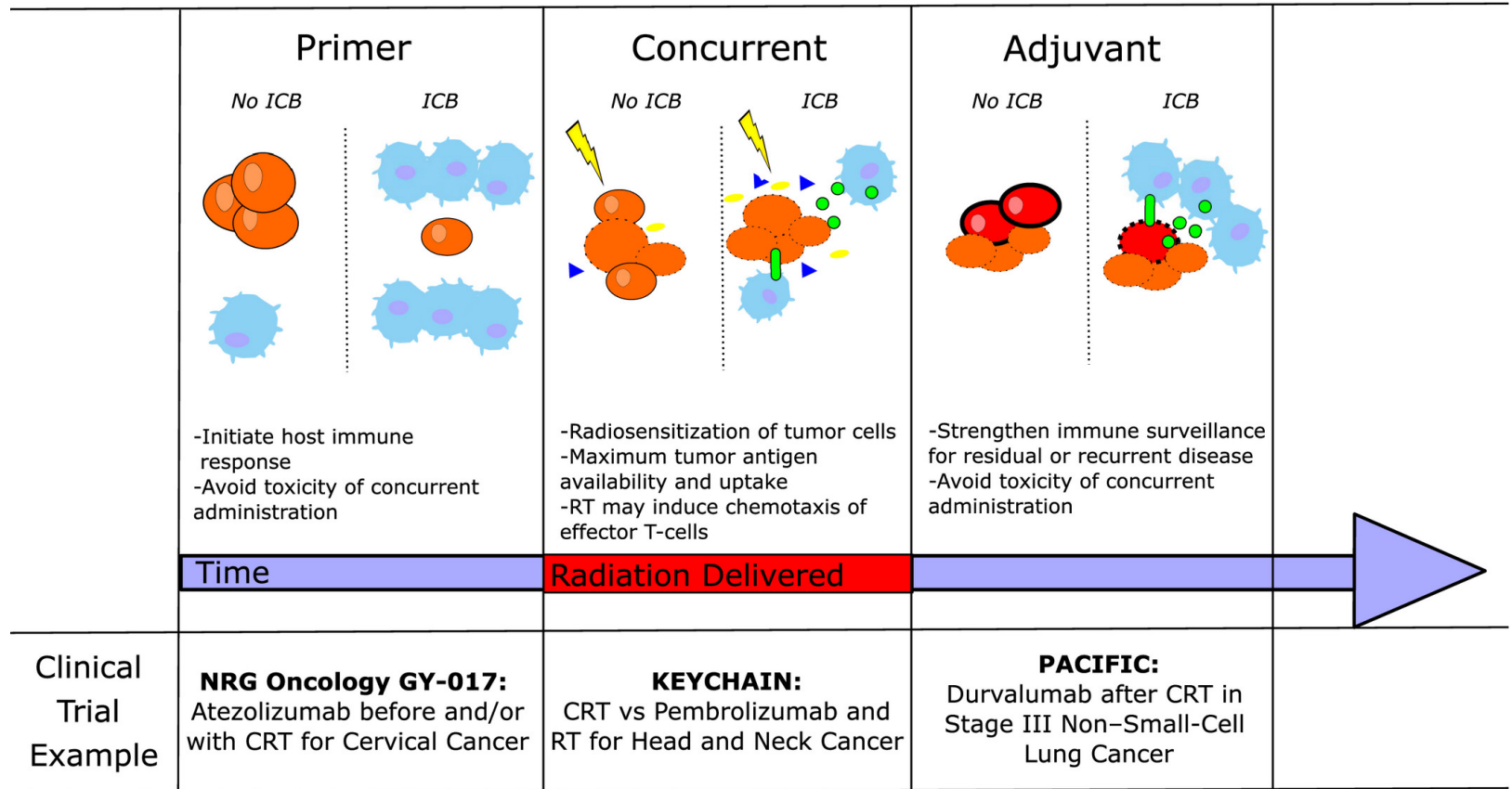
## CORINTH phase 1b/2, NCT04046133

Pembrolizumab: during and after CRT

# Does the combination sequence of CRT with immunotherapy matter in anal cancer?

	Primer		Concurrent		Adjuvant		
	No ICB	ICB	No ICB	ICB	No ICB	ICB	
							
	<ul style="list-style-type: none"> <li>-Initiate host immune response</li> <li>-Avoid toxicity of concurrent administration</li> </ul>		<ul style="list-style-type: none"> <li>-Radiosensitization of tumor cells</li> <li>-Maximum tumor antigen availability and uptake</li> <li>-RT may induce chemotaxis of effector T-cells</li> </ul>		<ul style="list-style-type: none"> <li>-Strengthen immune surveillance for residual or recurrent disease</li> <li>-Avoid toxicity of concurrent administration</li> </ul>		
	Time		Radiation Delivered		Time		
Clinical Trial Example	<b>NRG Oncology GY-017:</b> Atezolizumab before and/or with CRT for Cervical Cancer		<b>KEYCHAIN:</b> CRT vs Pembrolizumab and RT for Head and Neck Cancer		<b>PACIFIC:</b> Durvalumab after CRT in Stage III Non-Small-Cell Lung Cancer		

# Does the combination sequence of CRT with immunotherapy matter in anal cancer?



Anal cancer trials with ICI

**RADIANCE**

**RADIANCE  
CORINTH**

**RADIANCE  
CORINTH  
NCI/ECOG/ACRIN**



# Conclusions

- The immunomodulatory effect of HPV provides a rationale for combining immune checkpoint inhibitors (ICI) with CRT in locally-advanced non-metastatic anal cancer
- Promising data with PD-1/PD-L1 ICI in recurrent/metastatic anal cancer
- The impact of treatment sequence on the efficacy of CRT-immunotherapy is currently being investigated in different phase II/III clinical trials