

XXXIII CONGRESSO NAZIONALE AIRO

# AIRO2023

BOLOGNA,  
27-29 OTTOBRE 2023

PALAZZO DEI CONGRESSI

Radioterapia Oncologica: l'evoluzione al servizio dei pazienti

**Volumi di trattamento e frazionamento della dose nelle combinazioni radio-immunoterapiche: evidenze attuali e sfide future: Gastroenterico**

Mauro Loi

AOU Careggi-Università di Firenze



Associazione Italiana  
Radioterapia e Oncologia clinica

## No Conflict of Interest to disclose



- Rectal Cancer
- Esophageal Cancer
- Anal Cancer
- Pancreas
- HCC
- Future perspectives
- Take home message

## RECTAL CANCER

- Sinergy RT-ICI in preclinical models  
→ overcome RT-induced PDL1 expression +++  
*Dovedi Can Res 2014*
- ICI +++ d MMR/MSI-H (5%)  
→ instability=↑ neoantigen load
- VOLTAGE (p I/II, n=37): LCRT+Nivo  
→ p CR MSI-H 60%, MSS 30%  
*Yoshino ASCO 2019*
- NRG-GI002 (pII, n=178): FOLFOX+LCRT ± Pembro  
→ 3-year OS (95% vs. 87%; HR 0.35, p = 0.04)  
→ DFS=NS, NAR=NS: surrogate? *George ASCO 2023*

Radioterapia Oncologica:  
l'evoluzione al servizio dei pazienti

## ESMO

Phase III  
trialsNICHE (n=20)  
NICHE-2 (n=110)  
Cercek JCO (n=12)

## RECTAL CANCER

### UNION study design

A randomized and open-label phase III clinical trial (NCT04928807)

#### Key eligibility criteria

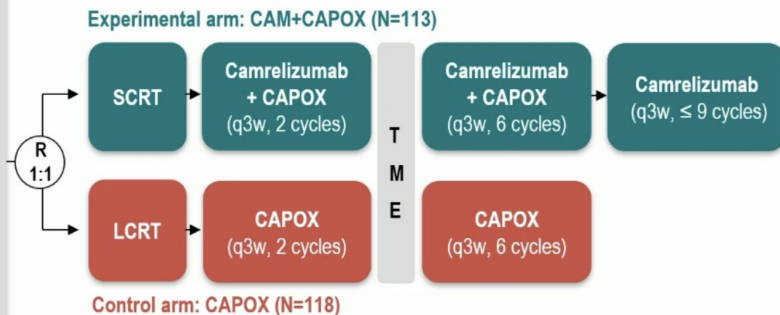
- Rectal adenocarcinoma (clinical stage T3-4 or N\*)
- No prior anti-tumor treatment and eligible for surgery
- Lower edge of the tumor was ≤ 10 cm from the anal verge
- ECOG PS 0 or 1  
(N=231)

#### Stratification factors

- Clinical T stage (≤ T3 vs T4)
- Clinical N stage (N0 vs N\*)

#### Enrolled time

- July 20, 2021-March 1, 2023



SCRT: 25 Gy/5 fractions.

LCRT: 50.4 Gy/28 fractions with concurrent capecitabine 825 mg/m<sup>2</sup>, po bid.

CAPOX: oxaliplatin 130 mg/m<sup>2</sup> iv d1; capecitabine 1000 mg/m<sup>2</sup> po bid, d1-14.

CAM: camrelizumab 200mg iv drip, q3w.

CAM+CAPOX arm: 1 week after SCRT, receive CAM + CAPOX.

CAPOX arm: 2 weeks after LCRT, receive CAPOX.

TME : total mesorectal excision, conducted within 10 weeks after the end of radiotherapy.

#### Primary endpoint :

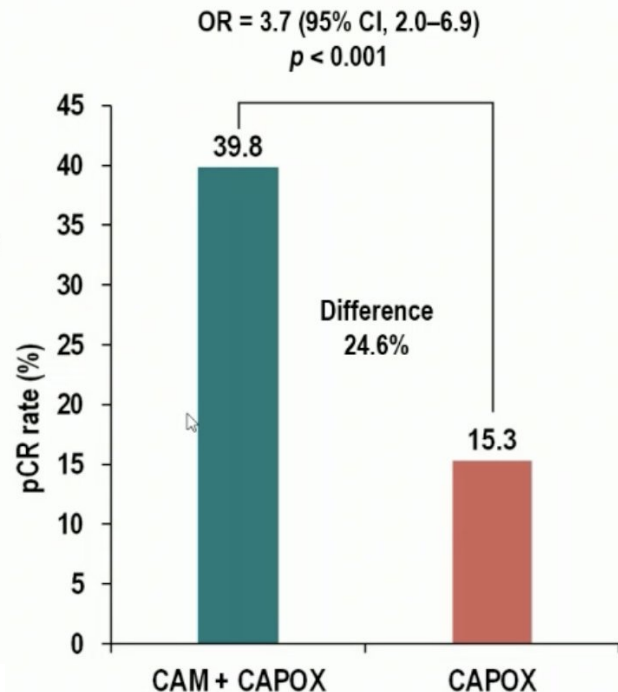
- BIRC assessed pCR rate (ypT0N0)

#### Key secondary endpoints:

- 3-year EFS rate
- OS

#### Secondary endpoints:

- 3-year DFS rate
- R0 resection rate
- Tumor regression grade
- Completion rate of neoadjuvant therapy
- Quality of life
- Safety



Lin ESMO 23

## RECTAL CANCER

- NCT04304209 → MSI: Sintilimab + observation or surgery  
→ MSS: LCRT ± Sintilimab + observation or surgery
- EOCG-ACRIN 2201 → SCRT+Nivolumab+Ipilimumab
- NCT04109755 → MSI: SCRT+Pembrolizumab

	STUDY	PHASE	DESIGN	ENDPOINT
<b>LCRT</b>	NCT03127007 (R-IMMUNE)	Phase 1/2	LC CRT±Atezolizumab → TME	AE, pCR
	NCT02948348	Phase 1/2	LC CRT + Nivo → TME	pCR
	NCT05245474	Phase 2	LCRT± Concurrent/Sequential Tislelizumab → TME	pCR
	NCT03299660	Phase 2	LC CRT → Avelumab → TME	pCR
	NCT03854799	Phase 2	LC CRT → Avelumab → TME	pCR
	NCT04621370 (PRIME-RT)	Phase 2	LCRT+ Durvalumab versus SCRT+ Durvalumab → FOLFOX	pCR, cCR
	NCT05507112	Phase 2	LC CRT ± Concurrent Tislelizumab → TME	pCR
	NCT03921684	Phase 2	LC CRT → FOLFOX + Nivolumab → TME	pCR
	NCT04124601	Phase 2	LC CRT±Nivo/Ipi	AE, Response
	NCT05009069	Phase 2	LCRT + Atezolizumab + Tiragolumab → TME	pCR
	NCT04293419 (DUREC)	Phase 2	FOLFOX + Durvalumab → LCCRT → TME	pCR
<b>SCRT</b>	NCT05576480	Phase 2	SCRT → Penpulimab + CAPEOX → TME	pCR
	NCT05086627	Phase 2	SCRT → CAPEOX ± Tislelizumab → TME → CAPEOX	pCR
	NCT03503630	Phase 2	SCRT → Avelumab + FOLFOX → TME	pCR
	NCT04751370	Phase 2	Nivo/Ipi → SCRT → Nivo/Ipi → TME	pCR
	NCT04503694	Phase 2	Rego + Nivo → SCRT → Rego+ Nivo → TME	pCR
	NCT05484024	Phase 2/3	SCRT → NACT + Sintilimab → W/W or TME	pCR, DFS

## Locoregional Failure During and After Short-course Radiotherapy Followed by Chemotherapy and Surgery Compared With Long-course Chemoradiotherapy and Surgery

*A 5-Year Follow-up of the RAPIDO Trial*

Colorectal cancer

### **TNT and local recurrence in the RAPIDO trial – untangling the puzzle**

[Robert Glynne-Jones](#)  & [James Hollingshead](#)



# AIRO2023

## ESOPHAGEAL

- Checkmate-577
  - 794 patients (71% ADC) with R0 yp T+orN+ after CROSS+S
  - Phase III 2:1 adjuvant Nivolumab vs Placebo
  - 2xDFS! (primary endpoint)
  - Reimbursement pending in Italy (OS data awaited)
  - Benefit independent for PD-L1 expression!

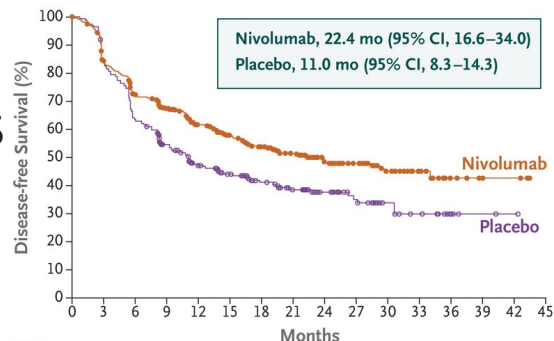
*Kelly NEJM 2022*

- SANO trial
  - CROSS followed by surgery versus observation in cCR
  - Non-inferior 2-yr OS (primary endpoint), improved HRQoL

*Van Der Wilk ESMO 2023*

Radioterapia Oncologica:  
l'evoluzione al servizio dei pazienti

Disease-free Survival in the Overall Population



No. at Risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0



- Sinergy RT-ICI in preclinical models → overcome RT-induced PDL1 expression +++

*Oh ASTRO 2016*

- Unoperable SCC unfit for radical CTRT : induction chemo+ICI+CTRT vs CTRT

→ Retrospective (n=137)

→ Non-significant increase in PFS and OS

*Peng ASTRO 2017*

- Unoperable SCC unfit for radical CTRT : RT 60Gy +Camrelizumab

→ Phase Ib (n=19)

→ Median OS 16 months

*Zhang Oncologist 2021*

# AIRO2023

## ESOPHAGEAL (ADC)

Radioterapia Oncologica:  
l'evoluzione al servizio dei pazienti

- ADC CTRT : CTRT+Pembro →S→ adjuvant Pembro  
→ Phase Ib/II (n=31)  
→ pCR 23%

*Zhu Clin Can Res 2022*

- ADC CTRT : CTRT+Atezo →S (PERFECT)  
→ Phase II (n=40)  
→ pCR 24%

*Van den Ende Clin Can Res 2022*

**Zhu et al**  
pCR: 23%

**CROSS**  
pCR: 25%

**PERFECT**  
pCR: 24%



## ESOPHAGEAL

STUDY	PHASE	DESIGN	ENDPOINT
NCT05650216, NCT05043688	Phase 2	Camrelizumab + CRT	pCR
NCT04229459	Phase 2	Nivolumab+ CRT	pCR
NCT03777813	Phase 2	Durvalumab +CRT vs. CRT	PFS
NCT05520619	Phase 2	Tislelizumab + CRT	PFS
NCT05387681	Phase 2	Envafohimab + CRT	pCR
NCT04929392	Phase 2	Pembrolizumab + CRT	pCR
NCT04888403	Phase 2	Toripalimab + CRT	pCR
NCT04973306	Phase 2/3	Tislelizumab + CRT vs. CRT	pCR, OS
NCT03604991	Phase 3	Pre-op Nivolumab + CRT vs. Pre-op CRT with postop adjuvant (Nivo vs. Nivo/Ipi)	pCR, DFS, OS
NCT04404491	Phase 3	Camrelizumab + RT vs. RT + CHT	PFS
NCT04821843	Phase 3	Nimotuzumab + CRT vs. Nimotuzumab + CHT	OS
NCT04821778	Phase 3	Nimotuzumab + CRT vs. CRT	OS
NCT05244798	Phase 3	Sintilimab + CHT vs. Sintilimab + CRT vs. CRT	pCR

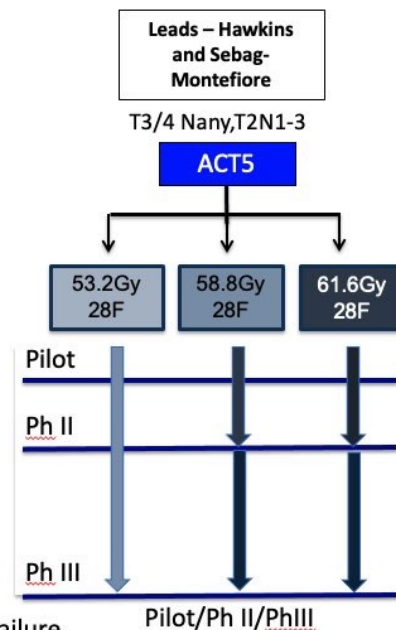
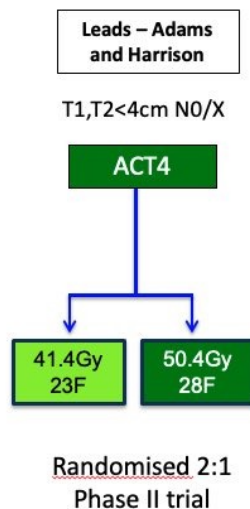
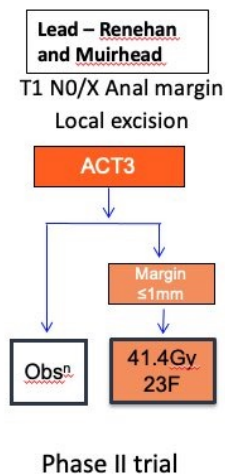


## ANAL CANAL SCC

- Standard CRT: relapse/persistence in 30% of cases in LA
  - 18-24% ORR of ICI as >1 line (NCI9673, Keynote-158) *Morris Lancet Oncol 2017*  
*Marabelle Lancet Gast Hep 2022*
- HPV involvement
  - Immunogenic in nature beyond PDL1 expression! *Mondini Mol Can Ther 2014*  
*Krishna Can Res 2018*
- HIV involvement
  - Immunosuppressive (?) → no diff in CD3, CD4, CD8, CD68, or LAG-3  
*Yanik Jama Oncol 2017*
- ECOG-ACRIN 2165: Phase III CRT (54/45 Gy/30#) +adjuvant Nivo versus follow-up
  - Waiting for...(primary endpoint: EFS)

STUDY	PHASE	STAGE	DESIGN	ENDPOINT
NCT04046133 (CORINTH)	Phase 1	III A/B	CRT + Pembrolizumab	AE, Response
NCT04230759 (RADIANCE)	Phase 2	IIB-IIIC	CRT 5FU/MMC±Durvalumab	DFS
NCT04929028	Phase 2	Low/High Risk HiV	CRT 5FU/MMC±Nivolumab	DFS
NCT05661188 (TIRANUS)	Phase 2	I-IIIB	CRT 5FU/MMC/Tiraglolumab/Atezolizumab	cCR
NCT03233711	Phase 3	I-IIIB	CRT 5FU/MMC±Nivolumab	DFS
NCT05374252	Phase 3	III	CRT 5FU/MMC±Sintilimab+Adjuvant Sintilimab 6months	DFS

## PLATO - Personalising RadioTherapy dose for Anal Cancer



Primary end point :- 3yr locoregional failure

# AIRO2023

## PANCREAS

Radioterapia Oncologica:  
l'evoluzione al servizio dei pazienti

- Poor immunogenicity of PDAC  
→ large desmoplastic stroma hampers immune infiltration  
→ low mutational burden!!  
→ failure of ICI therapy

*Brouwer Cell Onc 2019*

- Radiotherapy alone elicit insufficient immune response!



Original Article

Feasibility, safety, and efficacy of stereotactic body radiotherapy combined with intradermal heat-killed mycobacterium obuense (IMM-101) vaccination for non-progressive locally advanced pancreatic cancer, after induction chemotherapy with (modified)FOLFIRINOX – The LAPC-2 trial



*Van 't Land Radiother Oncol 2022*



RT is useless in  
pancreas cancer

So is immuno  
....





- Rahma et al: RTCT (50.4 Gy/28#+Cape ± Pembro) followed by surgery

→Phase 2 (n=37)

→No differences in immune cell infiltrate

*Rahma J Immunother Cancer 2021*

- CheckPAC : Phase II, mPC 15/1#+ Nivo ± Ipi (n=84)

→PR/SD 17% Nivo, 32% Nivo+Ipi

→Better OS associated with ↓CRP, IL-6, IL-8

*Chen JCO 2022*

- TRIPLE-R : Phase II, mPC 15/1#+ Nivo+Ipi+Tocilizumab (n=26)

→No meaningful activity

*Chen JCO 2022*



## PANCREAS

- NCT02704156: Phase II SBRT 35-40/5# +pembrolizumab+trametinib vs SBRT+gem (n=176)

→ ↑ OS [HR 0.69] vs GEM

→ ↑ PFS [HR 0,6] vs GEM

*Zhu Lancet Oncol 2022*

- Sub-analysis : impact of higher dose level (BED10 → >65)

→ ↑ PFS [7,9 VS 4.3 mo, HR 0.48, p=0,002]

→ Trend to significant effect on survival [15.1 vs. 12.4 months, HR 0.67, p=0,07]

*Zhu EclinMed 2023*

- Sub-analysis : biomarker analysis in experimental arm

→ ↑ OS correlated with PD-L1+/ TIL- and KRASmut

*Zhu Lancet Oncol 2023*

- RTOG 1112

→ Superior OS SBRT+Sorafenib vs Sorafenib

*Dawson IJROBP 2022*

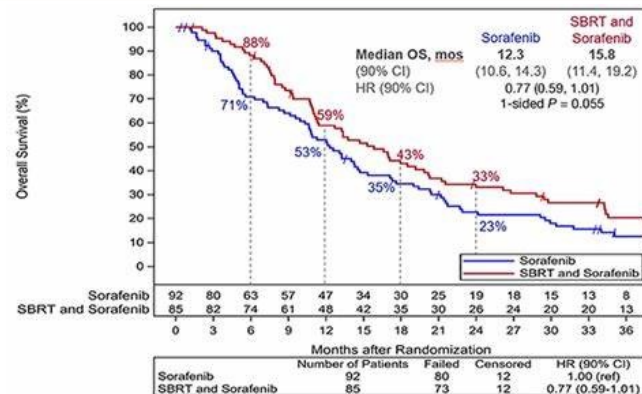
- But Sorafenib no longer SOC

→ Imbrave 150: Atezolizumab Bevacizumab **is** SOC

*Finn NEJM 2021*

→ Himalaya 3: Immunox2 (Durva+Treme «shot») **may become SOC**

*Abou Alpha evNEJM 2022*



- SBRT (40Gy/5#) +Nivo  $\pm$  Ipi  
→ Phase 1 (n=14), improved ORR Nivo +Ipi  
*Dawson IJROBP 2022*
- NCT05488522  
→ SBRT+Atezolizumab-Bevacizumab
- NCT04430452  
→ SBRT+Durva  $\pm$  Tremelimumab



- SPLEEN PRESERVATION

- Mean dose >10 Gy increased risk for infective mortality  
(severe >40 Gy)

*Gwynne Clin Onc 2020*

- CD4+ and CD8+ colony-forming capability -90% for 3 Gy

*Yovino Cancer Inv 2013*

- Lymphopenia correlates with response to RT and ICI

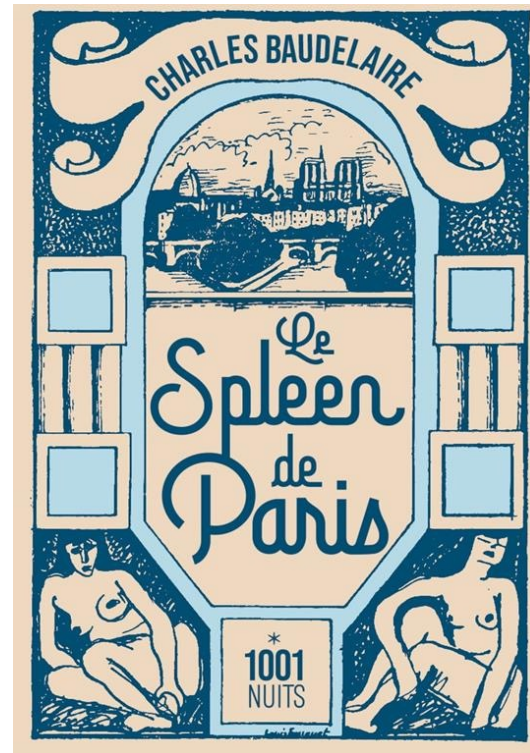
*Chen IJROBP 2020*

*Reddy Radiat Oncol 2022*

- Spleen may act as a reservoir for TILs

- OAR to protect or «niche»?

*Katz Front Oncol 2022*



- ENI
  - A staple of radiation treatment (emulation of the surgeon?)
  - Lymphnodes are also a primary hub for lymphocyte priming
  - Are we doing it all wrong?

nature communications



Article

<https://doi.org/10.1038/s41467-022-34676-w>

### **Elective nodal irradiation mitigates local and systemic immunity generated by combination radiation and immunotherapy in head and neck tumors**

- ENI ablates the immune response to RT 8x3 and anti CD25
  - ENI decreases T cell expansion in the DLNs and TME penetration
  - ENI omission results in higher LR recurrences
- ... that can be averted by sentinel node resection, or irradiation

*Darragh Nat Comm 2021*

# AIRO2023

## TAKE HOME MESSAGE

- RECTAL CANCER
  - RT+ICI ++MSS overcome RT-derived PDL1+
  - +++LCRT
  - is pCR a proper surrogate?
  
- ANAL CANAL
  - HPV and HIV: frenemies?
  - Not only for LA but also deescalate?
  - ENI?

Radioterapia Oncologica:  
l'evoluzione al servizio dei pazienti





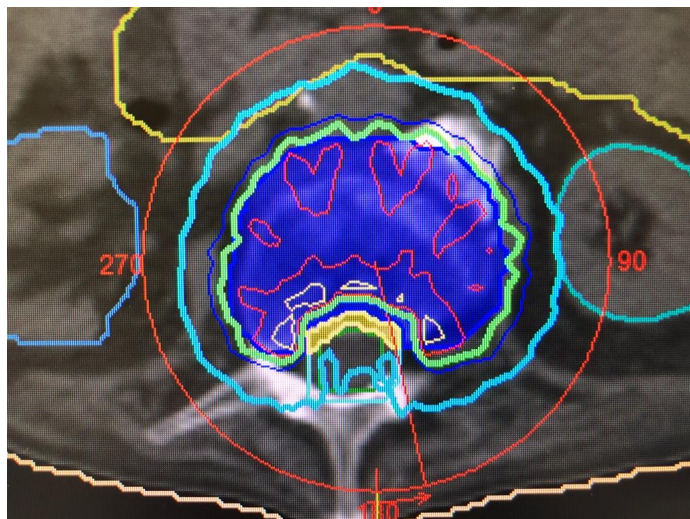
## TAKE HOME MESSAGE

- ESOPHAGEAL CANCER
  - Non operative strategies for cCR (SANO).. Immune consolidation?
  - Another succesful case of PACIFIC paradigm (CRT+immuno?) if OS benefit confirmed in ypT+
- PANCREATIC CANCER
  - Poorly immunogenic, scarce potential for RT alone to elicit immunity
  - Hints of sinergy for SBRT+ICI
  - No clues about patient selection or manipulation of TME  
(but this is the way....)
- HCC
  - Running behind Med Onc is a losing game
  - Need to develop SBRT-centered strategies

# AIRO2023

Radioterapia Oncologica:  
l'evoluzione al servizio dei pazienti

“thank you for  
your **ATTENTION**  
:)”



*Courtesy Dr Livia Marrazzo, UniFi*

