
# Take Home Messages

Ospedale San Gerardo

**S. Arcangeli**

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

# Dichiarazione di conflitto d’interesse

Stefano Arcangeli:

Astellas

Janssen

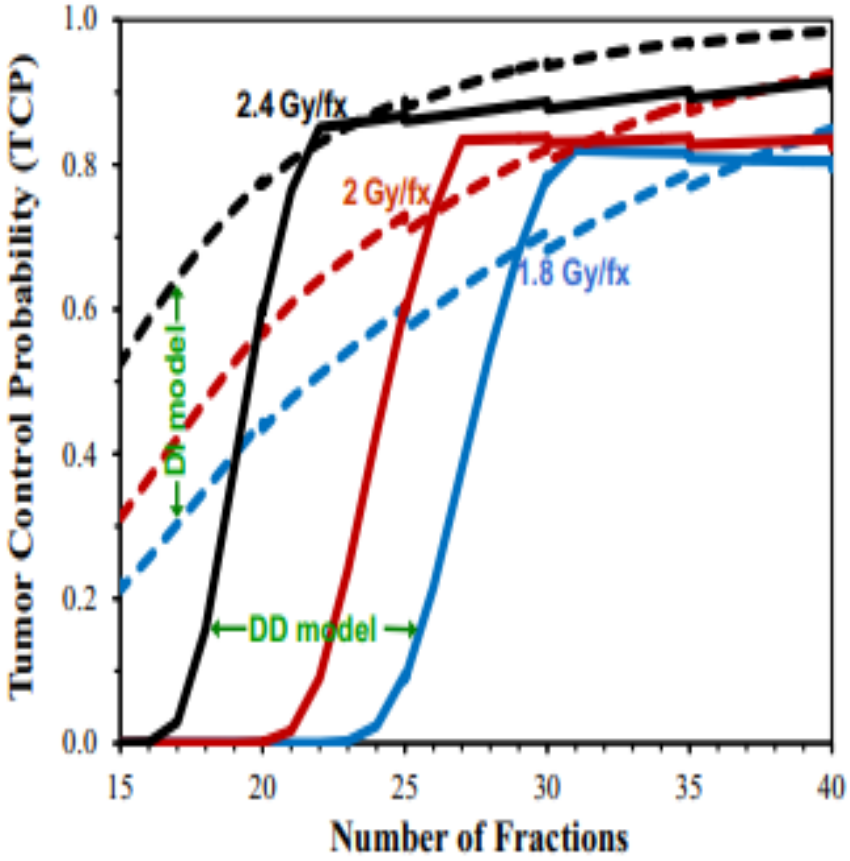
# Radiobiologia e frazionamenti alterati

Radiother Oncol. 2018 Apr;127(1):20-26. doi: 10.1016/j.radonc.2018.02.015. Epub 2018 Mar 10.

# Dose dependence of accelerated repopulation in head and neck cancer: Supporting evidence and clinical implications.

Shuryak I[1], Hall EJ[2], Brenner DJ[2].

The alternative dose-dependent model of AR provides significantly-improved descriptions of a wide range of randomized clinical data




For currently-used HNC fractionation schemes, **the last 5 fractions do not increase TCP**, but simply compensate for increased accelerated repopulation.

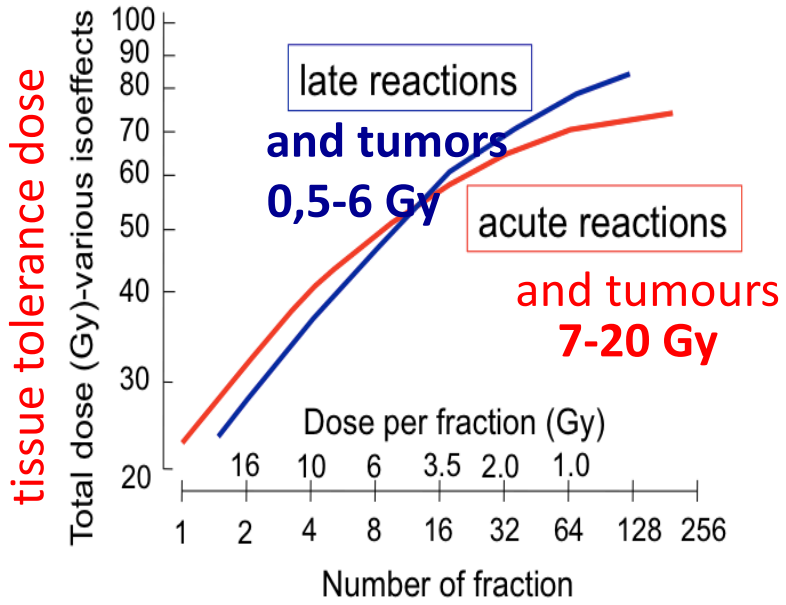
van Leeuwen *et al. Radiation Oncology* (2018) 13:96
https://doi.org/10.1186/s13014-018-1040-z

Radiation Oncology

REVIEW Open Access

# The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies

C. M. van Leeuwen[1], A. L. Oei[1,2], J. Crezee[1], A. Bel[1], N. A. P. Franken[1,2], L. J. A. Stalpers[1] and H. P. Kok[1*]



ACTA ONCOLOGICA
2018, VOL. 57, NO. 7, 883–894
https://doi.org/10.1080/0284186X.2018.1433874

Taylor & Francis
Taylor & Francis Group

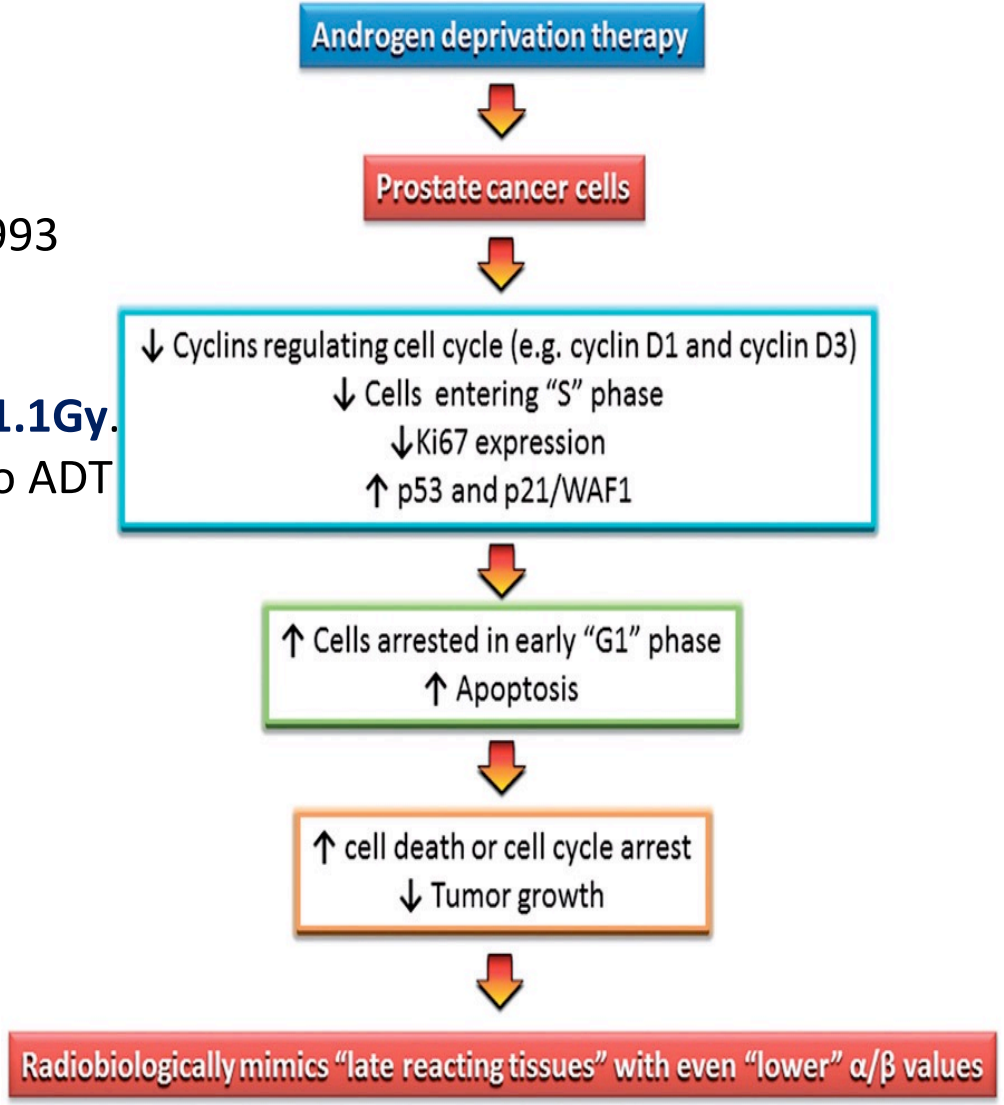
ORIGINAL ARTICLE

# Clinical estimation of α/β values for prostate cancer from isoeffective phase III randomized trials with moderately hypofractionated radiotherapy

Niloy R. Datta, Emanuel Stutz, Susanne Rogers and Stephan Bodis

usually assumed to be low (**1.0–1.8 Gy**)
Eight trials from seven studies, randomized 6993 patients between CRT and HRT

Clinically estimatedranged between**1.3 and 11.1Gy**.
The estimated values were inversely related to ADT usage



# Accelerated partial breast or whole breast irradiation after breast conservation surgery for patients with early breast cancer

## 10-year follow up results of the APBI IMRT Florence randomized phase 3 trial

**10-year cumulative IBTR incidence** in early breast cancer treated with **external APBI using IMRT** technique in **5 once-daily fractions (30 Gy in 5#)** is low and **not significantly different** from patients treated with CF-WBI

**Comparable LRR**, **DM**, **CBC**, **BCSS**, and **OS** rates

**Acute & Late toxicity** and **Cosmesis** evaluations significantly in **favor** of **APBI arm**

**APBI** might be considered a **standard alternative** to WBI in low risk early breast cancer patients

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RESEARCH ARTICLE

The Journal of Clinical Investigation

jci.org Volume 129 Number 2 February 2019

# Single-dose radiotherapy disables tumor cell homologous recombination via ischemia/reperfusion injury

Sahra Bodo,[1] Cécile Campagne,[1] Tin Htwe Thin,[1] Daniel S. Higginson,[1] H. Alberto Vargas,[2] Guoqiang Hua,[1] John D. Fuller,[3] Ellen Ackerstaff,[4] James Russell,[4] Zhigang Zhang,[5] Stefan Klingler,[3] HyungJoon Cho,[4] Matthew G. Kaag,[6] Yousef Mazaheri,[2] Andreas Rimner,[1] Katia Manova-Todorova,[7] Boris Epel,[8] Joan Zatcky,[1] Cristian R. Cleary,[1] Shyam S. Rao,[1] Yoshiya Yamada,[1] Michael J. Zelefsky,[1] Howard J. Halpern,[8] Jason A. Koutcher,[4] Carlos Cordon-Cardo,[9] Carlo Greco,[10] Adriana Haimovitz-Friedman,[1] Evis Sala,[2] Simon N. Powell,[1] Richard Kolesnick,[3] and Zvi Fuks[1,10]

[1]Department of Radiation Oncology, [2]Department of Radiology, [3]Laboratory of Signal Transduction, [4]Department of Medical Physics, [5]Department of Epidemiology and Biostatistics, [6]Department of Surgery,

ASMase-driven perfusion defects and consequent ROS/SSR–mediated HDR inactivation

ASMase-mediated microcirculatory vasoconstriction after SDRT

↓

ischemic stress response within parenchymal tumor cells

↓

ROS

↓

SUMO stress response

↓

depletion of chromatin- associated free SUMO3 (indispensable for HDR of DSBs)

24 Gy SDRT, but not 3×9 Gy fractionation, coupled early tumor ischemia/reperfusion to human cancer ablation.

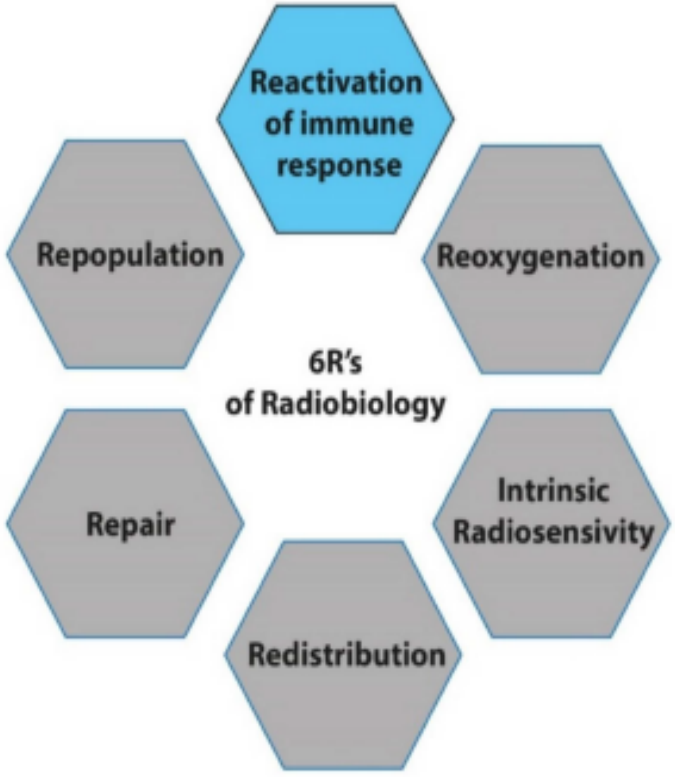
cancers

MDPI

*Review*

# The 6th R of Radiobiology: Reactivation of Anti-Tumor Immune Response

Jihane Boustani [1,†], Mathieu Grapin [1,†], Pierre-Antoine Laurent [1], Lionel Apetoh [2] and Céline Mirjolet [1,2,*]



# Importance of dose per fraction

Advances in Radiation Oncology (2018) 3, 486-493

advances
in radiation oncology

www.advancesradonc.org

Critical Review

## Generating antitumor immunity by targeted radiation therapy: Role of dose and fractionation

Eric C. Ko MD, PhD, Kimberly Thomas Benjamin MD, Silvia C. Formenti MD*

Postow MA, N Engl J Med. 2012;366:925- 31.
Hiniker SM, Transl Oncol. 2012;5:404-7.
Golden EB, Cancer Immunol Res. 2013;1:365-72
Claire Vanpouille-Box, *Clin Cancer Res* 2017.

In preclinical models:
6 Gy x5 (IFN gamma)
8 Gy x3 (IFN gamma)

Dose >10-12 Gy: immunosuppressive effects
20-30 Gy (Treg)

nature COMMUNICATIONS

ARTICLE

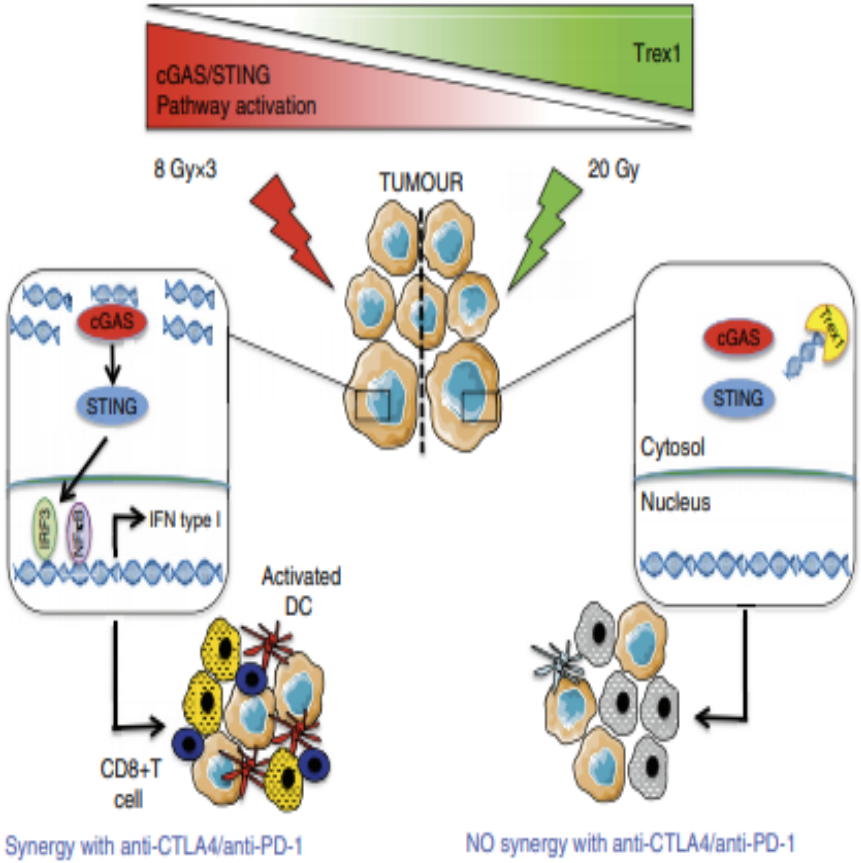
Received 27 Mar 2017 | Accepted 12 Apr 2017 | Published 9 Jun 2017

DOI: 10.1038/ncomms15618 OPEN

# DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity

Claire Vanpouille-Box[1], Amandine Alard[2,†], Molykutty J. Aryankalayil[3], Yasmeen Sarfraz[1], Julie M. Diamond[1], Robert J. Schneider[2], Giorgio Inghirami[4], C. Norman Coleman[3], Silvia C. Formenti[1] & Sandra Demaria[1,4]






# Tumori dell’ Encefalo

Neuro-Oncology
21(9), 1175–1183, 2019 | doi:10.1093/neuonc/noz068 | Advance Access date 12 April 2019

**Association between hippocampal dose and memory in survivors of childhood or adolescent low-grade glioma: a 10-year neurocognitive longitudinal study**

80 patients (6 -21 years )with LGG treated with RT to 54 Gy on a phase II trial

1. Survivors of pediatric low-grade gliomas experience decline in memory.
2. Greater hippocampal dose is associated with greater decline in memory.
3. Reducing hippocampal dose may represent a memory preserving treatment strategy.

**avoid hippocampal doses equal to or greater than 40 Gy**

Acharya et al. Neurooncol 2019, 21(9), 1175–1183

National Comprehensive Cancer Network®

# NCCN Guidelines Version 1.2019
# Central Nervous System Cancers

NCCN Guidelines Index
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Discussion

## PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

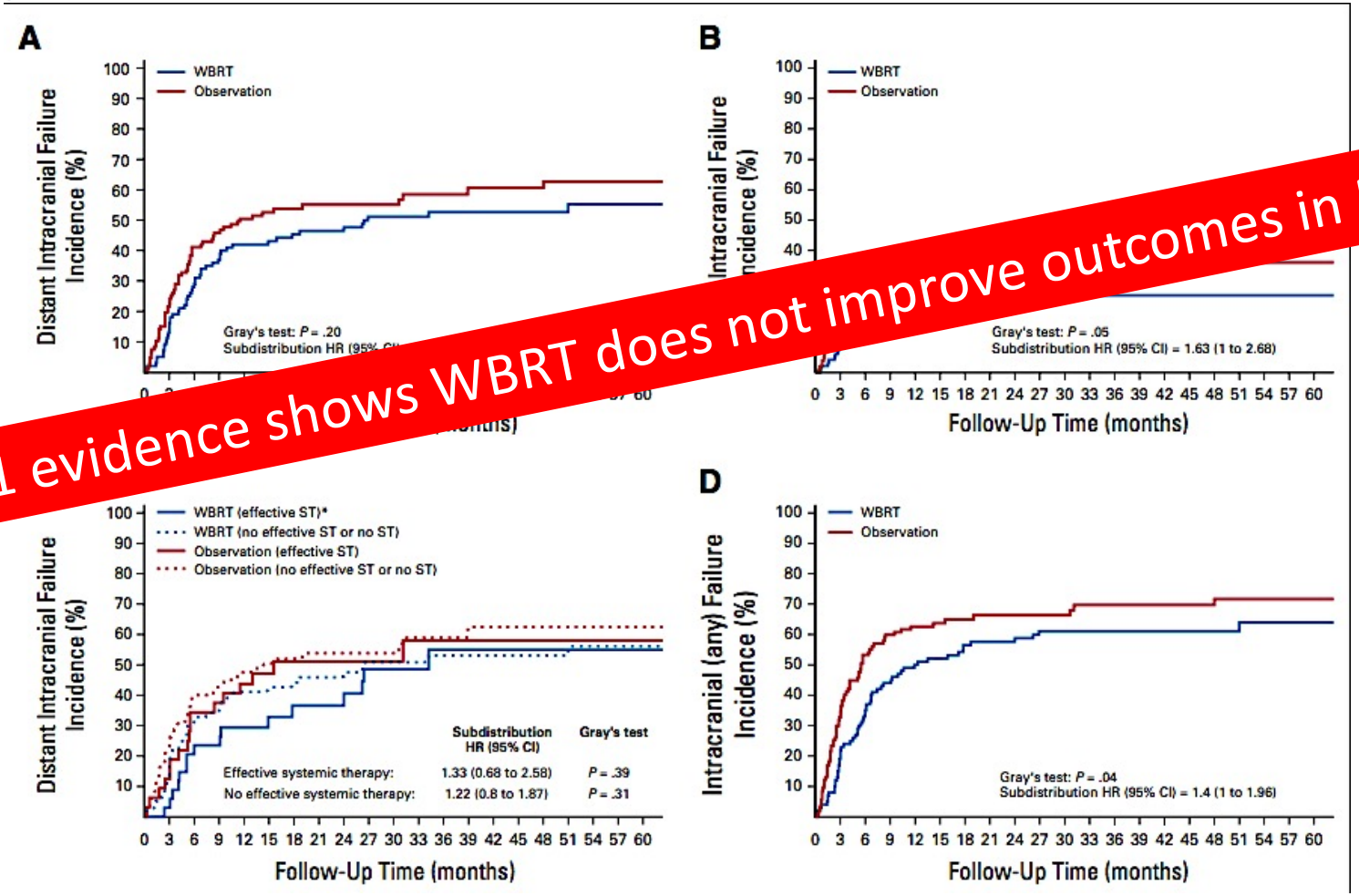
**Brain Metastases**

- WBRT: Doses vary between 20 and 40 Gy delivered in 5–20 fractions.
  - The standard regimens include 30 Gy in 10 fractions or 37.5 Gy in 15 fractions.
  - Nevertheless, 20 Gy in 5 fractions is a good option for patients with poor predicted prognosis.[19]
  - For patients with a better prognosis, consider memantine during and after WBRT for a total of 6 months.[20]
  - For patients with a better prognosis (4 months or greater), consider hippocampal-sparing WBRT.[21-22]

**For brain metastasis patients eligible to receive WBRT and whose survival is expected to be 4 months or longer, hippocampal avoidance using IMRT should be considered standard of care.**

original report

# Adjuvant Whole-Brain Radiation Therapy Compared With Observation After Local Treatment of Melanoma Brain Metastases: A Multicenter, Randomized Phase III Trial




This level-1 evidence shows WBRT does not improve outcomes in MBMs

Hong et al. 2019

JAMA | Original Investigation

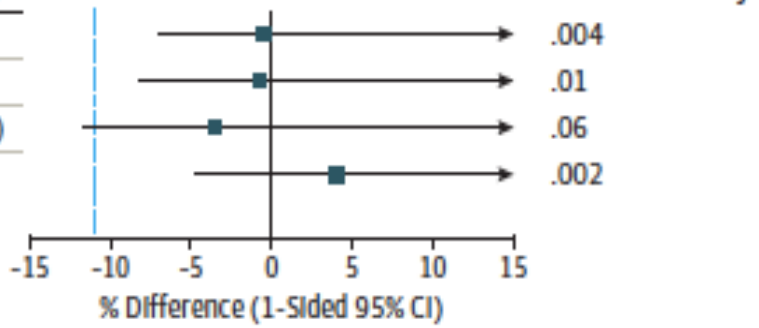
# Effect of Single-Fraction vs Multifraction Radiotherapy on Ambulatory Status Among Patients With Spinal Canal Compression From Metastatic Cancer

## The SCORAD Randomized Clinical Trial

- Eligible patients (n = 686) had metastatic cancer with spinal cord or cauda equina compression, life expectancy > 8 weeks, and no previous RT to the same area
- External beam 8Gy/1 fr RT (n 345) vs 20Gy/5 fr RT over 5 consecutive days (n341)

SF-RT is not non-inferior to MF-RT in patients with SCC from solid tumors

| | Single-Fraction Group | | Multifraction Group | | |
|---|---|---|---|---|---|
| Follow-up, wk | No. of Patients | Patients With Ambulatory Status Grade 1-2, No. (%) | No. of Patients | Patients With Ambulatory Status Grade | |
| 1 | 294 | 188 (63.9) | | | -0.4 (-6.9 to ) |
| 4 | 214 | | | (67.6) | -0.7 (-8.1 to ) |
| 8 | | | 176 | 128 (72.7) | -3.5 (-11.5 to ) |
| | | 102 (71.8) | 158 | 107 (67.7) | 4.1 (-4.6 to ) |

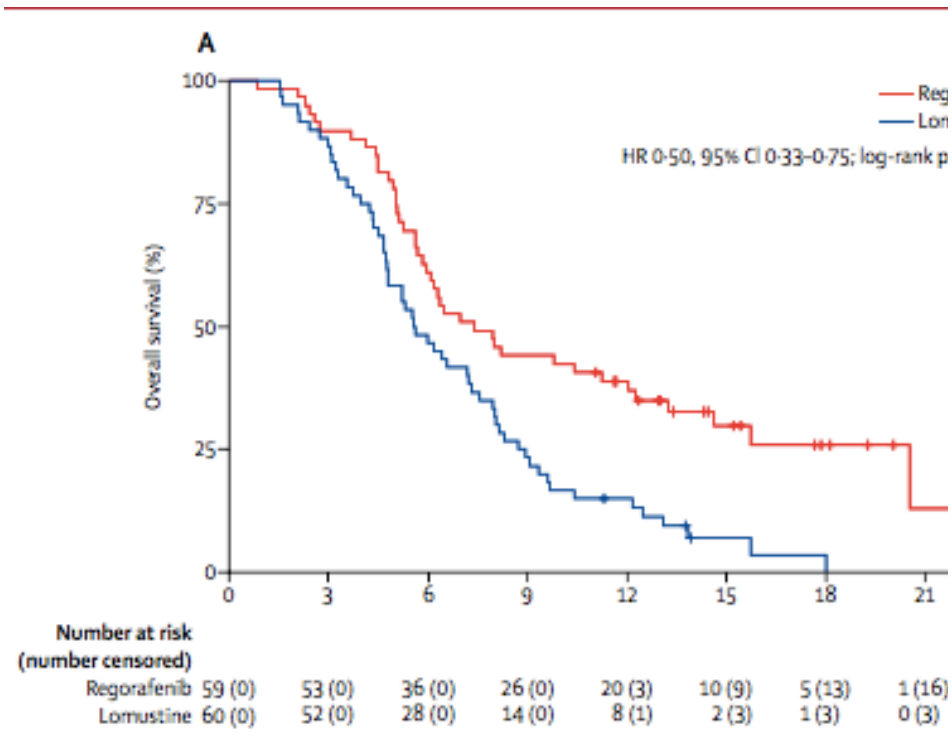


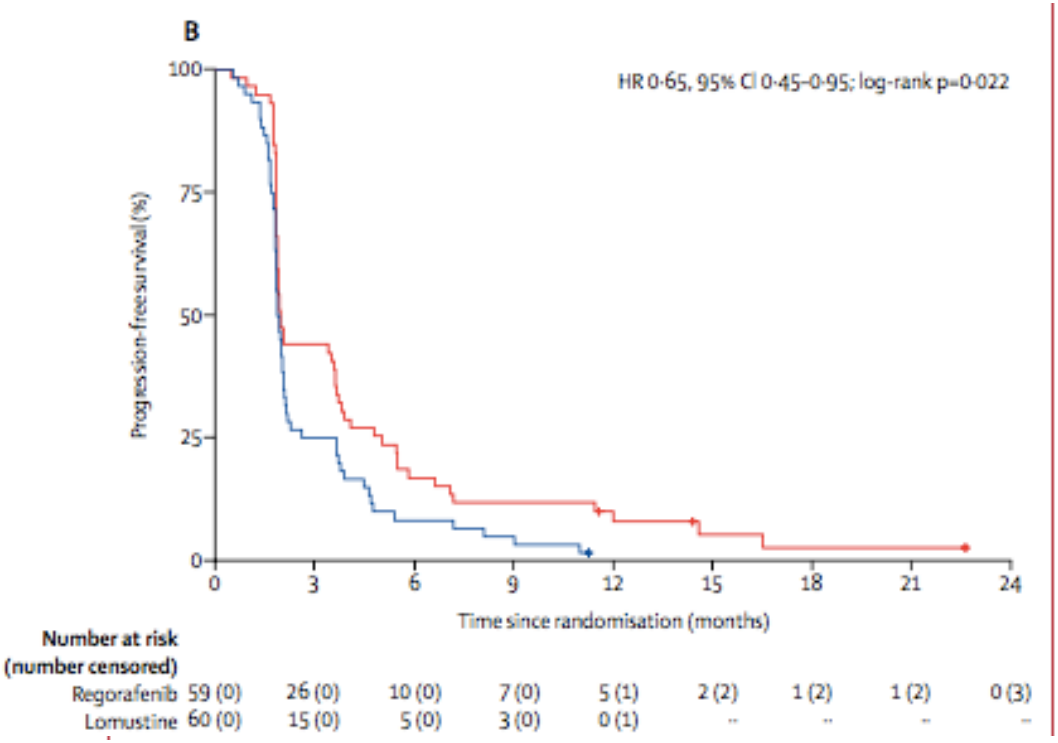

Hoskin et al. 2019

# Regorafenib compared with lomustine in patients with relapsed glioblastoma (REGOMA): a multicentre, open-label, randomised, controlled, phase 2 trial

*Giuseppe Lombardi, Gian Luca De Salvo, Alba Ariela Brandes, Marica Eoli, Roberta Rudà, Marina Faedi, Ivan Lolli, Andrea Pace, Bruno Daniele, Francesco Pasqualetti, Simona Rizzato, Luisa Bellu, Ardi Pambuku, Miriam Farina, Giovanna Magni, Stefano Indraccolo, Marina Paola Gardiman, Riccardo Soffietti, Vittorina Zagonel*

Lancet Oncol 2019




**Lombardi et al. 2019**

# Tumori Testa-Collo

# De-intensificazione della terapia

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

*Gillison M.L 2019*

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

*Mehanna H. 2019*

Phase II Trial of De-Intensified Chemoradiotherapy for Human Papillomavirus–Associated Oropharyngeal Squamous Cell Carcinoma

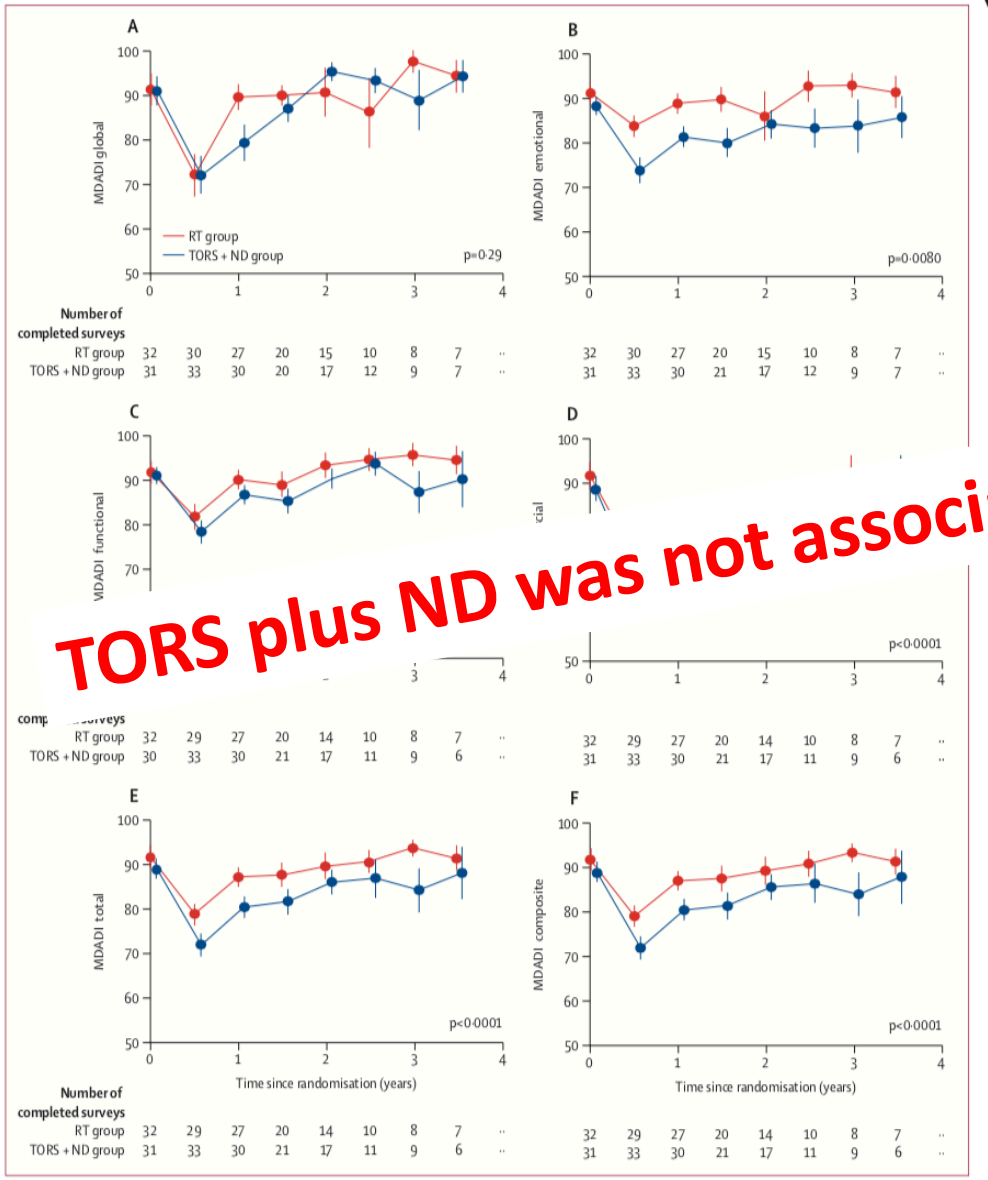
*Chera B.S. 2019*

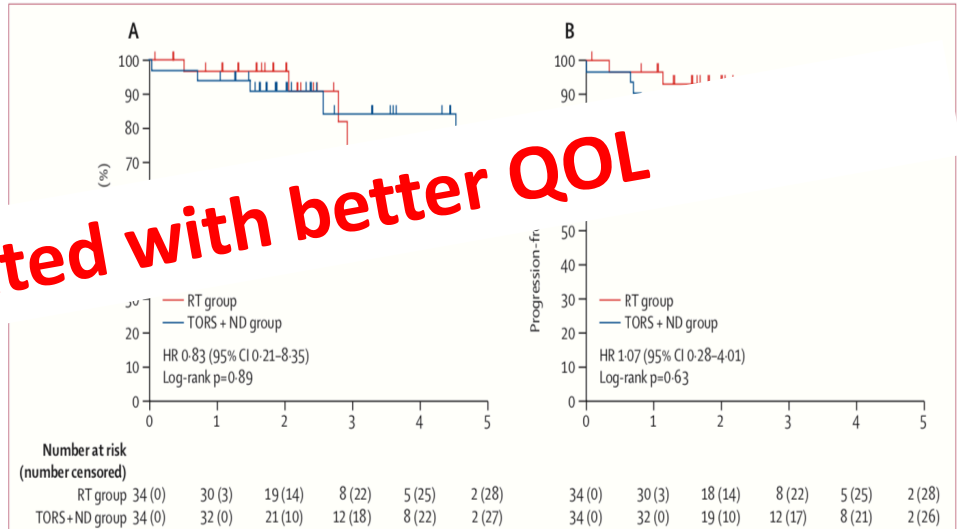
Phase II Evaluation of Aggressive Dose De-Escalation for Adjuvant Chemoradiotherapy in Human Papillomavirus–Associated Oropharynx Squamous Cell Carcinoma

*Ma D.J. 2019*

THE LANCET Oncology

# Radiotherapy versus transoral robotic surgery and neck dissection for oropharyngeal squamous cell carcinoma (ORATOR): an open-label, phase 2, randomised trial




**TORS plus ND was not associated with better QOL**

Nichols A.J. 2019

# Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma

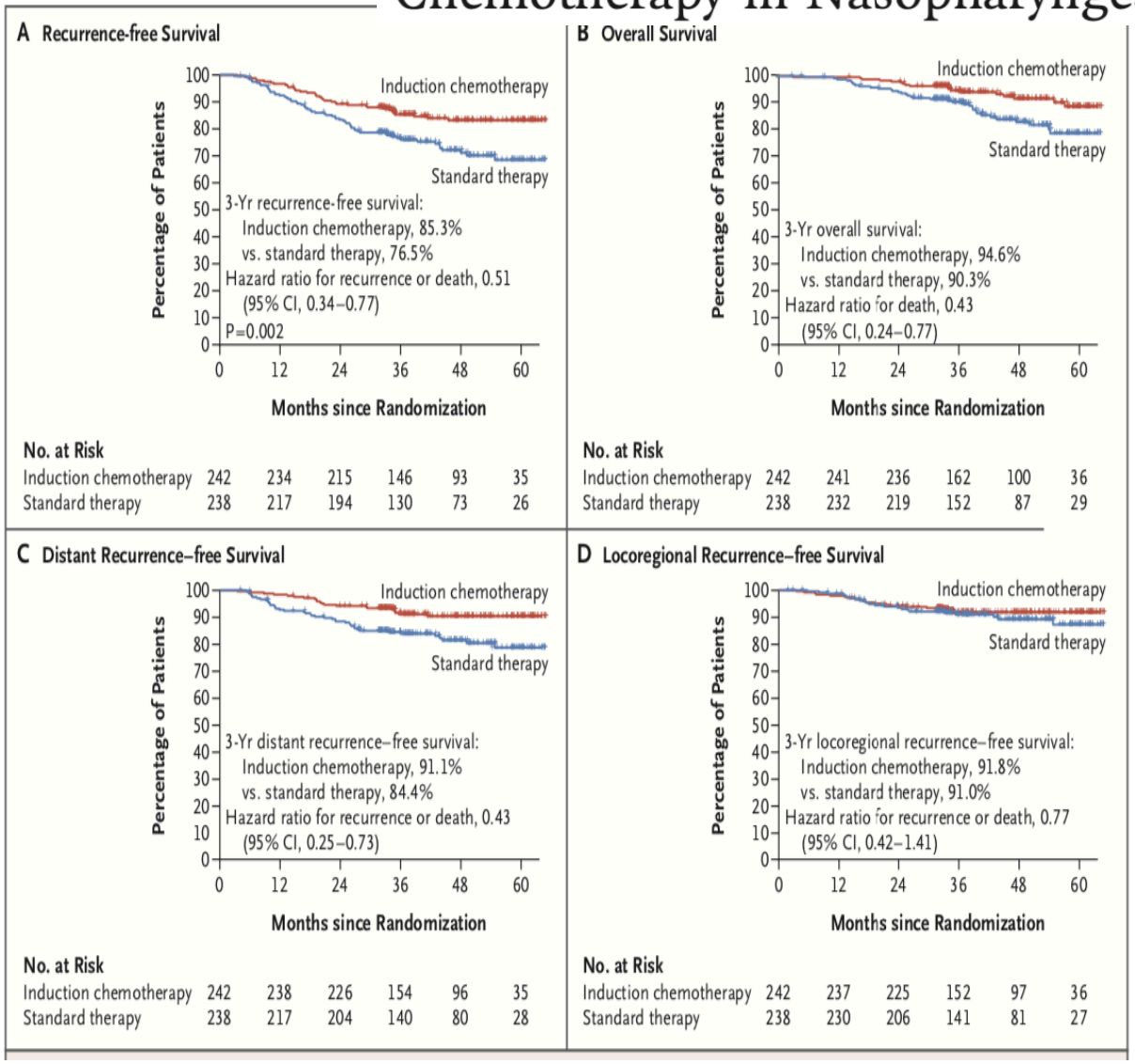
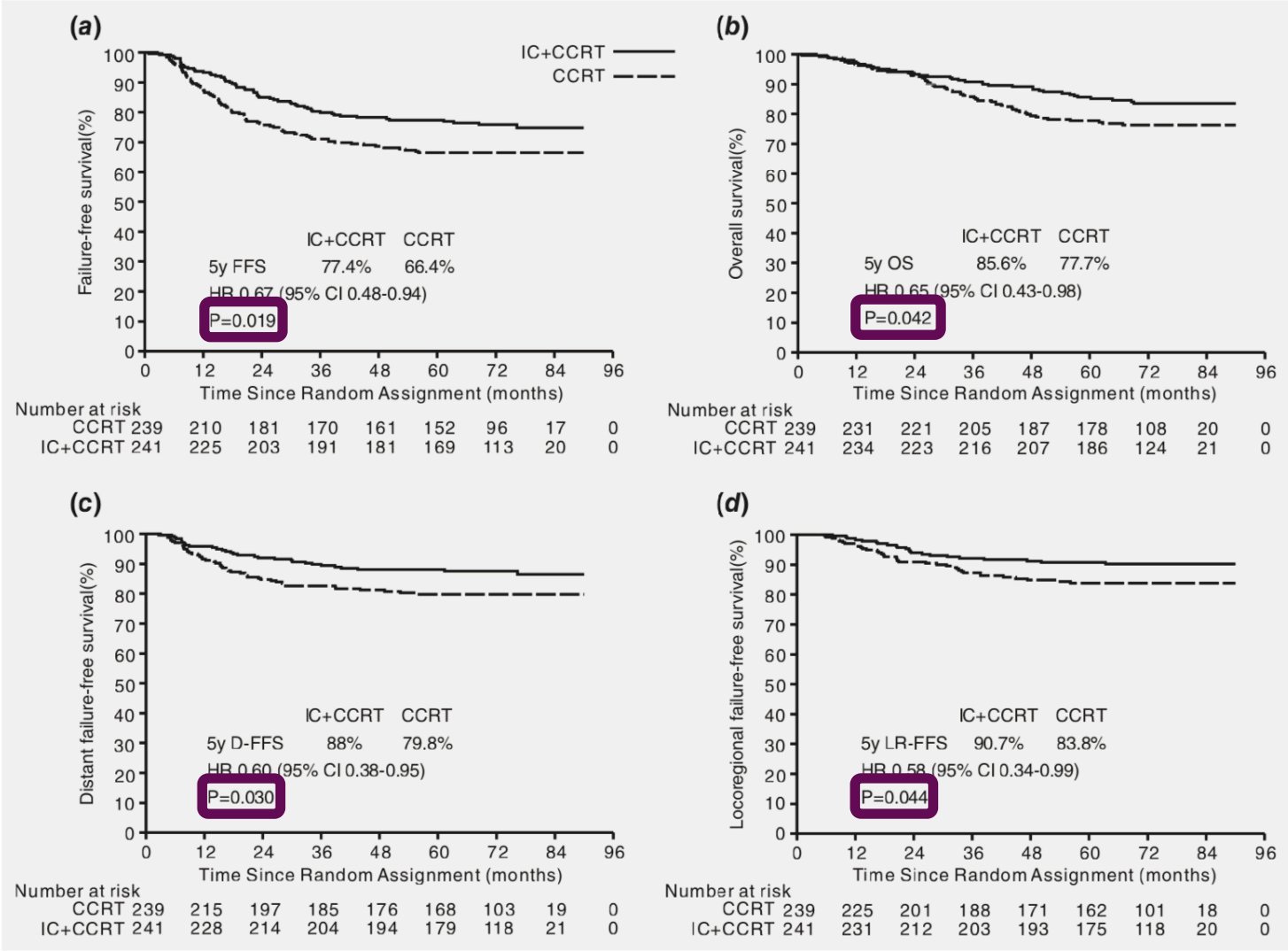



Table 2. Survival and Response to Treatment.*

| Variable | Induction Chemotherapy (N=242) | Standard Therapy (N=238) | Hazard Ratio (95% CI) |
|---|---|---|---|
| Recurrence-free survival | | | |
| Recurrence or death — no. (%) | 37 (15.3) | 63 (26.5) | |
| Percentage of patients alive and without recurrence at 3 yr (95% CI) | 85.3 (80.0–89.3) | 76.5 (70.4–81.5) | 0.51 (0.34–0.77) |
| Overall survival | | | |
| Death — no. (%) | 18 (7.4) | 35 (14.7) | |
| Percentage of patients alive at 3 yr (95% CI) | 94.6 (90.6–96.9) | 90.3 (85.6–93.5) | 0.43 (0.24–0.77) |
| Distant recurrence–free survival | | | |
| Distant metastasis or death — no. (%) | 23 (9.5) | 40 (16.8) | |
| Percentage of patients alive and without distant metastasis at 3 yr (95% CI) | 91.1 (86.4–94.2) | 84.4 (79.1–88.5) | 0.43 (0.25–0.73) |
| Locoregional recurrence–free survival | | | |
| Locoregional recurrence or death — no. (%) | 17 (7.0) | 22 (9.2) | |
| Percentage of patients alive and without locoregional recurrence at 3 yr (95% CI) | 91.8 (87.3–94.7) | 91.0 (86.2–94.0) | 0.77 (0.42–1.41) |
| Response to induction chemotherapy† | | | |
| Complete response — no./total no. (%) | 24/239 (10.0) | — | |
| Partial response — no./total no. (%) | 202/239 (84.5) | — | |
| Stable disease — no./total no. (%) | 10/239 (4.2) | — | |
| Progressive disease — no./total no. (%) | 3/239 (1.3) | — | |
| Response to whole treatment — no. (%) | | | |
| Complete response | 235 (97.1) | 230 (96.6) | |
| Partial response | 2 (0.8) | 5 (2.1) | |
| Progressive disease | 1 (0.4) | 1 (0.4) | |
| Could not be assessed | 4 (1.7) | 2 (0.8) | |

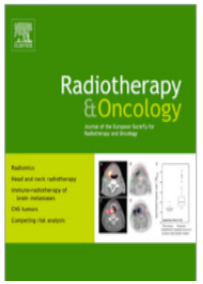
Zhang Y. 2019

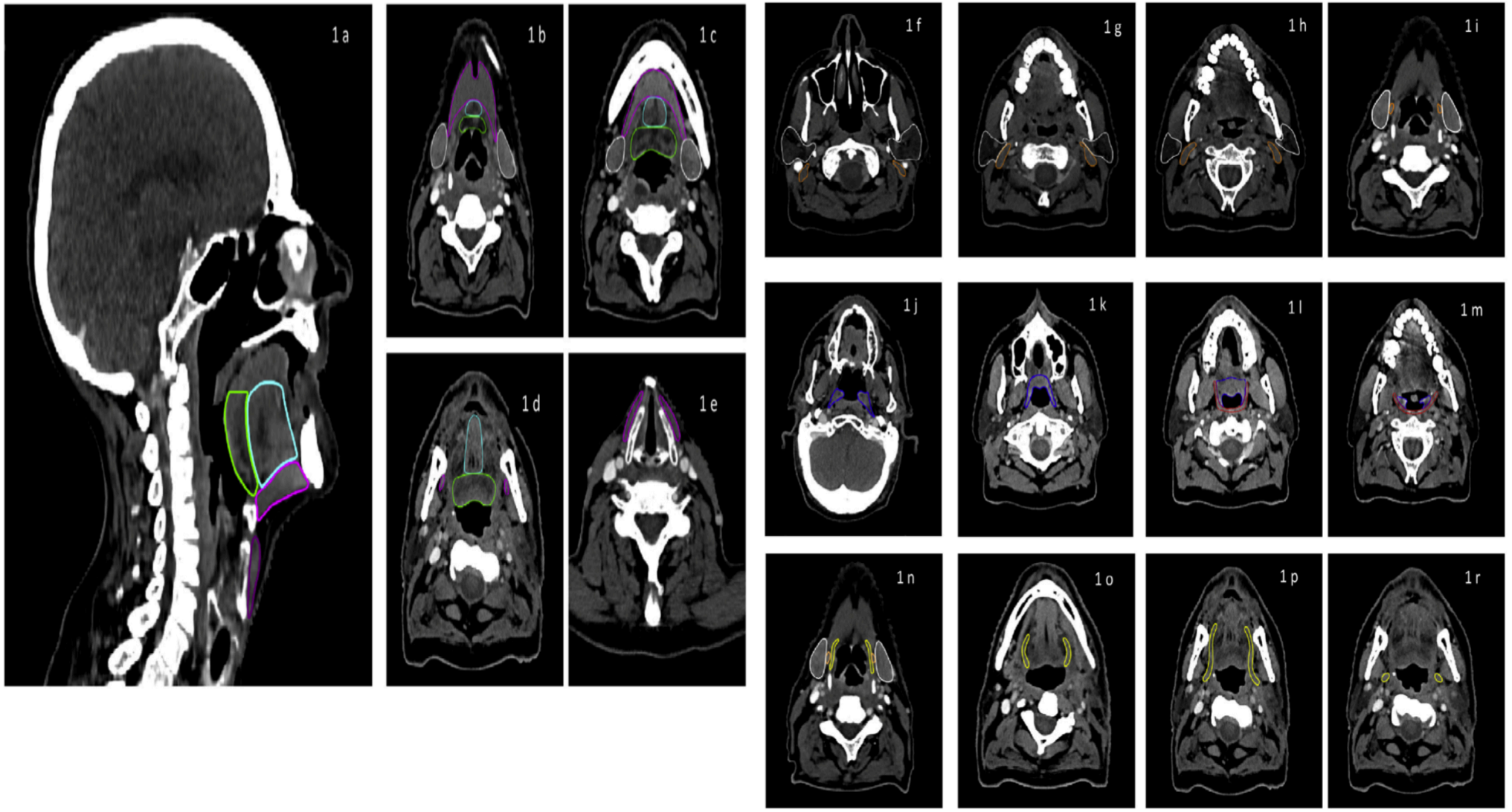

# Concurrent chemoradiotherapy with/without induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma: Long-term results of phase 3 randomized controlled trial




Li W.F. 2019

# Functional Swallowing Units (FSUs) as organs-at-risk for radiotherapy. PART 2: Advanced delineation guidelines for FSUs



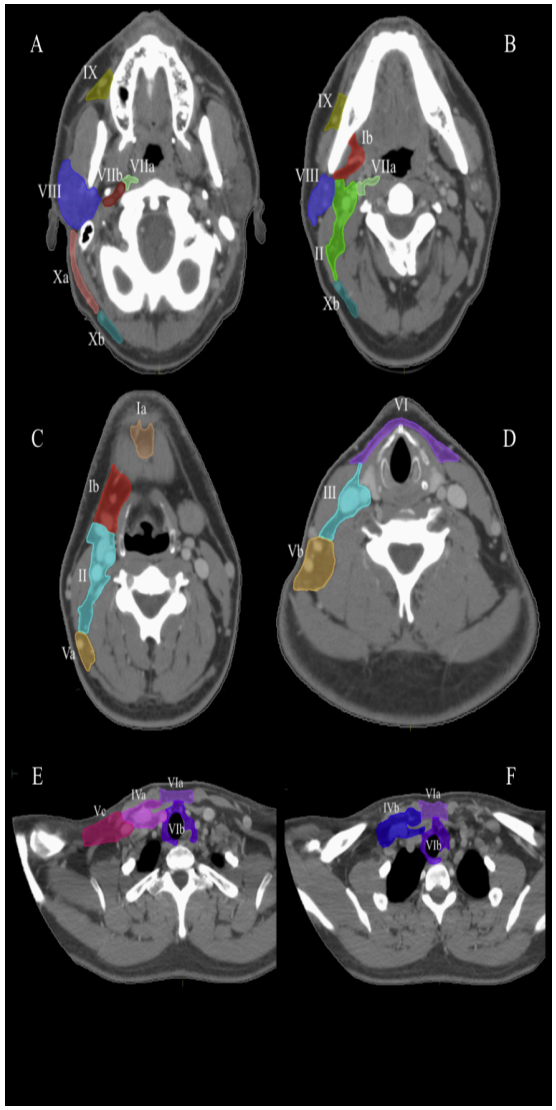




Gawryszuk A. 2019

# Selection of lymph node target volumes for definitive head and neck radiation therapy: a 2019 Update


Raccomandazioni per i livelli linfonodali da includere sia per N+ che per N- in base alla sottosede anatomica di localizzazione della malattia

**8th edition**
**UICC/AJCC**
**TNM**




## Robbins' classification

Livelli:

- Ia(sottomentonieri)
- Ib (sottomandibolari)
- II (giugulari sup)
- III (giugulari medi)
- IVa (giugulari inferiori)
- IVb (sovraclaveari mediali)
- Va and Vb (del triangolo posteriore sup. ed inf.)
- Vc (sovraclaveari laterali)
- VIa (giugulari ant)
- VIb (prelaringei, pretracheali, paratracheali)
- VIIa (retrofaringei)
- VIIb (retro-stiloidei)
- VIII (parotidei)
- IX (buccofaciali)
- Xa (retroauricolari and subauriculari)
- Xb (occipitali)

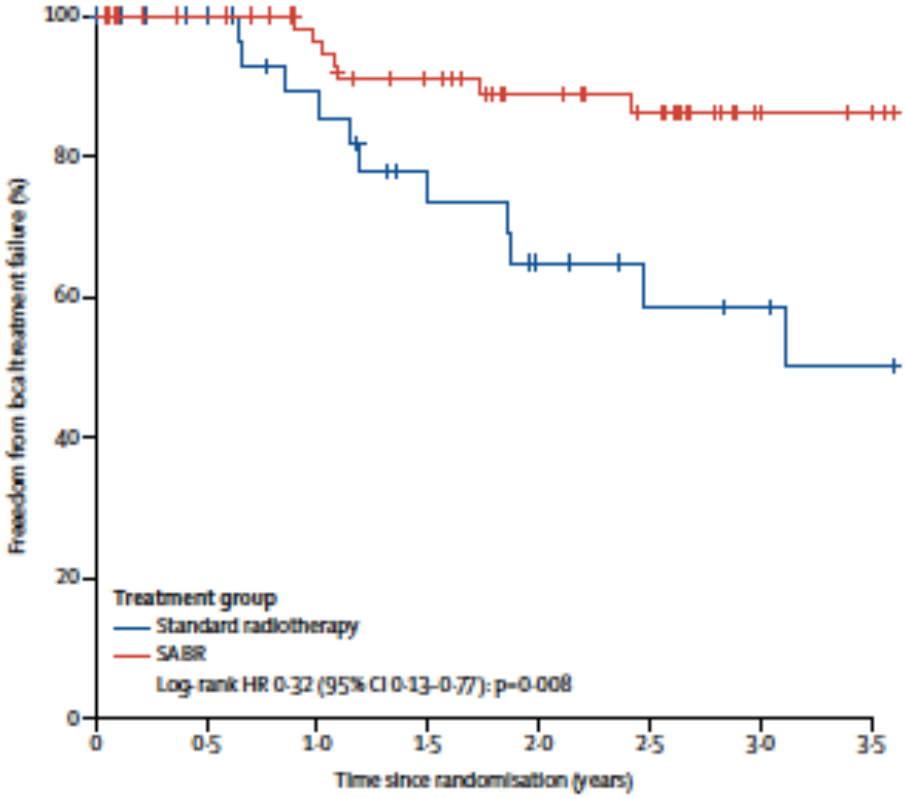
**Biau J. 2019**

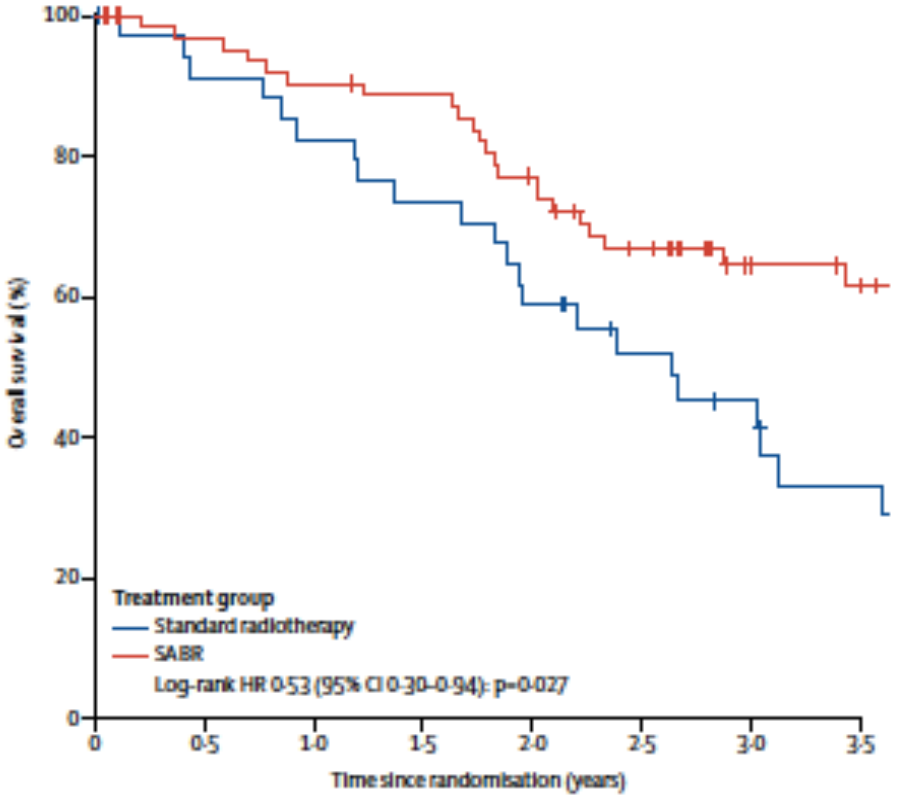
# Tumori del Torace

# Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial

Lancet Oncol 2019; 20: 494–503

SABR (54 Gy/3 fx or 48 Gy/4 fx) vs standard RT (66 Gy/33 fx or 50 Gy/20 fx)




Ball et al. 2019

Surgery is superior to SBRT in terms of:
Overall su

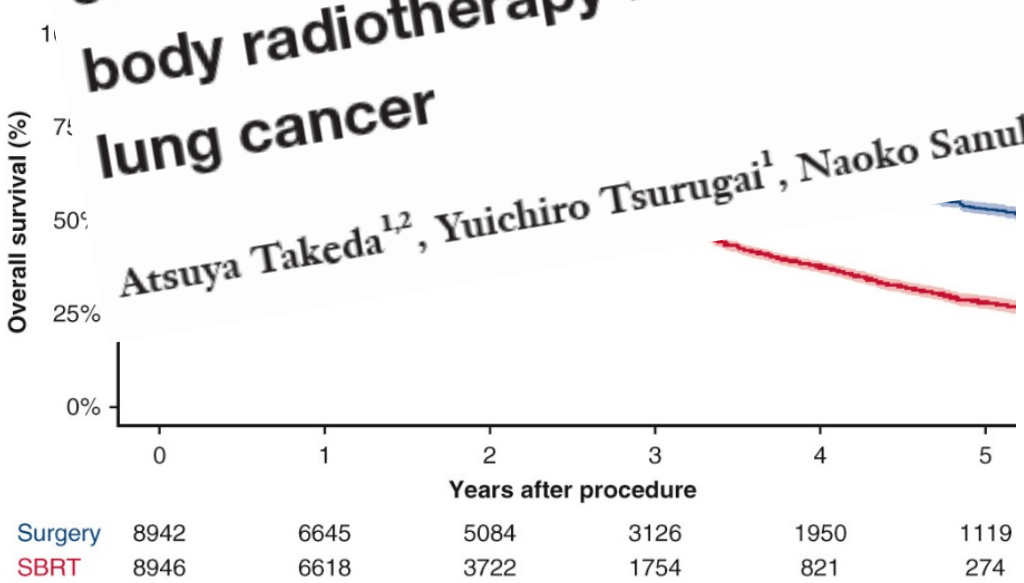
The Journal of Thoracic and Cardiovascular Surgery
JTCVS
AATS
< Previous Article January 2019 Volume 157, Issue 1, Pages 362–373.e8 Next Article >

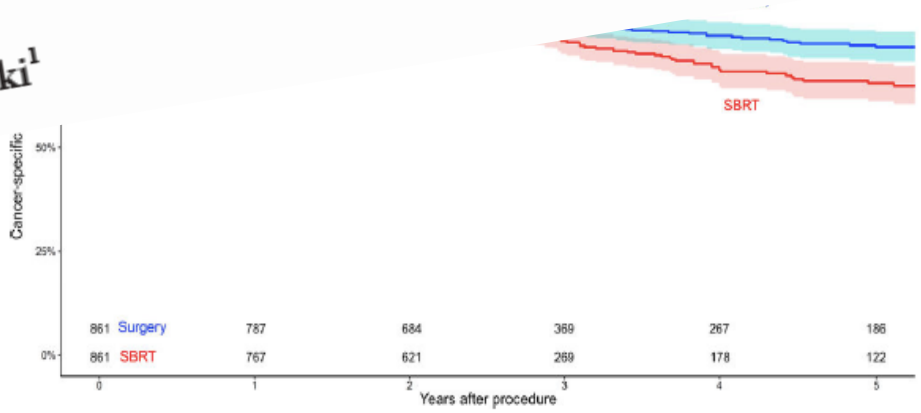
A systematic review and meta
radiation th

Editorial Commentary

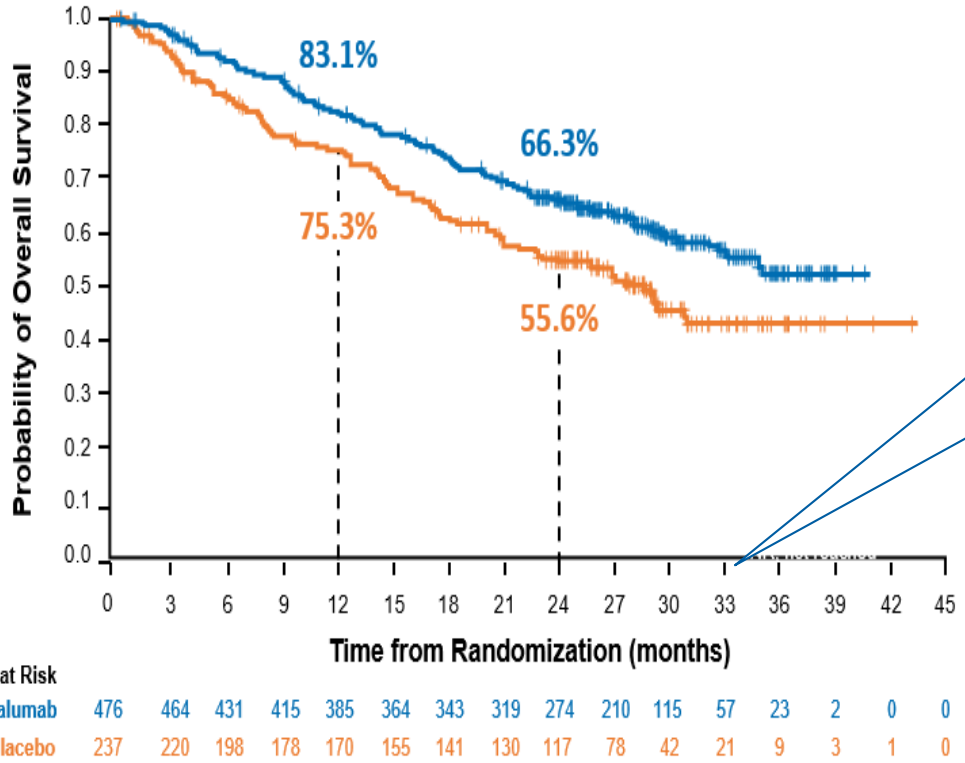
# Substantial imbalance that is never eliminated with propensity score matched analyses in comparing surgery to stereotactic body radiotherapy for patients with early-stage non-small cell lung cancer

Atsuya Takeda[1,2], Yuichiro Tsurugai[1], Naoko Sanuki[1]



# Overall Survival* (ITT)




**ASCO 2019**

Update from the PACIFIC trial

**3-y OS: 57.0% versus 43.5%**

**MS: NR versus 29,1 mo**

| | No. of events / No. of patients (%) | Median OS (95% CI) months |
|---|---|---|
| Durvalumab | 183/476 (38.4) | NR (34.7–NR) |
| Placebo | 116/237 (48.9) | 28.7 (22.9–NR) |

Scott JA et al, NEJM 2018

Scott JA et al, NEJM 2017

National Comprehensive Cancer Network®

**NCCN Guidelines Version 2.2020**
**Non-Small Cell Lung Cancer**

NCCN Guidelines Index
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Discussion

**Consolidation Therapy for Patients with Unresectable Stage III NSCLC, PS 0-1, and No Disease Progression After 2 or More Cycles of Definitive Chemoradiation**

**Durvalumab 10 mg/kg IV every 2 weeks for up to 12 months[7] (category 1)**

*Regimens can be used as preoperative/adjuvant chemotherapy/RT.
†Regimens can be used as definitive concurrent chemotherapy/RT.
‡Durvalumab may be used after any of the concurrent chemo/RT regimens listed above for eligible patients.

# Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

Lancet Oncol 2019

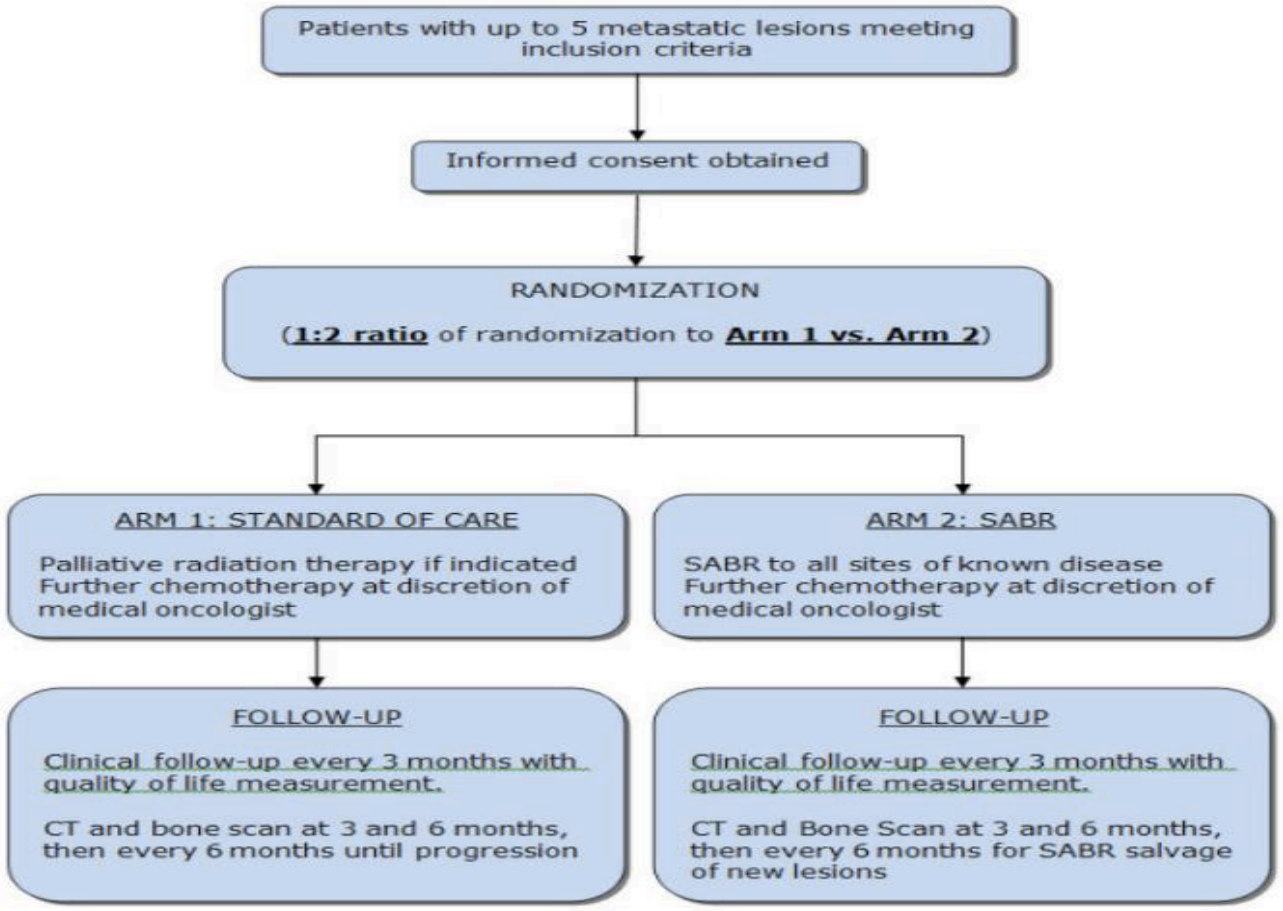


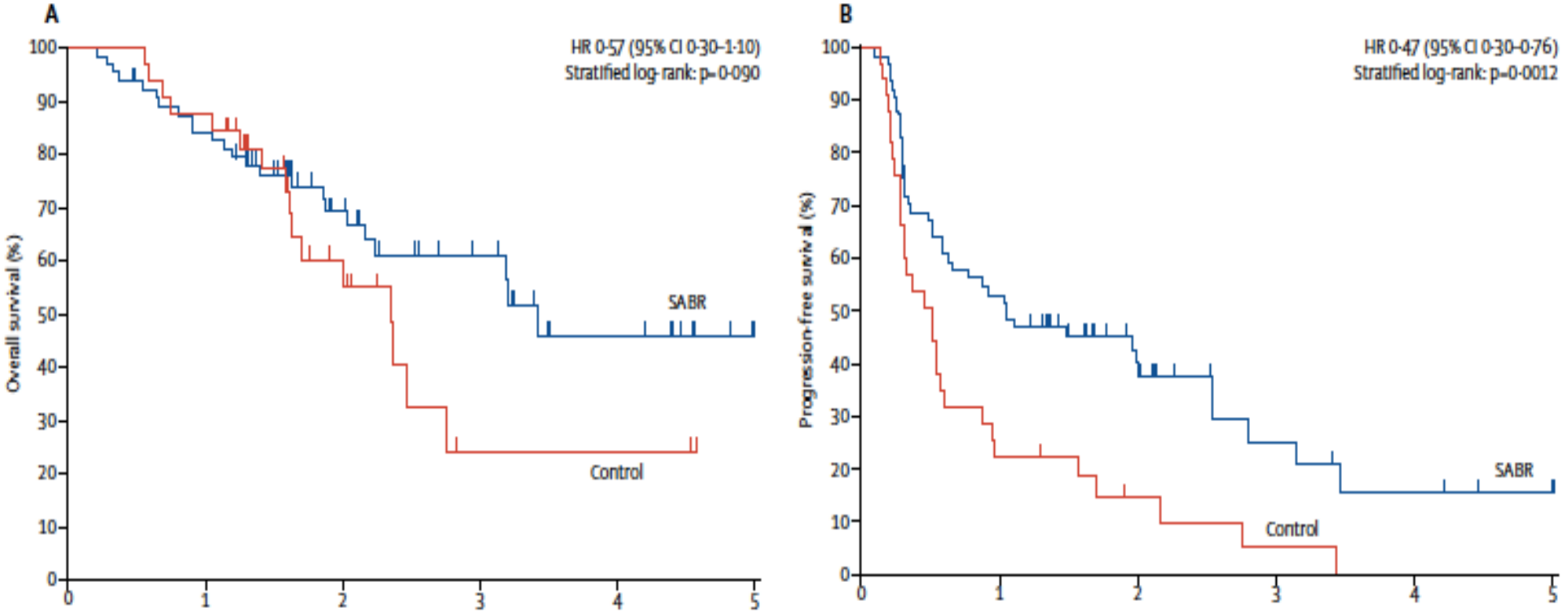

Figure 1
**Study design.** Patients with be randomized in a 1:2 ratio between Arm 1 (Standard of care) vs. Arm 2 (SABR).

**Palma et al. 2019**

# Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

*Lancet Oncol* 2019

Median follow up: 26 months




**Palma et al. 2019**

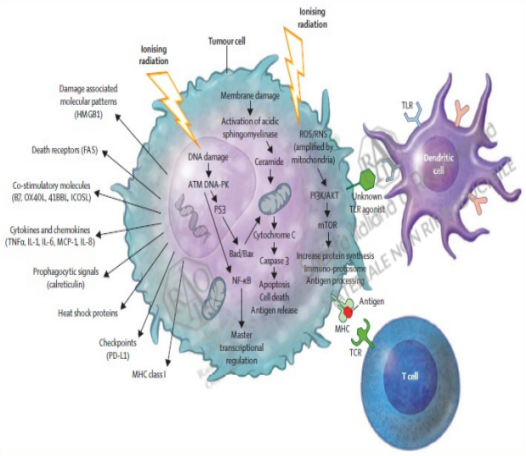
# Final Results of a Phase II Prospective Trial Evaluating the Combination of Stereotactic Body Radiotherapy (SBRT) with Concurrent Pembrolizumab in Patients with Metastatic Non-Small Cell Lung Cancer (NSCLC)

A.M. Campbell[1], W.L. Cai[1], D. Burkhardt[2], S.N. Gettinger[3], S.B. Goldberg[4], M. Amodio[2], S. Kaech[5], S. Krishnaswamy[2], R.H. Decker[6]

74

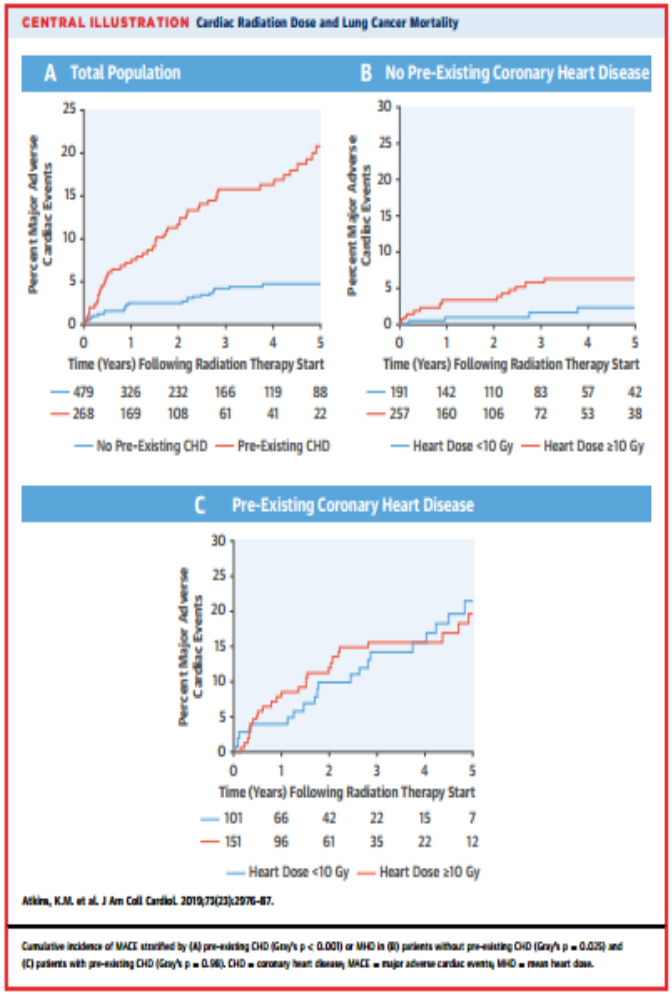

**2019 ASTRO Annual Meeting**

- Patients (56) with metastatic non–small cell lung cancer (NSCLC) who have experienced disease progression on immunotherapy may benefit from stereotactic body radiotherapy (SBRT) in terms of progression-free survival
- The addition of SBRT after progression on immunotherapy resulted in increased PFS, a systemic response rate of 9.52%, and a disease control rate of 57.14%
- Improved PFS correlated with an increased TIL score: pts with elevated TIL scores (2-3) showed improved progression free survival (PFS), with a mean of 215 versus 59 days



JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 73, NO. 23, 2019
© 2019 THE AUTHORS. PUBLISHED BY ELSEVIER ON BEHALF OF THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY-NC-ND LICENSE (http://creativecommons.org/licenses/by-nc-nd/4.0/).

# Cardiac Radiation Dose, Cardiac Disease, and Mortality in Patients With Lung Cancer




Cumulative incidence of MACE stratified by (A) pre-existing CHD (Gray's $p < 0.001$) or MHD in (B) patients without pre-existing CHD (Gray's $p = 0.025$) and (C) patients with pre-existing CHD (Gray's $p = 0.98$). CHD = coronary heart disease; MACE = major adverse cardiac events; MHD = mean heart dose.

- Il 10,3% dei pazienti ha sviluppato ≥1 MACE (major cardiac adverse event), evento più probabile nei pazienti positivi per coronaropatie (coronary heart disease, CHD; 18,7% vs. 5,6%; P> 0,0001)
- Nei pazienti CHD-negativi il trattamento con MHD ≥10 Gy rispetto a <10 Gy era associato a un rischio signicativamente maggiore di MACE (HR: 3,01; P=0,025) e di mortalità per qualunque causa (HR: 1,34; P=0,014).

La MHD è un predittore indipendente di MACE e di mortalità per qualunque causa entro 2 anni dalla radioterapia

Constraints:

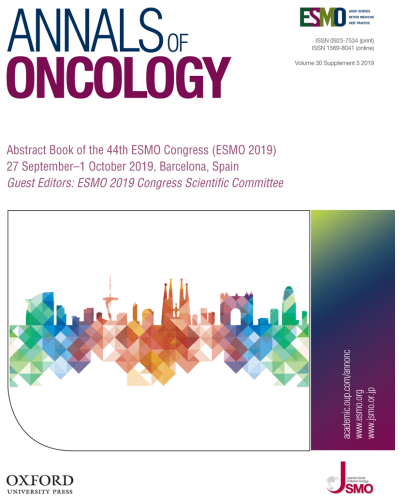
**MHD< 15 Gy V50< 25% V5≤ 60%**

**Atkins K.M. 2019**

**LBA89**

# PD-L1 expression, patterns of progression and patient-reported outcomes (PROs) with durvalumab plus platinum-etoposide in ES-SCLC: Results from CASPIAN

L. Paz-Ares[1], J.W. Goldman[2], M.C. Garassino[3], M. Dvorkin[4], D. Trukhin[5], G. Statsenko[6], K. Hotta[7], J.H. Ji[8], M.J. Hochmair[9], O. Voitko[10], L. Havel[11], A. Poltoratskiy[12], G. Losonczy[13], N. Reinmuth[14], Y. Shrestha[15], N. Patel[16], H. Mann[17], H. Jiang[18], M. Özgüroğlu[19], Y. Chen[20]




Una minoranza di pazienti con ES-SCLC ottiene un beneficio clinicamente rilevante dall'immunoterapia

L'espressione di PD-L1 è bassa e non ha alcun effetto significativo sugli esiti clinici (no biomarkers)

Trattare tutti i pazienti è costoso rispetto ai benefici ottenuti ed espone i pazienti a tossicità inutili

JAMA Network Open

Research Letter | Oncology

# Evolving Practice Patterns in the Use of Prophylactic Cranial Irradiation for Extensive-Stage Small Cell Lung Cancer

Olsi Gjyshi, MD, PhD; Ethan B. Ludmir, MD; Todd A. Pezzi, MD, MBA; David Boyce-Fappiano, MD; Amy E. Dursteler, MD; Timur Mitin, MD, PhD; Steven H. Lin, MD, PhD

Lancet Oncol. 2017 May;18(5):663-671. doi: 10.1016/S1470-2045(17)30230-9. Epub 2017 Mar 23.

**Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial.**

Takahashi T[1], Yamanaka T[2], Seto T[3], Harada H[4], Nokihara H[5], Saka H[6], Nishio M[7], Kaneda H[8], Takayama K[9], Ishimoto O[10], Takeda K[11], Yoshioka H[12], Tachihara M[13], Sakai H[14], Goto K[15], Yamamoto N[16].

Linee Guida NCCN: **equivalenza tra la sorveglianza con RM e PCI nell'ES-SCLC**

**Survey ASTRO** (569 su 3851 soci) sull'uso di PCI conseguente allo studio Takahashi, Lancet Oncol. 2017

L'uso di PCI tra i medici che conoscevano lo studio è diminuito dal 72% al 44%(pre vs post-pubblicazione)

Il tasso di continuazione dell'uso di PCI era dell'85% tra i medici che non conoscevano lo studio del 2017

- **il 47% dei rispondenti arruolerebbe pazienti affetti da SCLC in stadio limitato ed ES-SCLC**;
- il 15% arruolerebbe solo pazienti affetti da SCLC in stadio limitato;
- il 20% arruolerebbe solo pazienti affetti da ES-SCLC

# Pleural Mesothelioma – Role of Radiotherapy

## Radical Hemi-thoracic Radiotherapy vs. Palliative Radiotherapy for Malignant Pleural Mesothelioma

- Phase 3 study, 108 pts were randomized
- Radical hemithoracic radiotherapy (RHR) with IMRT and PET-guidance, to deliver up to 50 to 60 Gy, in patients undergoing non-radical lung-sparing surgery and chemotherapy
- Total mean lung dose < 22 Gy
- The intention-to-treat analysis showed a 2- year OS rate of 58% in the RHR arm vs. 28% in the PR arm (p=0.003)
- RHR **doubles survival** compared with palliative radiotherapy in patients with malignant pleural mesothelioma (MPM)
- Toxicity: G 3-4 pneumonitis in 5 pts

[Minatel E, Trovo M et al, ESTRO 38 – 2019, *Abstract OC-0500]*

# Sarcomi Tessuti molli


# STRASS (EORTC 62092): A phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma.

Sylvie Bonvalot, Alessandro Gronchi, Cecile Le Pechoux, Carol Jane Swallow, Dirk C. Strauss, Pierre Meeus, Frits van Coevorden, Stephan Stoldt, Eberhard Stoeckle, Piotr Rutkowski, Claudia Sangalli, Charles Honoré, Marco Rastrelli, Chandrajit Raut, Peter Chung, Marco Fiore, Saskia Litiere, Sandrine Marreaud, Hans Gelderblom, Rick L.M. Haas

266 pts affected by retroperitoneal sarcoma [198 (74.5%) Liposarcoma]

Patients were randomized 1:1

preoperative RT (3D-CRT or IMRT) 50.4 Gy followed by surgery (RT/S group)

surgery alone (S group)

Primary endpoint abdominal relapse free survival (ARFS)

3-year ARFS 66.0% in RT/S vs. 58.7% in S group (HR = 0.84, p=0.340)

In liposarcoma group 3-year ARFS 71.6% in RT/S and 60.4% in S group (HR = 0.64, p =0.049)

EClinicalMedicine 9 (2019) 35–43

Contents lists available at ScienceDirect

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EClinicalMedicine
Published by THE LANCET

Research Paper

# Trabectedin and RAdiotherapy in Soft Tissue Sarcoma (TRASTS): Results of a Phase I Study in Myxoid Liposarcoma from Spanish (GEIS), Italian (ISG), French (FSG) Sarcoma Groups

Alessandro Gronchi [a,*], Nadia Hindi [b,c], Josefina Cruz [d], Jean-Yves Blay [e], Antonio Lopez-Pousa [f], Antoine Italiano [g], Rosa Alvarez [h], Antonio Gutierrez [i], Inmaculada Rincón [c], Claudia Sangalli [a], Jose Luis Pérez Aguiar [d], Jesús Romero [j], Carlo Morosi [a], Marie Pierre Sunyach [e], Roberta Sanfilippo [a], Cleofe Romagosa [k], Dominique Ranchere-Vince [e], Angelo P. Dei Tos [l,m], Paolo G. Casali [a,b,c,d,e,f,g,h,i,j,k,l,m,n], Javier Martin-Broto [b,c]

14 patients (7M and 7F) with mixoid liposarcoma of the extremities or the trunk wall
median age 36-years (range 24–70); median tumor size of 12.5 cm (range 7–20 cm)

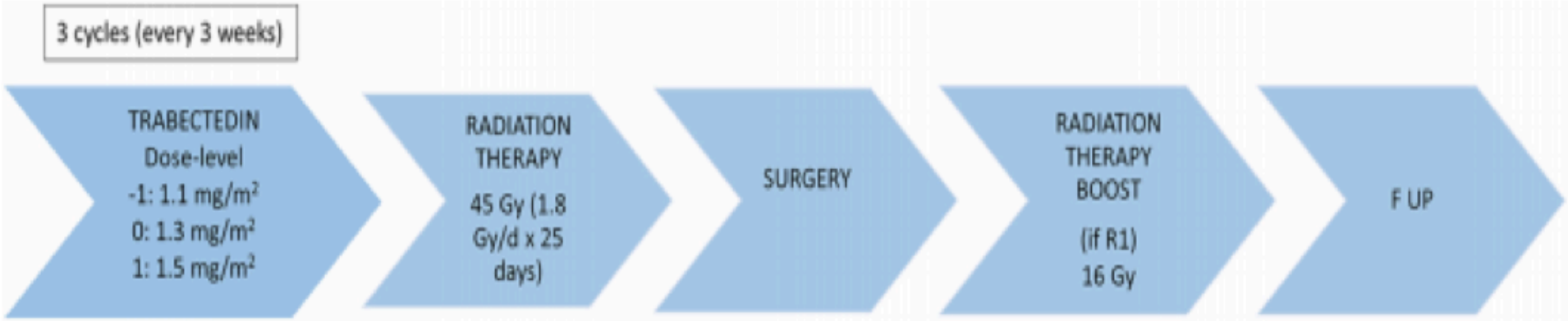


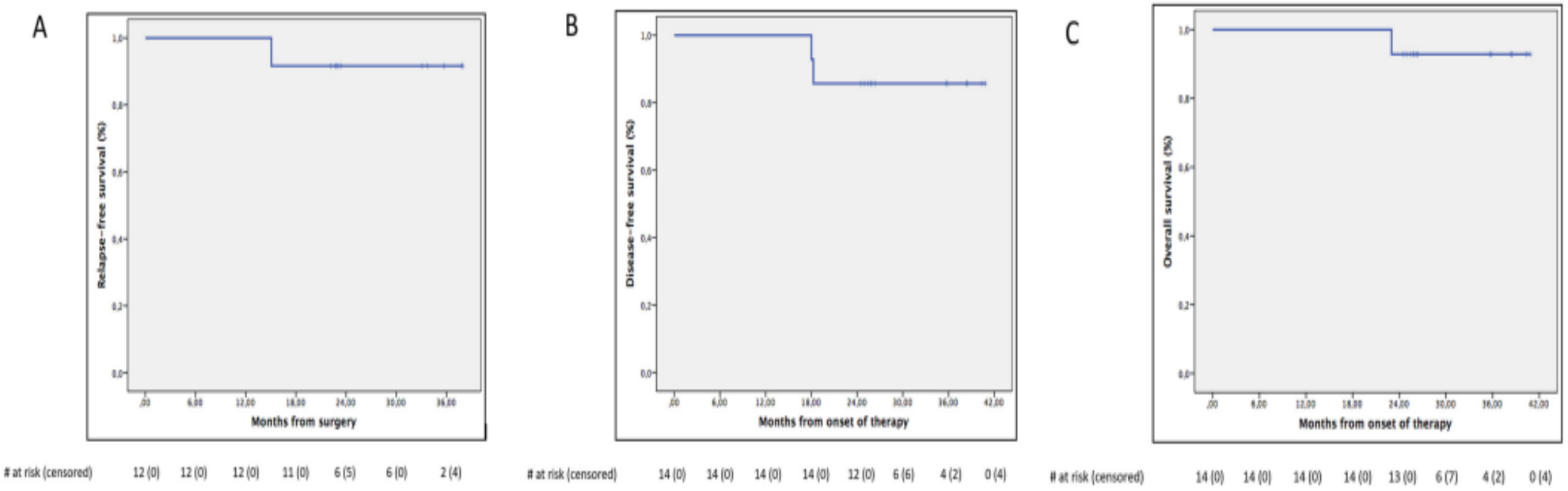

**Fig. 1.** Outline of the trial design.

# Pathology

Median visible residual tumor in the surgical specimen was 5% (0–60)

9/12 patients (75%) with ≤10% visible remaining tumor

3/12 (25%) had a complete pathological response



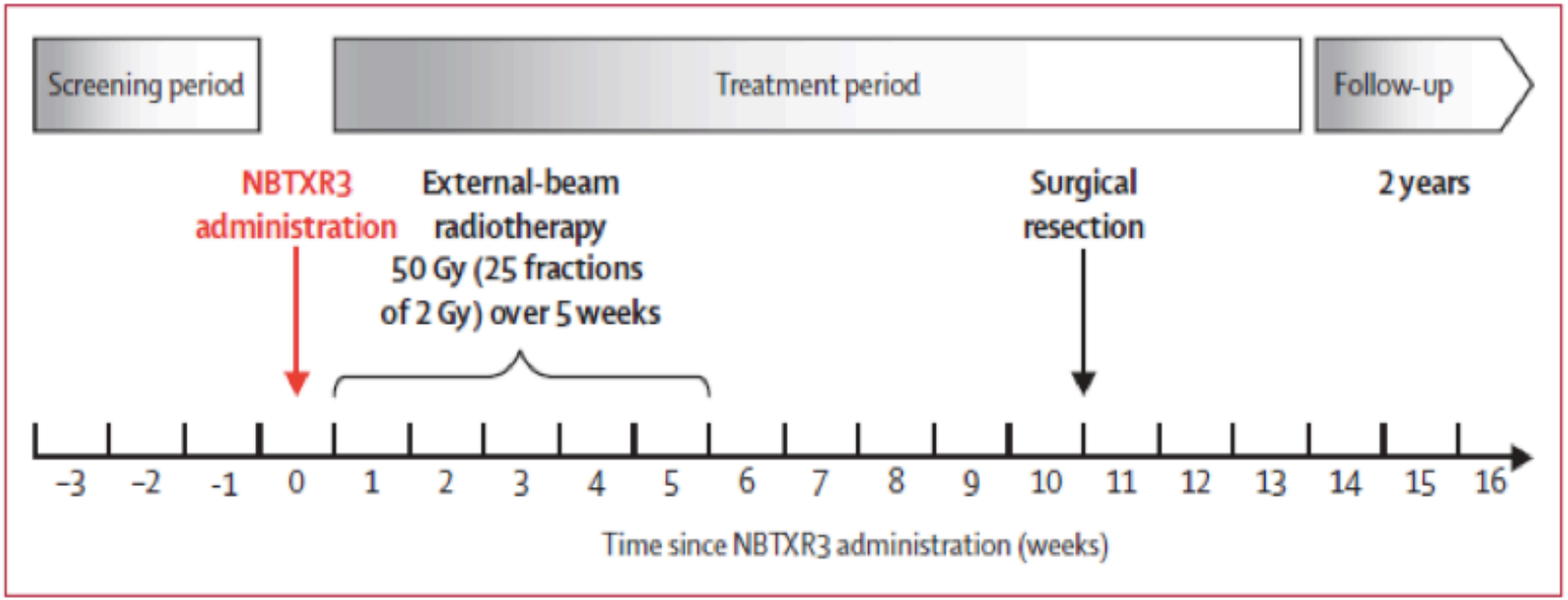

Gronchi A et al. eClinicalMedicine 9:35-43, 2019

# NBTXR3, a first-in-class radioenhancer hafnium oxide nanoparticle, plus radiotherapy versus radiotherapy alone in patients with locally advanced soft-tissue sarcoma (Act.In.Sarc): a multicentre, phase 2–3, randomised, controlled trial

*Sylvie Bonvalot, Piotr L Rutkowski, Juliette Thariat, Sébastien Carrère, Anne Ducassou, Marie-Pierre Sunyach, Peter Agoston, Angela Hong, Augustin Mervoyer, Marco Rastrelli, Victor Moreno, Rubi K Li, Béatrice Tiangco, Antonio Casado Herraez, Alessandro Gronchi, László Mangel, Teresa Sy-Ortin, Peter Hohenberger, Thierry de Baère, Axel Le Cesne, Sylvie Helfre, Esma Saada-Bouzid, Aneta Borkowska, Rodica Anghel, Ann Co, Michael Gebhart, Guy Kantor, Angel Montero, Herbert H Loong, Ramona Vergés, Lore Lapeire, Sorin Dema, Gabriel Kacso, Lyn Austen, Laurence Moureau-Zabotto, Vincent Servois, Eva Wardelmann, Philippe Terrier, Alexander J Lazar, Judith V M G Bovée, Cécile Le Péchoux, Zsusanna Papai*

**179 adult patients with locally advanced soft-tissue sarcoma of the extremity or trunk wall**

**89 in the NBTXR3 plus radiotherapy group and 90 in the radiotherapy alone group**




Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

| | NBTXR3 and radiotherapy group (n=87) | Radiotherapy alone group (n=89) | p value |
|---|---|---|---|
| **Primary endpoint** | | | |
| Pathological complete responses, n (%)* | 14 (16%) | 7 (8%) | 0·044 |
| **Secondary endpoints** | | | |
| R0 resections† | 67 (77%) | 57 (64%) | 0·042 |
| Resection margin‡ | | | .. |
| NA | 2/83 (2%) | 4/86 (5%) | |
| R0 | 67/83 (81%) | 57/86 (66%) | .. |
| R1 | 9/83 (11%) | 19/86 (22%) | .. |
| R2 | 5/83 (6%) | 5/86 (6%) | .. |

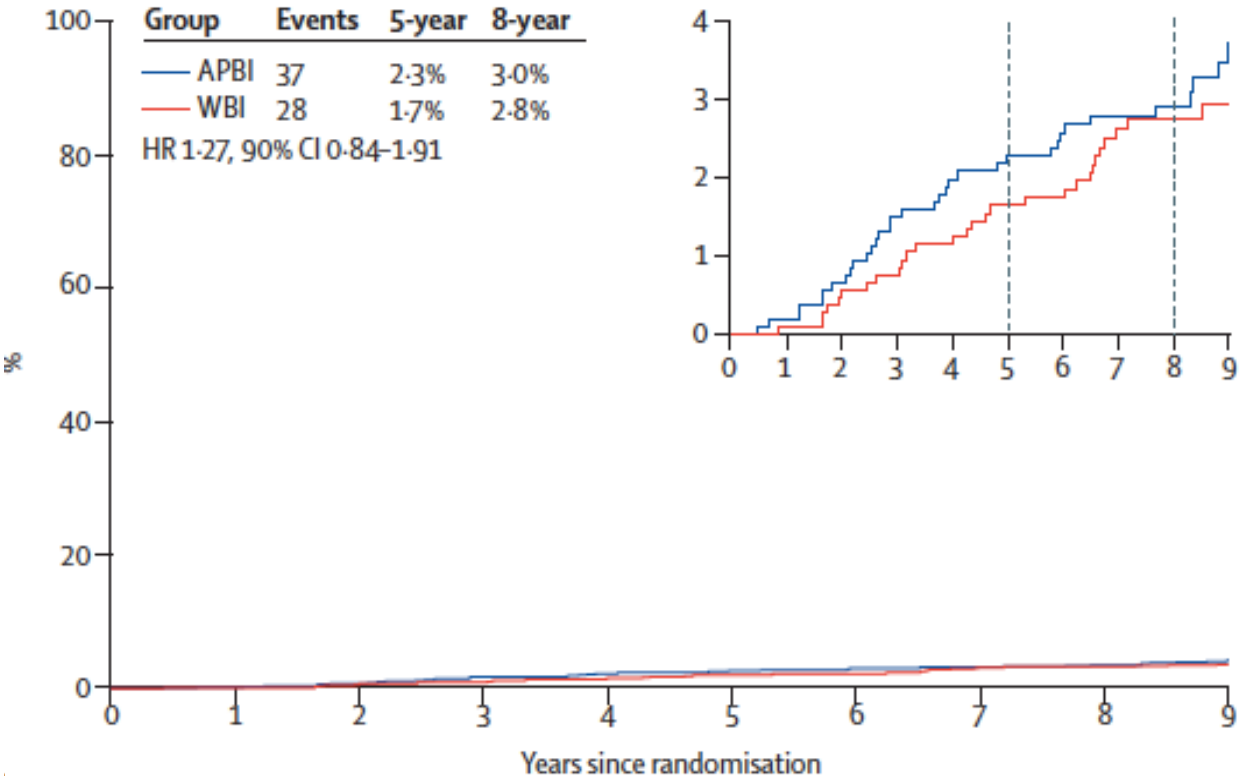
Bonvalot S et al. Lancet Oncol. 2019 Aug;20(8):1148-1159

# Neoplasie mammarie

# External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial

*Lancet* 2019; 394: 2165-72

Women ≥ 40 years with DCIS or node-negative breast cancer treated by BCS
APBI: 38.5 Gy/10 fx b.i.d vs WBRT (50 Gy/25 fx or 42.5/16 fx)




| | APBI | WBI |
|---|---|---|
| Total patients | 1070 | 1065 |
| Ipsilateral breast tumour recurrence | 37 (3·5%) | 28 (2·6%) |
| Regional recurrence | 4 (0·4%) | 2 (0·2%) |
| Distant recurrence | 20 (1·9%) | 18 (1·7%) |
| Contralateral breast cancer | 29 (2·7%) | 38 (3·6%) |
| Non-breast second cancer* | 84 (7·9%) | 57 (5·4%) |
| Death | 25 (2·3%) | 27 (2·5%) |
| Any event | 199 (19%) | 170 (16%) |

Data are n (%) unless otherwise specified. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. *Site of second cancers are provided in the appendix (p 8).

***Table 2:*** **Event types as a first event by treatment group**

***Wheelan et al. 2019***

# External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial

*Lancet* 2019; 394: 2165-72

| | APBI (n=1070) | | | WBI (n=1065) | | |
|---|---|---|---|---|---|---|
| | Grade 2 | Grade 3 | Total | Grade 2 | Grade 3 | Total |
| **Acute period** | | | | | | |
| Radiation dermatitis | 101 (9·4%) | 1 (<0·5%) | 102 (9·5%) | 322 (30·2%) | 6 (0·6%) | 328 (30·8%) |
| Fatigue | 130 (12·1%) | 9 (0·8%) | 139 (13·0%) | 146 (13·7%) | 5 (0·5%) | 151 (14·0%) |
| Breast swelling | 63 (5·9%) | 1 (<0·5%) | 64 (6·0%) | 90 (8·5%) | 1 (<0·5%) | 91 (8·5%) |
| Breast pain | 69 (6·4%) | 2 (<0·5%) | 71 (6·6%) | 78 (7·3%) | 4 (<0·5%) | 82 (7·7%) |
| Pneumonitis | 2 (<0·5%) | 0 | 2 (<0·5%) | 7 (0·7%) | 1 (<0·5%) | 8 (0·8%) |
| Any acute toxicity | 281 (26·3%) | 19 (1·8%) | 300 (28·0%) | 466 (43·8%) | 18 (1·7%) | 484 (45·4%) |
| **Late period** | | | | | | |
| Induration or fibrosis | 214 (20·0%) | 31 (2·9%) | 245 (22·9%) | 48 (4·5%) | 1 (<0·5%) | 49 (4·6%) |
| Telangiectasia | 86 (8·0%) | 13 (1·2%) | 99 (9·3%) | 39 (3·7%) | 0 | 39 (3·7%) |
| Breast pain | 48 (4·5%) | 3 (<0·5%) | 51 (4·8%) | 19 (1·8%) | 1 (<0·5%) | 20 (1·9%) |
| Chest wall pain | 26 (2·4%) | 4 (<0·5%) | 30 (2·8%) | 3 (<0·5%) | 0 | 3 (<0·5%) |
| Fatty necrosis | 24 (2·2%) | 5 (0·5%) | 29 (2·7%) | 2 (<0·5%) | 2 (<0·5%) | 4 (<0·5%) |
| Any late toxicity | 298 (27·9%) | 48 (4·5%) | 346 (32·3%) | 131 (12·3%) | 11 (1·0%) | 142 (13·3%) |

Data are n (%) unless otherwise specified. APBI=accelerated partial breast irradiation. WBI=whole breast irradiation. *Worst grade experienced by patients in the acute period (within 3 months from start of radiotherapy), and in the late period (beyond 3 months).

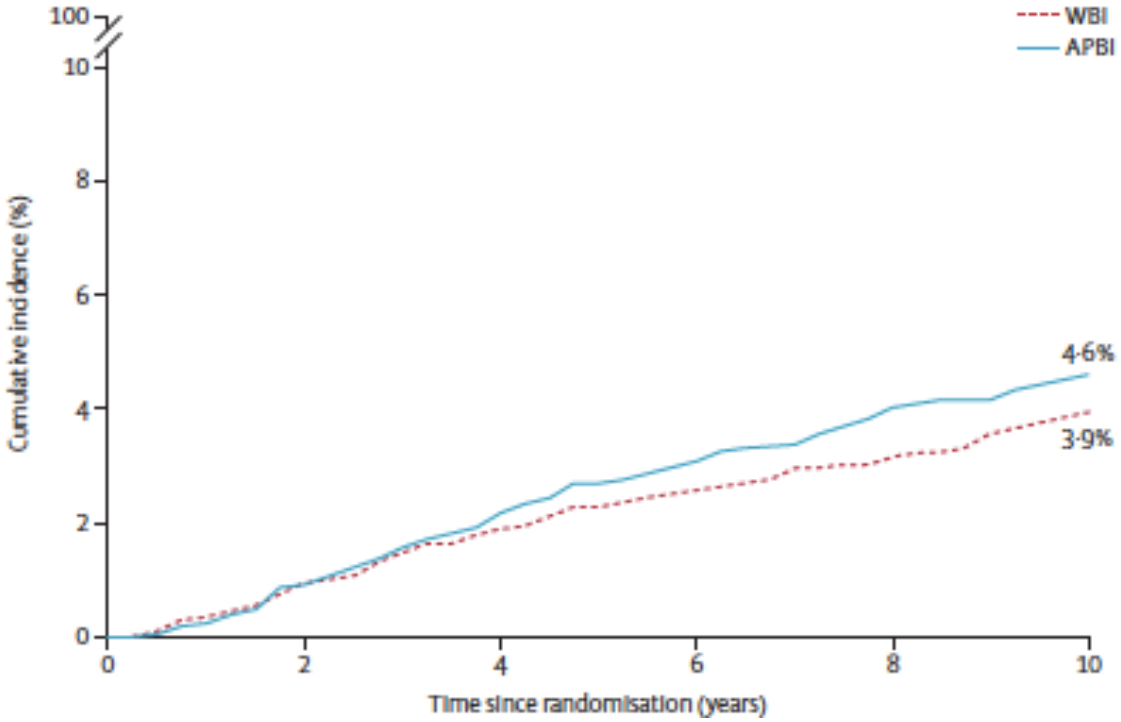
***Table 3:*** **Radiation toxicity* by treatment and period**

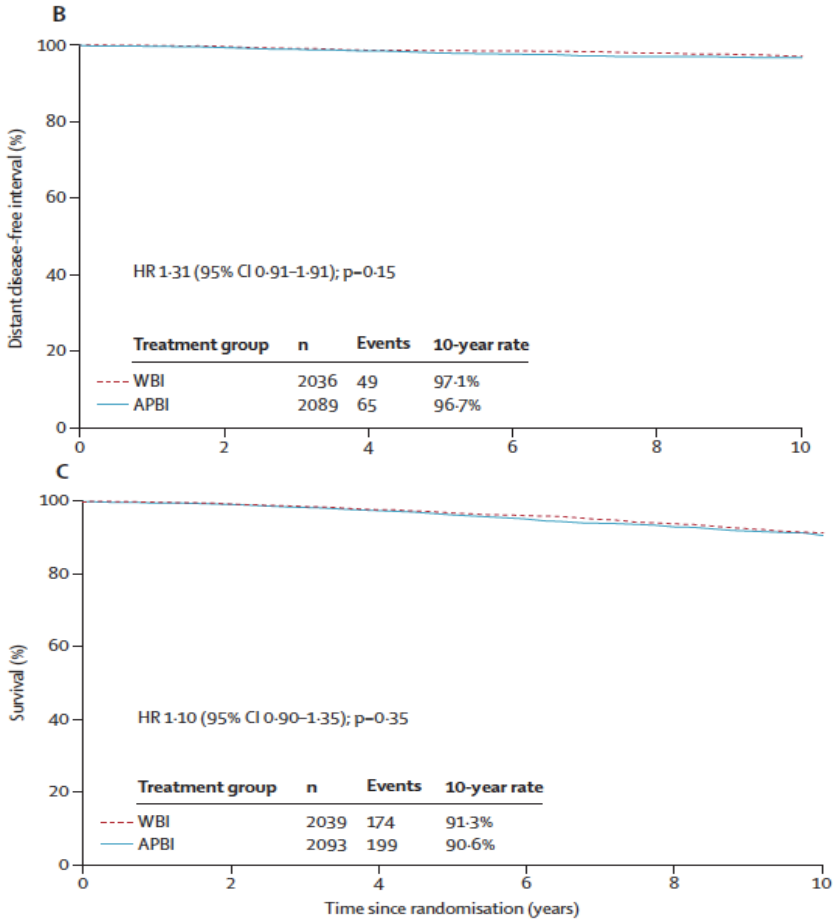
***Wheelan et al. 2019***

# Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial

Lancet 2019; 394: 2155–64

Women ≥ 18 years with early breast cancer (all histologies) treated by lumpectomy
APBI: HDR BT 34 Gy or 38.5 Gy/10 fx b.i.d  vs WBRT (50 Gy/25)




*Vicini et al. 2019*

# Accelerated partial breast or whole breast irradiation after breast conservation surgery for patients with early breast cancer

## 10-year follow up results of the APBI IMRT Florence randomized phase 3 trial

**10-year cumulative IBTR incidence** in early breast cancer treated with **external APBI using IMRT** technique in **5 once-daily fractions (30 Gy in 5#)** is low and **not significantly different** from patients treated with CF-WBI

**Comparable LRR**, **DM**, **CBC**, **BCSS**, and **OS** rates

**Acute & Late toxicity** and **Cosmesis** evaluations significantly in **favor** of **APBI arm**

**APBI** might be considered a **standard alternative** to WBI in low risk early breast cancer patients

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Associazione Italiana
Radioterapia e Oncologia clinica

2019

# *Best Clinical Practice*
# nella Radioterapia della Mammella

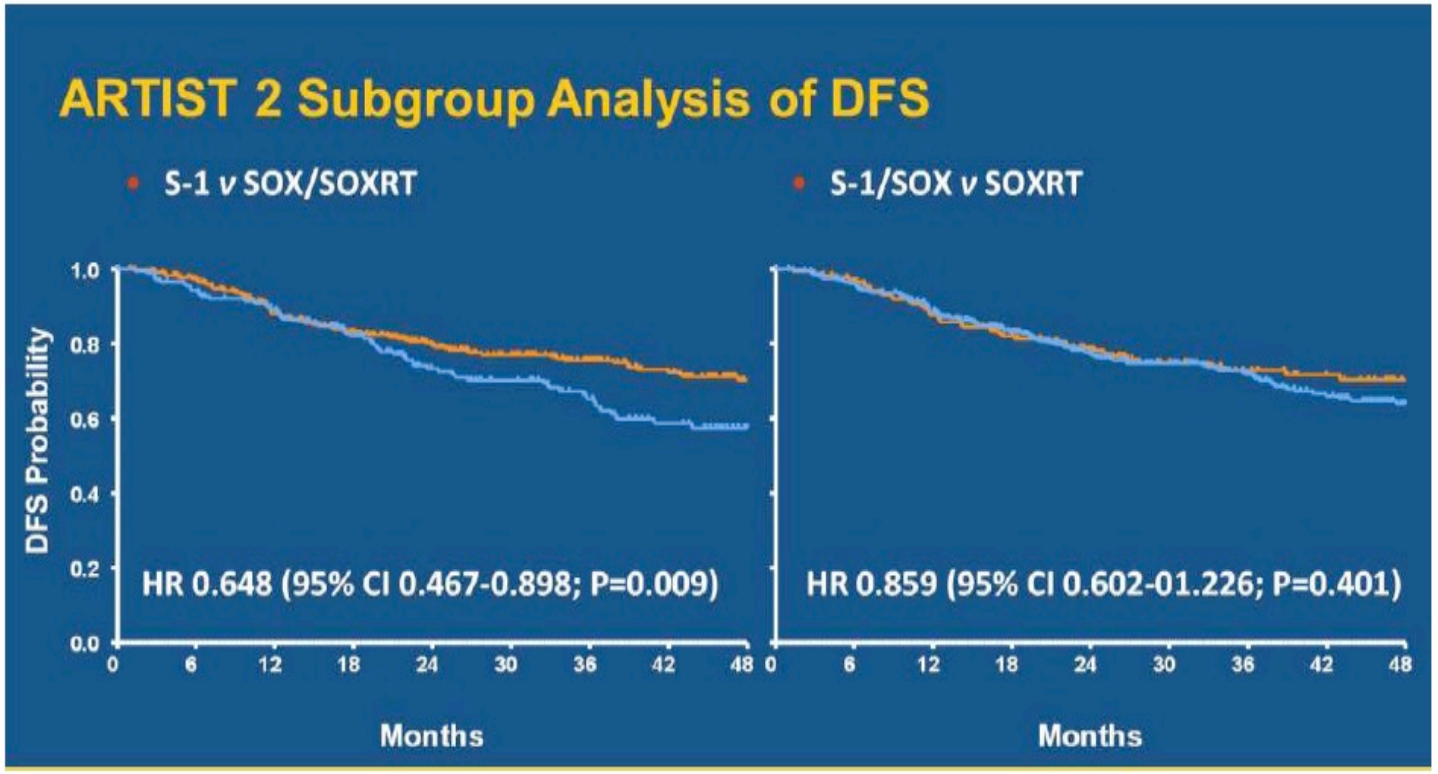
Gruppo di Lavoro per la Patologia Mammaria

# Tumori dell’apparato gastroenterico

# ARTIST-2 Trial: Results

**Resectable gastric cancer**

- Adjuvant SOX or SOX + RT were superior in terms of DFS compared to S-1 monotherapy
- No additional benefit with chemo-radiotherapy




PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

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Park SH et al, ASCO 2019

# Perioperative CT

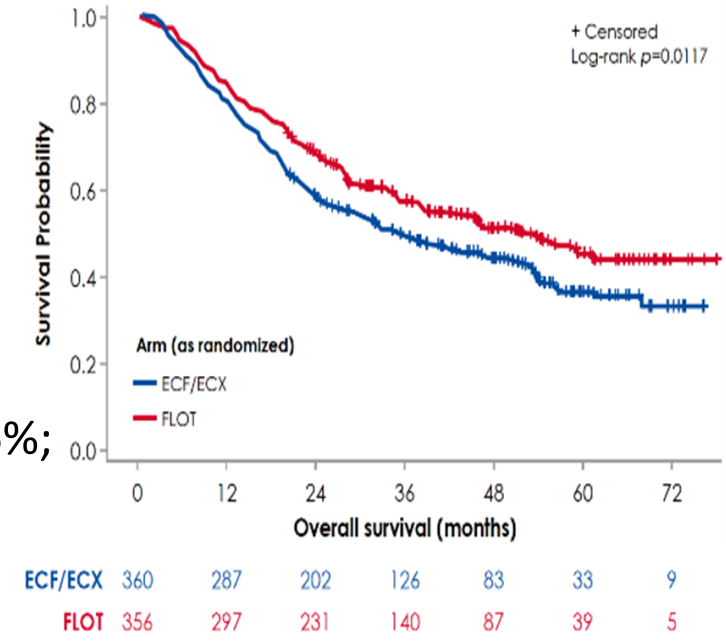
**Locally advanced gastric cancer**

## Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial

Salah-Eddin Al-Batran, Nils Homann, Claudia Pauligk, Thorsten O Goetze, Johannes Meiler, Stefan Kasper, Hans-Georg Kopp, Frank Mayer, Georg Martin Haag, Kim Luley, Udo Lindig, Wolff Schmiegel, Michael Pohl, Jan Stoehlmacher, Gunnar Folprecht, Stephan Probst, Nicole Prasnikar, Wolfgang Fischbach, Rolf Mahlberg, Jörg Trojan, Michael Koenigsmann, Uwe M Martens, Peter Thuss-Patience, Matthias Egger, Andreas Block, Volker Heinemann, Gerald Illerhaus, Markus Moehler, Michael Schenk, Frank Kullmann, Dirk M Behringer, Michael Heike, Daniel Pink, Christian Teschendorf, Carmen Löhr, Helga Bernhard, Gunter Schuch, Volker Rethwisch, Ludwig Fischer von Weikersthal, Jörg T Hartmann, Michael Kneba, Severin Daum, Karsten Schulmann, Jörg Weniger, Sebastian Belle, Timo Gaiser, Fuat S Oduncu, Martina Güntner, Wael Hozaeel, Alexander Reichart, Elke Jäger, Thomas Kraus, Stefan Mönig, Wolf O Bechstein, Martin Schuler, Harald Schmalenberg*, Ralf D Hofheinz*, on behalf of the FLOT4-AIO

cT2 or higher
nodal positive (cN+)

pCR ECF: 16% vs FLOT 6%; p=0,02).




| | ECF/ECX | FLOT |
|---|---|---|
| mOS | 35 months [27-46] | 50 months [38-na] |
| HR | 0.77 [0.63-0.94] p=0.012 (log rank) | |

| OS rate* | ECF/ECX | FLOT |
|---|---|---|
| 2y | 59% | 68% |
| 3y | 48% | 57% |
| 5y | 36% | 45% |

*projected OS rate

Al Batran SE et Al, Lancet 2019

# Neoadj CTRT in adenoca GEJ

Gastric Cancer (2019) 22:245–254
https://doi.org/10.1007/s10120-018-0901-3

REVIEW ARTICLE

## Neoadjuvant chemoradiotherapy or chemotherapy for gastroesophageal junction adenocarcinoma: A systematic review and meta-analysis

Fausto Petrelli[1] · Michele Ghidini[2] · Sandro Barni[1] · Giovanni Sgroi[3] · Rodolfo Passalacqua[2] · Gianluca Tomasello[2]

Odds ratio of **pCR** was **2.8** in favor of **CTRT** (95% CI 2.27–3.47;*P* < 0.001).

**CTRT** improved **locoregional recurrences rate** (OR 0.6, 95% CI 0.39–0.91; *P* = 0.01)

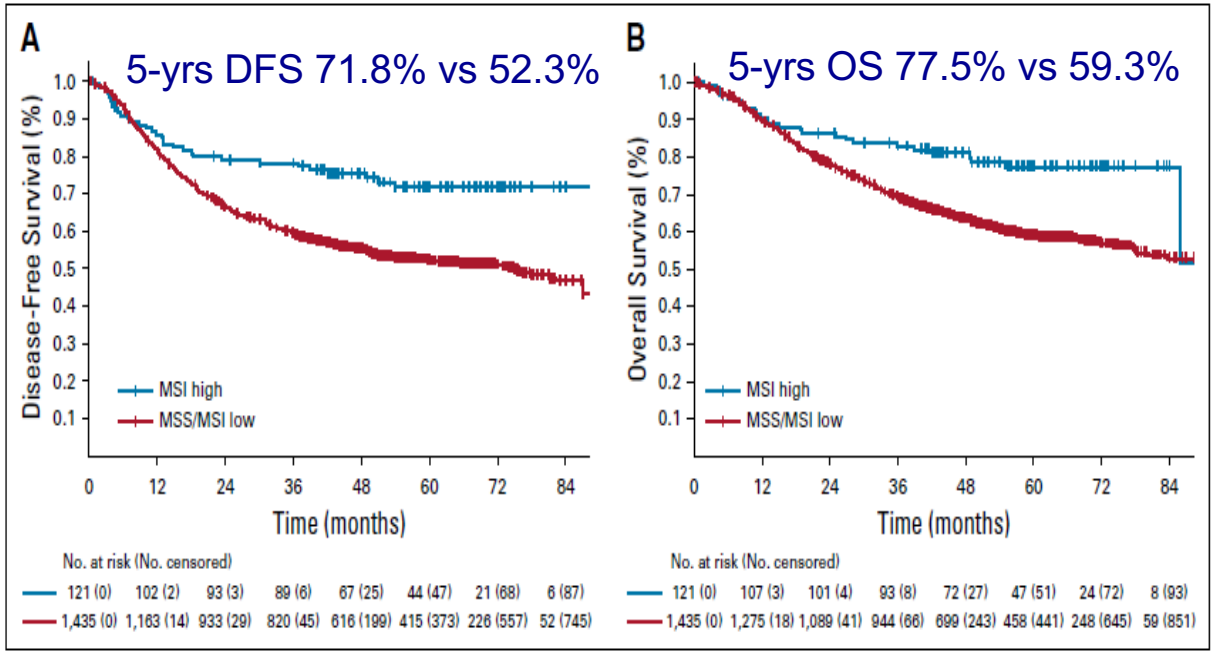
**CTRT DID NOT** improved **distant metastases** rate (OR 0.81, 95% CI 0.59–1.11; *P* = 0.19)

original report

# Individual Patient Data Meta-Analysis of the Value of Microsatellite Instability As a Biomarker in Gastric Cancer

Filippo Pietrantonio, MD[1,2]; Rosalba Miceli, PhD[1]; Alessandra Raimondi, MD[1]; Young Woo Kim, MD, PhD[3]; Won Ki Kang, MD[4]; Ruth E. Langley, MD, PhD[5]; Yoon Young Choi, MD[6]; Kyoung-Mee Kim, MD, PhD[4]; Matthew Guy Nankivell, MSc[5]; Federica Morano, MD[1]; Andrew Wotherspoon, MBBCh[8]; Nicola Valeri, MD, PhD[8,9]; Myeong-Cherl Kook, MD, PhD[3]; Ji Yeong An, MD, PhD[4]; Heike I. Grabsch, MD, PhD, MBA[10,11]; Giovanni Fucà, MD[1]; Sung Hoon Noh, MD, PhD[6]; Tae Sung Sohn, PhD[4]; Sung Kim, MD[4]; Maria Di Bartolomeo, MD[1]; David Cunningham, MD[8]; Jeeyun Lee, MD[4]; Jae-Ho Cheong, MD, PhD[6]; and Elizabeth Catherine Smyth, MD[11]

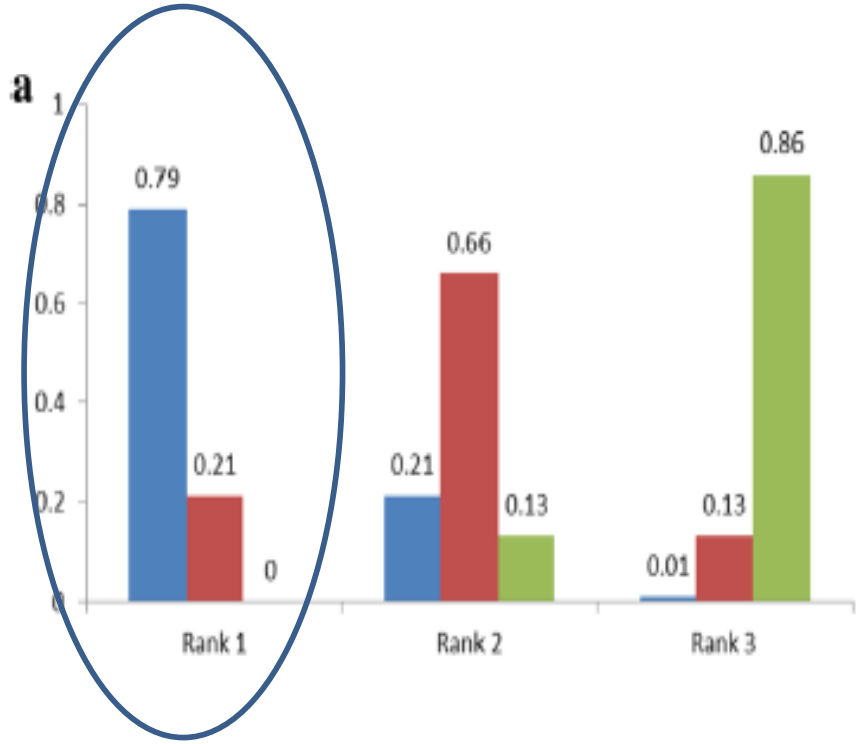
- IPD meta-analysis of prognostic/predictive role of MSI in resected GC pts from MAGIC, CLASSIC, ARTIST and ITACA-S
- 121/1156 **(7.8%)** had MSI-H and had **longer DFS**
- **MSI-H** pts **did not benefit from chemotherapy**



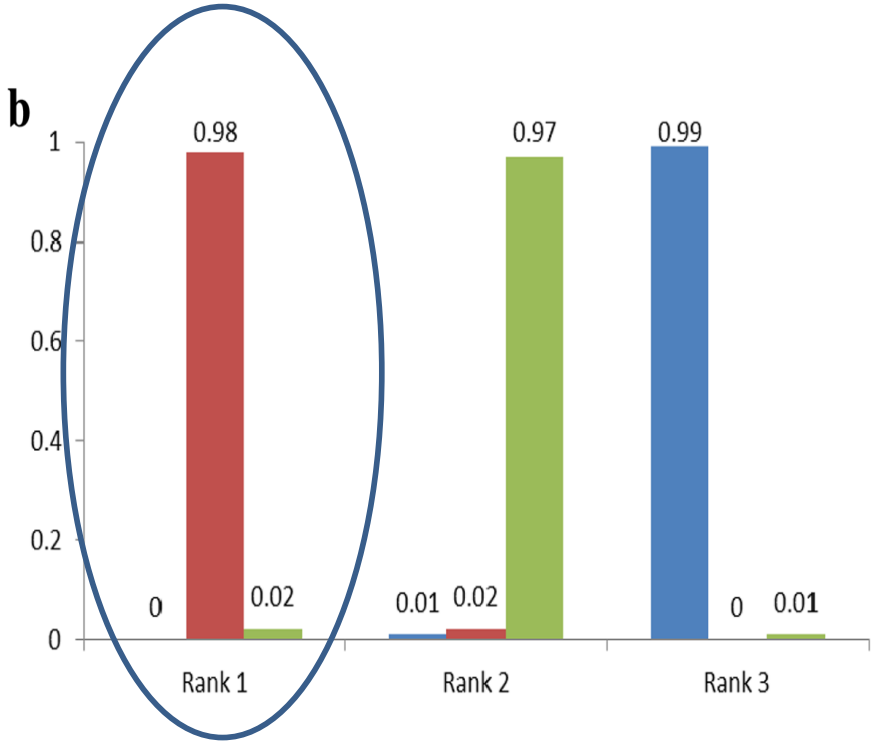

Pietrantonio et al, J Clin Oncol 2019

# Preoperative CTRT vs CT vs upfront S

## R0 resection




## Overall Survival



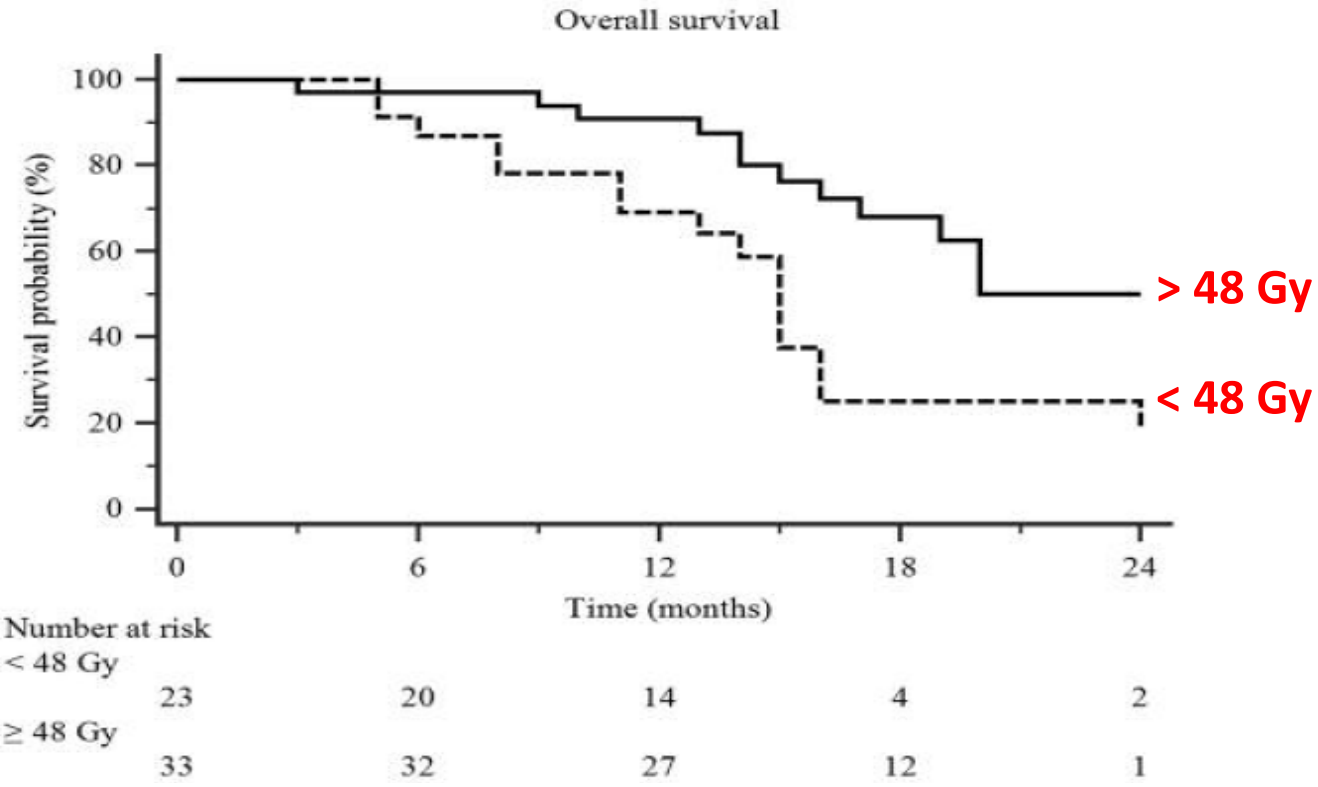

chemoradiotherapy  Chemotherapy  Upfront surgery

Hu et al. Radiation Oncology (2019)

# Sterebody Radiotherapy

## Higher Biologically Effective Dose Predicts Survival in SBRT of Pancreatic Cancer: A Multicentric Analysis (PAULA-1)

ALESSANDRA ARCELLI[1], ALESSANDRA GUIDO[1], MILLY BUWENGE[1], NICOLA SIMONI[2], RENZO MAZZAROTTO[2], GABRIELLA MACCHIA[3], FRANCESCO DEODATO[3], SAVINO CILLA[4], PIERLUIGI BONOMO[5], VALERIO SCOTTI[6], LILIANA BELGIOIA[7], GIORGIO TOLENTO[1], FRANCESCO CELLINI[8], ELISA GRASSI[9], MARIACRISTINA DI MARCO[9], RICCARDO CASADEI[10], ALESSIO G. MORGANTI[1] and SILVIA CAMMELLI[1]



# Preoperative intensification

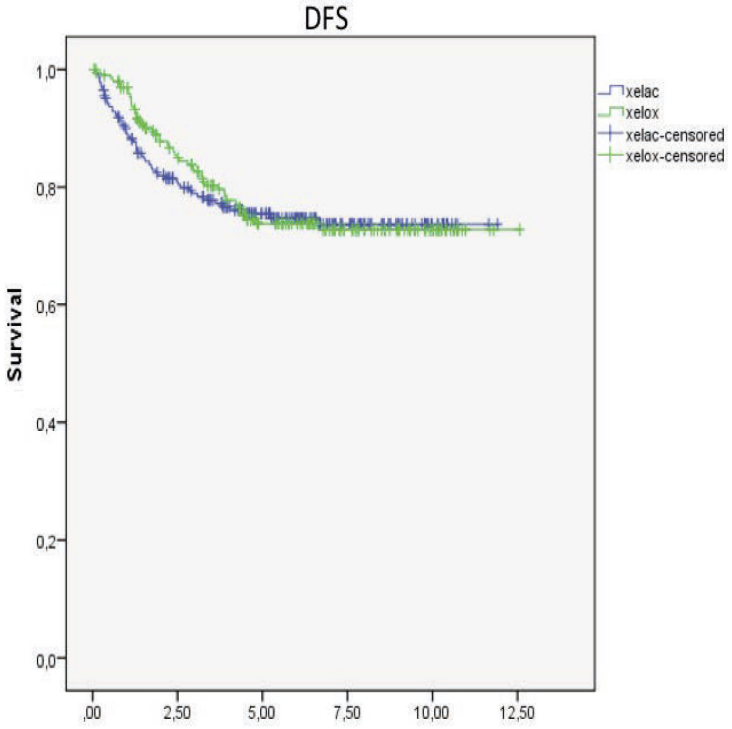
Contents lists available at ScienceDirect

Radiotherapy and Oncology

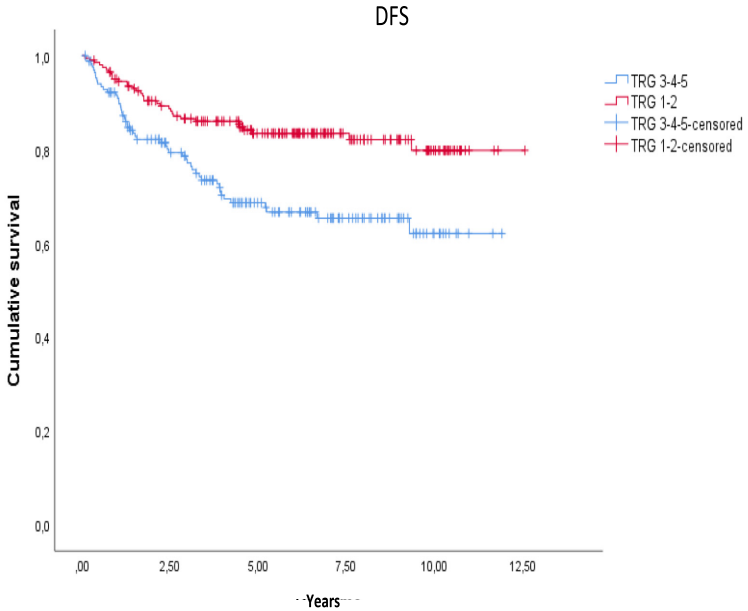
journal homepage: www.thegreenjournal.com

The INTERACT Trial: Long-term results of a randomised trial on preoperative capecitabine-based radiochemotherapy intensified by concomitant boost or oxaliplatin, for cT2 (distal)–cT3 rectal cancer

All patients




According to TRG




Valentini V et al. Radiother Oncol 2019

# Total Neoadjuvant Therapy

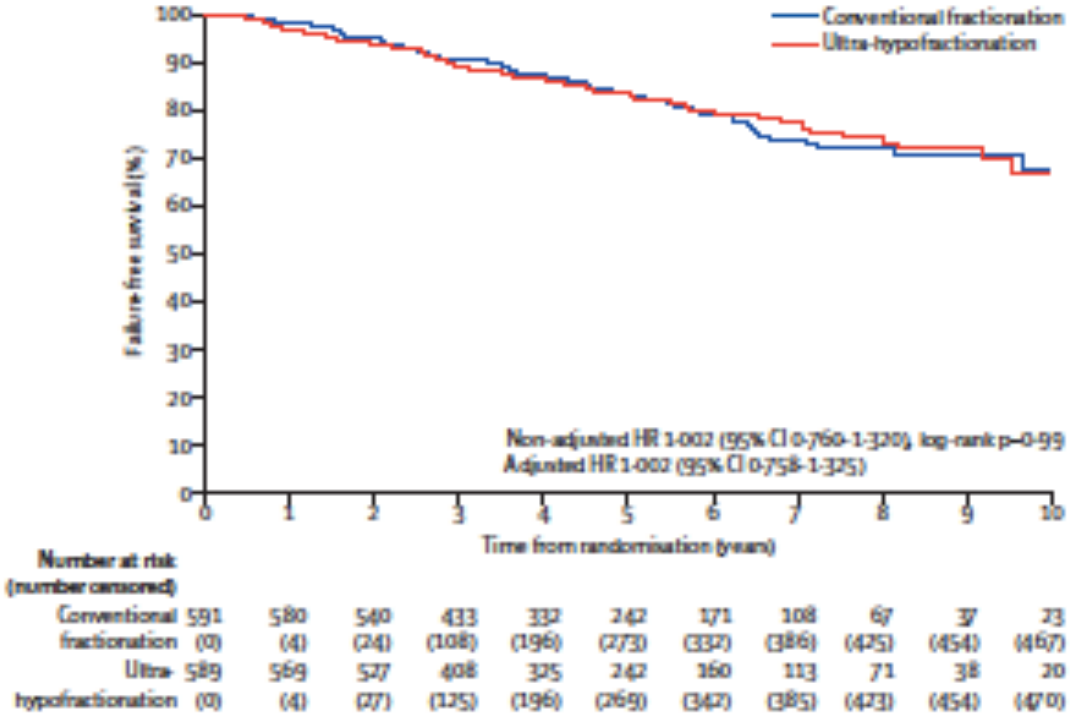
| End point | GROUP A | GROUP B |
|---|---|---|
| **pCR** (pTONO) | **17%** (p < 0.001)* | **25%** (p= 0.21)* |
| **pCR + cCR** (10 pts rejected surgery) | 21% | **28%** |
| **R0 resection** | 92% | 90% |
| **Sphincter saving** | 68% | 72% |
| **TRG 4-3** | 41% | **50%** |
| **Low NAR score** | 26% | **35%** |
| **Good quality TME** | 85% | 82% |
| **CRM ≤ 1 mm** | 10% | 7% |

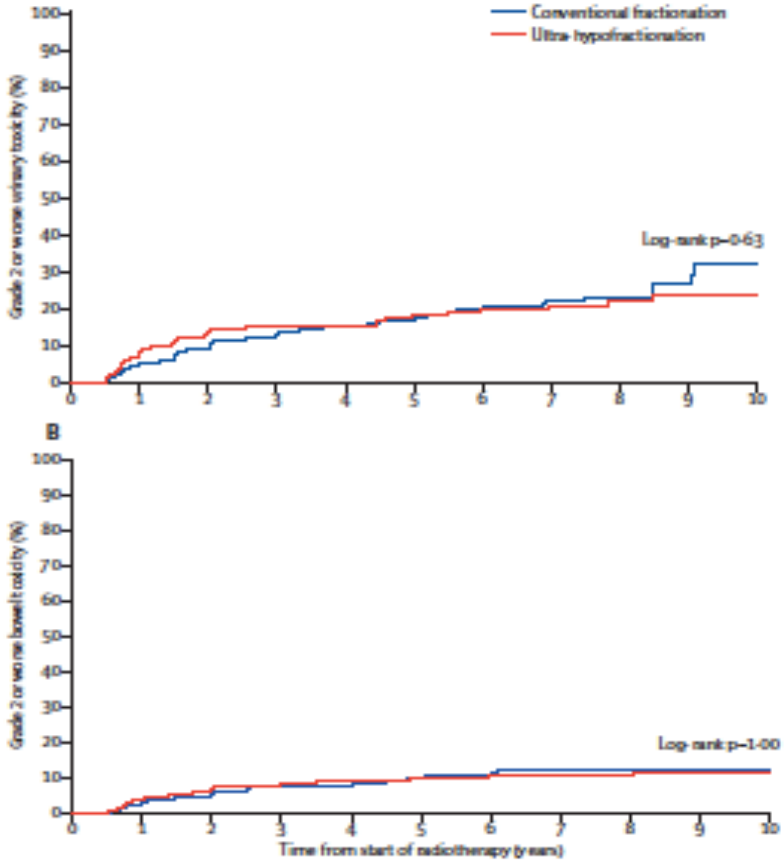
# Neoplasie dell’apparato urogenitale maschile e tumori della prostata

# Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial

Lancet 2019; 394: 385–95

Intermediate to high risk PCa
Ultrahypofractionated RT (42.7 Gy/7 fx) vs standard RT (78 Gy/39 fx)
No ADT allowed



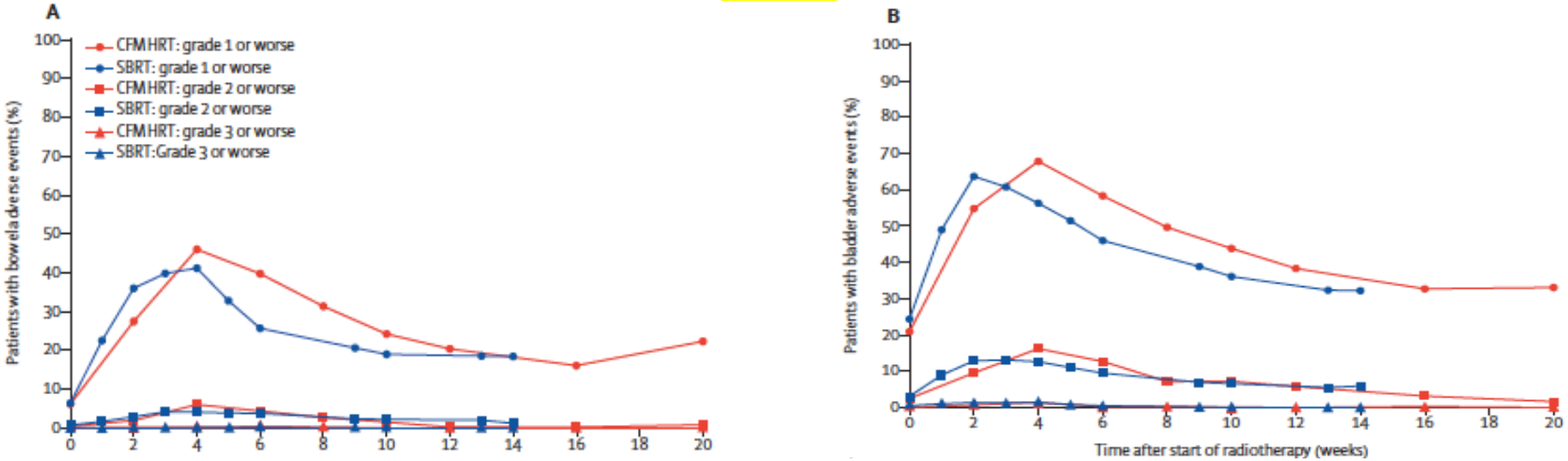




*Widmark et al. 2019*

# Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial

Lancet Oncol 2019; 20: 1531–43

NCCN low-risk or intermediate-risk disease
SBRT (36.25 Gy/5 fx) vs standard RT (78 Gy/39 fx or 62 Gy/20 fx)
No ADT allowed




| | Conventionally fractionated or moderately hypofractionated radiotherapy (n=432) | | | | Stereotactic body radiotherapy (n=415) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
| Gastrointestinal | 264 (61%) | 49 (11%) | 4 (1%) | 0 | 219 (53%) | 42 (10%) | 1 (<1%) | 0 |
| Genitourinary | 254 (59%) | 111 (26%) | 6 (1%) | 1 (<1%) | 236 (57%) | 86 (21%) | 8 (2%) | 2 (<1%) |

Data are n (%). No death due to adverse events were reported.

*Table 2:* Radiation Therapy Oncology Group adverse events

***Brand et al. 2019***

Journal Pre-proof


Comparison of outcomes and toxicity between extreme and moderate radiotherapy hypofractionation in localized prostate cancer: a propensity score analysis

Giulia Marvaso, MD, Delia Ciardo, MSc, Sara Gandini, MSc, Giulia Riva, MD, Emanuele Frigo, MD, Stefania Volpe, MD, Cristiana Fodor, MSc, Dario Zerini, MD, Damaris Patricia Rojas, MD, Stefania Comi, MSc, Raffaella Cambria, MSc, Federica Cattani, MSc, Gennaro Musi, MD, Ottavio De Cobelli, MD, Roberto Orecchia, MD, Barbara A. Jereczek-Fossa, MD, PhD

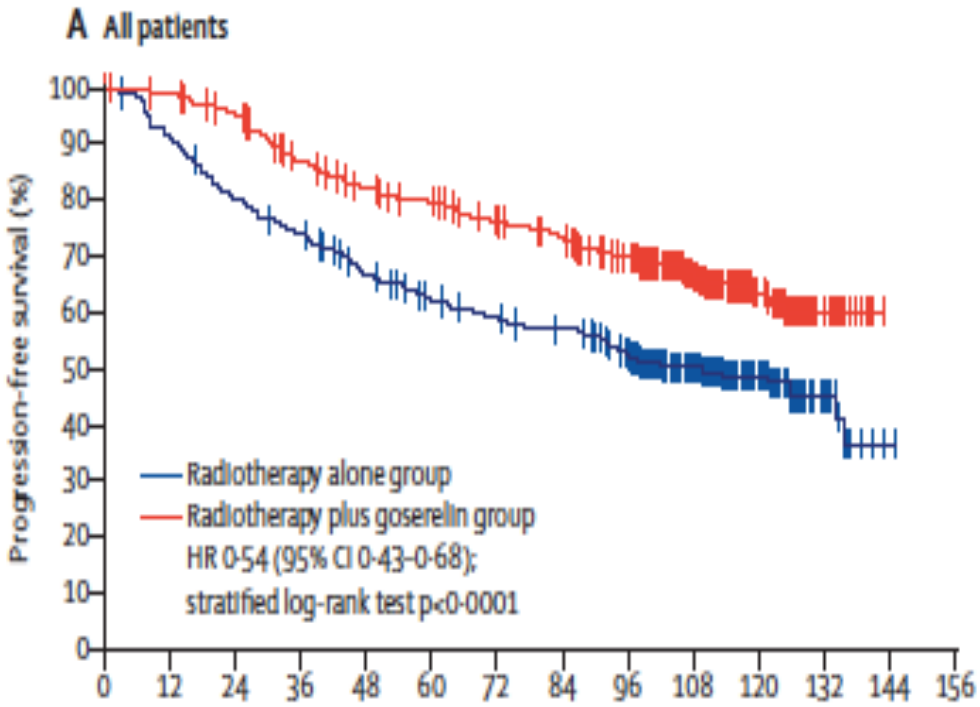
**Table 5:** Multivariate Cox proportional hazard models on late GI and GU (G>1). Hazard Ratio (HR) and 95% Confidence intervals for the whole cohort and matched subgroups.

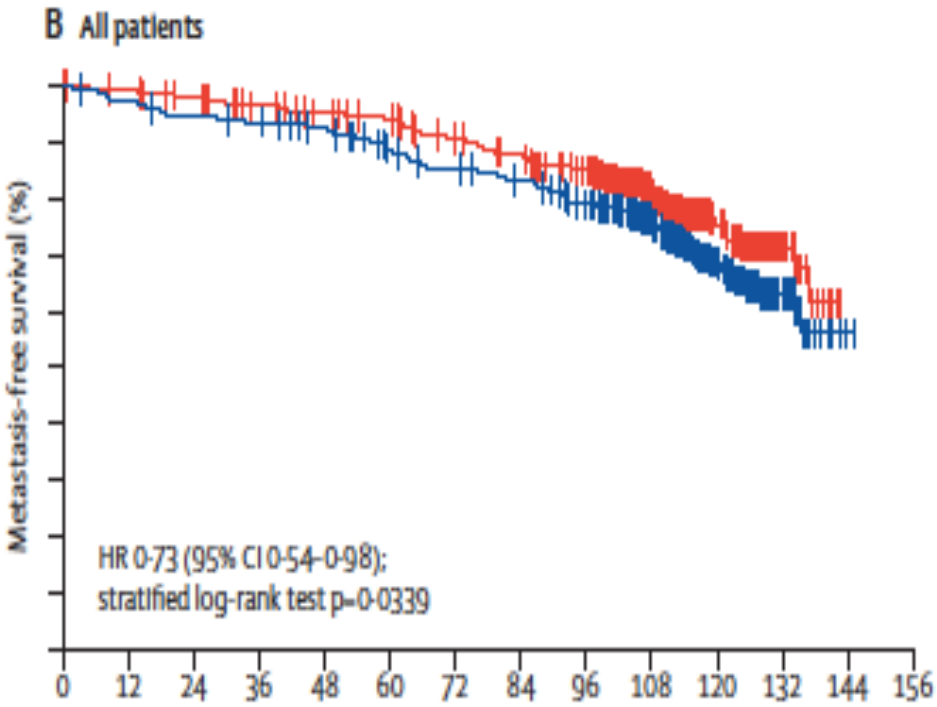
| | | HR | Low 95%CI | Up 95%CI | P-value |
|---|---|---|---|---|---|
| **Analysis stratified by propensity score (n=421)** | | | | | |
| **Gastro-Intestinal Toxicity** | | | | | |
| Fractionation | MH-RT *vs* EH-RT | 1.49 | 0.32 | 7.02 | 0.61 |
| Age | | 1.07 | 0.96 | 1.19 | 0.24 |
| Comorbidities | Yes vs No | 0.53 | 0.11 | 2.62 | 0.43 |
| **Genito-Urinary Toxicity** | | | | | |
| Fractionation | MH-RT *vs* EH-RT | 0.46 | 0.19 | 1.07 | 0.07 |
| Age | | 0.95 | 0.91 | 1.00 | 0.04 |
| Comorbidities | Yes vs No | 1.85 | 0.42 | 8.15 | 0.42 |
| **Subgroup analysis on patients matched by propensity score (n=226)** | | | | | |
| **Gastro-Intestinal Toxicity** | | | | | |
| Fractionation | MH-RT *vs* EH-RT | 1.19 | 0.25 | 5.60 | 0.82 |
| Age | | 1.07 | 0.94 | 1.21 | 0.32 |
| Comorbidities | Yes vs No | 0.17 | 0.03 | 0.87 | 0.03 |
| **Genito-Urinary Toxicity** | | | | | |
| Fractionation | MH-RT *vs* EH-RT | 0.40 | 0.15 | 1.04 | 0.06 |
| Age | | 1.03 | 0.96 | 1.10 | 0.39 |
| Comorbidities | Yes vs No | 1.39 | 0.19 | 10.47 | 0.75 |

# Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial

*Lancet Oncol* 2019

Median pre-SRT: 0.3 ng/mL
Treatment arms: SRT vs SRT + 6 months GnRH agonist
SRT dose: 66 Gy



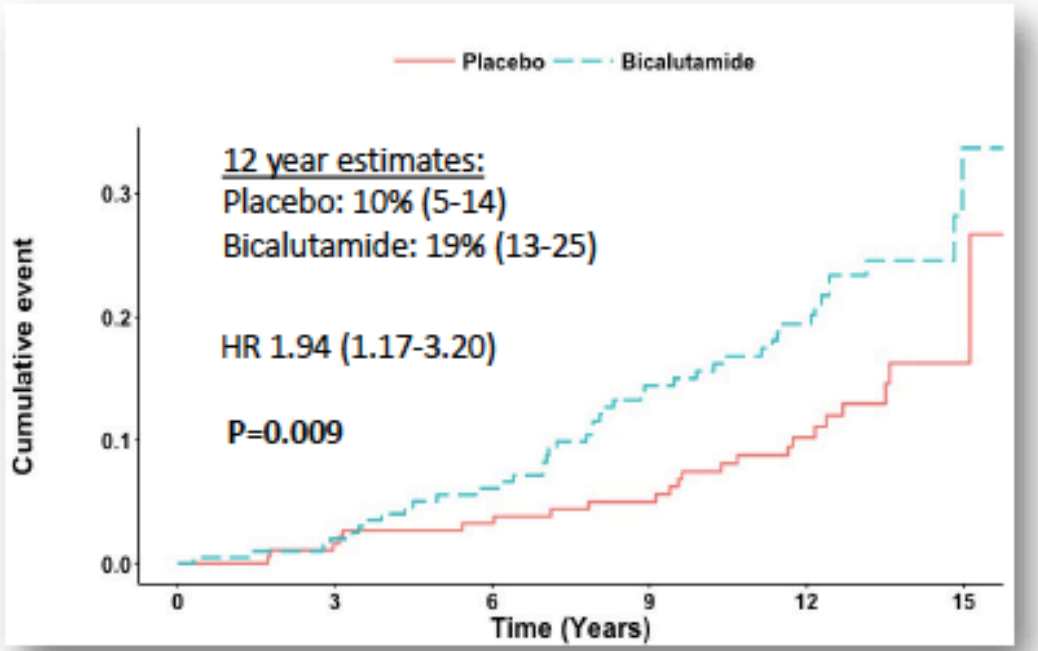

*Carne et al. 2019*

# Two Years of Anti-Androgen Treatment Increases Other-Cause Mortality in Men Receiving Early Salvage Radiotherapy:

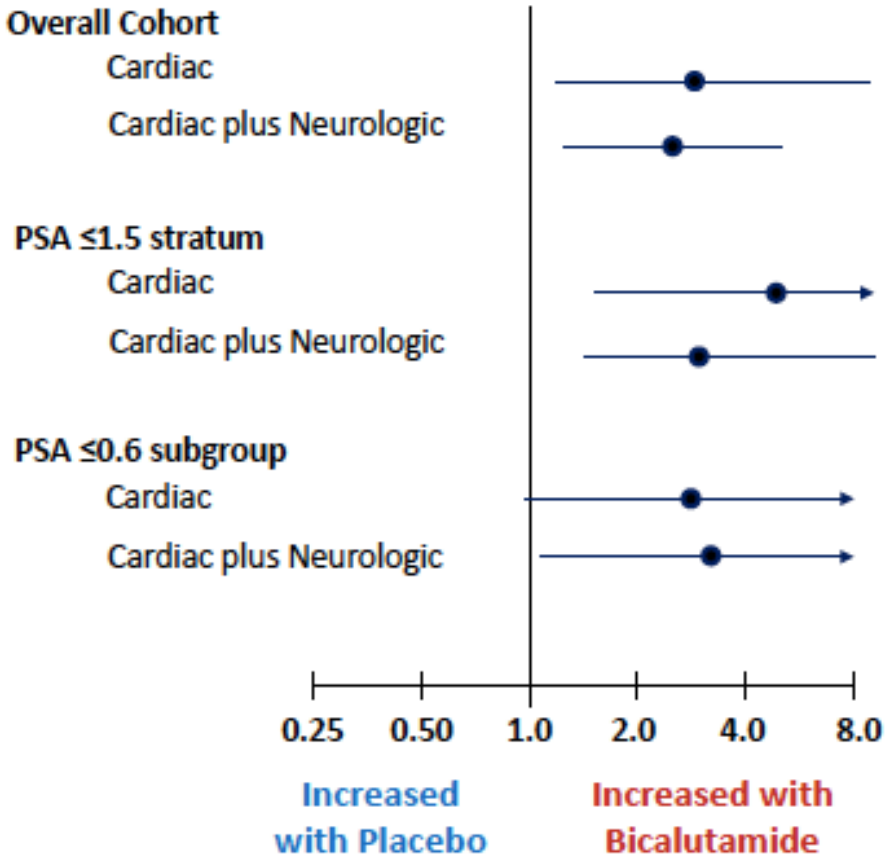
## *A Secondary Analysis of the NRG Oncology/ RTOG 9601 Randomized Phase III Trial*

**Other-Cause Mortality**

PSA 0.2-0.6 ng/mL

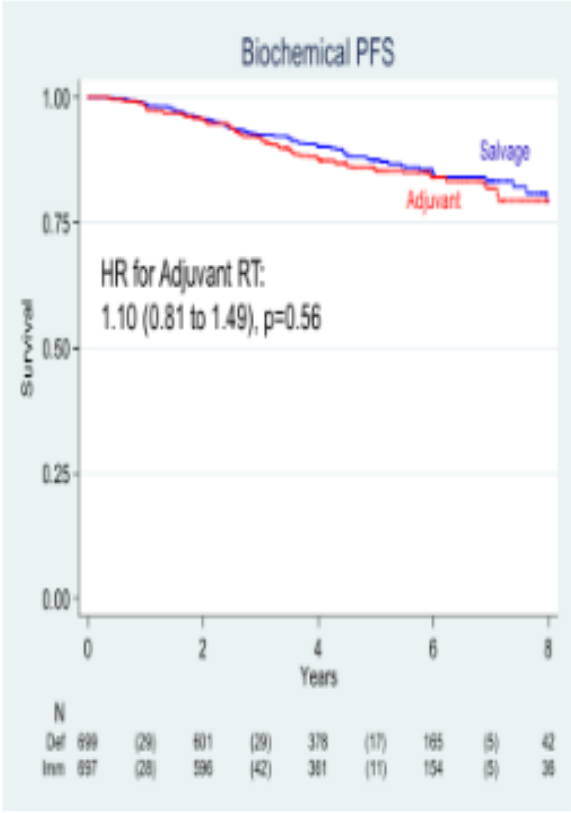



**Odds Ratio for Grade 3-5 Event**



# TIMING OF RADIOTHERAPY (RT) AFTER RADICAL PROSTATECTOMY (RP)

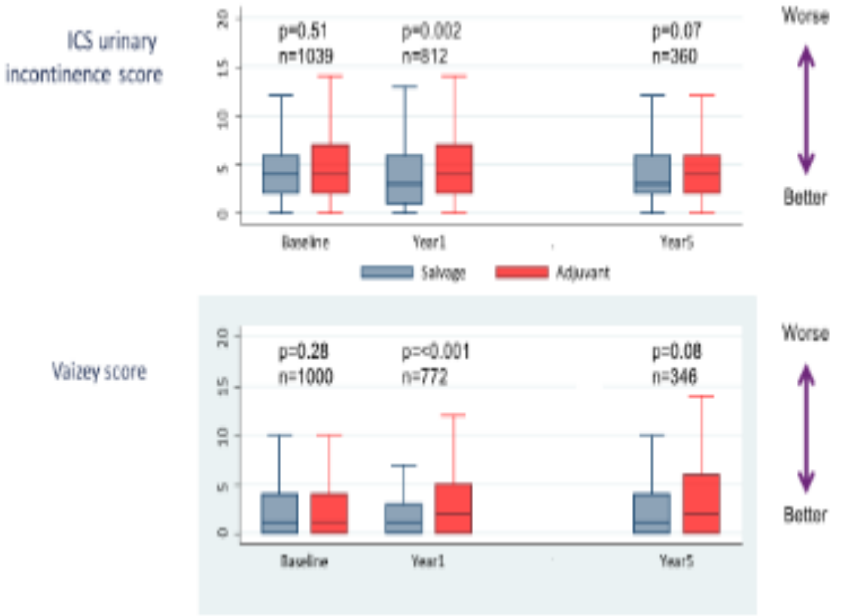
## LBA5191, Parker et al. **RADICALS-RT**




Events:
87 Adjuvant RT
82 Salvage RT

- Safety profile: increased GI and GU toxicities in the adjuvant group

## Patient Reported Outcomes




BARCELONA 2019 ESMO congress

International Journal of
Radiation Oncology
biology • physics
Official Journal of the American Society for Radiation Oncology
ASTRO



# A Phase III Multi-Centre Randomised Trial comparing adjuvant versus early salvage Radiotherapy following a Radical Prostatectomy: Results of the TROG 08.03 and ANZUP "RAVES" Trial

## Conclusion



Similar FFBF rates were shown between ART and SRT, but we did not meet the protocol defined level set for non-inferiority. SRT spares approximately half of men from pelvic radiotherapy, and is associated with significantly lower levels of GU toxicity.

## ONGOING PHASE III CLINICAL TRIALS EVALUATING ADT + ANDROGEN AXIS INHIBITION IN mHSPC

| Trial Name | Arms | # Pts. | 1° endpoint | NCT # | Anticipated Read-out |
|---|---|---|---|---|---|
| ENZA-MET | ADT +/- doce + enza vs. NSAA | 1100 | OS | NCT02446405 | 2020 |
| ARCHES | ADT +/- doce + enza vs. placebo | 1100 | rPFS | NCT02677896 | 2023 |
| TITAN | ADT +/- doce + apa vs. placebo | 1000 | OS | NCT02489318 | 2021 |
| ARASENS | ADT + doce + ODM-201 vs. placebo | 1300 | OS | NCT02799602 | 2022 |
| S1216 | ADT + TAK-700 vs. bicalutamide | 1304 | OS | NCT01809691 | 2022 |
| PEACE-1 | ADT +/- doce, +/- RT, +/- abi | 916 | OS, rPFS | NCT01957436 | 2020 |

# TITAN

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer

Kim N. Chi, M.D., Neeraj Agarwal, M.D., Anders Bjartell, M.D., Byung Ha Chung, M.D., Andrea J. Pereira de Santana Gomes, M.D., Robert Given, M.D., Álvaro Juárez Soto, M.D., Axel S. Merseburger, M.D., Mustafa Özgüroğlu, M.D., Hirotsugu Uemura, M.D., Dingwei Ye, M.D., Kris Deprince, M.D., Vahid Naini, Pharm.D., Jinhui Li, Ph.D., Shinta Cheng, M.D., Margaret K. Yu, M.D., Ke Zhang, Ph.D., Julie S. Larsen, Pharm.D., Sharon McCarthy, B.Pharm., and Simon Chowdhury, M.D., for the TITAN Investigators*

Chi et al NEJM 2019

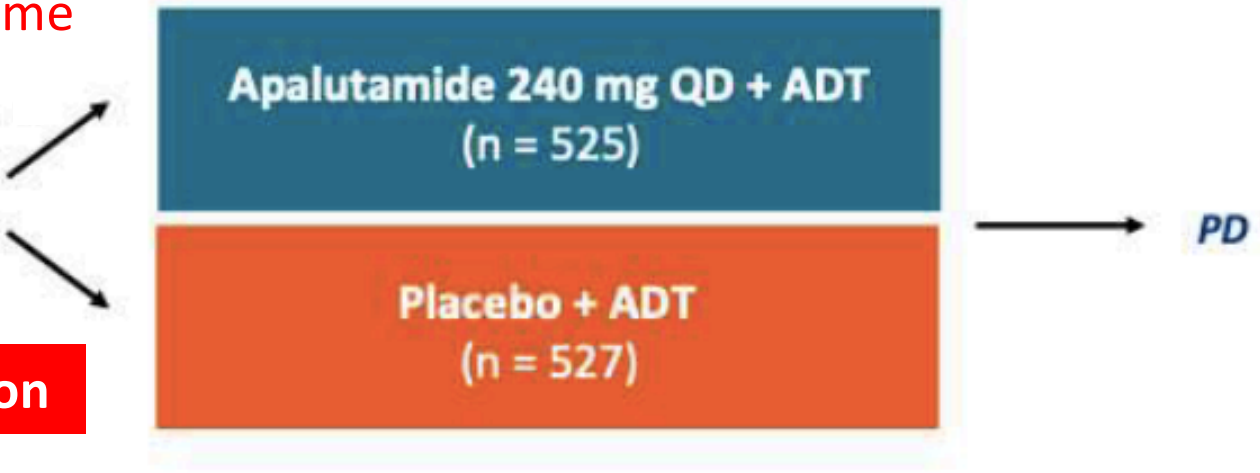
# TITAN – Study design

- International, randomized, double-blind, placebo-controlled phase III trial

63% high volume

Patients with metastatic castration-sensitive prostate cancer; ECOG PS 0/1; prior ADT ≤ 6 mos for mCSPC or ≤ 3 yrs for local disease
(N = 1052)

**"All-comers" patient population**



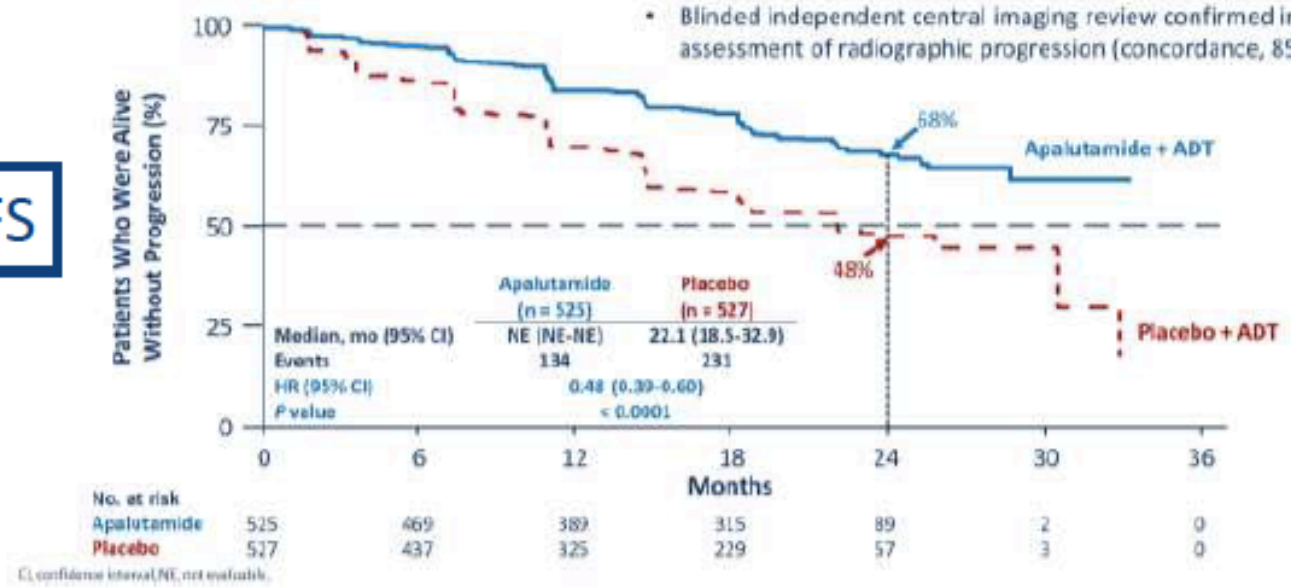

Primary endpoints: OS, radiographic PFS

Secondary endpoints: time to pain progression, time to SRE, time to chronic opioid use, time to cytotoxic chemotherapy

Exploratory endpoints including: time to PSA progression, PFS2

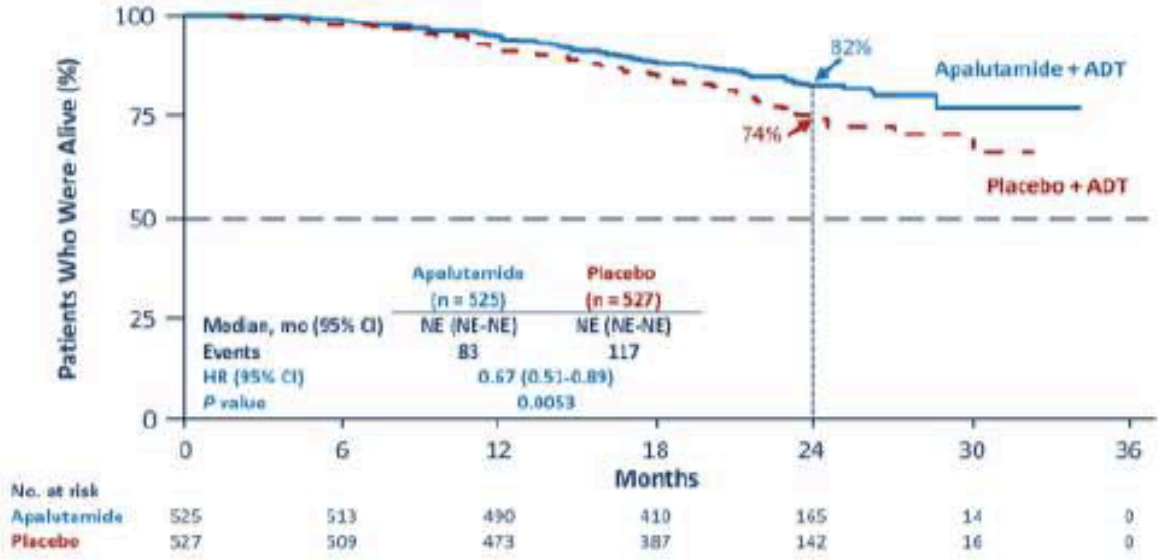
# TITAN – Results

rPFS




**Apalutamide significaIntly reduced risk of rPFS or death by 52%**

OS




**Apalutamide significaIntly reduced risk of death by 33%**

# ENZAMET

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer

I.D. Davis, A.J. Martin, M.R. Stockler, S. Begbie, K.N. Chi, S. Chowdhury, X. Coskinas, M. Frydenberg, W.E. Hague, L.G. Horvath, A.M. Joshua, N.J. Lawrence, G. Marx, J. McCaffrey, R. McDermott, M. McJannett, S.A. North, F. Parnis, W. Parulekar, D.W. Pook, M.N. Reaume, S.K. Sandhu, A. Tan, T.H. Tan, A. Thomson, E. Tu, F. Vera-Badillo, S.G. Williams, S. Yip, A.Y. Zhang, R.R. Zielinski, and C.J. Sweeney, for the ENZAMET Trial Investigators and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group*

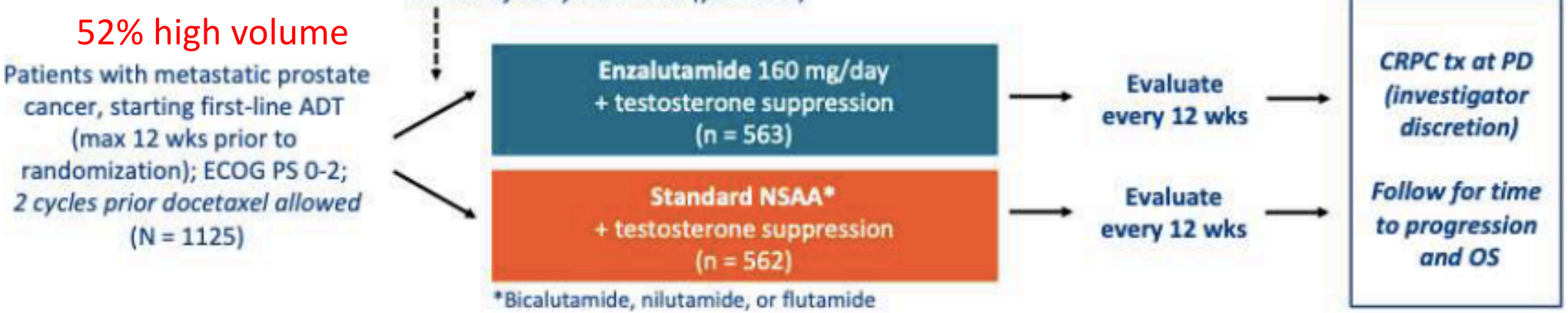
Davis et al NEJM 2019

# ENZAMET – Study Design

- Phase III, randomized, open-label, multicenter clinical trial

*Stratified by volume of metastases (high vs low), antiresorptive therapy (yes vs no), ECOG PS (0/1 vs 2), comorbidities (ACE-27: 0/1 vs 2/3), study site, planned use of early docetaxel (yes vs no)*

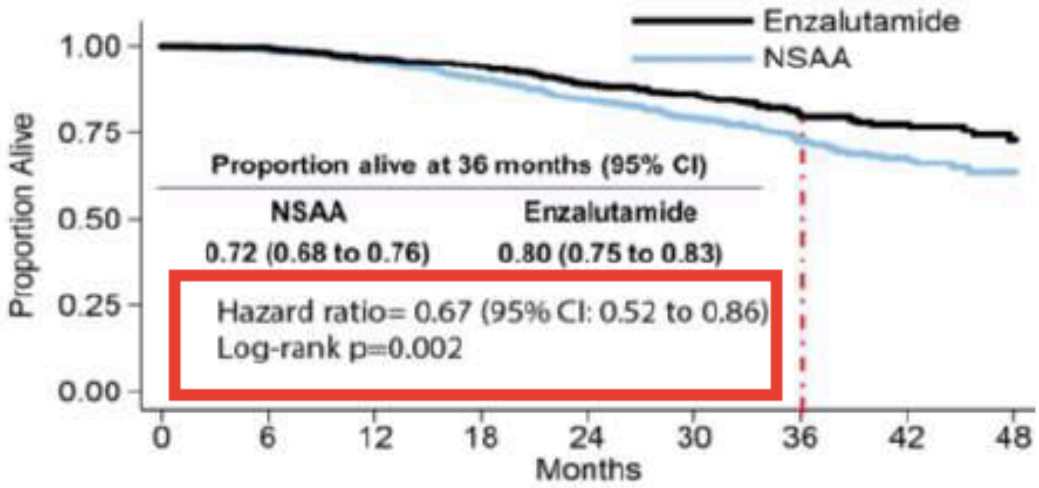
52% high volume




- Primary endpoint: OS
- Secondary endpoints: PSA PFS (including clinical progression if occurring first), clinical PFS, AEs, HRQoL

# ENZAMET – Results

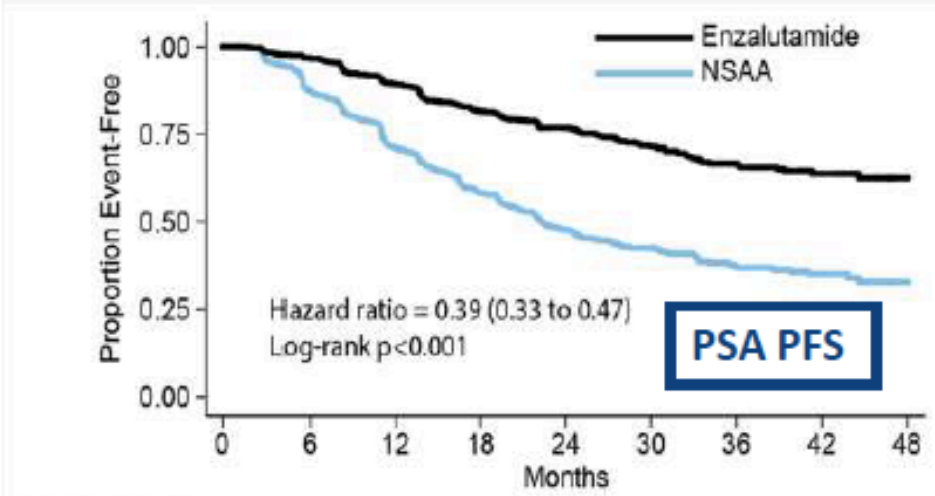
## Primary endpoint: OS




**Number at risk**

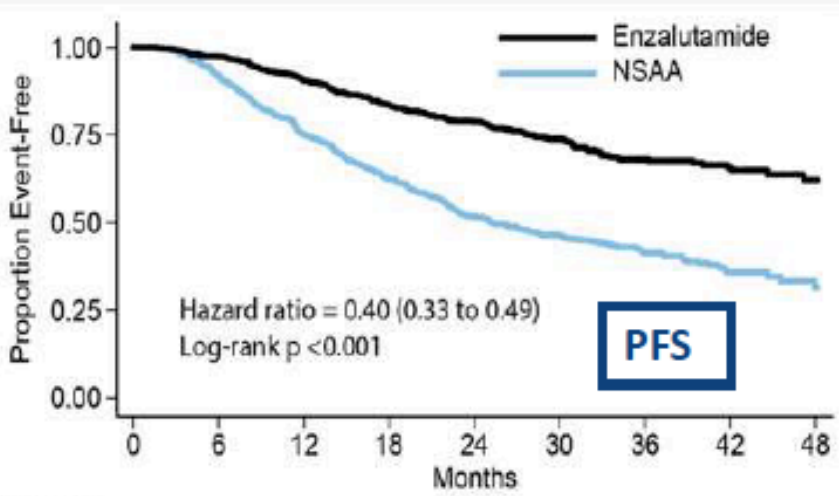
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NSAA | 562 | 551 | 531 | 501 | 452 | 311 | 174 | 86 | 32 |
| Enzalutamide | 563 | 558 | 541 | 527 | 480 | 340 | 189 | 106 | 45 |

## Secondary endpoint: PFS (PCWG2)




**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NSAA | 562 | 486 | 395 | 322 | 249 | 161 | 78 | 44 | 17 |
| Enzalutamide | 563 | 543 | 500 | 455 | 411 | 269 | 146 | 77 | 34 |




**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| NSAA | 562 | 512 | 418 | 346 | 272 | 182 | 96 | 50 | 17 |
| Enzalutamide | 563 | 547 | 507 | 468 | 424 | 284 | 156 | 84 | 36 |

# Treatment Options in mHSPC

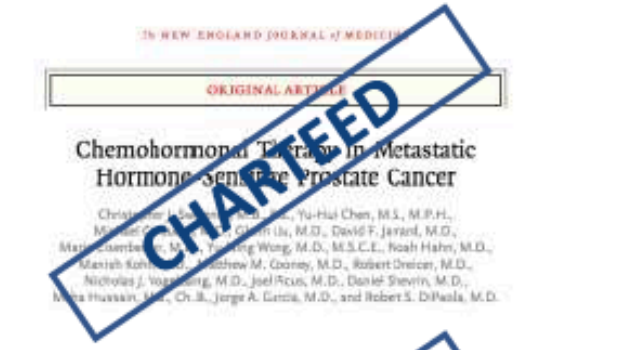
**DOCETAXEL**

**ABIRATERONE**

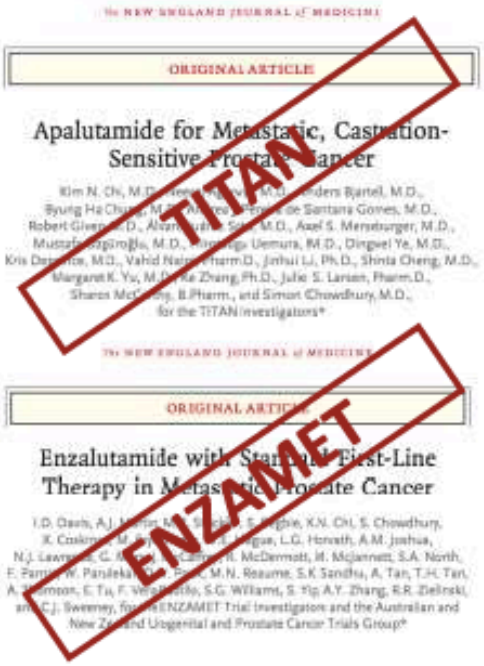
**ENZALUTAMIDE**

**APALUTAMIDE**

**2015** → **2017** → **2019**



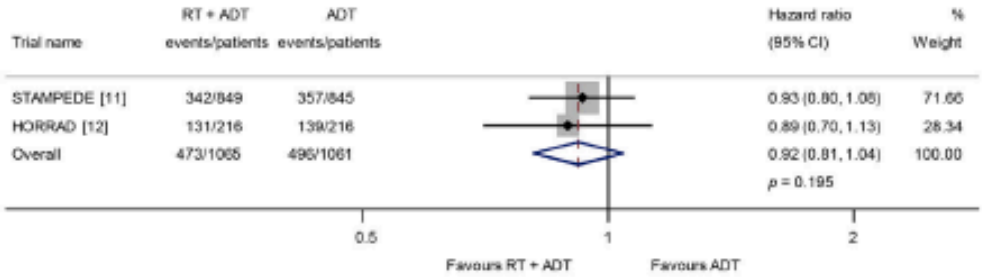




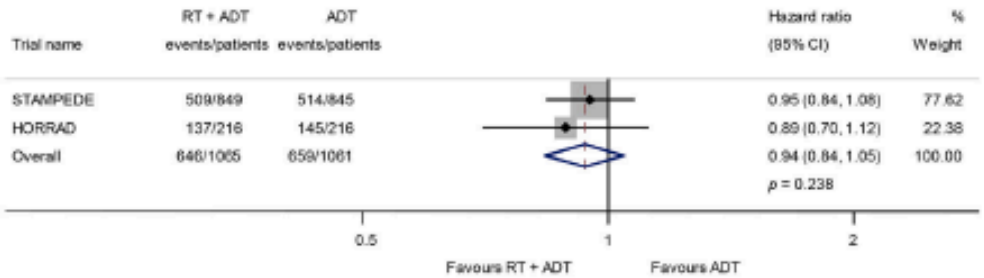

Prostate Cancer

# Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis

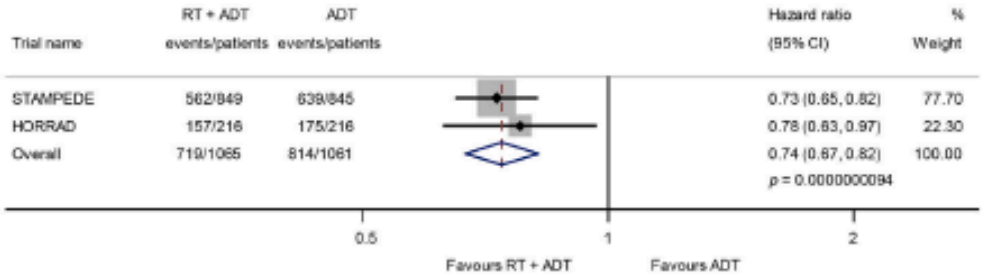
**OS**



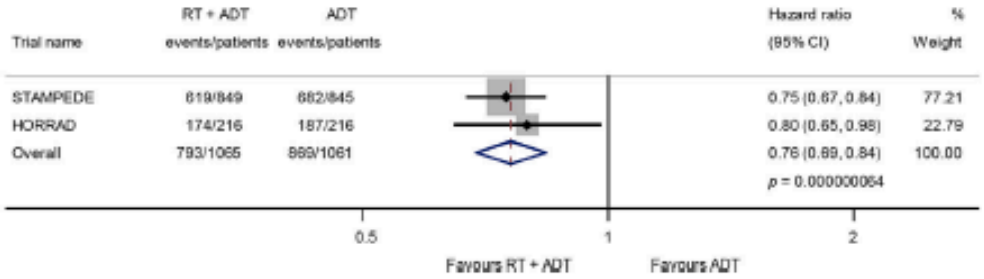

**PFS**




**bPFS**



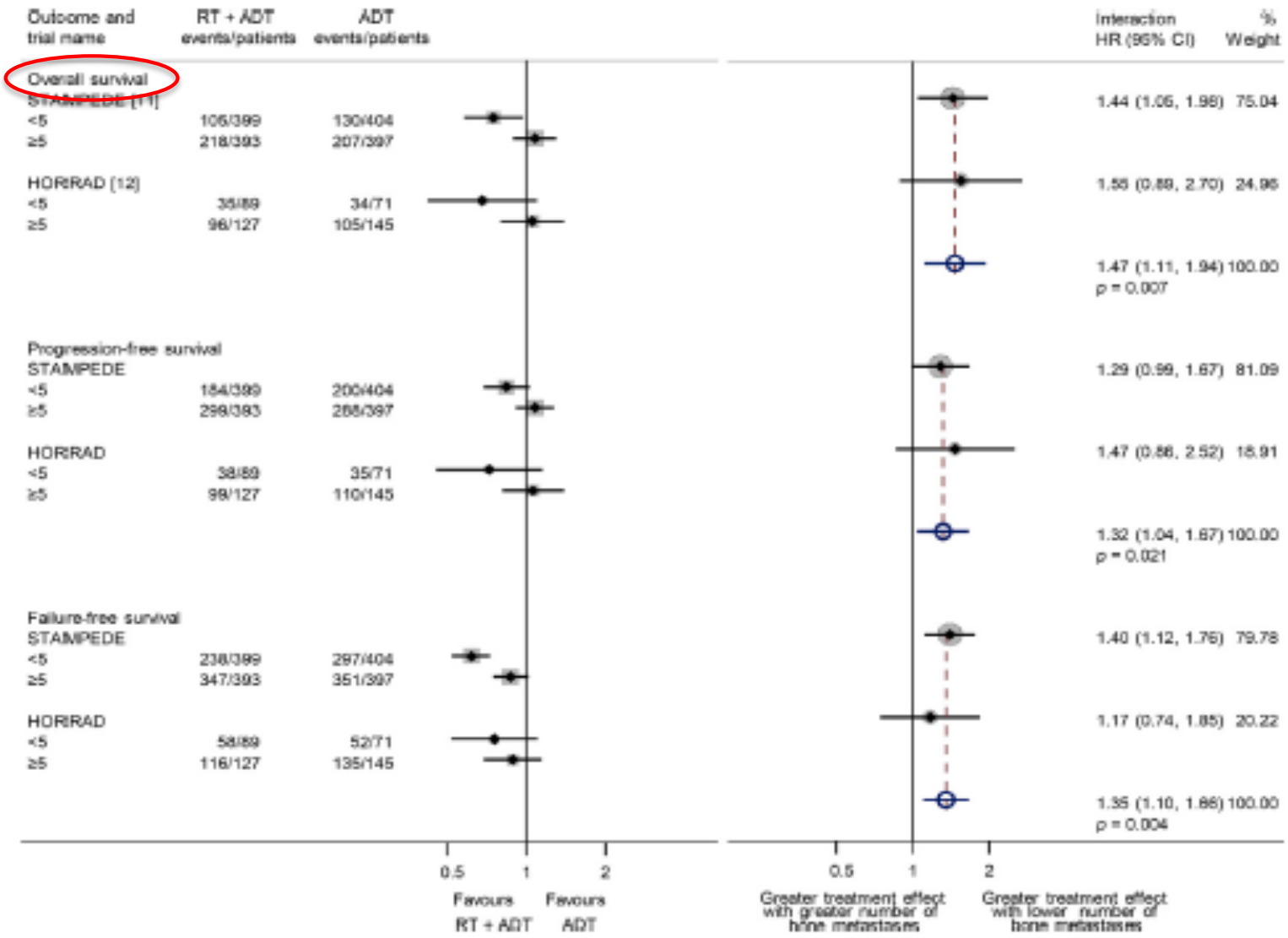

**FFS**




*Burdett et al. 2019*


Prostate Cancer

# Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis



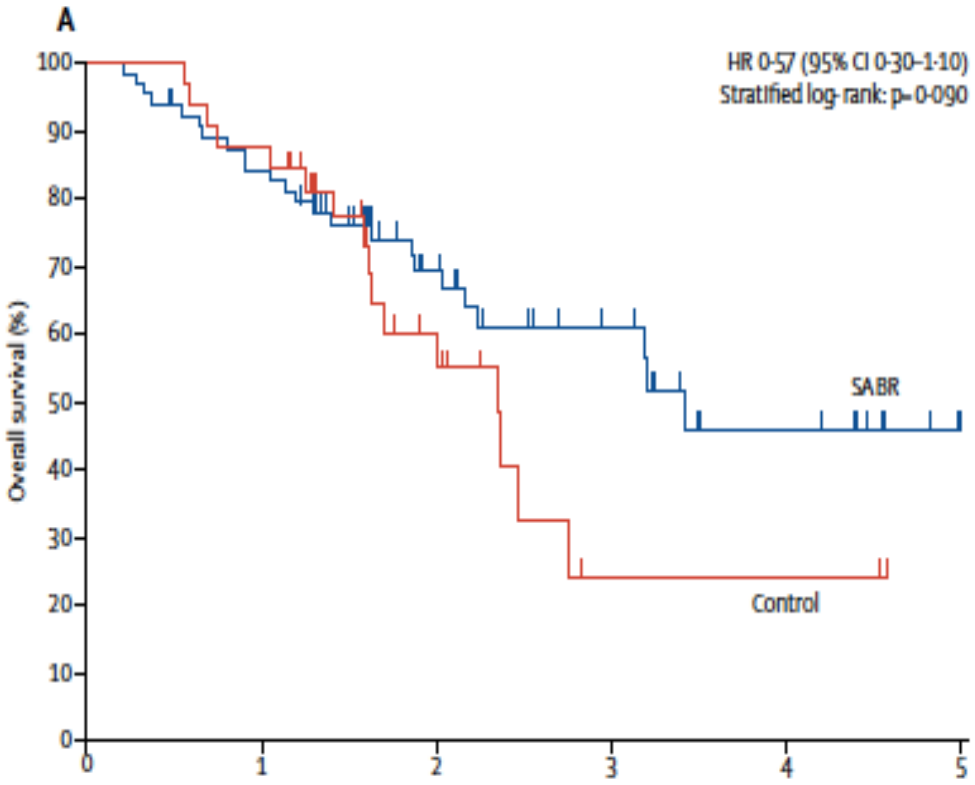

***Burdett et al. 2019***

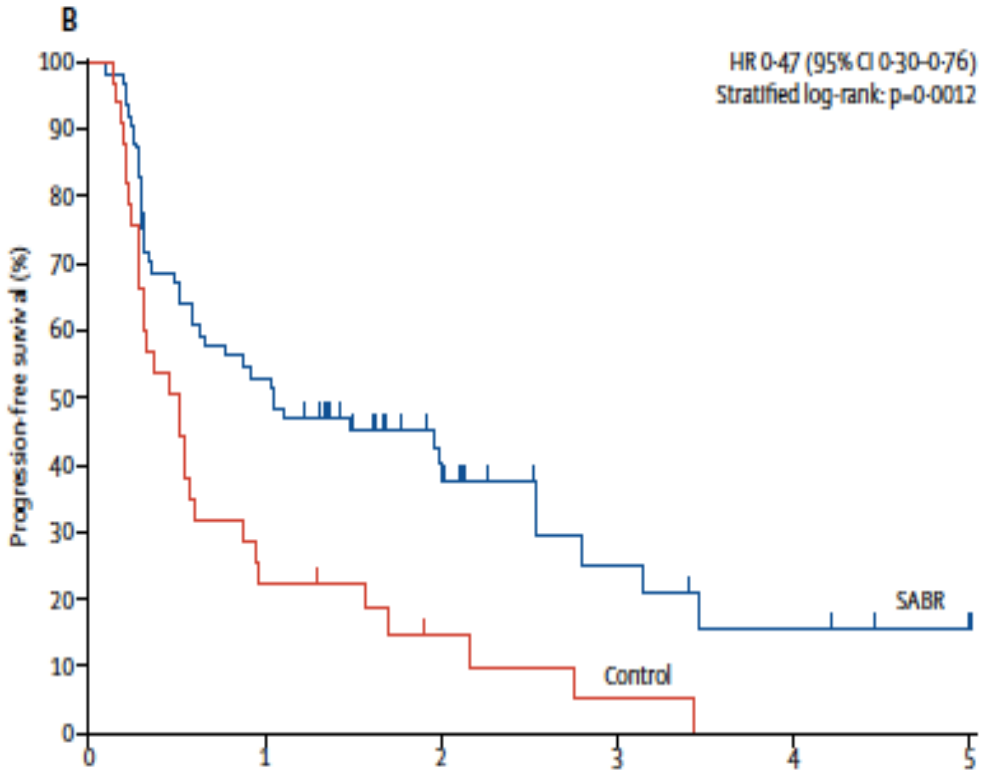
# Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial

*Lancet Oncol* 2019

Median follow up: 26 months

20% prostate cancer patients




**Palma et al. 2019**

# SBRT to oligoprogressive-mCRPCa:

# next-line systemic treatment free survival (NEST)

30 pts with CRPC

SBRT/surgery + 1-3 progressive mets (maintaining systemic therapy)

**MAIN FINDINGS:**

- **median NEST-free survival: 16 months**
- **progression-free survival: 10 months**
- **only minor radiotherapy- or surgery-related toxicity**

Berghen C et al. Eur Urol Oncol 2019 Sep 23. pii: S2588-9311


Thank you