UNIVERSITÀ DEGLI STUDI FIRENZE

BREAST CANCER

Prof. Lorenzo Livi
Radioterapia Oncologica
Università di Firenze

- 1. Radiotherapy
  a) Whole breast RT
  b) Partial breast RT
  c) IORT
  d) Nodal Irradiation
- 2. Chemotherapy
  a) HER 2 pos
  b) HER2 neg
  c) Endocrine therapy

1.a) Whole breast RT

The Lancet Oncology 2015

Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial

Harry Bartelink, Philippe Maingon, Philip Poortmans, Caroline Weltens, Alain Fourquet, Jos Jager, Dominic Schinagl, Bing Oei, Carla Rodenhuis, Jean-Claude Horiot, Henk Struikmans, Erik Van Limbergen, Youlia Kirova, Paula Elkhuizen, Rudolf Bongartz, Raymond Miralbell, David Morgan, Jean-Bernard Dubois, Vincent Remouchamps, René-Olivier Mirimanoff, Sandra Collette, Laurence Collette; on behalf of the European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups

Findings Between May 24, 1989, and June 25, 1996, 2657 patients were randomly assigned to receive no radiation boost and 2661 patients randomly assigned to receive a radiation boost. Median follow-up was 17·2 years (IQR 13·0–19·0). 20-year overall survival was 59·7% (99% CI 56·3–63·0) in the boost group versus 61·1% (57·6–64·3) in the no boost group, hazard ratio (HR) 1·05 (99% CI 0·92–1·19, p=0·323). Ipsilateral breast tumour recurrence was the first treatment failure for 354 patients (13%) in the no boost group versus 237 patients (9%) in the boost group, HR 0·65 (99% CI 0·52–0·81, p<0·0001). The 20-year cumulative incidence of ipsilatelal breast tumour recurrence was 16·4% (99% CI 14·1–18·8) in the no boost group versus 12·0% (9·8–14·4) in the boost group. Mastectomies as first salvage treatment for ipsilateral breast tumour recurrence occurred in 279 (79%) of 354 patients in the no boost group versus 178 (75%) of 237 in the boost group. The cumulative incidence of severe fibrosis at 20 years was 1·8% (99% CI 1·1–2·5) in the no boost group versus 5·2% (99% CI 3·9–6·4) in the boost group (p<0·0001).

Interpretation A radiation boost after whole-breast irradiation has no effect on long-term overall survival, but can improve local control, with the largest absolute benefit in young patients, although it increases the risk of moderate to severe fibrosis. The extra radiation dose can be avoided in most patients older than age 60 years.

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1.b) Partial breast RT

The Lancet Oncology 2015

5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial

Vratislav Strnad, Oliver J Ott, Guido Hildebrandt, Daniela Kauer-Dorner, Hellen Knauerhase, Tibor Major, Jaroslaw Lyczek, Jose Luis Guinot, Jürgen Dunst, Cristina Gutierrez Miguelez, Pavel Slampa, Michael Allgäuer, Kristina Lössl, Bülent Polat, György Kovács, Arnt-René Fischedick, Thomas G Wendt, Rainer Fietkau, Marion Hindemith, Alexandra Resch, Anna Kulik, Leo Arribas, Peter Niehoff, Fernando Guedea, Annika Schlamann, Richard Pötter, Christine Gall, Martina Malzer, Wolfgang Uter, Csaba Polgár, on behalf of the Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (GEC-ESTRO)

Summary

Background In a phase 3, randomised, non-inferiority trial, accelerated partial breast irradiation (APBI) for patients with stage 0, I, and IIA breast cancer who underwent breast-conserving treatment was compared with whole-breast irradiation. Here, we present 5-year follow-up results.

Methods We did a phase 3, randomised, non-inferiority trial at 16 hospitals and medical centres in seven European countries. 1184 patients with low-risk invasive and ductal carcinoma in situ treated with breast-conserving surgery were centrally randomised to either whole-breast irradiation or APBI using multicatheter brachytherapy. The primary endpoint was local recurrence. Analysis was done according to treatment received. This trial is registered with ClinicalTrials.gov, number NCT00402519.

Findings Between April 20, 2004, and July 30, 2009, 551 patients had whole-breast irradiation with tumour-bed boost and 633 patients received APBI using interstitial multicatheter brachytherapy. At 5-year follow-up, nine patients treated with APBI and five patients receiving whole-breast irradiation had a local recurrence; the cumulative incidence of local recurrence was 1·44% (95% CI 0·51–2·38) with APBI and 0·92% (0·12–1·73) with whole-breast irradiation (difference 0·52%, 95% CI –0·72 to 1·75; p=0·42). No grade 4 late side-effects were reported. The 5-year risk of grade 2–3 late side-effects to the skin was 3·2% with APBI versus 5·7% with whole-breast irradiation (p=0·08), and 5-year risk of grade 2–3 subcutaneous tissue late side-effects was 7·6% versus 6·3% (p=0·53). The risk of severe (grade 3) fibrosis at 5 years was 0·2% with whole-breast irradiation and 0% with APBI (p=0·46).

Interpretation The difference between treatments was below the relevance margin of 3 percentage points. Therefore, adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery in patients with early breast cancer is not inferior to adjuvant whole-breast irradiation with respect to 5-year local control, disease-free survival, and overall survival.

Adjuvant APBI using multicatheter brachytherapy after breast-conserving surgery in patients with early breast cancer **is not inferior to adjuvant whole-breast irradiation** with respect to **5-year local control, disease-free survival, and overall survival**

ECC 2015 & ASTRO 2015

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1.b) Partial breast RT

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journal homepage: www.thegreenjournal.com

GEC ESTRO Recommendations

Recommendations from GEC ESTRO Breast Cancer Working Group (I): Target definition and target delineation for accelerated or boost Partial Breast Irradiation using multicatheter interstitial brachytherapy after breast conserving closed cavity surgery

Vratislav Strnad [a,*], Jean-Michel Hannoun-Levi [b], Jose-Luis Guinot [c], Kristina Lössl [d], Daniela Kauer-Dorner [e], Alexandra Resch [e], György Kovács [f], Tibor Major [g], Erik Van Limbergen [h], On behalf of Working Group Breast Cancer of GEC-ESTRO

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1.b) Partial breast RT

Summary of proposed recommendations

According to the GEC-ESTRO Breast Cancer Working Group the following information and procedures are primarily needed for an appropriate delineation of CTV (PTV):

1. DETAILED KNOWLEDGE about primary surgical procedure (type of surgery, use, number and location of surgical clips, tumour bed related position of the skin scar), about all details of the pathology report including size of the resection margins in at least 6 directions, as well as about preoperative imaging (mammograms and/or MRI and/or ultrasound).
2. Identification of the TUMOUR LOCALIZATION before breast conserving surgery inside the breast and translation of this information into current CT imaging data set.
3. Calculation of the size of the TOTAL SAFETY MARGINS needed to cover the CTV in all 6 directions that should be at least 2 cm from the tumour.
4. DEFINITION OF TARGET – CTV/PTV.
5. DELINEATION OF THE TARGET – CTV/PTV.

For target delineation after closed cavity surgery we recommend the following steps

1. Perform a CT with marks on the scar.
2. Delineation of clips.
3. Delineation of surgical bed – whole surgical scar (WS) inside breast.
4. Delineation of ImTV (Imaging correlated Target Volume).
5. Delineation of ETB (Estimated Tumour Bed).
6. Delineation of CTV (Clinical Target Volume).
7. Delineation of PTV (Planning Target Volume).

In case of oncoplastic surgery no recommendations can be given but in selected cases of limited rotational flaps the CTV can be defined as the sum of the clipped area (CA) and the distance of 20 mm minus the smallest surgical free margin (SFM) defined by the pathologist (CTV = CA + (20-SFM). The PTV is defined as the CTV + 10 mm.

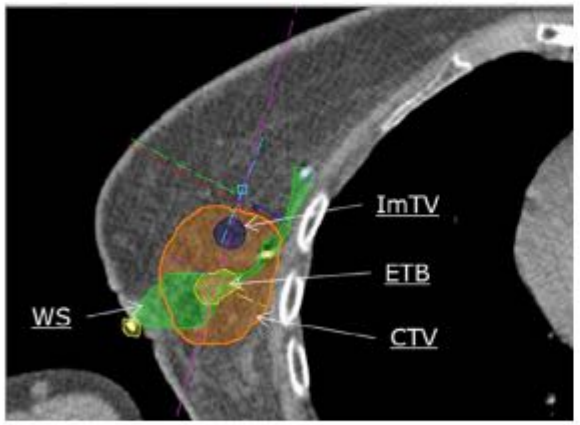

Fig. 4. Clinical Target Volume (CTV).

Strnad et al. Radiother Oncol 2015

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1.b) Partial breast RT

No significant difference in term of IBRT and OS between two arms; APBI displayed a significantly better toxicity profile

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Available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial

Lorenzo Livi [a], Icro Meattini [a,*], Livia Marrazzo [b], Gabriele Simontacchi [a], Stefania Pallotta [b], Calogero Saieva [c], Fabiola Paiar [a], Vieri Scotti [a], Carla De Luca Cardillo [a], Paolo Bastiani [d], Lorenzo Orzalesi [e], Donato Casella [e], Luis Sanchez [e], Jacopo Nori [f], Massimiliano Fambrini [g], Simonetta Bianchi [h]

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[d] *Radiotherapy Unit, Azienda Sanitaria 10, University of Florence, Florence, Italy*
[e] *Department of Surgery, University of Florence, Florence, Italy*
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1.b) Partial breast RT

International Journal of Radiation Oncology biology • physics

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Clinical Investigation

Preoperative Single-Fraction Partial Breast Radiation Therapy: A Novel Phase 1, Dose-Escalation Protocol With Radiation Response Biomarkers

Janet K. Horton, MD,* Rachel C. Blitzblau, MD, PhD,* Sua Yoo, PhD,* Joseph Geradts, MD,† Zheng Chang, PhD,* Jay A. Baker, MD,‡ Gregory S. Georgiade, MD,§ Wei Chen, PhD,‖ Sharareh Siamakpour-Reihani, PhD,* Chunhao Wang, BS,* Gloria Broadwater, MS,¶ Jeff Groth, BA,† Manisha Palta, MD,* Mark Dewhirst, DVM, PhD,* William T. Barry, PhD,#,** Eileen A. Duffy, RGN,* Jen-Tsan A. Chi, MD, PhD,††,‡‡ and E. Shelley Hwang, MD§

Preoperative single-dose radiation therapy to intact breast tumors is well tolerated. Radiation response is marked by early indicators of cell death in this biologically favorable patient cohort. Preoperative radiation should be tested in future clinical trials because it has the potential to challenge the current treatment paradigm and provide a path forward to identify radiation response biomarkers.

1.c) IORT

International Journal of Radiation Oncology biology • physics

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EDITORIAL

Pride, Prejudice, or Science: Attitudes Towards the Results of the TARGIT-A Trial of Targeted Intraoperative Radiation Therapy for Breast Cancer

Jayant S. Vaidya, MBBS, MS, DNB, FRCS, PhD,*,**,†† Max Bulsara, PhD,‡ Frederik Wenz, MD,† David Joseph, MD, FRCR,§ Christobel Saunders, FRCS,||,¶¶ Samuele Massarut, MD,§§ Henrik Flyger, MD,‡‡ Wolfgang Eiermann, MD,## Michael Alvarado, MD,¶¶ Laura Esserman, MD, MBA,¶¶ Mary Falzon, FRCPath,# Chris Brew-Graves, MSc,* Ingrid Potyka, PhD,* Jeffrey S. Tobias, MD, FRCR,¶ and Michael Baum, MBBS, MD, FRCS*, on behalf of the TARGIT trialists' group

The level 1 randomized evidence produced by the TARGIT-A trial shows that TARGIT-IORT with Intrabeam during lumpectomy, is effective and has fewer side effects than the conventional alternative of whole breast radiation therapy.

1.c) IORT

Replies:

Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):957-8. doi: 10.1016/j.ijrobp.2015.05.027. Epub 2015 Jul 14.

In Regard to Vaidya et al.

Kirby A[1], Hanna G[2], Wilcox M[3], MacKenzie M[3].

Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):952-3. doi: 10.1016/j.ijrobp.2015.05.032. Epub 2015 Jul 14.

In Regard to Vaidya et al.

Wazer DE[1], Hepel JT[2], Riker AI[3], Harness JK[4], Chung C[5], Khan AJ[6], Offersen BV[7], Poortmans P[8], Taghian A[9].

Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):959-60. doi: 10.1016/j.ijrobp.2015.05.028. Epub 2015 Jul 14.

In Regard to Vaidya et al.

Kaidar-Person O[1], Wygoda M[2], Symon Z[3], Corn BW[4], Kuten A[5].

Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):960-1. doi: 10.1016/j.ijrobp.2015.05.030. Epub 2015 Jul 14.

In Regard to Vaidya et al.

Meattini I[1], Boersma L[2], Livi L[1], Kirkove C[3], Gabryś D[4], Somaiah N[5], Remouchamps V[6], Elkhuizen PH[7], Kirova Y[8], Rivera S[9].

The number of events and length of follow-up in TARGIT-A is too short

basic errors in the justification of the margin of NI

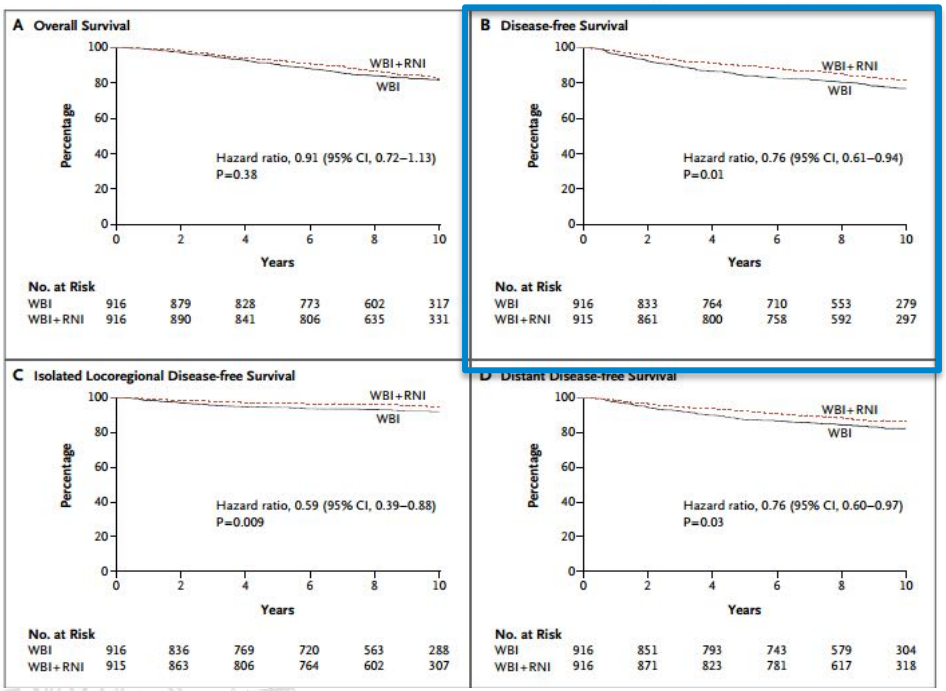
1.e) Nodal RT

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 23, 2015 VOL. 373 NO. 4

Regional Nodal Irradiation in Early-Stage Breast Cancer

Timothy J. Whelan, B.M., B.Ch., Ivo A. Olivotto, M.D., Wendy R. Parulekar, M.D., Ida Ackerman, M.D., Boon H. Chua, M.B., B.S., Ph.D., Abdenour Nabid, M.D., Katherine A. Vallis, M.B., B.S., Ph.D., Julia R. White, M.D., Pierre Rousseau, M.D., Andre Fortin, M.D., Lori J. Pierce, M.D., Lee Manchul, M.D., Susan Chafe, M.D., Maureen C. Nolan, M.D., Peter Craighead, M.D., Julie Bowen, M.D., David R. McCready, M.D., Kathleen I. Pritchard, M.D., Karen Gelmon, M.D., Yvonne Murray, B.Sc., Judy-Anne W. Chapman, Ph.D., Bingshu E. Chen, Ph.D., and Mark N. Levine, M.D., for the MA.20 Study Investigators*



Among women with **node-positive or high risk node-negative** breast cancer, the addition of **regional nodal irradiation** to whole-breast irradiation **did not improve OS**, but **reduced the rate of breast-cancer recurrence**

1.e) Nodal RT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

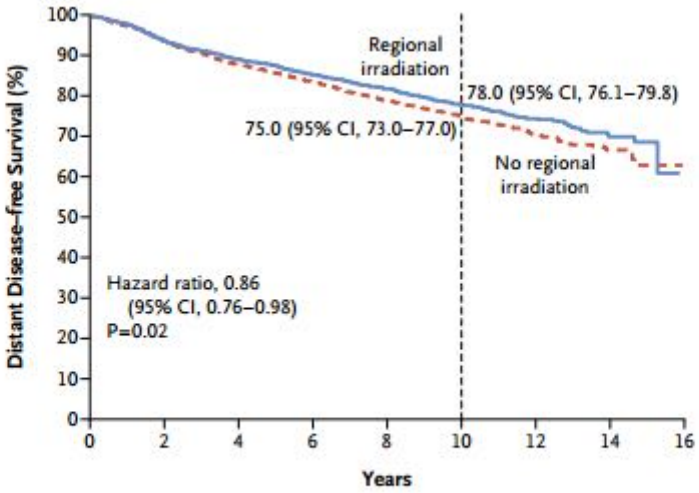
Internal Mammary and Medial Supraclavicular Irradiation in Breast Cancer

P.M. Poortmans, S. Collette, C. Kirkove, E. Van Limbergen, V. Budach, H. Struikmans, L. Collette, A. Fourquet, P. Maingon, M. Valli, K. De Winter, S. Marnitz, I. Barillot, L. Scandolaro, E. Vonk, C. Rodenhuis, H. Marsiglia, N. Weidner, G. van Tienhoven, C. Glanzmann, A. Kuten, R. Arriagada, H. Bartelink, and W. Van den Bogaert, for the EORTC Radiation Oncology and Breast Cancer Groups*

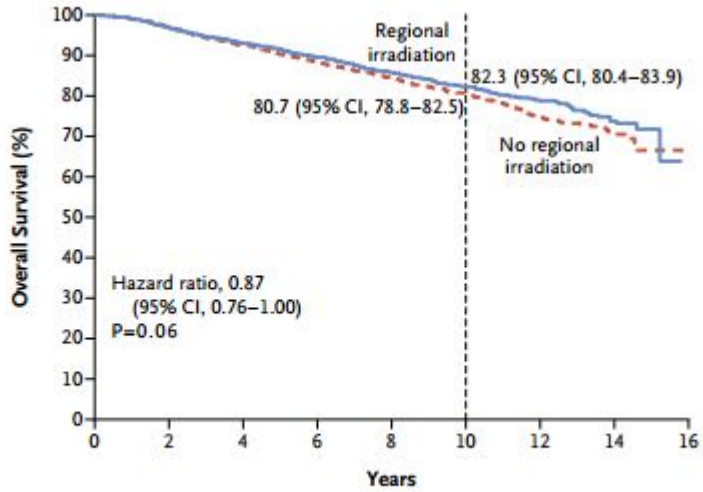
CONCLUSIONS

In patients with early-stage breast cancer, irradiation of the regional nodes had a marginal effect on overall survival. Disease-free survival and distant disease-free survival were improved, and breast-cancer mortality was reduced. (Funded by Fonds Cancer; ClinicalTrials.gov number, NCT00002851.)

1.e) Nodal RT



No. at Risk									No. of Events
No regional irradiation	2002	1862	1728	1606	1382	890	403	113	523
Regional irradiation	2002	1866	1764	1650	1464	939	437	117	462



No. at Risk									No. of Events
No regional irradiation	2002	1926	1819	1698	1475	969	434	119	429
Regional irradiation	2002	1931	1839	1732	1532	988	466	124	382

Poortmans et al. NEJM 2015

2.a) HER2 pos **The Lancet Oncology 2015**

Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial

Sara A Hurvitz, Fabrice Andre, Zefei Jiang, Zhimin Shao, Max S Mano, Silvia P Neciosup, Ling-Min Tseng, Qingyuan Zhang, Kunwei Shen, Donggeng Liu, Lydia M Dreosti, Howard A Burris, Masakazu Toi, Marc E Buyse, David Cabaribere, Mary-Ann Lindsay, Shantha Rao, Lida Bubuteishvili Pacaud, Tetiana Taran, Dennis Slamon

Findings Between Sept 10, 2009, and Dec 16, 2012, 719 patients were randomly assigned to receive everolimus (n=480) or placebo (n=239). Median follow-up was 41·3 months (IQR 35·4–46·6). In the full population, median progression-free survival was 14·95 months (95% CI 14·55–17·91) with everolimus versus 14·49 months (12·29–17·08) with placebo (hazard ratio 0·89, 95% CI 0·73–1·08; p=0·1166). In the HR-negative subpopulation (n=311), median progression-free survival with everolimus was 20·27 months (95% CI 14·95–24·08) versus 13·08 months (10·05–16·56) with placebo (hazard ratio 0·66, 95% CI 0·48–0·91; p=0·0049); however, the protocol-specified significance threshold (p=0·0044) was not crossed. The most common adverse events with everolimus were stomatitis (314 [67%] of 472 patients in the everolimus group *vs* 77 [32%] of 238 patients in the placebo group), diarrhoea (267 [57%] *vs* 111 [47%] patients), and alopecia (221 [47%] *vs* 125 [53%]). The most frequently reported grade 3 or 4 adverse events in the everolimus group versus the placebo group were neutropenia (117 [25%] *vs* 35 [15%]), stomatitis (59 [13%] *vs* three [1%]), anaemia (46 [10%] *vs* six [3%]) and diarrhoea (43 [9%] *vs* 10 [4%]) On-treatment adverse event-related deaths were reported in 17 (4%) patients in the everolimus group and none in the placebo group.

Interpretation Although progression-free survival was not significantly different between groups in the full analysis population, the 7·2 months prolongation we noted with the addition of everolimus in the HR-negative, HER2-positive population warrants further investigation, even if it did not meet prespecified criteria for significance. The safety profile was generally consistent with what was previously reported in BOLERO-3. Proactive monitoring and early management of adverse events in patients given everolimus and chemotherapy is crucial.

2.a) HER2 pos

Feasibility and Cardiac Safety of Trastuzumab Emtansine After Anthracycline-Based Chemotherapy As (neo)Adjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Early-Stage Breast Cancer

Ian E. Krop, Thomas M. Suter, Chau T. Dang, Luc Dirix, Gilles Romieu, Claudio Zamagni, Marc L. Citron, Mario Campone, Na Xu, Melanie Smitt, and Luca Gianni

A B S T R A C T

Purpose
Trastuzumab emtansine (T-DM1), an antibody–drug conjugate comprising the cytotoxic agent DM1, a stable linker, and trastuzumab, has demonstrated substantial activity in human epidermal growth factor receptor 2 (HER2) –positive metastatic breast cancer, raising interest in evaluating the feasibility and cardiac safety of T-DM1 in early-stage breast cancer (EBC).

Patients and Methods
Patients (N = 153) with HER2-positive EBC and prechemotherapy left ventricular ejection fraction (LVEF) ≥ 55% received (neo)adjuvant doxorubicin plus cyclophosphamide or fluorouracil plus epirubicin plus cyclophosphamide followed by T-DM1 for four cycles. Patients could then receive three to four cycles of optional docetaxel with or without trastuzumab. T-DM1 was then resumed with optional radiotherapy (sequential or concurrent) for 1 year (planned) of HER2-directed therapy. The coprimary end points were rate of prespecified cardiac events and safety.

Results
Median follow-up was 24.6 months. No prespecified cardiac events or symptomatic congestive heart failures were reported. Four patients (2.7%) had asymptomatic LVEF declines (≥ 10 percentage points from baseline to LVEF < 50%), leading to T-DM1 discontinuation in one patient. Of 148 patients who received ≥ one cycle of T-DM1, 82.4% completed the planned 1-year duration of HER2-directed therapy. During T-DM1 treatment, 38.5% and 2.7% of patients experienced grade 3 and 4 adverse events, respectively. Approximately 95% of patients receiving T-DM1 plus radiotherapy completed ≥ 95% of the planned radiation dose with delay ≤ 5 days.

Conclusion
Use of T-DM1 for approximately 1 year after anthracycline-based chemotherapy was feasible and generally well tolerated by patients with HER2-positive EBC, providing support for phase III trials of T-DM1 in this setting.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

2.a) HER2 pos

ASCO

Phase III, randomized study of trastuzumab emtansine (T-DM1) ± pertuzumab (P) vs trastuzumab + taxane (HT) for first-line treatment of HER2-positive MBC: Primary results from the MARIANNE study.

Meeting:
2015 ASCO Annual Meeting

Session Type and Session Title:
Oral Abstract Session, Breast Cancer—HER2/ER

Author(s):
Paul Anthony Ellis, Carlos H. Barrios, Wolfgang Eiermann, Masakazu Toi, Young-Hyuck Im, Pier Franco Conte, Miguel Martin, Tadeusz Pienkowski, Xavier B. Pivot, Howard A. Burris, Alexander Strasak, Monika Patre, Edith A. Perez; Guy's Hospital and Sarah Cannon Research Institute, London, United Kingdom; PUCRS School of Medicine, Porto Alegre, Brazil; Interdisciplinary Oncology Center, Munich, Germany; Graduate School of Medicine, Kyoto University, Kyoto, Japan; Samsung Medical Center, Seoul, South Korea; Department of Surgery, Oncology and Gastroenterology, University of Padova and Istituto Oncologico Veneto, Padova, Italy; Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense de Madrid, Madrid, Spain; Postgraduate Medical Education Center, Warsaw, Poland; University Hospital Jean Minjoz, Besançon, France; Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN; F. Hoffmann-La Roche Ltd, Basel, Switzerland; F. Hoffmann-La Roche Ltd., Basel, Switzerland; Mayo Clinic, Jacksonville, FL

Conclusions: These data demonstrate non-inferiority in PFS between T-DM1–containing arms and control. T-DM1–containing regimens were associated with a different toxicity profile than the control regimen. Clinical trial information: **NCT01120184**

2.a) HER2 pos

JAMA Oncology

Original Investigation

Association of Stromal Tumor-Infiltrating Lymphocytes With Recurrence-Free Survival in the N9831 Adjuvant Trial in Patients With Early-Stage HER2-Positive Breast Cancer

Edith A. Perez, MD; Karla V. Ballman, PhD; Kathy S. Tenner, BS; E. Aubrey Thompson, PhD; Sunil S. Badve, MD; Helen Bailey, MD; Frederick L. Baehner, MD

CONCLUSIONS AND RELEVANCE This analysis of participants in the N9831 trial found that the presence of STILs was prognostically associated with RFS in patients treated with chemotherapy alone but not in patients treated with chemotherapy plus trastuzumab. High levels of STILs were associated with lack of trastuzumab therapy benefit, in contrast to a previously reported association between increased levels of STILs and increased trastuzumab benefit in HER2-positive patients.

JAMA Oncol. Published online October 15, 2015.

2.b) HER2 neg

The Lancet Oncology 2015

Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial

Helena M Earl, Louise Hiller, Janet A Dunn, Clare Blenkinsop, Louise Grybowicz, Anne-Laure Vallier, Jean Abraham, Jeremy Thomas, Elena Provenzano, Luke Hughes-Davies, Ioannis Gounaris, Karen McAdam, Stephen Chan, Rizvana Ahmad, Tamas Hickish, Stephen Houston, Daniel Rea, John Bartlett, Carlos Caldas, David A Cameron, Larry Hayward, for the ARTemis Investigators

Findings Between May 7, 2009, and Jan 9, 2013, we randomly allocated 800 participants to D-FEC (n=401) and Bev+D-FEC (n=399). 781 patients were available for the primary endpoint analysis. Significantly more patients in the bevacizumab group achieved a pathological complete response compared with those treated with chemotherapy alone: 87 (22%, 95% CI 18–27) of 388 patients in the Bev+D-FEC group compared with 66 (17%, 13–21) of 393 patients in the D-FEC group (p=0·03). Grade 3 and 4 toxicities were reported at expected levels in both groups, although more patients had grade 4 neutropenia in the Bev+D-FEC group than in the D-FEC group (85 [22%] *vs* 68 [17%]).

Interpretation Addition of four cycles of bevacizumab to D-FEC in HER2-negative early breast cancer significantly improved pathological complete response. However, whether the improvement in pathological complete response will lead to improved disease-free and overall survival outcomes is unknown and will be reported after longer follow-up. Meta-analysis of available neoadjuvant trials is likely to be the only way to define subgroups of early breast cancer that would have clinically significant long-term benefit from bevacizumab treatment.

2.b) HER2 neg

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 16, 2015 VOL. 373 NO. 3

Palbociclib in Hormone-Receptor–Positive Advanced Breast Cancer

Nicholas C. Turner, M.D., Ph.D., Jungsil Ro, M.D., Fabrice André, M.D., Ph.D., Sherene Loi, M.D., Ph.D., Sunil Verma, M.D., Hiroji Iwata, M.D., Nadia Harbeck, M.D., Sibylle Loibl, M.D., Cynthia Huang Bartlett, M.D., Ke Zhang, Ph.D., Carla Giorgetti, Ph.D., Sophia Randolph, M.D., Ph.D., Maria Koehler, M.D., Ph.D., and Massimo Cristofanilli, M.D.

RESULTS

The median progression-free survival was 9.2 months (95% confidence interval [CI], 7.5 to not estimable) with palbociclib–fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) with placebo–fulvestrant (hazard ratio for disease progression or death, 0.42; 95% CI, 0.32 to 0.56; P<0.001). The most common grade 3 or 4 adverse events in the palbociclib–fulvestrant group were neutropenia (62.0%, vs. 0.6% in the placebo–fulvestrant group), leukopenia (25.2% vs. 0.6%), anemia (2.6% vs. 1.7%), thrombocytopenia (2.3% vs. 0%), and fatigue (2.0% vs. 1.2%). Febrile neutropenia was reported in 0.6% of palbociclib-treated patients and 0.6% of placebo-treated patients. The rate of discontinuation due to adverse events was 2.6% with palbociclib and 1.7% with placebo.

CONCLUSIONS

Among patients with hormone-receptor–positive metastatic breast cancer who had progression of disease during prior endocrine therapy, palbociclib combined with fulvestrant resulted in longer progression-free survival than fulvestrant alone.

2.b) HER2 neg

Cisplatin plus gemcitabine versus paclitaxel plus gemcitabine as first-line therapy for metastatic triple-negative breast cancer (CBCSG006): a randomised, open-label, multicentre, phase 3 trial

Xi-Chun Hu, Jian Zhang*, Bing-He Xu, Li Cai, Joseph Ragaz, Zhong-Hua Wang, Bi-Yun Wang, Yue-E Teng, Zhong-Sheng Tong, Yue-Yin Pan, Yong-Mei Yin, Chang-Ping Wu, Ze-Fei Jiang, Xiao-Jia Wang, Gu-Yin Lou, Dong-Geng Liu, Ji-Feng Feng, Jian-Feng Luo, Kang Sun, Ya-Jia Gu, Jiong Wu, Zhi-Min Shao*

Findings From Jan 14, 2011, to Nov 14, 2013, 240 patients were assessed for eligibility and randomly assigned to treatment (120 in the cisplatin plus gemcitabine group and 120 in the paclitaxel plus gemcitabine group). 236 patients received at least one dose of assigned chemotherapy and were included in the modified intention-to-treat analysis (118 per group). After a median follow-up of 16·3 months (IQR 14·4–26·8) in the cisplatin plus gemcitabine group and 15·9 months (10·7–25·4) in the paclitaxel plus gemcitabine group, the hazard ratio for progression-free survival was 0·692 (95% CI 0·523–0·915; $p_{non\text{-}inferiority}<0·0001$, $p_{superiority}=0·009$, thus cisplatin plus gemcitabine was both non-inferior to and superior to paclitaxel plus gemcitabine. Median progression-free survival was 7·73 months (95% CI 6·16–9·30) in the cisplatin plus gemcitabine group and 6·47 months (5·76–7·18) in the paclitaxel plus gemcitabine group. Grade 3 or 4 adverse events that differed significantly between the two groups included nausea (eight [7%] *vs* one [<1%]), vomiting (13 [11%] *vs* one [<1%]), musculoskeletal pain (none *vs* ten [8%]), anaemia (39 [33%] *vs* six [5%]), and thrombocytopenia (38 [32%] *vs* three [3%]), for the cisplatin plus gemcitabine compared with the paclitaxel plus gemcitabine groups, respectively. In addition, patients in the cisplatin plus gemcitabine group had significantly fewer events of grade 1–4 alopecia (12 [10%] *vs* 42 [36%]) and peripheral neuropathy (27 [23%] *vs* 60 [51%]), but more grade 1–4 anorexia (33 [28%] *vs* 10 [8%]), constipation (29 [25%] *vs* 11 [9%]), hypomagnesaemia (27 [23%] *vs* five [4%]), and hypokalaemia (10 [8%] *vs* two [2%]). Serious drug-related adverse events were seen in three patients in the paclitaxel plus gemcitabine group (interstitial pneumonia, anaphylaxis, and severe neutropenia) and four in the cisplatin plus gemcitabine group (pathological bone fracture, thrombocytopenia with subcutaneous haemorrhage, severe anaemia, and cardiogenic syncope). There were no treatment-related deaths.

Interpretation Cisplatin plus gemcitabine could be an alternative or even the preferred first-line chemotherapy strategy for patients with metastatic triple-negative breast cancer.

2.c) Endocrine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjuvant Ovarian Suppression in Premenopausal Breast Cancer

Prudence A. Francis, M.D., Meredith M. Regan, Sc.D., Gini F. Fleming, M.D., István Láng, M.D., Eva Ciruelos, M.D., Meritxell Bellet, M.D., Hervé R. Bonnefoi, M.D., Miguel A. Climent, M.D., Gian Antonio Da Prada, M.D., Harold J. Burstein, M.D., Ph.D., Silvana Martino, D.O., Nancy E. Davidson, M.D., Charles E. Geyer, Jr., M.D., Barbara A. Walley, M.D., Robert Coleman, M.B., B.S., M.D., Pierre Kerbrat, M.D., Stefan Buchholz, M.D., James N. Ingle, M.D., Eric P. Winer, M.D., Manuela Rabaglio-Poretti, M.D., Rudolf Maibach, Ph.D., Barbara Ruepp, Pharm.D., Anita Giobbie-Hurder, M.S., Karen N. Price, B.S., Marco Colleoni, M.D., Giuseppe Viale, M.D., Alan S. Coates, M.D., Aron Goldhirsch, M.D., and Richard D. Gelber, Ph.D., for the SOFT Investigators and the International Breast Cancer Study Group*

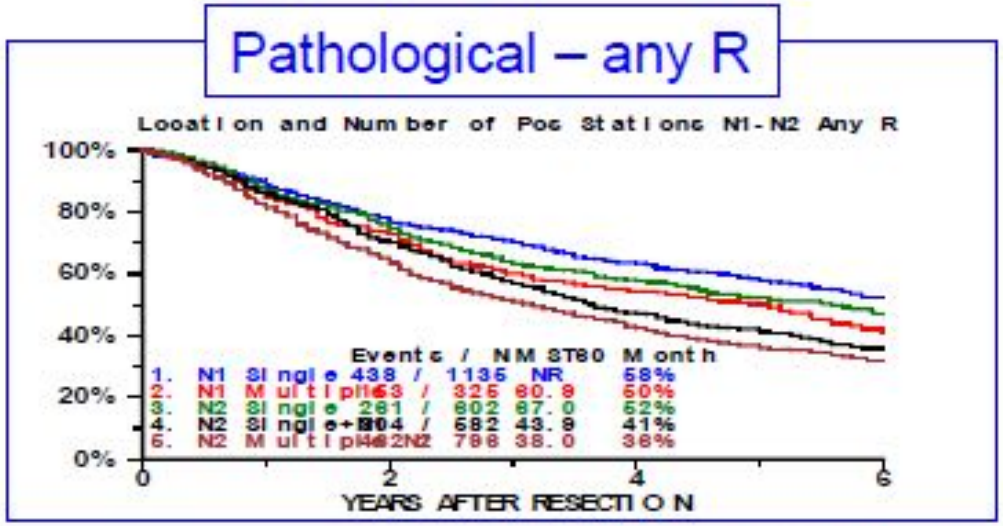
CONCLUSIONS

Adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall study population. However, for women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy and who remained premenopausal, the addition of ovarian suppression improved disease outcomes. Further improvement was seen with the use of exemestane plus ovarian suppression. (Funded by Pfizer and others; SOFT ClinicalTrials.gov number, NCT00066690.)

LUNG CANCER

Novità nella classificazione del NSCLC

Nuova proposta TNM: 8ª edizione



N1 Single = N1a
N1 Multiple = N1b
N2 Single N2 (“skip mets”) = N2a1
N2 Single N2 + N1 = N2a2
N2 Multiple N2 = N2b

Il differente interessamento *linfonodale* ha un impatto prognostico sulla sopravvivenza nei pazienti

Nuova proposta TNM: 8ª edizione

Recommendations

- M1a: as it is
- M1b: single metastasis in a single organ
- M1c: multiple metastases in a single organ or in several organs

Stratificazione prognostica dei pazienti *metastatici*

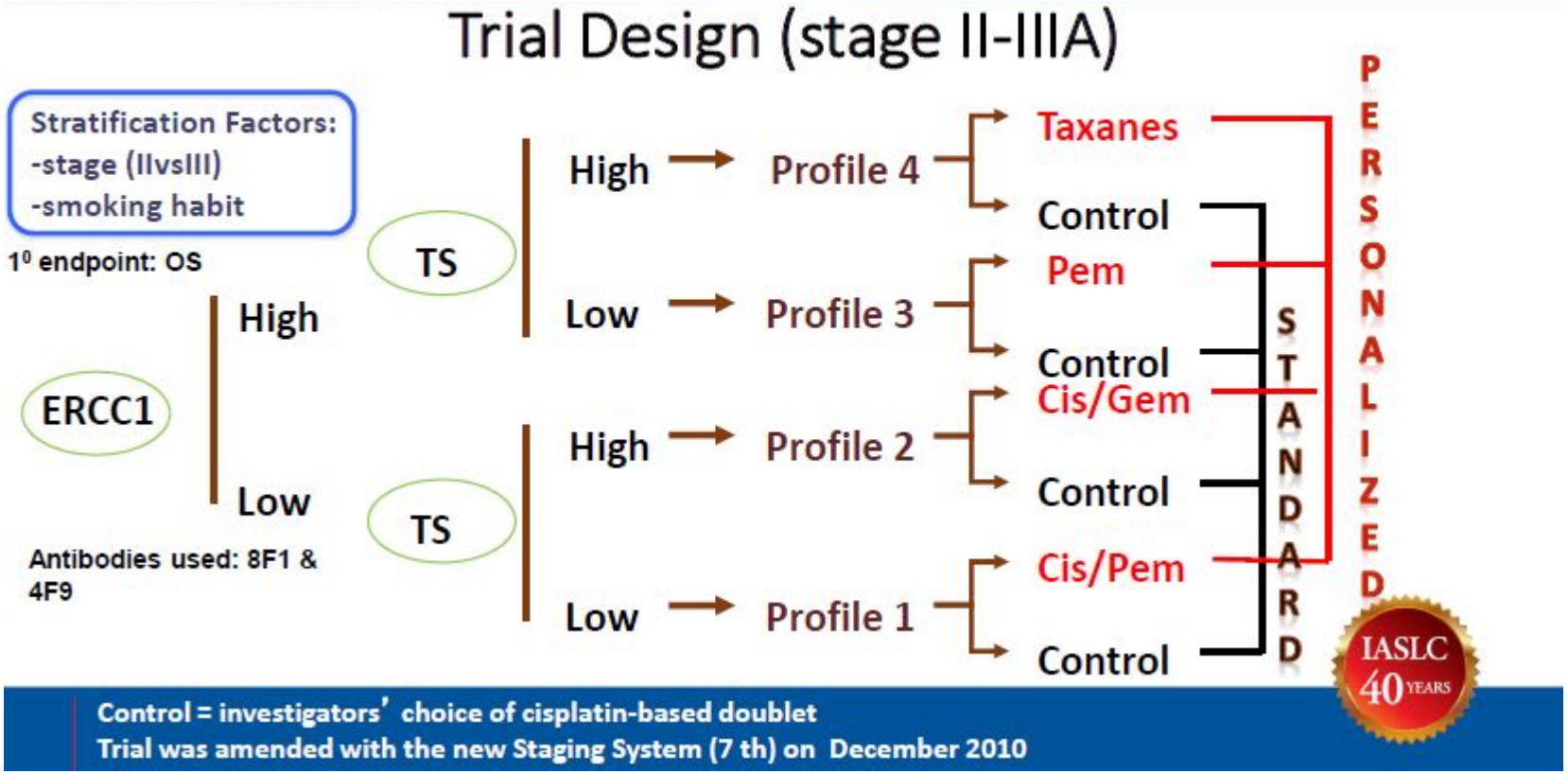
Novità nel trattamento adiuvante

Novità nel trattamento adiuvante

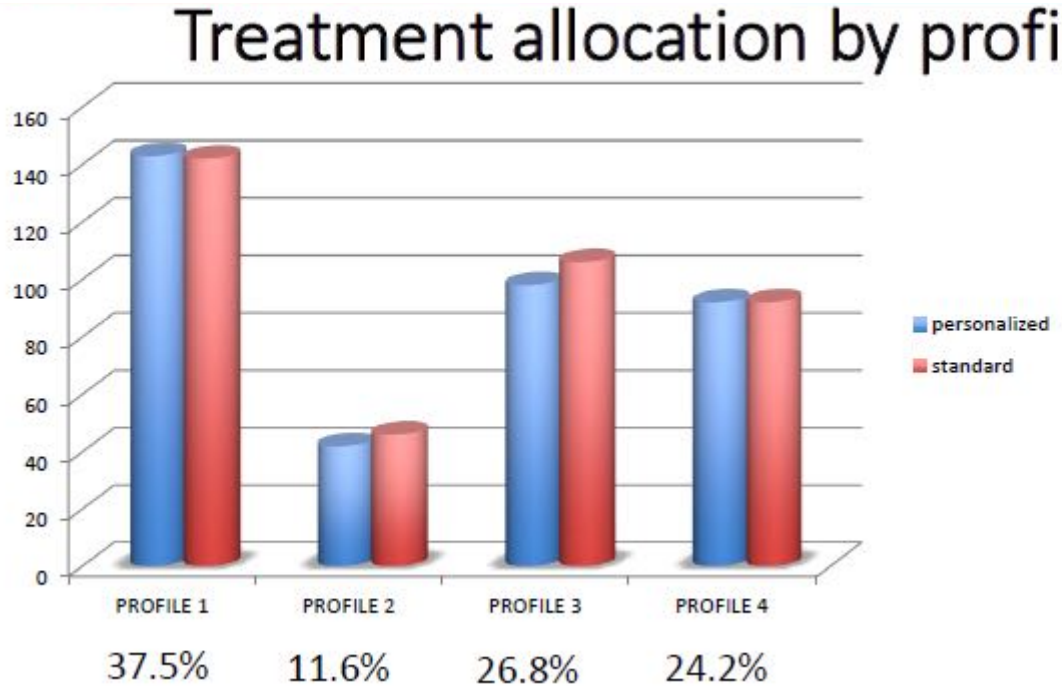
IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 • DENVER, COLORADO, USA

Preliminary Results of the International Tailored Chemotherapy Adjuvant Trial: the ITACA Trial

Silvia Novello[1], Christian Grohe[2], Michael Geissler[3], Monika Heidi Serke[4], Ida Colantonio[5], Andreas Meyer[6], Erich Stoelben[7], Francesco Cognetti[8], Wolfgang Schutte[9], Cornelia Kropf-Sanchen [10], Giuseppe Valmadre[11], Oscar Alabiso[12], Valter Torri[13], Valentina Monica[1], Giorgio Vittorio Scagliotti[1], Mauro Papotti[1] Christian Manegold [14].



- Chemioterapia adiuvante personalizzata in base a:
  - Espressione ERCC1 → sensibilità a cisplatino
  - Espressione Timidilato Sintetasi (TS) → sensibilità a pemetrexed



PROFILE1:
ERCC1 low, TS low
PROFILE2:
ERCC1 low, TS high
PROFILE3:
ERCC1 high, TS low
PROFILE4:
ERCC1 high, TS high

Accrual terminato → in attesa di risultati

Novità nel trattamento stereotassico

SBRT e early stage NSCLC: la problematica dell'accrual

- **ROSEL**

sponsorizzato da *The Netherlands Organisation for Health Research end Development*, è stato aperto a 9 centri olandesi nel 2008, ma è stato **chiuso nel 2010 dopo aver arruolato 22 pazienti su 960 previsti.**

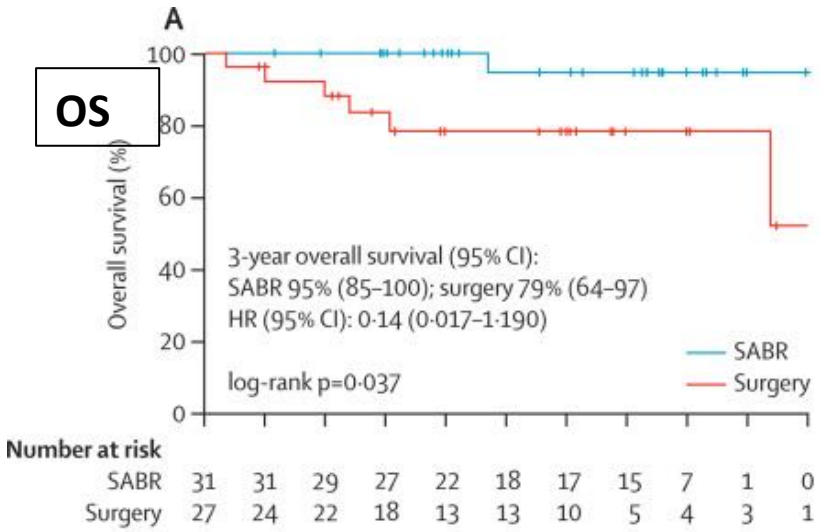
- **STARS**

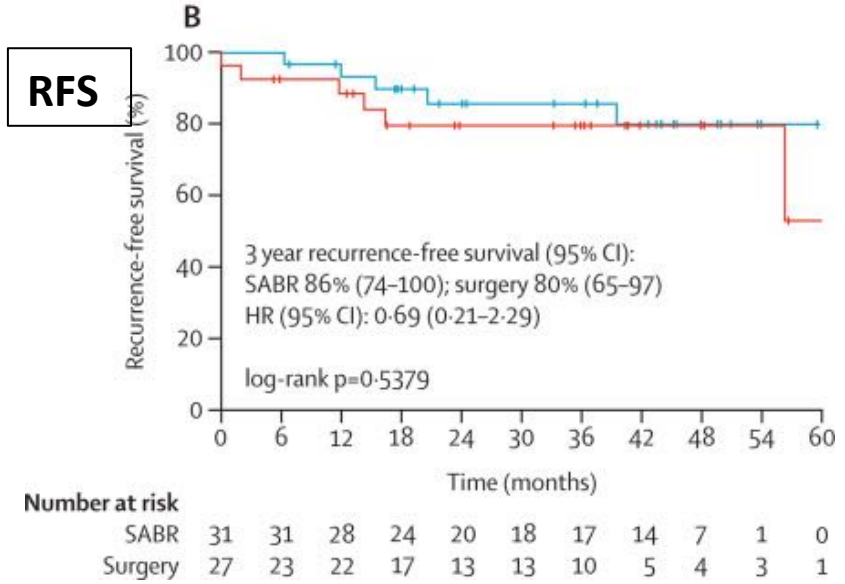
sponsorizzato da *Accuray©*, è stato aperto a 15 centri nel 2009, **chiuso nel 2013 con l'arruolamento di 36 pazienti dei 1030 previsti dallo studio.**

- **ACOSOG**

sponsorizzato dall'*American College of Surgeons*, è stato aperto a 53 centri nel 2011 e **chiuso nel 2013, arruolando 10 di 420 pazienti totali.**

SBRT vs chirurgia: evidenze più recenti

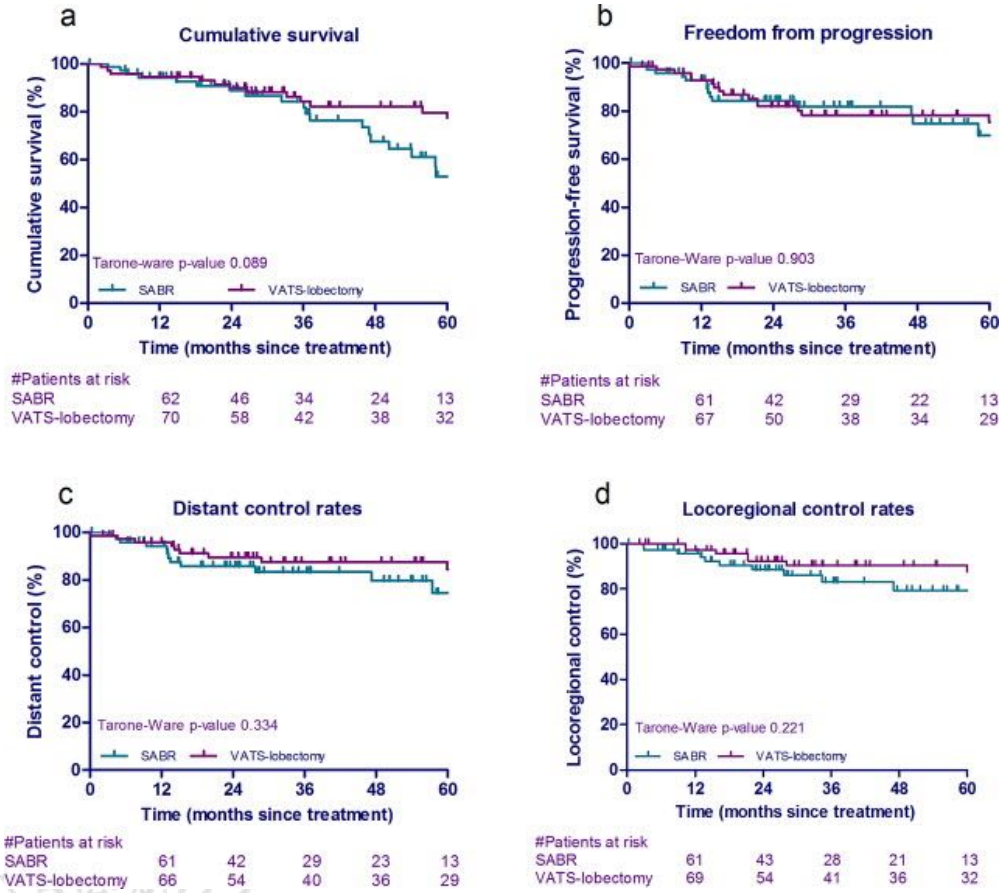




Nessuna differenza in termini di OS,RFS e insorgenza di metastasi a distanza fra SBRT e chirurgia

Chang JY et al. Lancet Oncol 2015

SBRT vs Chirurgia in NSCLC "early stage"



- 577 pazienti: 96 VATS o lobectomie + 481 SABR pazienti.
- Nessuna differenza statisticamente significativa in termini di OS, LC e metastasi a distanza fra i due gruppi di pazienti

Mokhles S et a. Lung Cancer 2015

SBRT nella popolazione geriatrica

Stereotactic Body Radiation Therapy Versus No Treatment for Early Stage Non–Small Cell Lung Cancer in Medically Inoperable Elderly Patients: A National Cancer Data Base Analysis

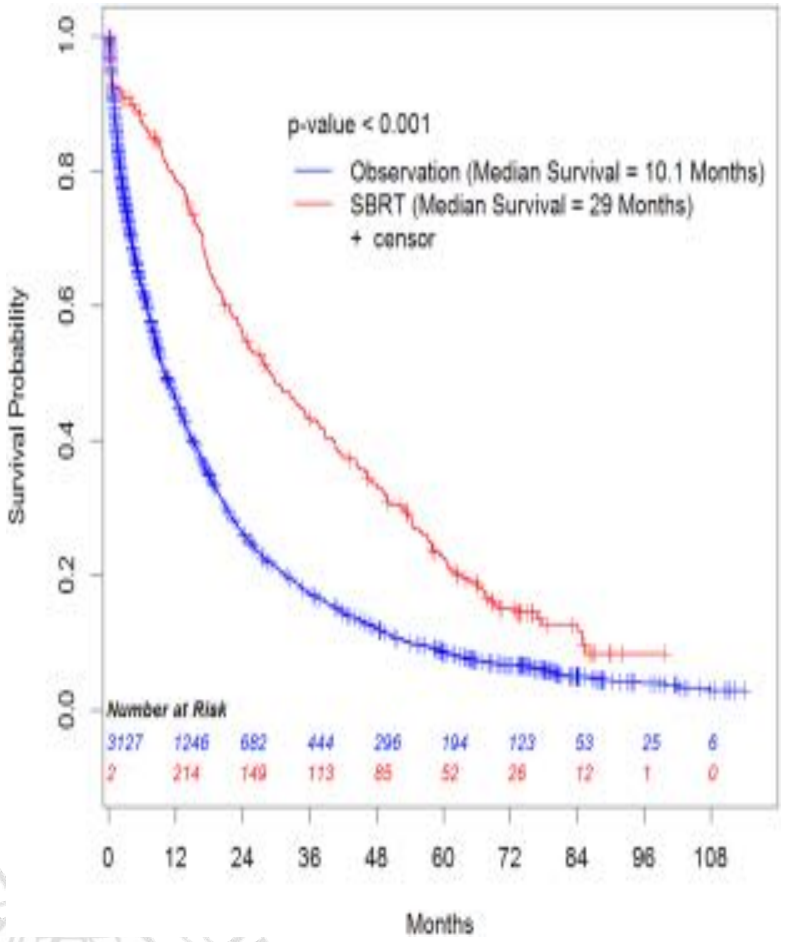
Ronica H. Nanda, MD[1,2]; Yuan Liu, PhD[2,3,4]; Theresa W. Gillespie, PhD[2,3]; John L. Mikell, MD[1,2]; Suresh S. Ramalingam, MD[2,5]; Felix G. Fernandez, MD[2,6]; Walter J. Curran, MD[1,2]; Joseph Lipscomb, PhD[2,4]; and Kristin A. Higgins, MD[1,2]

- Pazienti con età ≥ 70 anni (cT1-T3 cN0)
- 3147 pazienti ricavati da database nazionale US
- SBRT eseguita in 289 pazienti (82.%) vs sola osservazione nei restanti 2889 (91.2%)
- Comorbidità valutate con Charlston Score omogenee fra i due gruppi

Nanda RH et al. Cancer 2015

UNIVERSITÀ DEGLI STUDI FIRENZE

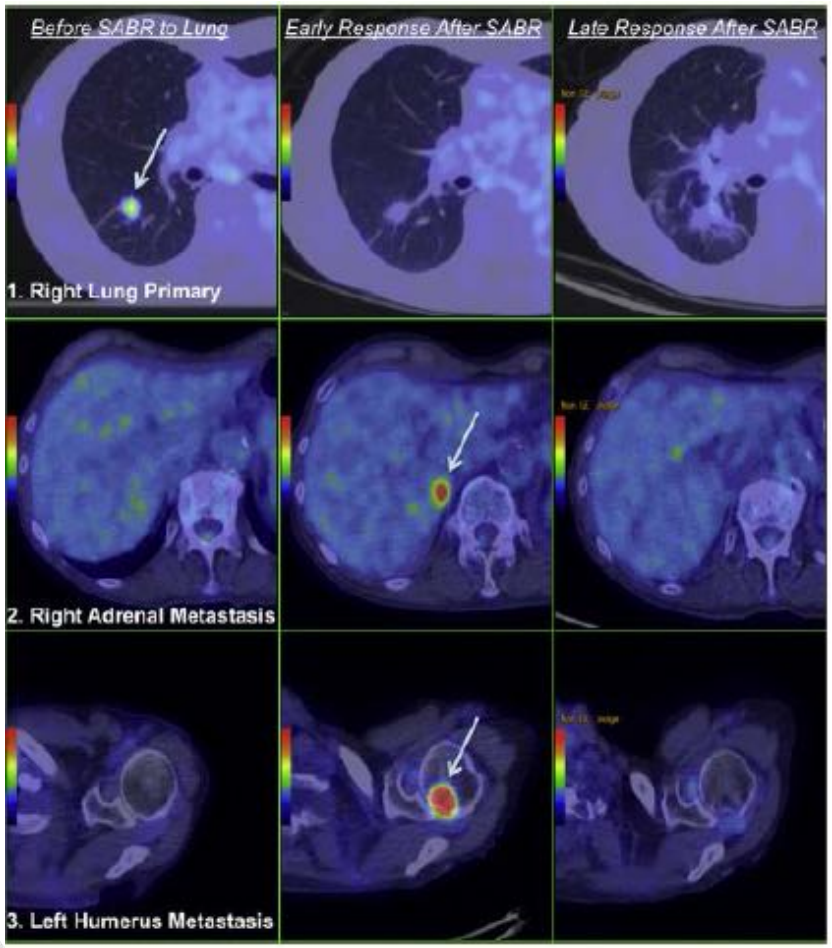
SBRT nella popolazione geriatrica

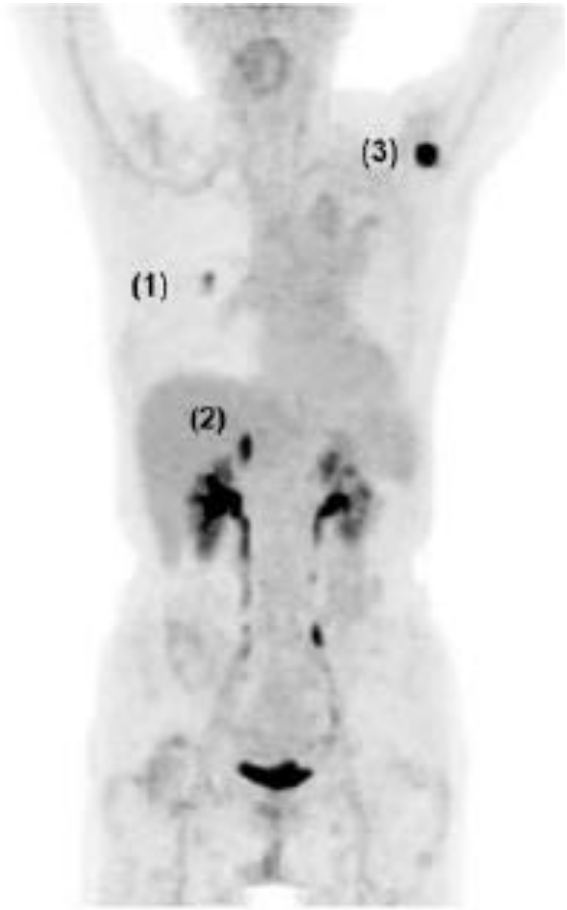


- Miglioramento della sopravvivenza grazie a SBRT in tutti i gruppi di età analizzati
- **OS mediana**: 29.1 vs 10.1 mesi **(p <0.001)**
- Beneficio della SBRT costante ed indipendente dal numero di comorbidità.

Nanda RH et al. Cancer 2015

Immunogenicità della SBRT (1)





Siva S et al. JTO 2013

Immunogenicità della SBRT (2)

Determination of peripheral blood immune cells during SABRT and surgery for early stage NSCLC (Hamlet study)

Erasmus MC Cancer Institute

- Observational cohort study
- Stage I and IIa NSCLC, pathological proven
- Blood samples on week 1,2,3,4,5,6, after start of therapy
- Flowcytometric analysis of different immune cells,
  - Both fresh and frozen
  - Before and after stimulation

Prospettive dello studio HAMLET

- La SBRT ma non la chirurgia, stimola l'attivazione delle cell T, inducendo una risposta anti-tumore specifica.
- L' iperspressione di PD-1 indotta dalla risposta immunitaria fa propendere per un utilizzo clinico di inibitori di PD(L)-1 associati alla SBRT

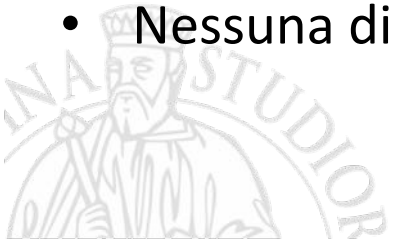
UNIVERSITÀ DEGLI STUDI FIRENZE

Novità nel trattamento del NSCLC localmente avanzato

Quale chemioterapia va associata alla RT? Le novità del WCLC 2015

OUTCOME	CDDP-ETOP	CBDCA-TAX	P-VALUE
ORR	58 %	56%	0,28
3y- SURVIVAL	30%	25%	0,5
PFS	11,2 months	9,3 months	0,15
LR	36%	37%	0,64
DM	43%	43%	0,9

- Revisione sistematica di CBDCA+TAXOLO vs CDDP+ ETOPOSIDE in associazione a RT
- 84 studi analizzati
- Nessuna differenza in termini di outcome fra i due regimi chemioterapici



WCLC 8/9/2015

Quale chemioterapia va associata alla RT? Le novità del WCLC 2015

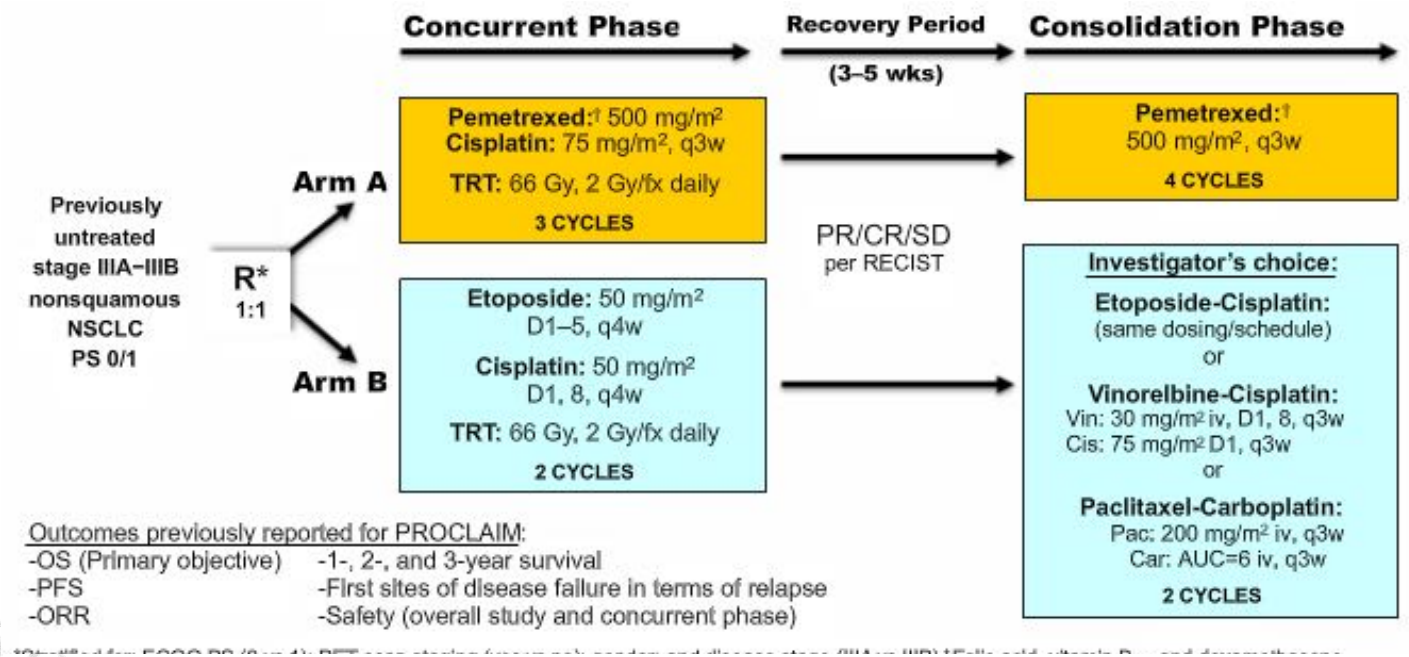
TOXICITY > grade 3	CDDP-ETOP	CBDCA-TAX	P-VALUE
PNEUMONITIS	9%	7%	0,17
ESOPHAGITIS	20%	15%	0,18
NAUSEA/VOMIT	20%	9%	0,018
ANEMIA	16%	8%	0,06
TROMBOCITOPENIA	14%	6%	0,001
NEUTROPENIA	54%	23%	<0,0001

Maggiore tossicità soggettiva ed ematologica dell'associazione CDDP +ETOPOSIDE a parità di dose e frazionamento della radioterapia

ORAL SESSION 8/9/2015

Quale chemioterapia va associata alla RT? Le novità di ASCO e WCLC 2015

RISULTATI DI SAFETY della chemioterapia di consolidamento dello studio PROCLAIM



WCLC 8/9/2015

Quale chemioterapia va associata alla RT? Le novità del WCLC 2015

RISULTATI DI SAFETY della chemioterapia di consolidamento dello studio PROCLAIM

- ASCO 2015 (Senan): nessuna differenza significativa nei due bracci di chemioterapia

  → il pemetrexed può essere utilizzato nei NSCLC-non squamosi in associazione alla RT.

- Nel **CONSOLIDAMENTO** → migliore tollerabilità del pemetrexed

Tematiche emergenti nel trattamento del NSCLC localmente avanzato

1. Trattamento dei pazienti EGFR+/ALK
2. DNA circolante
3. Immunoterapia

Trattamento "mutation-driven" nei pazienti in stadio III

Weight Loss (in prior 6 mos.)	Stratification Stage	Chemotherapy
1. ≤ 5%	1. IIIA	1. cisplatin & etoposide
2. > 5%	2. IIIB	2. paclitaxel & carboplatin

EGFR TK Mutation Cohort

RANDOMIZE

Arm 1: Induction Therapy: Erlotinib, 150 mg/day for 12 weeks* → Concurrent †chemotherapy and IMRT or 3D-CRT 60 Gy in 30 fxs

Arm 2: Concurrent †chemotherapy and radiation, 60 Gy

ALK Tran L Cohort

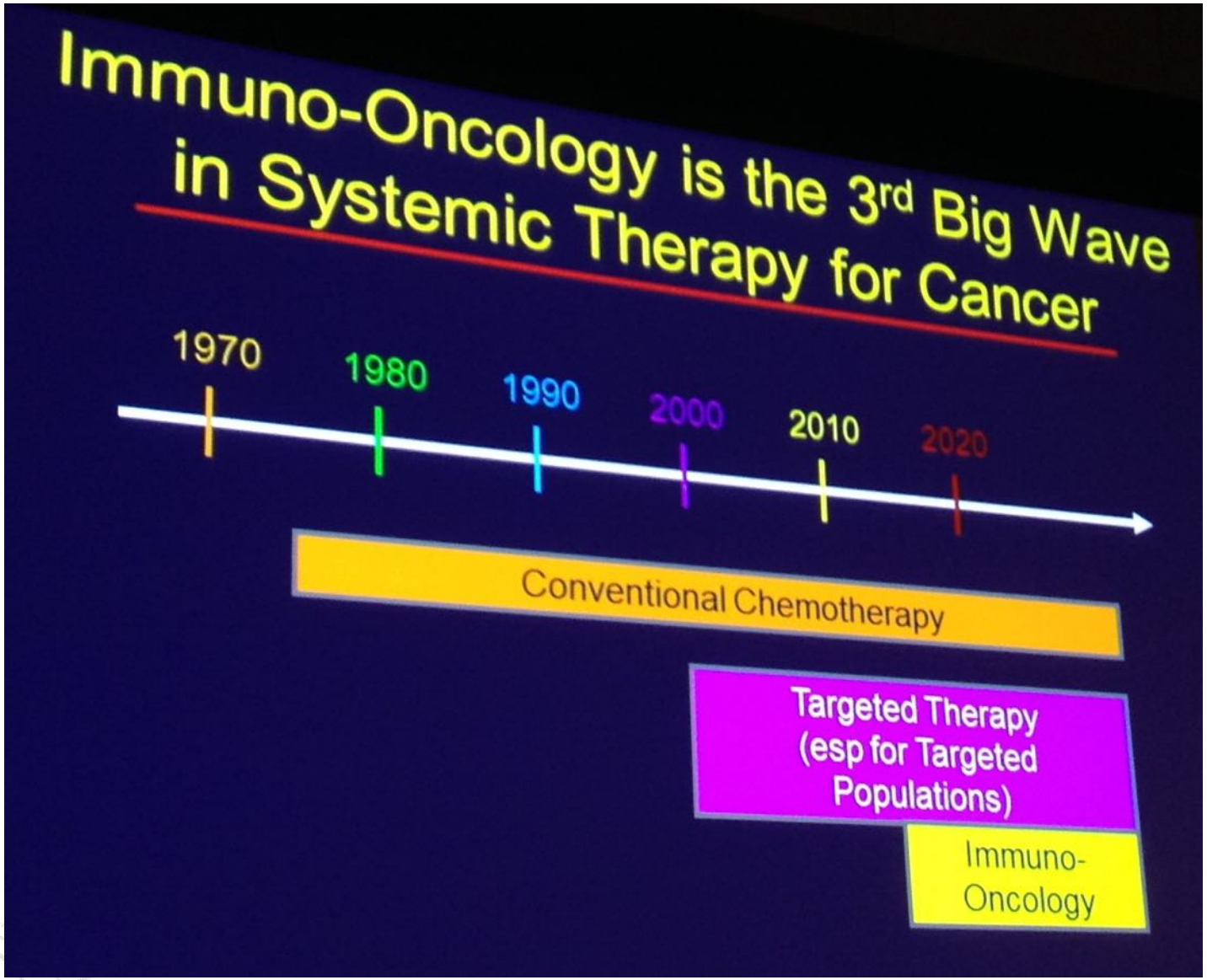
RANDOMIZE

Arm 3: Induction Therapy: Crizotinib, 250 mg/bid for 12 weeks* → Concurrent †chemotherapy and IMRT or 3D-CRT 60 Gy in 30 fxs

Arm 4: Concurrent †chemotherapy and radiation, 60 Gy

RTOG 1306

ACCRUAL IN CORSO……


Immuno-Oncology is the 3rd Big Wave in Systemic Therapy for Cancer
1970
1980
1990
2000
2010
2020
Conventional Chemotherapy
Targeted Therapy (esp for Targeted Populations)
Immuno-Oncology

Ruolo dell'immunologia nell'outcome dei pazienti in stadio III

Progression free survival

	HR [95% CI]	p-value
Performance status		0.58
≥ 1 vs. 0	1.2 [0.6 ; 2.4]	
Stage		0.05
IIIb vs. IIIa	1.9 [1.0 ; 3.8]	
Thoracic surgery		0.18
Yes vs. No	0.5 [0.2 ; 1.3]	
Histology		0.65
Other vs. AdenoK	0.9 [0.4 ; 1.7]	
PDL1		**0.03**
Positive vs. Negative	2.1 [1.1 ; 4.0]	

Overall survival

	HR [95% CI]	p-value
Performance status		0.07
≥ 1 vs. 0	2.0 [0.9 ; 4.1]	
Stage		0.03
IIIb vs. IIIa	2.3 [1.1 ; 4.6]	
Thoracic surgery		0.06
Yes vs. No	0.4 [0.1 ; 1.0]	
Histology		0.37
Other vs. AdenoK	0.7 [0.4 ; 1.4]	
PDL1		**0.01**
Positive vs. Negative	2.4 [1.2 ; 4.7]	

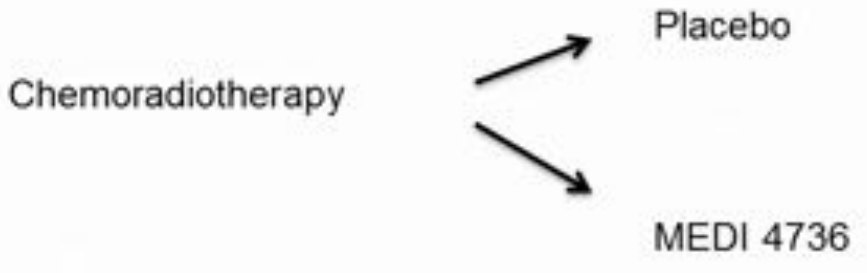
IASLC

- L'espressione di PDL1 impatta su PFS e OS in pazienti trattati con CTRT

Besse B; WCLC 9/9/2015

Immunoterapia e Stadio III: prospettive future

PACIFIC PD-L1 Phase III Trial (MEDI 4736)



Planned accrual: 702 pts, >100 sites
Endpoints: PFS, OS

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Novità nel trattamento del NSCLC in IV stadio

Immunoterapia nel IV stadio

ORIGINAL ARTICLE

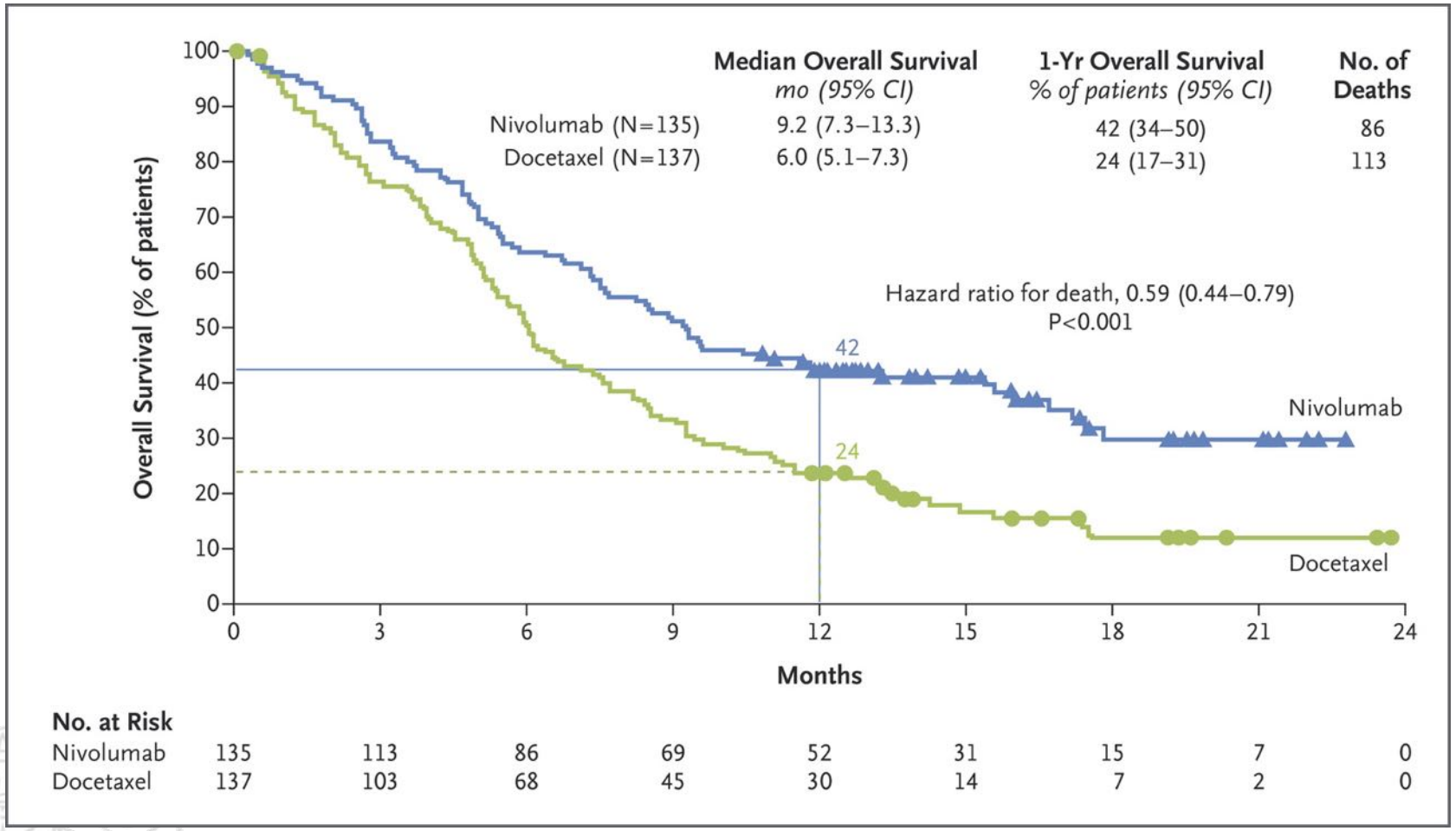
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D.,

- 272 pazienti
- Nivolumab vs Docetaxel (II linea)
- **OS**: 9.2 vs 6 mesi

Brahmer J et al. NEJM 2015

Immunoterapia nel IV stadio



Brahmer J et al. N Engl J Med 2015

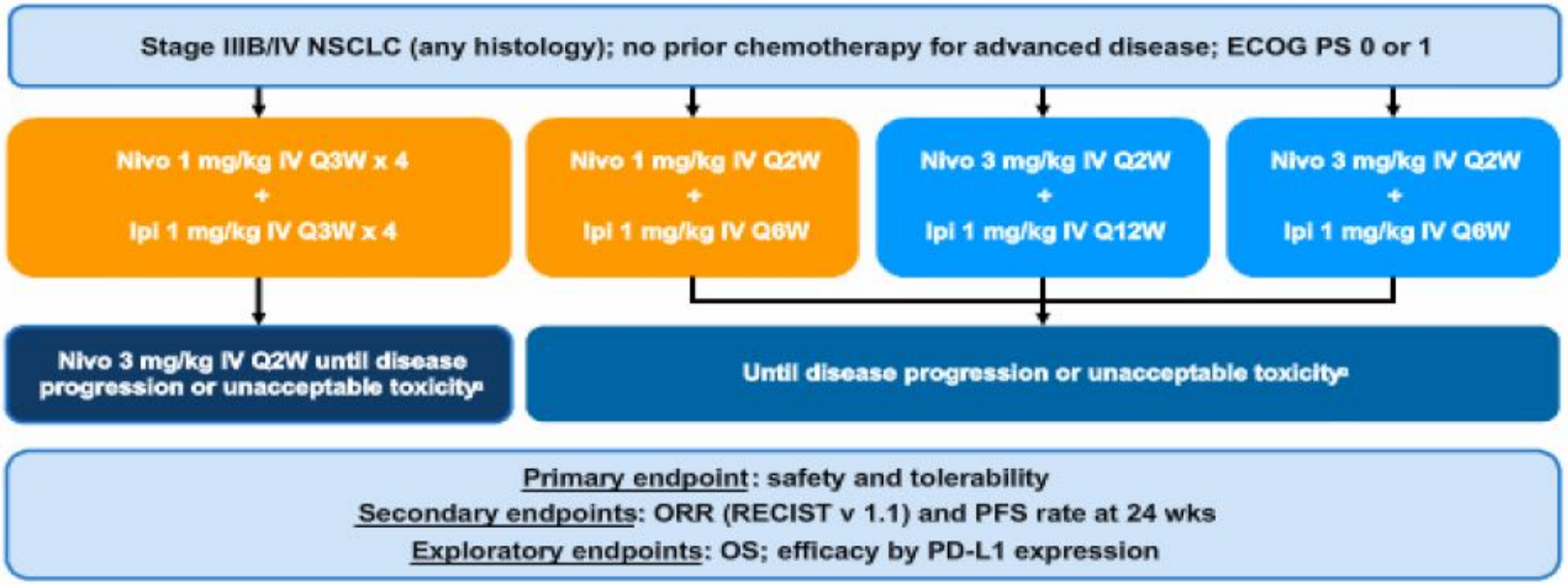
UNIVERSITÀ DEGLI STUDI FIRENZE

Prospettive emergenti

IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

CheckMate 012 Study Design: Nivolumab Plus Ipilimumab



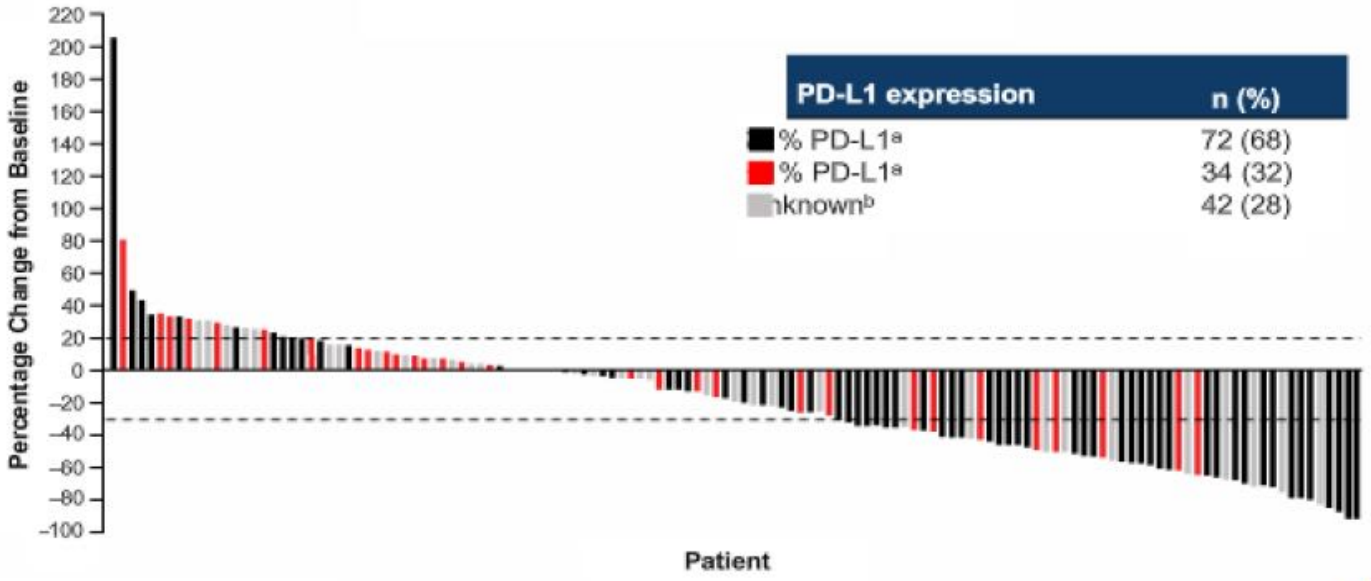
- Here, we report results from new cohorts explored to permit synergistic activity and acceptable safety profile of combination treatment with nivolumab and ipilimuma

[a]Patients tolerating study treatment permitted to continue treatment beyond RECIST v1.1-defined progression if considered to be deriving clinical benefit

IASLC 40 YEARS

HOD 01: highlight of previous day – Presenting YL WU, China

Best Percentage Change in Target Lesion Tumor Burden by Tumor PD-L1 Expression



[a]Based on patients with known PD-L1 expression
[b]Based on all treated patients
Includes all patients with baseline target lesion and ≥1 post-baseline assessment of target lesion. Positive change in tumor burden indicates tumor growth; negative chan
burden indicates tumor reduction. Not all reductions of ≥30% from baseline are PRs

IASLC

Nivolumab + Ipilimumab hanno mostrato un'alto livello di attività con risposta clinica rilevante e duratura nel tempo

Buon profilo di tossicità (G3-4 inferiori al 10%)

Attività clinica indipendente dall'espressione tumorale di PDL1

Possibile nuovo algoritmo di trattamento del NSCLC