CUrative **R**adiotherapy to the primary tumor vs. b**E**st supportive care in patients with initially metastatic **C**ervical carcinoma **(CURE-C trial)**

EORTC ROG-GCG-QLG

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EORTC

GYNECOLOGIC CANCER INTERGROUP

An Organization of International Cooperative Groups for Clinical Trials in Gynecologic Cancers

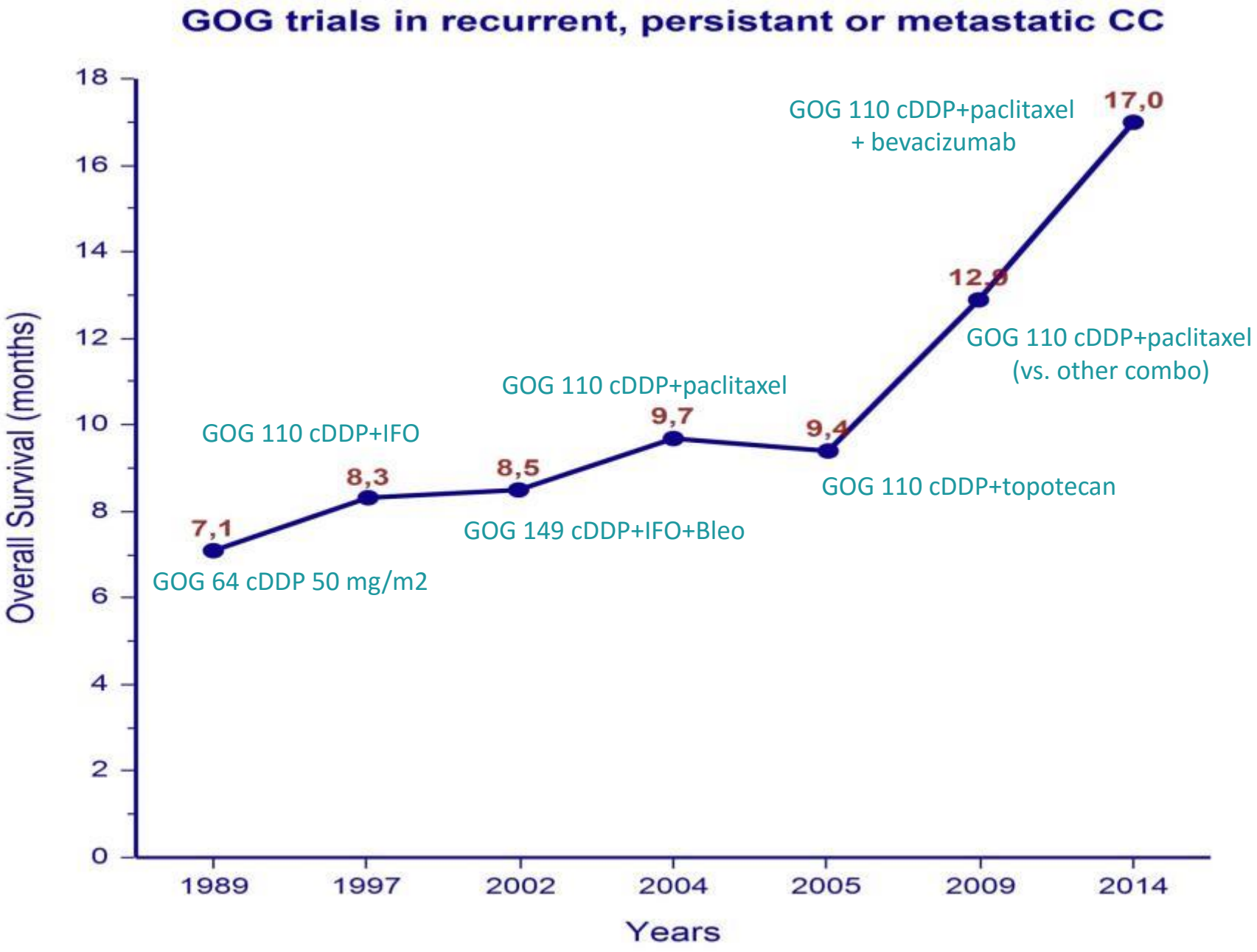
The future of cancer therapy

Introduction

- Metastatic stage IVB disease present in 15-20% of CC patients at diagnosis

- Platinum-based chemotherapy +/- individualized radiotherapy standard of care in metastatic disease (NCCN 2.2015)

No radomized trial of radiotherapy in the setting of primary metastatic CC


GOG trials in recurrent, persistant or metastatic CC
Overall Survival (months)
18
16
14
12
10
8
6
4
2
0
1989
1997
2002
2004
2005
2009
2014
Years
7,1
8,3
8,5
9,7
9,4
12,9
17,0
GOG 64 cDDP 50 mg/m2
GOG 110 cDDP+IFO
GOG 149 cDDP+IFO+Bleo
GOG 110 cDDP+paclitaxel
GOG 110 cDDP+topotecan
GOG 110 cDDP+paclitaxel
(vs. other combo)
GOG 110 cDDP+paclitaxel
+ bevacizumab

Introduction

Pelvic/para-aortic progression is still a very common cause of death even in initially metastatic cervical carcinoma: causing hydronephrosis and renal failure with uremia, bleeding, thromboembolism, pelvic organ fistulas or tumor necrosis with consequent lethal sepsis

Furthermore, primary cancer cells continue to disseminate to generate more metastatic foci (Lyng 2006, Su 2012, Donat 2014)

Distant metastases remain asymptomatic for a long time and represent a direct cause of death less frequently (e.g. liver failure, carcinomatous lung lymphangoitis, brain edema, etc.)

Radiotherapy of the primary cervical carcinoma and pelvic/para-aortic lymph nodes to a "curative" dose as used in locally advanced disease may have a huge potential to improve outcomes in initially metastatic CC

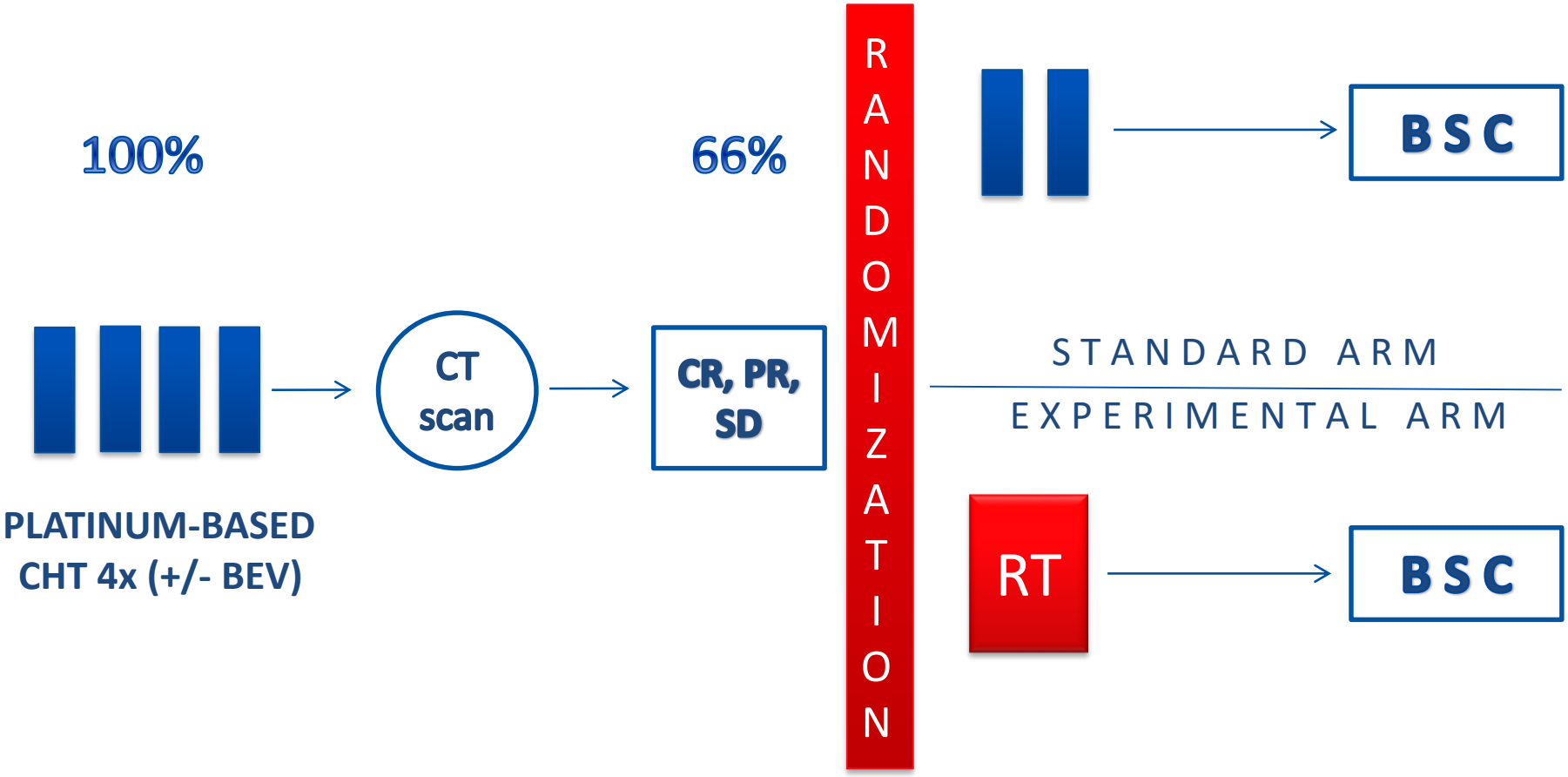
Purpose

To prove the superiority of primary tumor radiotherapy to "curative" doses over palliative treatment (best supportive care) in the setting of initially metastatic stage IVB cervical carcinoma in patients with response after standard platinum-based systemic chemotherapy

Inclusion criteria

- Histologically confirmed cancer of the uterine cervix
- Stage IVB metastatic disease
- No clinical evidence of brain metastases
- Presence of untreated primary cervical carcinoma
- No need for urgent upfront radiotherapy for life threating symptoms
- No previous RT treatment in the pelvis or para-aortic area
- No prior history of Crohn's disease, ulcerative colitis; or other chronic bowel disease
- Performance status 0-2
- Life expectancy ≥ 6 months
- Adequate hematological formulae

Phase II randomized trial



BSC: including palliative RT up to 40Gy BED2 in case of symptomatic progression, 2nd line CHT, etc.

Endpoints

Primary: **Time to progression**

Secondary:

- **Quality of life (A Translational part of the research)**
- **Overall Survival**
- **Treatment toxicity**
- **Evaluation of treatment feasibility in a multi-institutional setting**

Stratification factors

- Response to initial chemotherapy by RECIST criteria: CR, PR vs. SD
- Performance status
- Bevacizumab yes/no

Statistics

Due to the variability of the BSC, a comparative phase II design is proposed

As proposed by Korn et al (JCO 2001), a phase II comparative screening design can be implemented as a superiority phase III trial design with an increased type I error and optimistic treatment effect

For this trial, using a one sided log-rank test at a level of significance of 10% (alpha), to test for a HR=0.63 (increase from 50% to 65% event-free survival at 12 months) at 80% power would need about:

- 80 events ~100 patients in 1:1 randomization.

The event-free curves between the two arms will be compared with a non-parametric test stratified for the stratification factors

With the above assumptions, a hazard ratio of minimum would need to be observed 0.75 to reach significance