

Interactive Clinical Case Systemic Therapy for Endometrial Cancer: A New Standard?

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Systemic Therapy of Endometrial Cancer

Part 1

Adjuvant Therapy of Locally Advanced Disease

No Adjuvant Therapy

Role of External Beam Radiotherapy (EBRT)

Role of EBRT + Chemotherapy

Role of Adjuvant Chemotherapy

Role of Hormonal Therapy

My Choice

No Adjuvant Therapy

Role of External Beam Radiotherapy (EBRT)

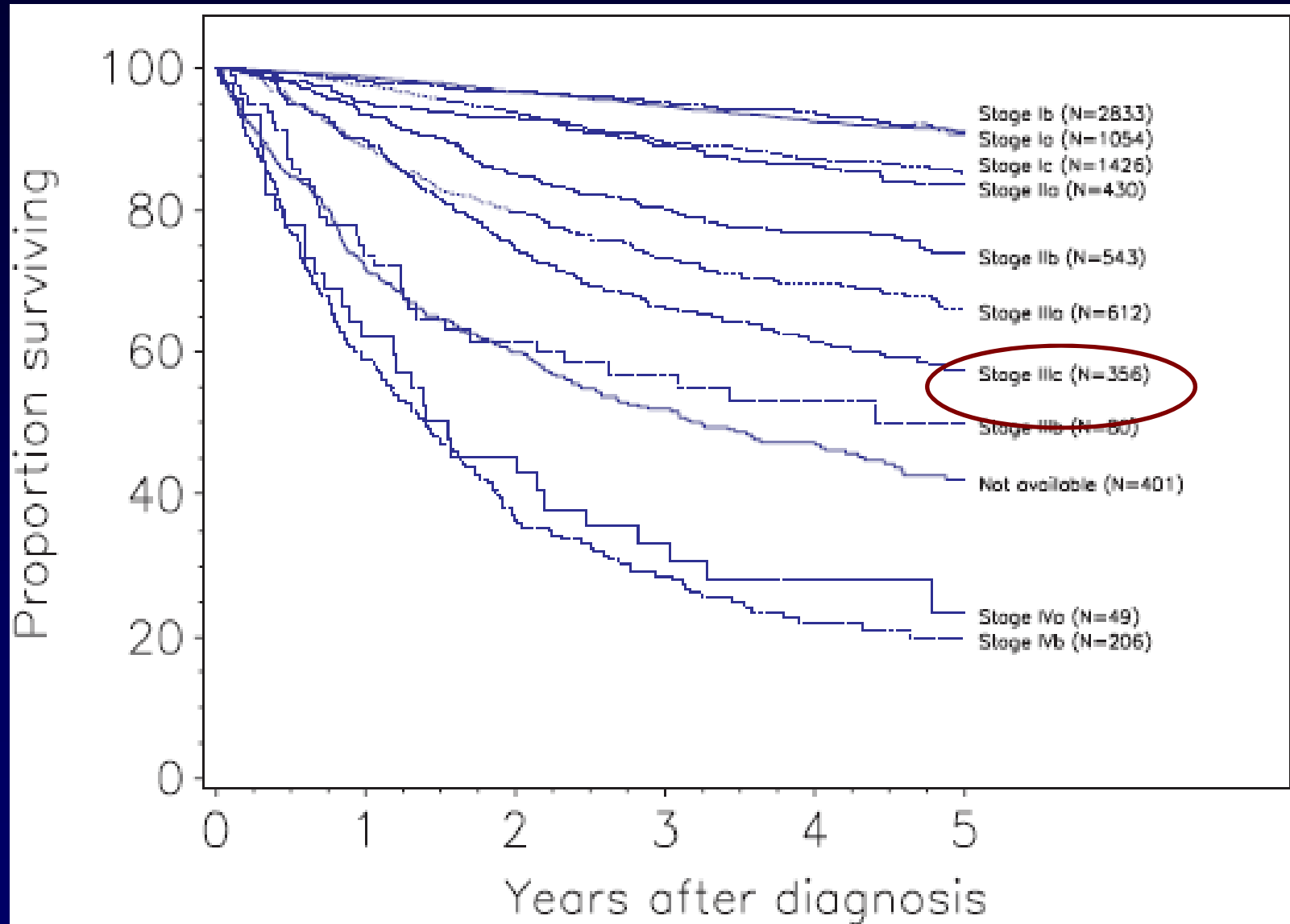
Role of Adjuvant Endocrine Therapy

Role of Hormonal Therapy

My Choice

FIGO: 5-Year Survival

n = 7990 (surgical stage)



No Adjuvant Therapy

Role of External Beam Radiotherapy (EBRT)

Role of Hormonal Therapy

My Choice

Adjuvant EBRT

Oslo trial: Aalders J, et al. *Obstet & Gynecol.* 1980;56(4):419-427.

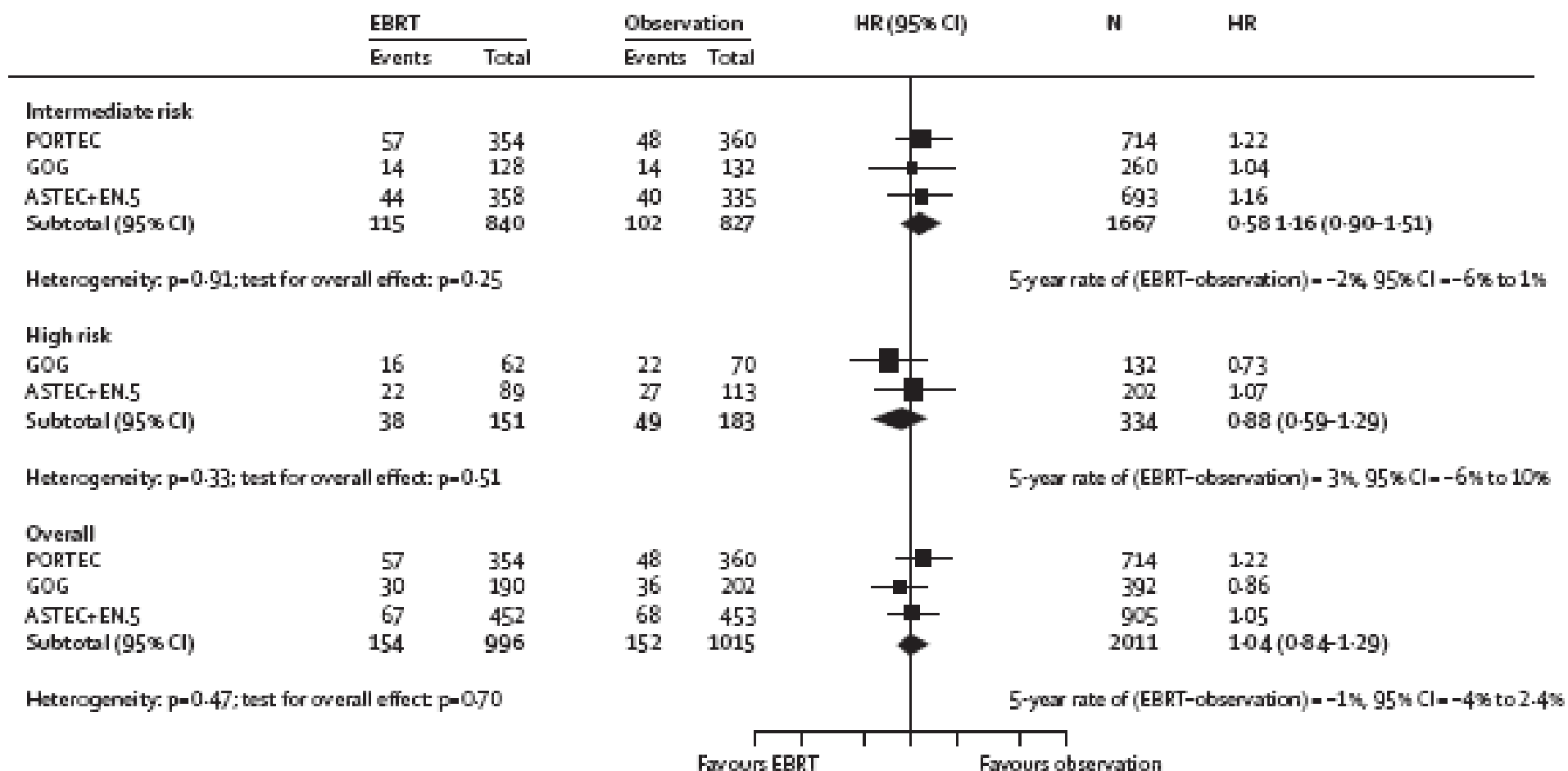
Portec 1: Creutzberg CL, et al. *Lancet.* 2000;355(9213):1404-1411.

GOG 99: Keys HM, et al. *Gynecol Oncol.* 2004;92(3):744-751.

ASTEAC: Blake P, et al. *Lancet.* 2009;373(9658):137-146.

Meta-Analysis PORTEC, GOG-99, ASTEC

A Overall survival

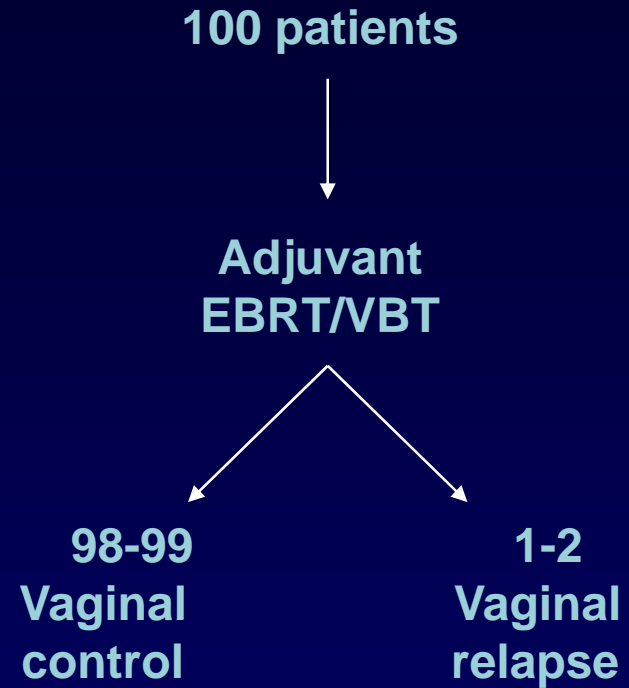


Blake P, et al. *Lancet*. 2009;373(9658):137-146.

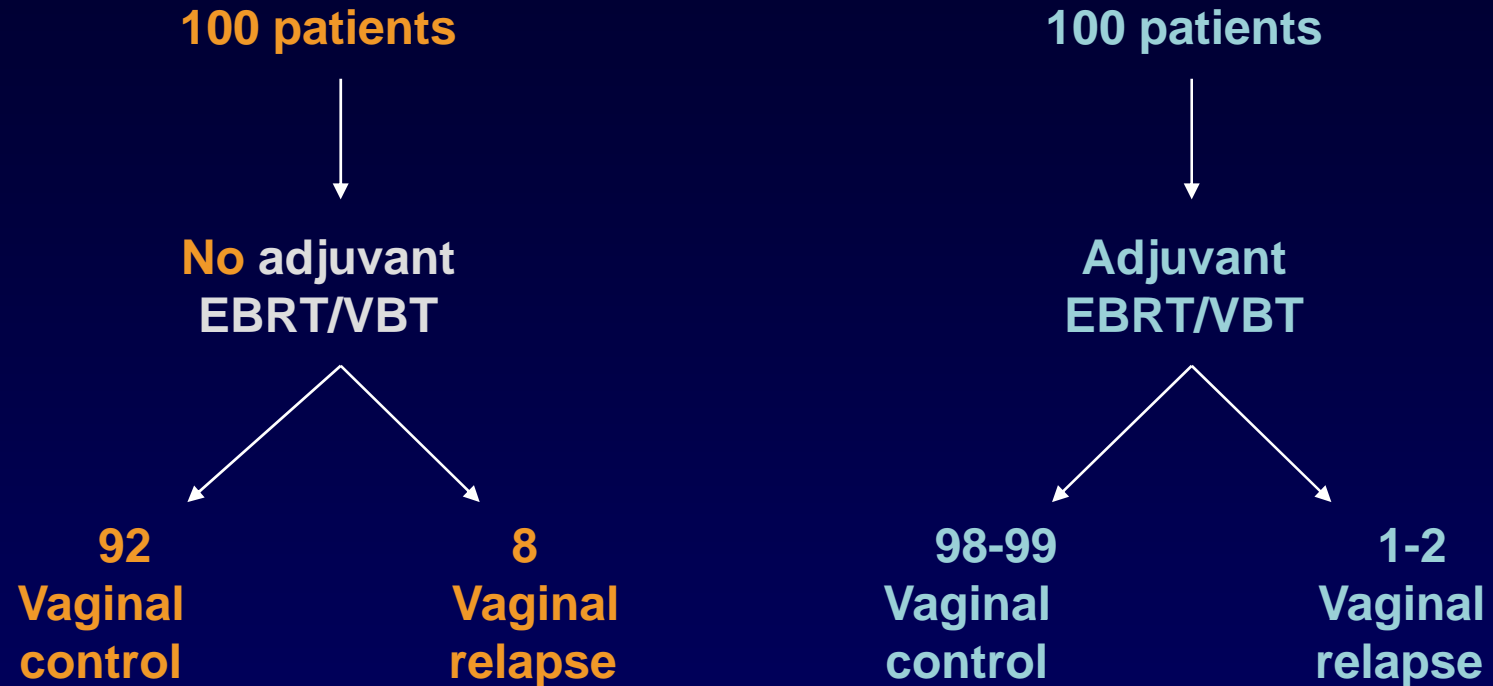
Adjuvant EBRT/BT Conclusion

- **EBRT - no effect on survival** **Level 1a**
- **EBRT – improves local control** **Level 1a**
- **EBRT – acute & late complications** **Level 1a**
- **BT – gives same local control as EBRT
though less toxic** **Level 1b**

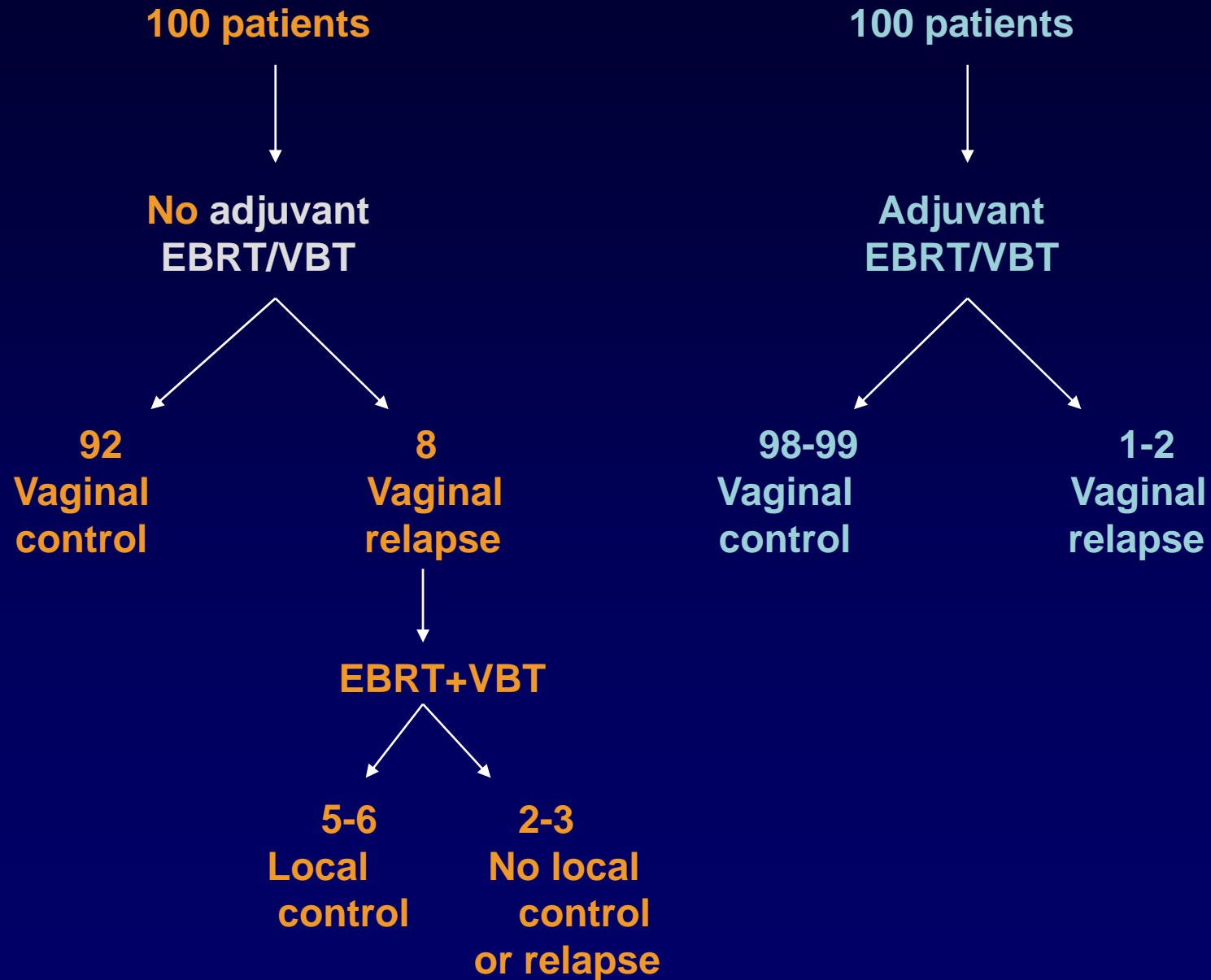
Local Control



Local Control



Local Control



No Adjuvant Therapy

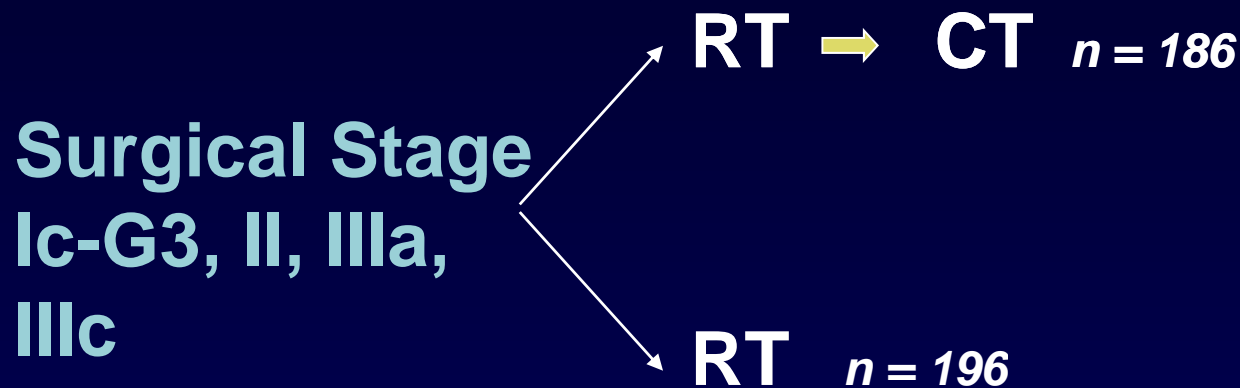
Role of External Beam Radiotherapy (EBRT)

Role of EBRT + Chemotherapy

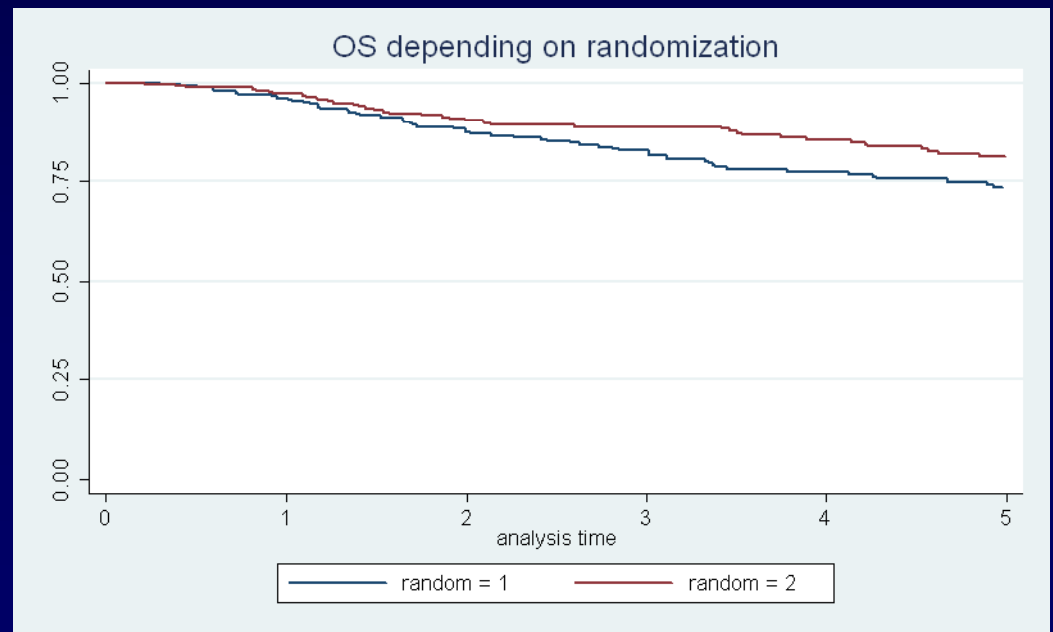
Role of Adjuvant Chemotherapy

Role of Hormonal Therapy

NSGO EC-9501/EORTC-55991/ILIADE + MANGO



HR 0.68 (CI 0.46-1.0) $P = .047$;
estimated difference in 5-year OS
8% from 73% to 81%



Högberg T, et al. *J Clin Oncol.* 2007;25(18S): Abstract 5503.

No Adjuvant Therapy

Role of External Beam Radiotherapy (EBRT)

Role of EBRT + Chemotherapy

Role of Adjuvant Chemotherapy

Role of Hormonal Therapy

Adjuvant Chemotherapy

Italian trial: Maggi R, et al. *Br J Cancer*. 2006;95(3):266-271.

JGOG trial: Susumu N, et al. *Gynecol Oncol*. 2008;108(1):226-233.

Postop Adj Chemo Italian Trial

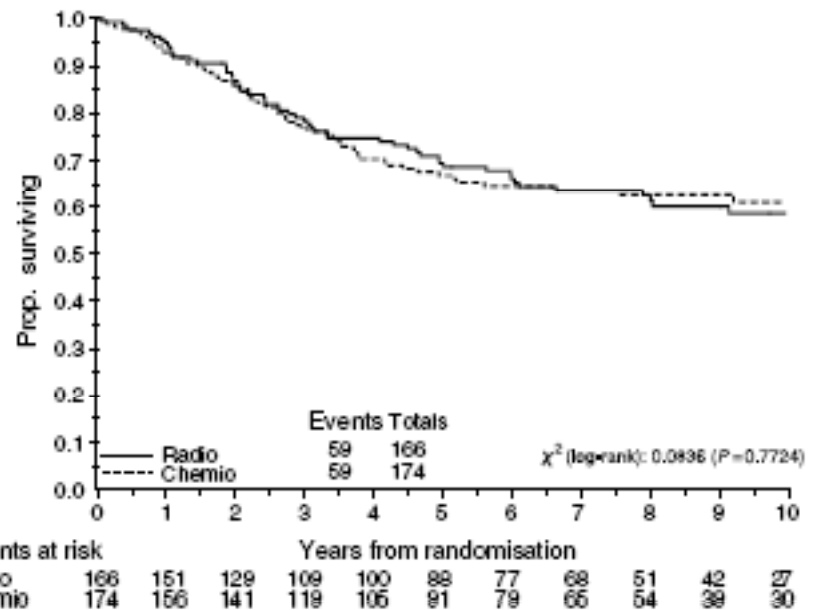


Figure 2 Overall survival of patients with high-risk endometrial carcinoma (stage IcG3, IIg3 with myometrial invasion >50% and III) receiving adjuvant radiotherapy (Radio) or chemotherapy (Chemio). Five-year overall survival was 69% and 66% respectively for adjuvant radiotherapy and chemotherapy.

**Surgical Stage
Ic-G3, II-G3, III**

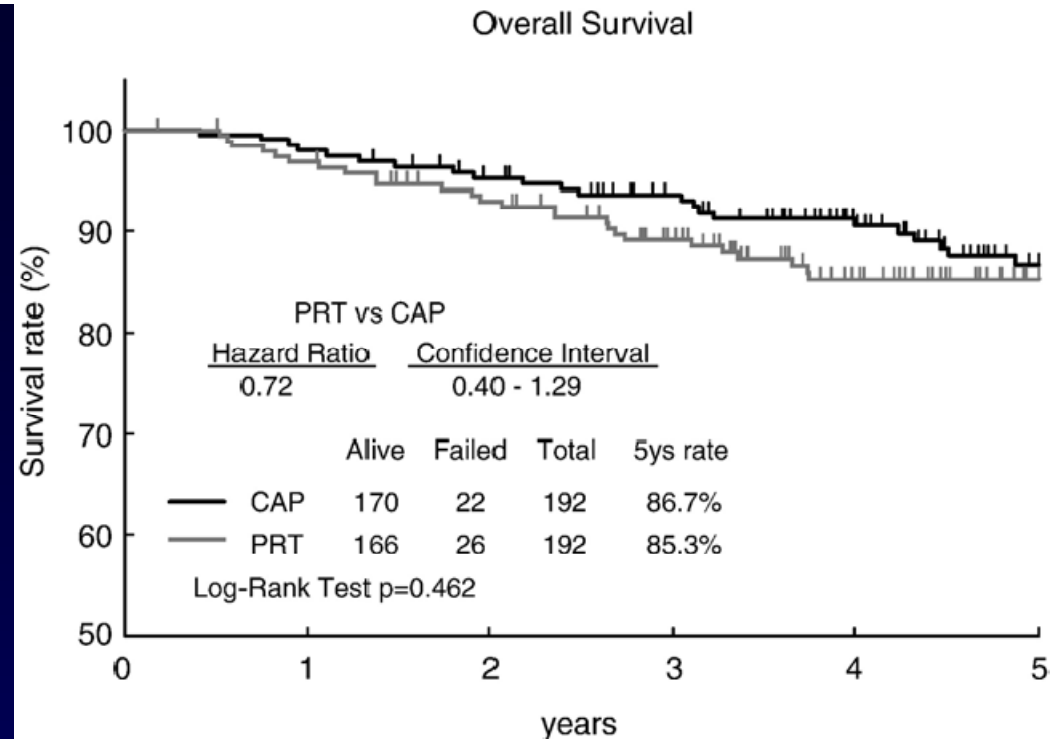
CT *n* = 177

**Cyclophos 600 + Doxorubicin 45 + Cisplatin 50
q 4 weeks, 5 courses**

RT *n* = 168

45-50 Gy

Postop Adj Chemo JGOG Trial



Surgical Stage
Ic-G1-3, II, III

CT *n* = 192

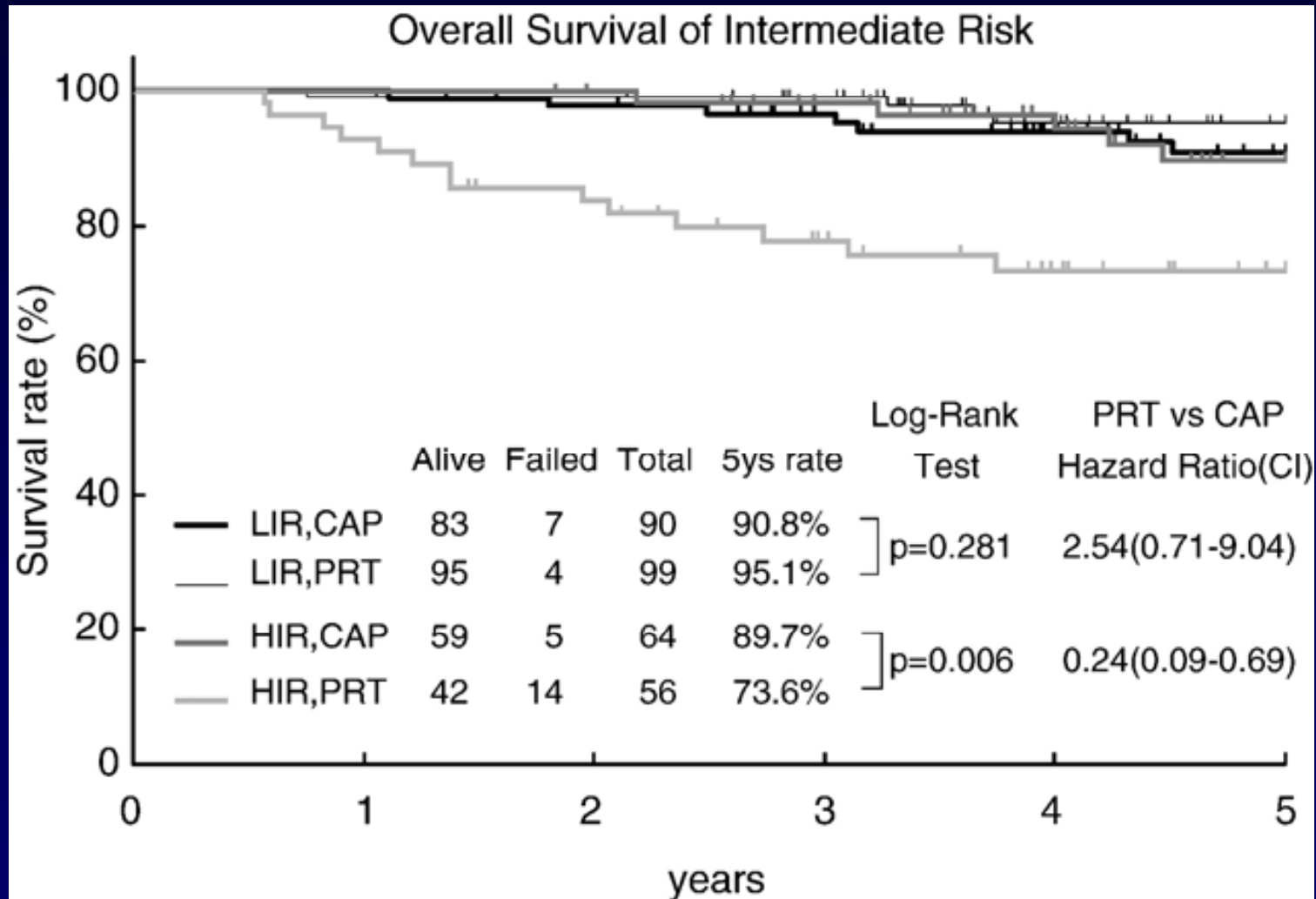
*Cyclophos 333 + Doxorubicin 40 + Cisplatin 50
q 4 weeks, 3 courses*

RT *n* = 193

45-50 Gy

Postop Adj Chemo JGOG Trial

Subgroup analysis



Susumu N, et al. *Gynecol Oncol.* 2008;108(1):226-233.

No Adjuvant Therapy

Role of External Beam Radiotherapy (EBRT)

Role of EBRT + Chemotherapy

Role of Adjuvant Chemotherapy

Role of Hormonal Therapy

Adjuvant Hormonal Therapy

- **Systemic review of 9 randomized trials**
- **The available evidence does not demonstrate any benefit for adjuvant hormonal therapy**
- **The use of hormonal therapy is not recommended as adjuvant treatment**

No Adjuvant Therapy

Role of External Beam Radiotherapy (EBRT)

Role of EBRT + Chemotherapy

Role of Adjuvant Chemotherapy

Role of Hormonal Therapy

My Choice

My Choice

**Patient should be offered to enter in
a clinical trial**

Outside Clinical Trial: Carboplatin-Paclitaxel

Systemic Therapy of Endometrial Cancer

Part 2

Management of Metastatic Disease

Hormonal Therapy

Surgery of Lung Metastases

Cis-Doxo Rechallenge

Other Combinations

Targeted Therapy

Hormonal Therapy

- **Low level of evidence: Only phase II trials or retrospective cohorts**
- **May be an option in old women with comorbidity where chemotherapy is contraindicated and low-grade ER/PR–positive disease**

- **Progestins:**
 - **OS ca. 19 months**
 - » Thigpen JT, et al. *J Clin Oncol.* 1999;17(6):1736-1744.
 - » Leutz, et al. *J Clin Oncol.* 2004;14:357-36
 - » Decruze SB, et al. *Int J Gynecol Cancer.* 2007;17(5):964-978.
- **SERMs:**
 - **Tamoxifen: RR ca. 10%**
 - » Thigpen T, et al. *J Clin Oncol.* 2001;19(2):364-367.
 - **Tamoxifen + Progestin: RR 27% to 30%; OS 2.7-3.0 months**
 - » Fiorica JV, et al. *Gynecol Oncol.* 2004;92(1):10-14.
 - » Whitney CW, et al. *Gynecol Oncol.* 2004;92(1):4-9.
- **Aromatase Inhibitors: (Anastrozole, Letrozole)**
 - **RR ca. 10%**
 - » Rose PG, et al. *Gynecol Oncol.* 2000;78(2):212-216.
 - » Ma BB, et al. *Int J Gynecol Cancer.* 2004;14(4):650-658.
- **Gonadotropin-Releasing Hormone (GnRH) Agonists: (eg, Goserelin)**
 - **RR 0% to 28%; PFS ca. 2 months**
 - » Asbury RF, et al. *Am J Clin Oncol.* 2002;25(6):557-560.

Hormonal Therapy

Surgery of Lung Metastases

Cis-Doxo Rechallenge

Other Combinations

Targeted Therapy

Surgery of Lung Metastases

Not Evidence Based

Only case reports

Gücer F, et al. *Int J Gynecol Cancer*. 2005;15(6):1160-1162.

Hormonal Therapy

Surgery of Lung Metastases

Cis-Doxo Rechallenge

Other Combinations

Targeted Therapy

Chemotherapy Regimen

GOG-122: Randall ME, et al. *J Clin Oncol*. 2006;24(1):36-44.

EORTC 55872: Aapro MS, et al. *Ann Oncol*. 2003;14(3):441-448.

GOG-107: Thigpen JT, et al. *J Clin Oncol*. 2004;22(19):3902-3908.

GOG: Fleming GF, et al. *Ann Oncol*. 2004;15(8):1173-1178.

GOG: Fleming GF, et al. *J Clin Oncol*. 2004;22(11):2159-2166.

Sorbe B, et al. *Int J Gynecol Cancer*. 2008;18(4):803-808.

Michener CM, et al. *J Cancer Res Clin Oncol*. 2005;131(9):581-584.

Chemo for FIGO III-IV GOG 122

Surgical Stage
III – IV

RT (WAI) *n* = 202
30 + 15 Gy

CT *n* = 194
Doxo 60 + Cisplat 50
q 3 weeks, 8 courses

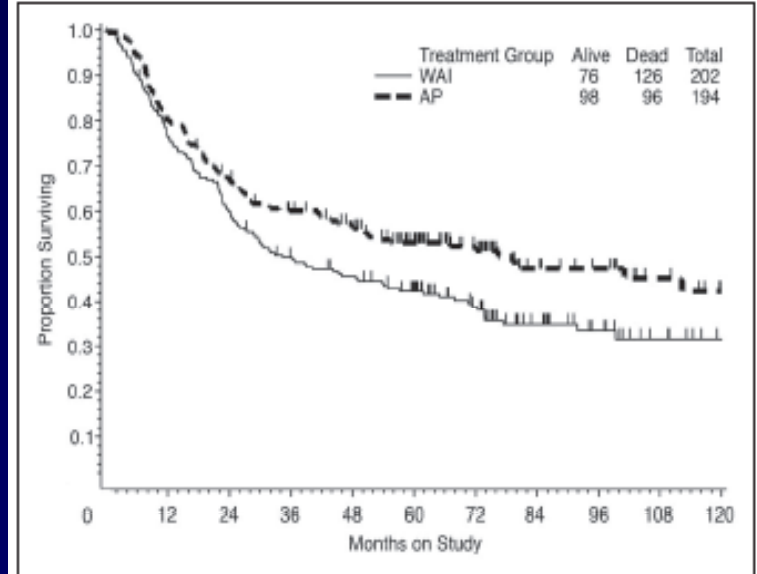
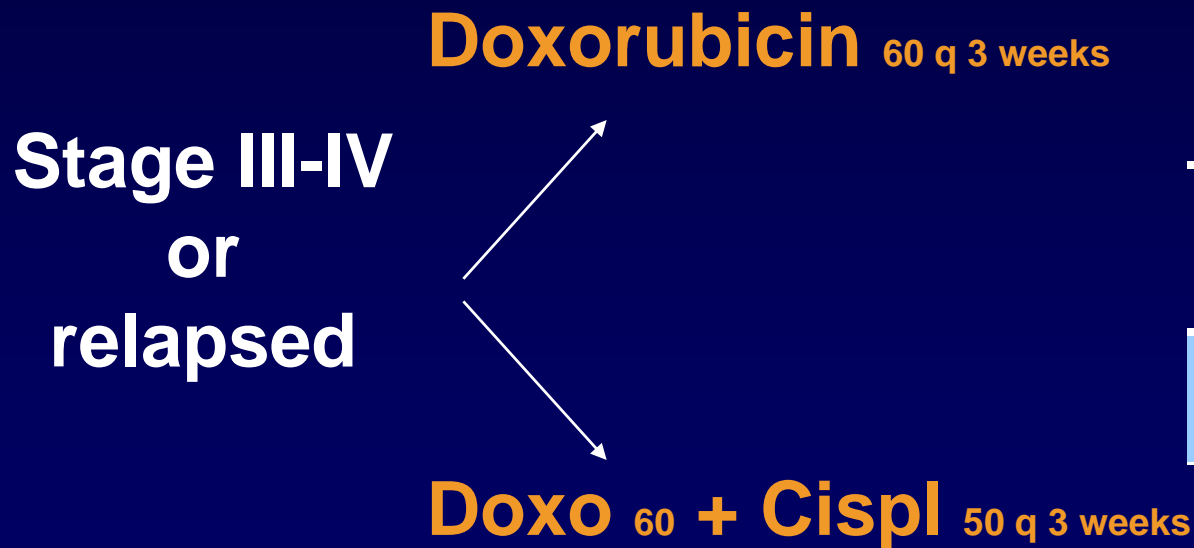


Fig 2. Survival by randomized treatment group. AP, doxorubicin and cisplatin; WAI, whole-abdominal irradiation.

First-Line Therapy for Stage III-IV or Relapsed Disease



Aapro: Phase III; n = 177

	Doxo	Doxo+ Cis
ORR	17%	43%
OS	7 mo	9 mo

Thigpen: Phase III; n = 299

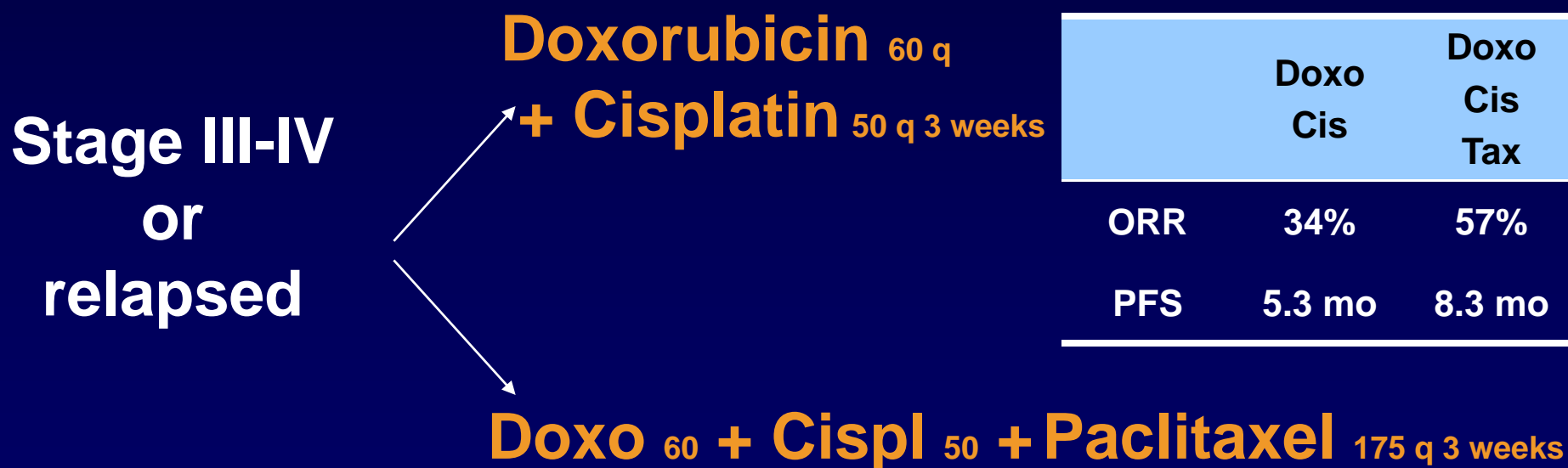
	Doxo	Doxo+ Cis
ORR	25%	42%
PFS	3.8 mo	5.7 mo
OS	9.2 mo	9.0 mo

Aapro MS, et al. *Ann Oncol.* 2003;14(3):441-448.

Thigpen JT, et al. *J Clin Oncol.* 2004;22(19):3902-3908.

First-Line Therapy for Stage III-IV or Relapsed Disease

Phase III; n = 299



First-Line Therapy for Stage III-IV or Relapsed Disease

Phase II

n = 66

Stage III-IV
or
relapsed

→ **Carbo** AUC 5 + **Paclitaxel** 175 q 3 weeks

ORR	67%
PFS	14 mo

First-Line Therapy for Stage III-IV or Relapsed Disease

Phase II

Stage III-IV
or
relapsed



Carbo AUC 5 + **Paclitaxel** 175 q 3 weeks

Similar activity as with Cis+Doxo

Chemotherapy—Conclusion

**Chemotherapy improves survival
for stage III & IV
and for relapsed disease
(Level 1a)**

Hormonal Therapy

Surgery of Lung Metastases

Cis-Doxo Rechallenge

Other Combinations

Targeted Therapy

- **mTOR Inhibitors:**

- **Temsirolimus and other compounds**

- *RR 7% to 26%; SD 40% to 50%*

- » Oza AM, et al. *J Clin Oncol.* 2006;24(18S): Abstract 3003.

- » Slomovitz BM, et al. *Gyn Oncol.* 2007; 104(3Suppl 1): Abstract 70.

- » Colombo N, et al. *J Clin Oncol.* 2007;25(18): Abstract 5516.

- » Oza AM, et al. *J Clin Oncol.* 2008;26(May 20 suppl): Abstract 5...

- **Angiogenesis:**

- **Bevacizumab: *RR ca. 10%***

- » Wright JD, et al. *Anticancer Res.* 2007;27(5B):3525-3528.

- **VEGF-Trap: *modest activity***

- » Ongoing trials

- **Tyrosine Kinase Inhibitors: *modest activity***

- » Ongoing trials

Hormonal Therapy

Surgery of Lung Metastases

Cis-Doxo Rechallenge

Other Combinations

Targeted Therapy

My Choice

My Choice

**Patient should be offered to enter in
a clinical trial**

Outside Clinical Trial: Carboplatin-Paclitaxel

ENGOT-NESTEC: Network Study in Endometrial Cancer
under the ENGOT umbrella and in cooperation with the Mayo clinic.

Clinically presumed:
 FIGO IB-II any histo type,
 FIGO I A G3 endometrioid,
 FIGO IA/B histo type II

- (R) Mayo trial (Dowdy, Mariani)
 AGO ECLAT trial (Emons)
- (R) NSGO trial (Hogberg)
- (R) AGO/NOGGO trial (Sehouli)
- (R) DGCG trial (Mirza)

