Practical Management of the GYN-Oncology Patient Discussing Real Life Cases

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Case study

- 49 yr old woman, vaginal bleeding. Clinical examination + MRI = tumor of the cervix-6.4 cm- no evidence of parametrial invasion nor vaginal- biopsy: adenocarcinoma
- Laparoscopic para-aortic lymph node dissection: negative
- Chemoradiation (cisplatin)

Case study

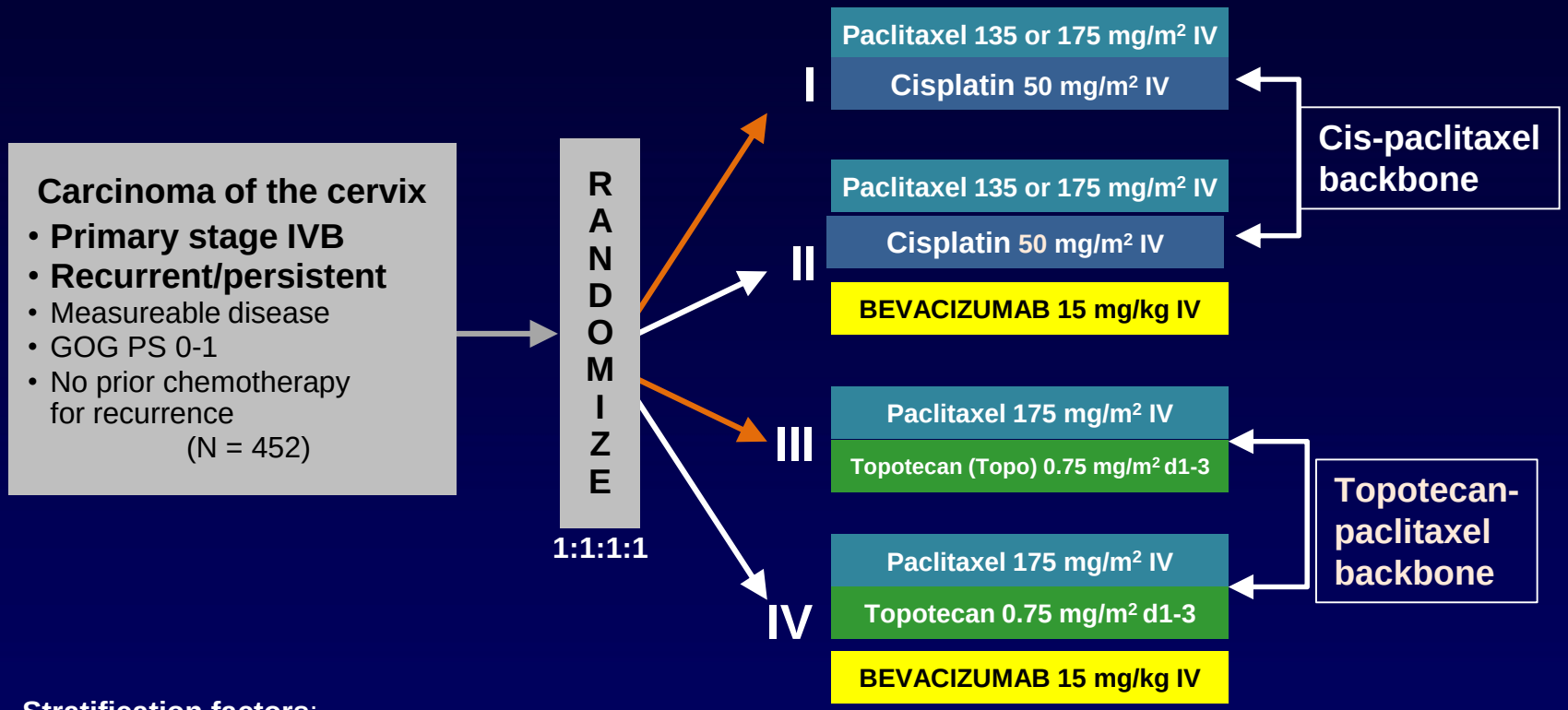
- 1 year later: relapse in the pelvis and peritoneum. Left hydronephrosis. Normal renal function.
- Pelvic MRI: 6cm mass between bladder and rectum without sign of mucosa invasion

Three Decades: Recurrent and Metastatic Cervical Cancer

- **Cisplatin (Cis) 50 mg/m2 plus paclitaxel (Pac) 135 mg/m2 is standard therapy (GOG)**
  - **Alternative is carboplatin plus paclitaxel**
- **Gynecologic Oncology Group (GOG) 204 (2009)**
  - **Phase III randomized trial of 4 platinum-based chemotherapy doublets: Cisplatin plus paclitaxel remained standard for GOG**
- **Majority of patients with recurrent cervical cancer treated with cisplatin-based chemoradiation for locally advanced disease**
- **New therapeutic options needed:**
  - **Non-platinum chemotherapy doublets?**
  - **Anti-angiogenesis therapy?**

Tewari KS, et al. *Curr Oncol Rep.* 2005;7(6):419-434. Monk BJ, et al. *J Clin Oncol.* 2007;25(20):2952-2965. Tewari KS, et al. *Onkologie.* 2008;32(10):552-554. *Monk BJ, et al. *J Clin Oncol.* 2009;27(28):4649-4655. Tewari KS, et al. *Semin Oncol.* 2009;36(2):170-180. Tewari KS, et al. *Clin Adv Hematol Oncol.* 2010;8(2):108-115. Tewari KS. *Am J Hematol Oncol.* 2010;9:31-34. Tewari KS. *Clin Ovarian Cancer.* 2011;4:90-93.

GOG 240: Schema



Stratification factors:

- **Stage IVB vs recurrent/ persistent disease**
- **Performance status**
- **Prior cisplatin Rx as radiation-sensitizer**

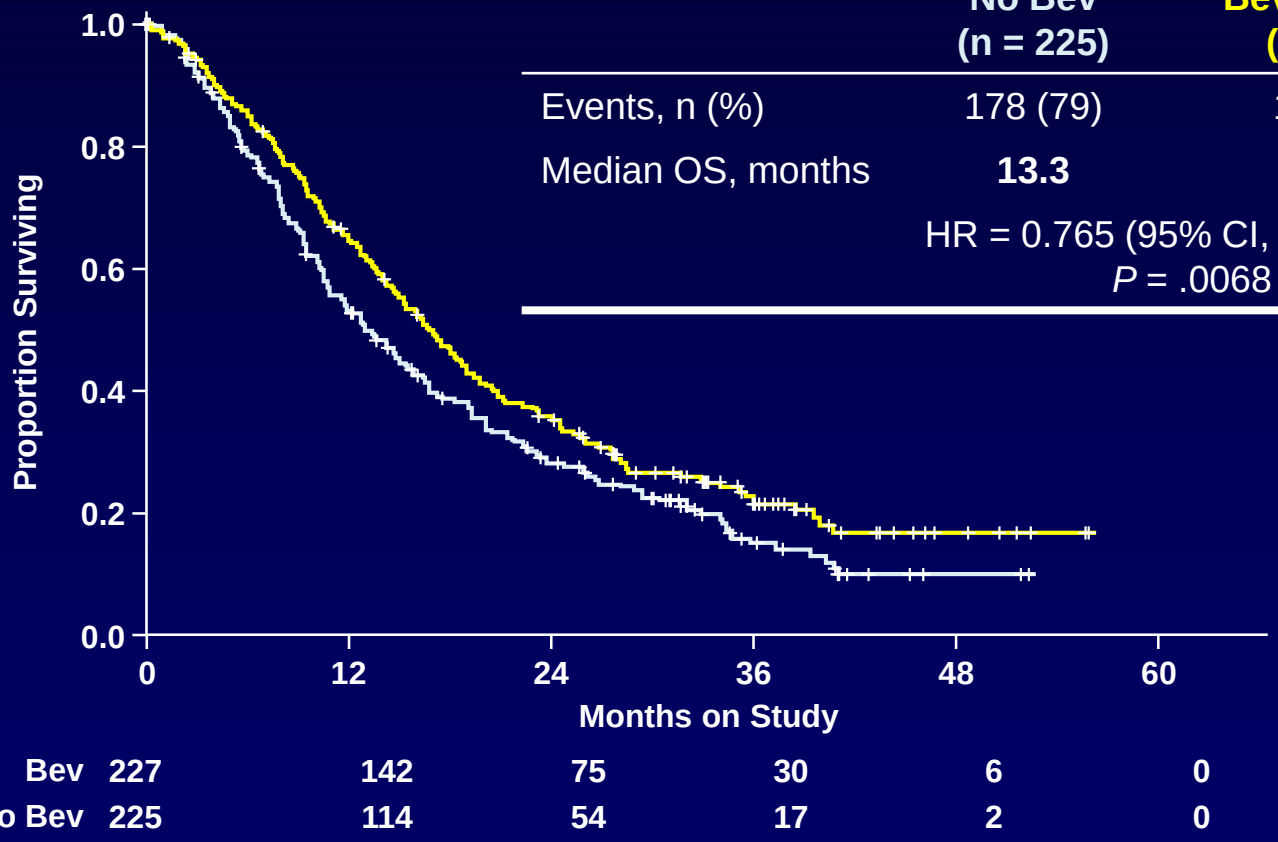
q21d Rx to PD, toxicity, CR

CR, complete response; PD, progressive disease; PS, performance status; q21d, every 21 days; Rx, treatment

National Institutes of Health. Available at: http://clinicaltrials.gov/ct2/show/NCT00803062. Accessed January 7, 2015.

GOG 240.6: Final Protocol-Specified OS ChemoRx vs ChemoRx Plus Bev

	No Bev (n = 225)	Bevacizumab (n = 227)
Events, n (%)	178 (79)	170 (75)
Median OS, months	**13.3**	**16.8**
	HR = 0.765 (95% CI, 0.62–0.95) *P* = .0068	



Tewari KS, et al. *Ann Oncol.* 2014;25(Suppl 4): Abstract LBA26.

Moore Criteria

- Performance status>0
- Pelvic disease
- African-American ancestry
- Disease-free interval<1 year
- Prior platinum exposure

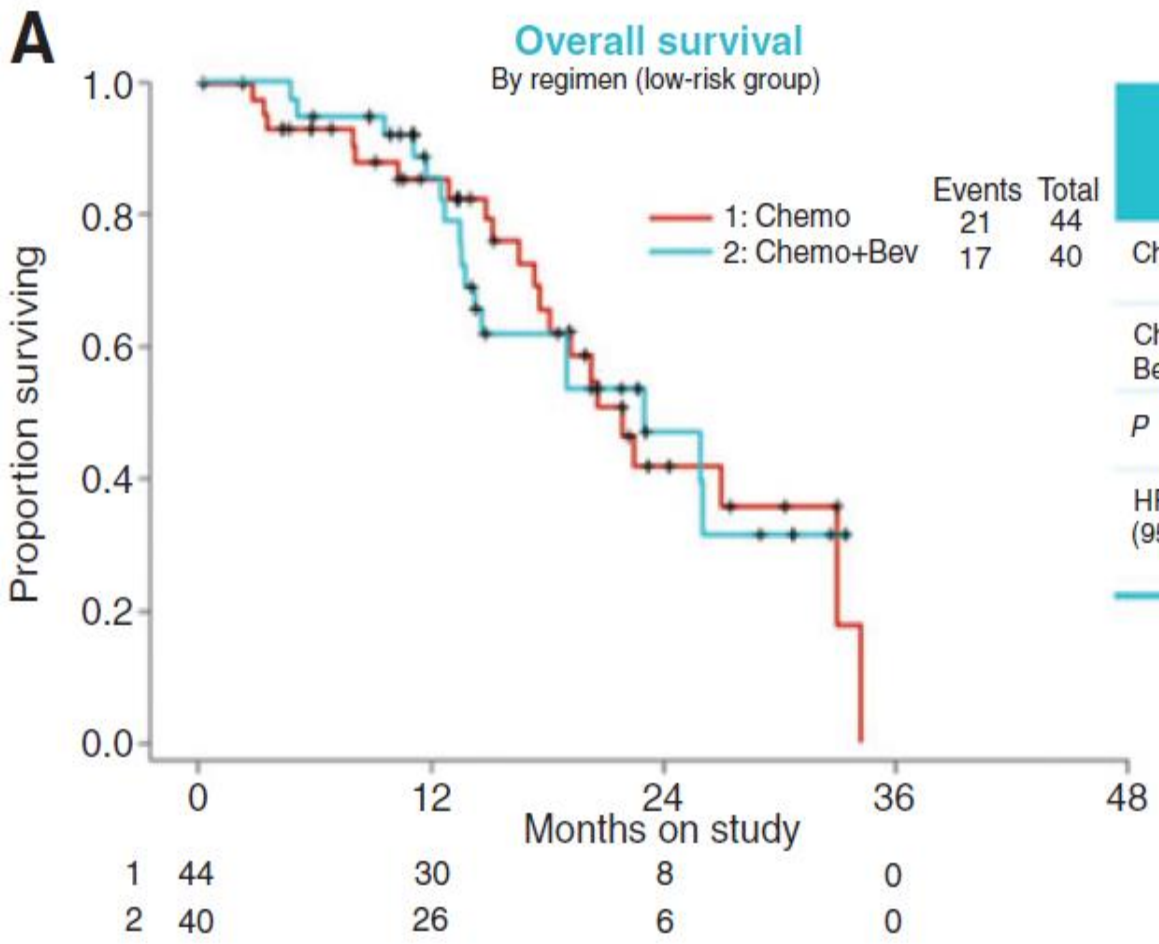
Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

Prognosis according to Moore Criteria

- Low risk: 0-1 factors
- Mid risk: 2-3 factors
- High risk: 4-5 factors

Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

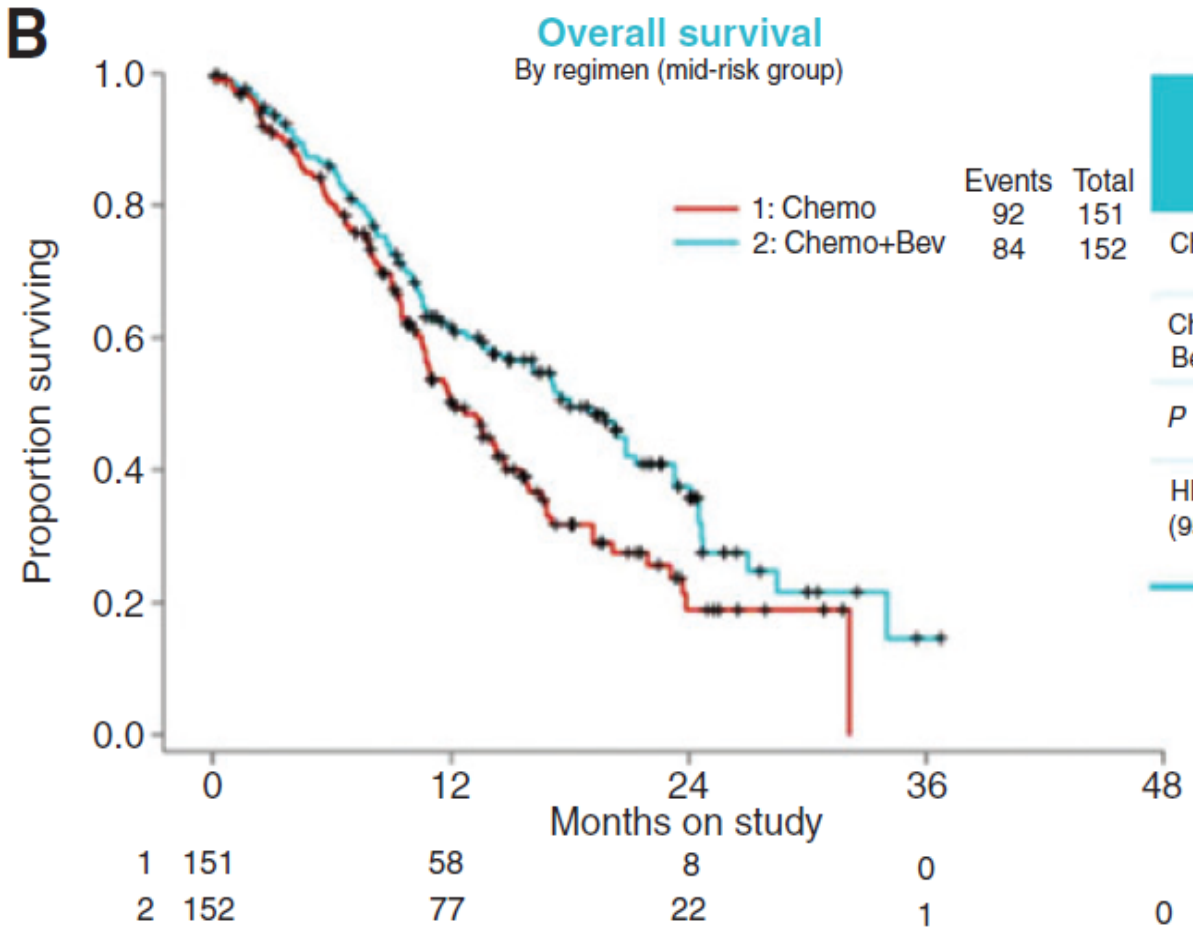
Overall Survival by regimen



	Median OS (mo)	Median PFS (mo)	RR (%)
Chemo	21.8	8.0	52.0
Chemo + Bev	22.9	10.9	62.5
P	0.9087	0.2903	<0.3435
HR (95% CI)	0.96 (0.51–1.83)	0.85 (0.53–1.37)	1.522 (0.64–3.64)

Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

Overall Survival by regimen

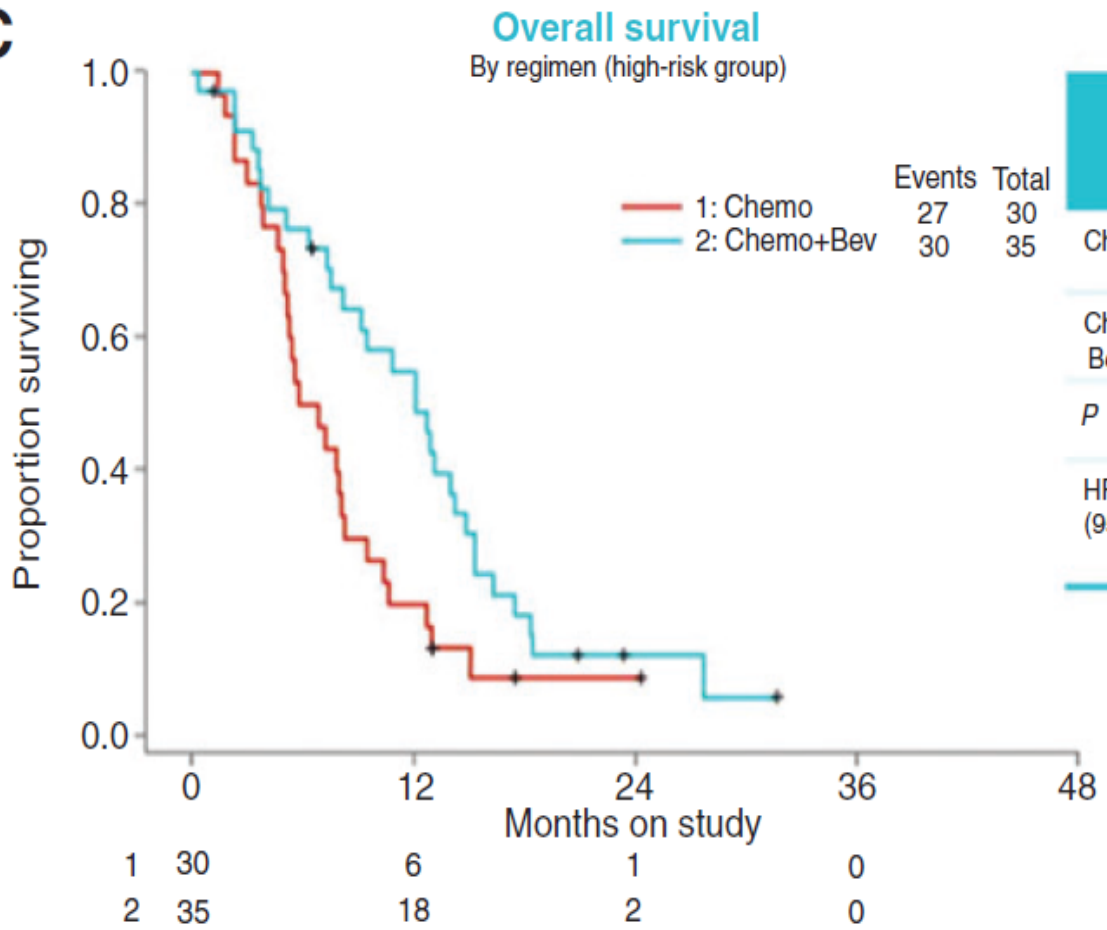


	Median OS (mo)	Median PFS (mo)	RR (%)
Chemo	12.1	5.8	36.0
Chemo + Bev	17.9	7.9	50.7
P	0.0094	0.0047	<0.0087
HR (95% CI)	0.673 (0.51–0.91)	0.694 (0.54–0.89)	1.844 (1.16–2.92)

Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

Overall Survival by risk regimen

C



	Median OS (mo)	Median PFS (mo)	RR (%)
Chemo	6.3	3.0	13.0
Chemo + Bev	12.1	6.0	22.9
P	0.0196	0.0272	<0.3190
HR (95% CI)	0.536 (0.32–0.905)	0.506 (0.277–0.926)	1.926 (0.52–7.18)

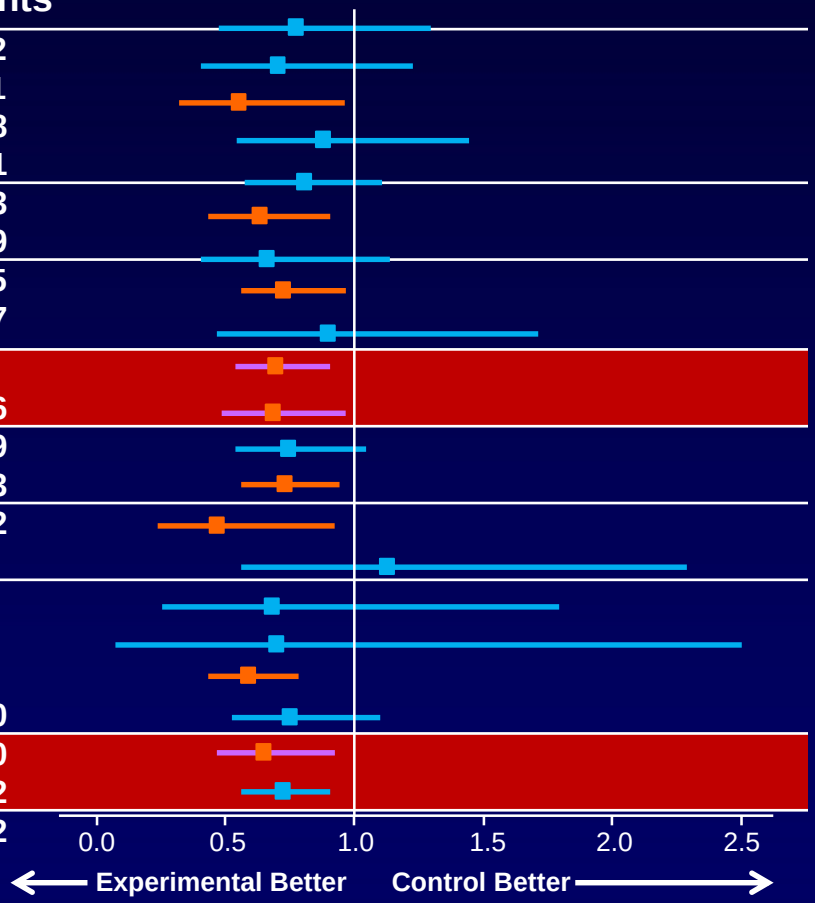
Tewari et al.Clin Cancer Res; 21(24) December 15, 2015

Bevacizumab approved in recurrent/metastatic cervix cancer

- FDA: August 14, 2014
- EMA: April 8, 2015
- France

GOG 240.2: OS and Prognostic Factors

Subgroup		No. of patients
Age	Age ≤40 years	112
	40 <age ≤48 years	111
	48 <age ≤56 years	108
	56 years <age	121
Performance status	0	263
	1	189
Prior platinum RT	No	115
	Yes	337
Disease status	Advanced	76
	Recurrent/persistent	376
Topotecan treatment	No	229
	Yes	223
Race	Not black	392
	Black	60
Histology	Adenocarcinoma	86
	Adenosquamous	44
	Other	12
	Squamous	310
Pelvic disease	No	210
	Yes	242
Overall		452



Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

GOG 240.2: Treatment Exposure and Specific Adverse Events (AEs)

Adverse Event, n (%)	Chemo Alone (n = 219)	Chemo + Bev (n = 220)
Grade 5 AE(s)	4 (1.8)	4 (1.8)
GI events, non-fistula (grade ≥2)	96 (44)	114 (52)
GI fistula (grade ≥3)*	0 (0)	7 (3)
GI perforation (grade ≥3)	0 (0)	5 (2)
GU fistula (grade ≥3)*	1 (0)	6 (2)
Pain (grade ≥2)	62 (28)	71 (32)
Hypertension (grade ≥2)*	4 (2)	54 (25)
Proteinuria (grade ≥3)	0 (0)	4 (2)
Neutropenia (grade ≥4)*	57 (26)	78 (35)
Febrile neutropenia (grade ≥3)	12 (5)	12 (5)
Thromboembolism (grade ≥3)*	3 (1)	18 (8)
Bleeding CNS (any grade)	0 (0)	0 (0)
GI (grade ≥3)	1 (0)	4 (1)
GU (grade ≥3)	1 (0)	6 (3)

*$P<.05$

Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

Vaginal Fistulae

222 patients

GI-vaginal fistula: 0 patients (0%)
GU-vaginal fistula: 3 patients (1.4%)

218 patients

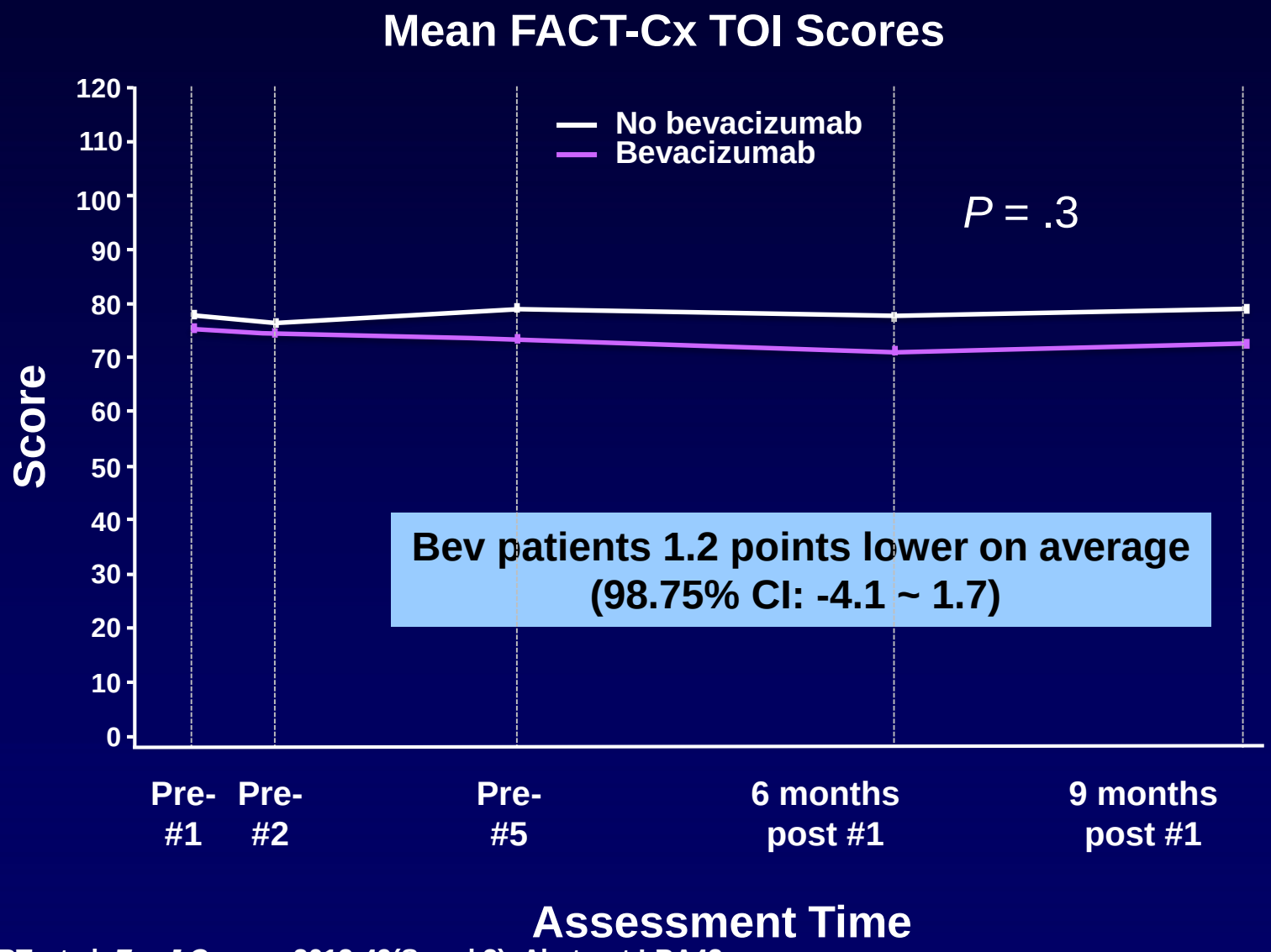
GI-vaginal fistula G3: 7 patients (3%)
GU-vaginal fistula: 4 patients (1.8%)
GI fistula: 1 patient (0.5%)

In a separate analysis of the GOG 240 study, all fistulae events were re-graded:

- None of the fistulae were associated with peritonitis, sepsis or death. Among the patients who developed GI-vaginal fistulae, all (100%) had received prior pelvic radiation therapy compared to 80% in the overall population.

Willmott L, et al. Presented at the 15th Biennial Meeting of the International Gynecologic Cancer Society; 8-11 November, 2014: Melbourne, Australia. [abstract] CT, chemotherapy; GI, gastrointestinal; GU, genitourinary

GOG 240.3: HRQoL Mean FACT-Cx TOI



Penson RT, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract LBA42.

Who is the Best Candidate for Bevacizumab?

GOG 240: Eligibility Criteria

- Recurrent/persistent or metastatic disease
- Frontline excluding chemotherapy with radiation
- Squamous cell carcinoma (SCCA), adenocarcinoma (AC), adenosquamous carcinoma (AS)
- GOG performance status 0-1
- Normal renal function (Cr < 1.3)
- No bleeding or nonhealing ulcer, other nonhealing wound, or fistula
- Malnutrition corrected

GOG 240.2: Conclusions

- **Bevacizumab plus chemotherapy significantly improves OS in stage IVB, recurrent or persistent cervical carcinoma**
  - **Nearly 4-month improvement in OS is clinically significant**
  - **Increase in median PFS and overall response rate are also demonstrated**
  - **Benefit seen even when recurrent disease is in irradiated pelvis**
- **Bevacizumab treatment is associated with a higher rate of AEs**
  - **3% to 8% rate of known bevacizumab-related Aes**
  - **The improvement in OS with bevacizumab treatment was not accompanied by a significant decrease in HRQoL**

Tewari KS, et al. *J Clin Oncol*. 2013;31(Suppl): Abstract 3.

Back up slides

GOG 240.1: Toxicity

Cis-Pac Backbone vs Topo-Pac Backbone

		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Leukopenia	**Cis-Pac**	45	27	70	60	10	0
	Topo-Pac	30	28	42	71	33	0
Nausea	**Cis-Pac**	82	78	36	16	0	0
	Topo-Pac	103	71	26	4	0	0
Vomiting	**Cis-Pac**	145	29	28	10	0	0
	Topo-Pac	161	27	11	5	0	0
Metabolic	**Cis-Pac**	115	42	28	26	1	0
	Topo-Pac	130	35	26	11	2	0
Neurosensory	**Cis-Pac**	96	65	35	16	0	0
	Topo-Pac	87	82	30	5	0	0
Allergy	**Cis-Pac**	172	16	17	7	0	0
	Topo-Pac	193	7	1	3	0	0