The British Association of Gynaecological Pathologists

Cervix Cancer: Conventional and New Treatment Approaches

Melanie Powell
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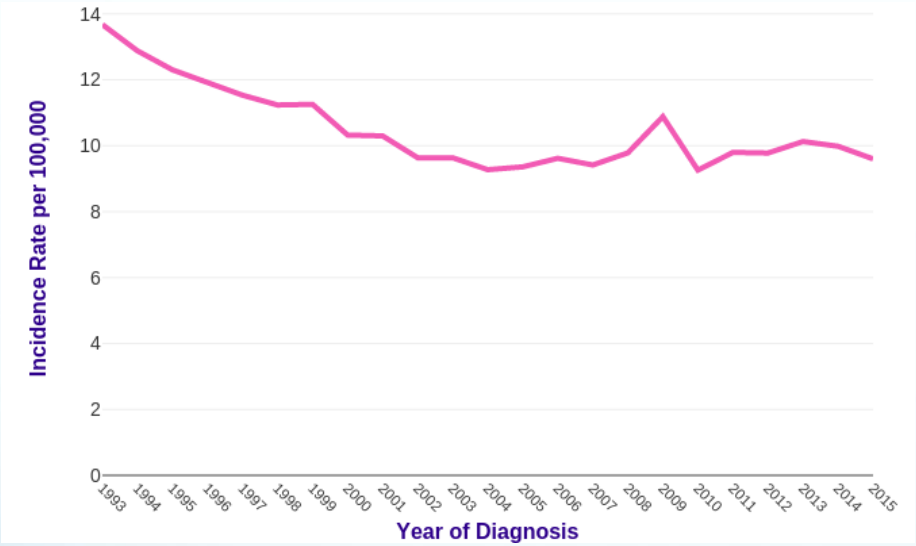
Barts Health NHS Trust

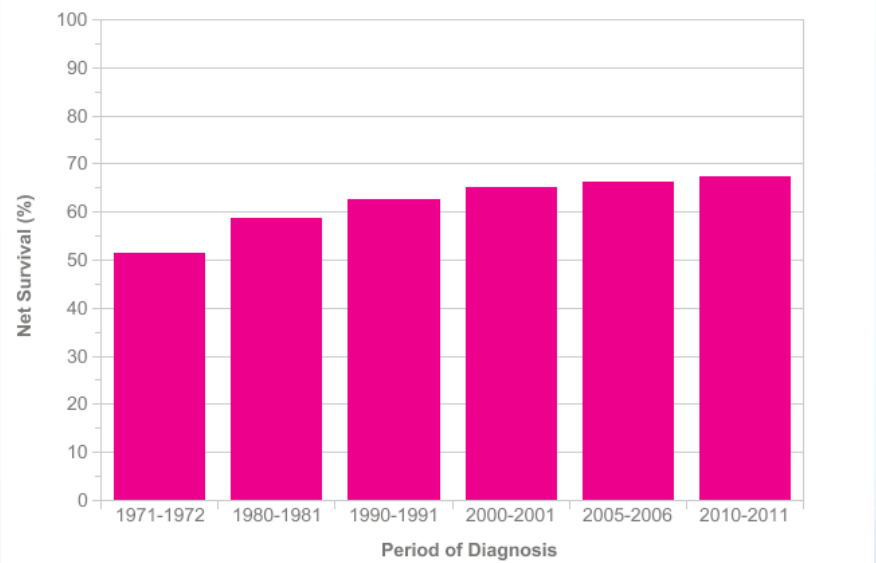


The Basics

- 4th commonest cancer in women world wide
- Over 500 000 per year
- UK Incidence 9 per 100 000
- Peak incidence 25 to 29 years
- Incidence predicted to increase by 40% over next 20 years with peak occurring in age 55-59
- 67% 5 year survival

Trends over time

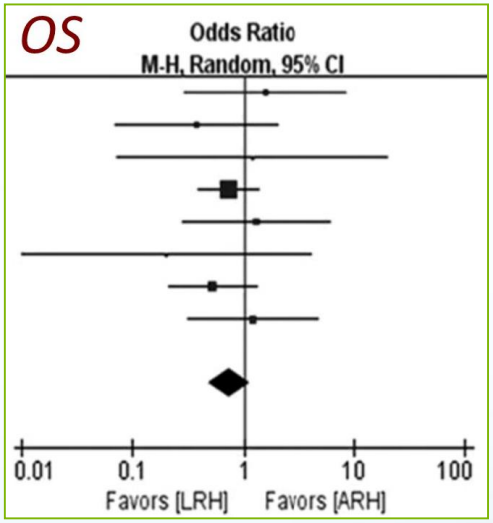




Cancer Research UK

The rise and rise of minimally invasive surgery

- 23 studies N=4205
- Surgical outcomes
  - ↑ operating time
  - ↓ blood loss
  - ↓Time in hospital
  - ↓Bladder problems

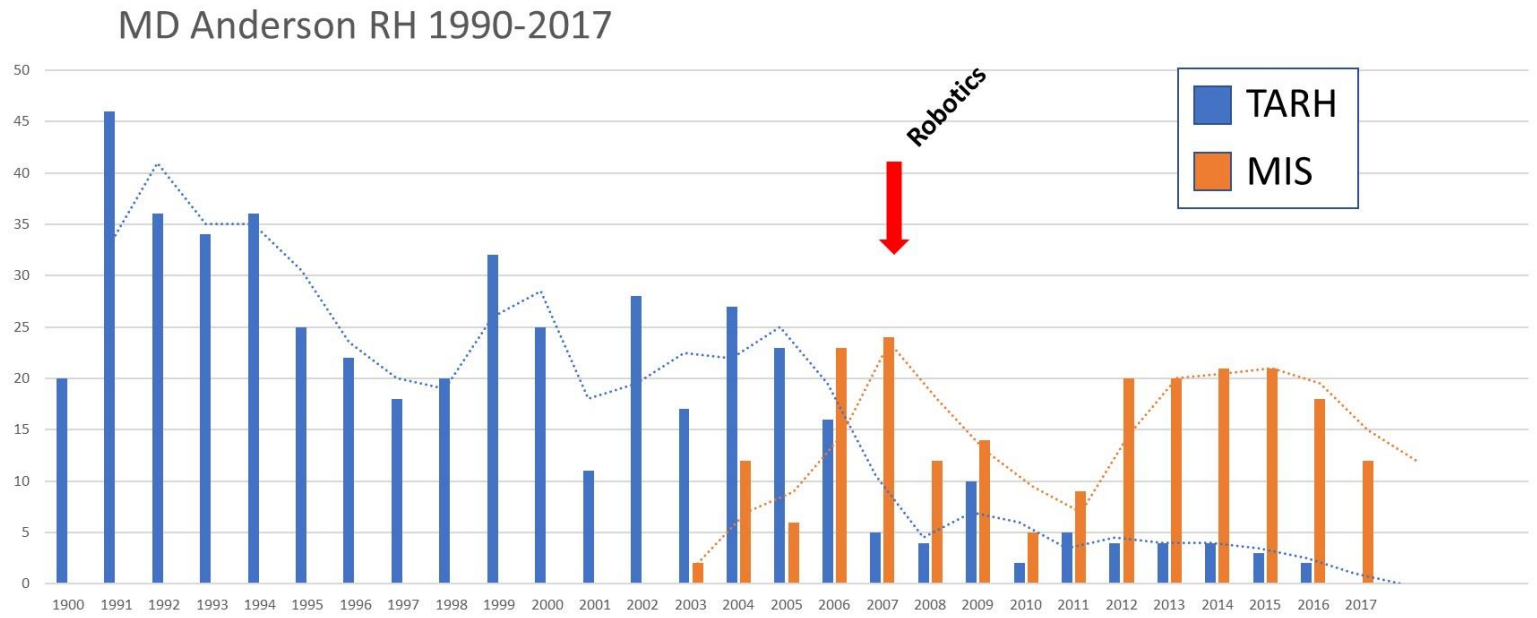


'LRH outweighs ARH in most essential aspects'

Laparoscopic Radical Hysterectomy in Early Stage Cervical Cancer: A Systematic Review and Meta-Analysis Zhao et al. J. Laparoendosc Adv Surg Tech 27:1132 (2017)

The rise and rise of minimally invasive surgery

The adoption of MIS RH at MD Anderson



Courtesy Pedro Ramirez

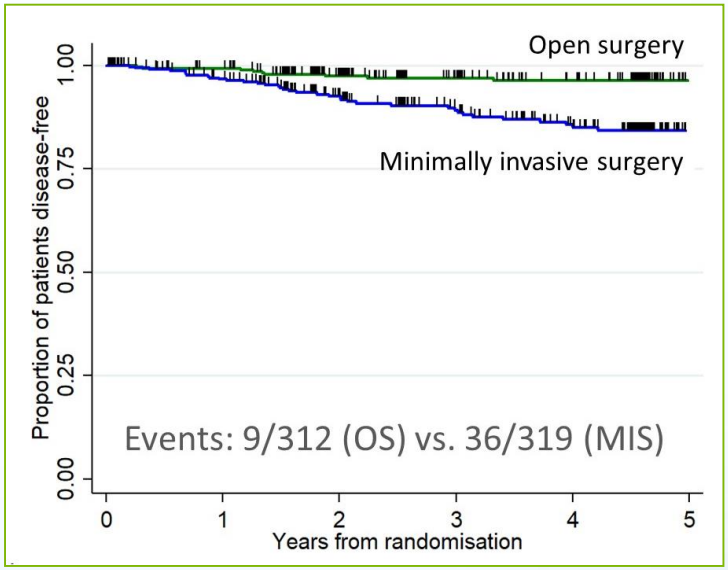
The rise and rise of minimally invasive surgery

Does a reduction in operative morbidity lead to a better outcome for patients?

Laparoscopic Approach in Cervical Cancer LACC Trial

- Ia1LVSI+;Ia2, IB1
- N=631
- Premature closure by DSMC
- **PFS HR 4.0 (CI;1.9-8.2)**

  96.5% (open) v 86% (MIS)



Ramirez NEJM 379 2018

Laparoscopic Approach in Cervical Cancer LACC Trial

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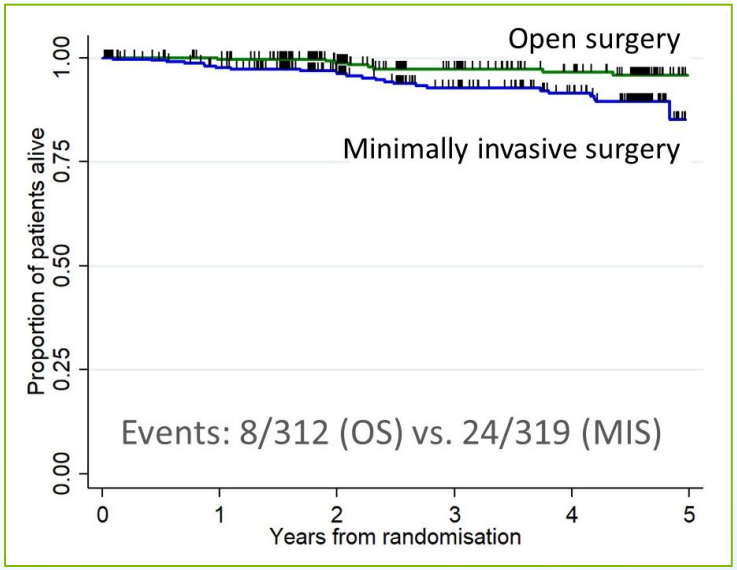
- PFS HR 4.0 (CI;1.9-8.2)
- **OS HR 2.86 (CI; 1.3-6.4)**

  99% (open) v 94% (MIS)



Ramirez NEJM 379 2018

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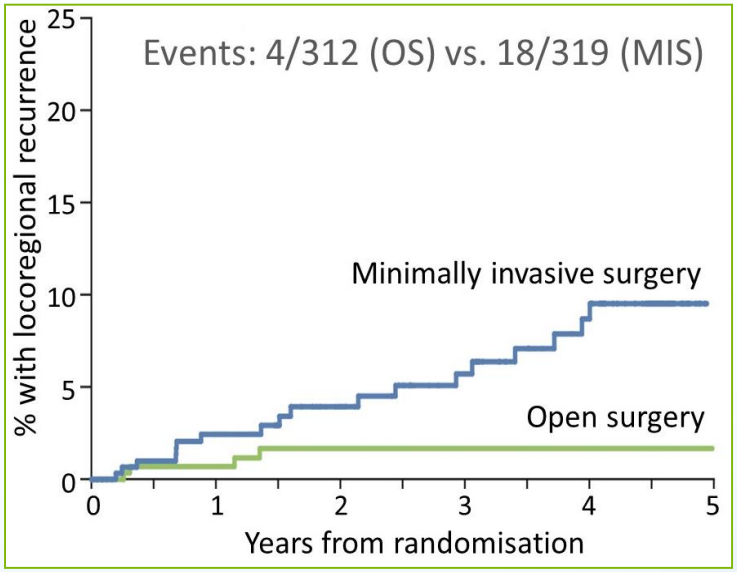
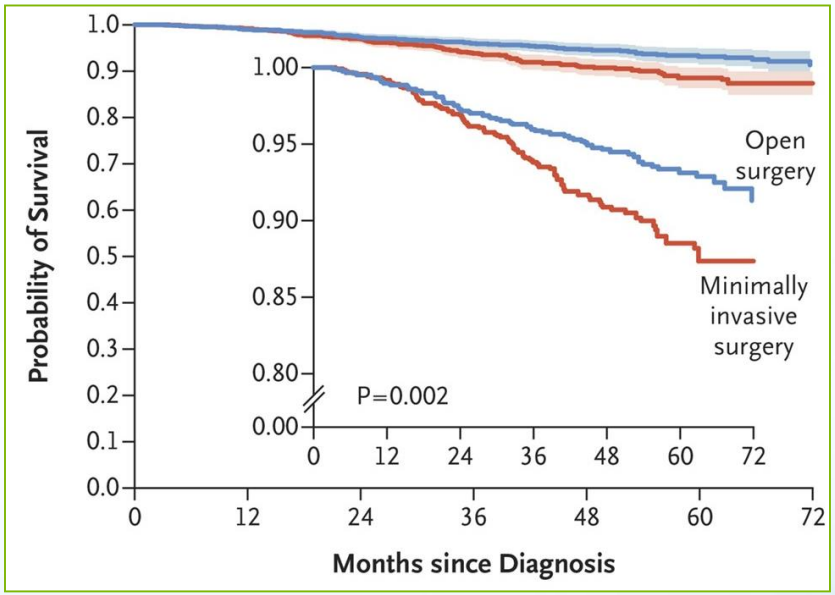
- OS HR 2.86 (CI; 1.3-6.4)
- **LR HR 4.26 9(CI; 1.4-12.6)**



Ramirez NEJM 379 2018

Comparison of Open v MIS Radical Hysterectomy

- Nat Cancer Data Base search
  - Rad Hyst 2010-13
  - Stage Ia2 and IB (FIGO2009)
- Median FU 48 months
- MIS 48% inc risk of death
  - At 4 years 9.1% (MIS) v 5.3% (Open)



Melamed NEJM 379 2018

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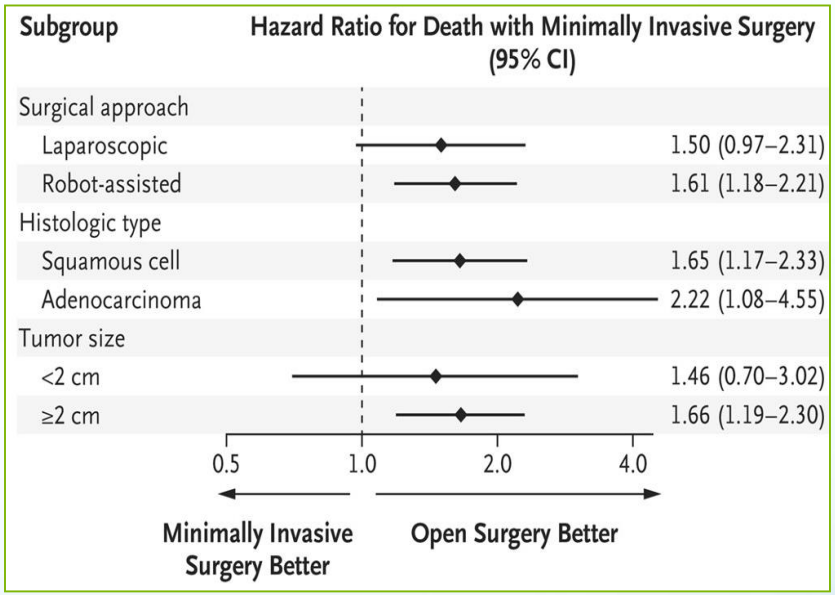

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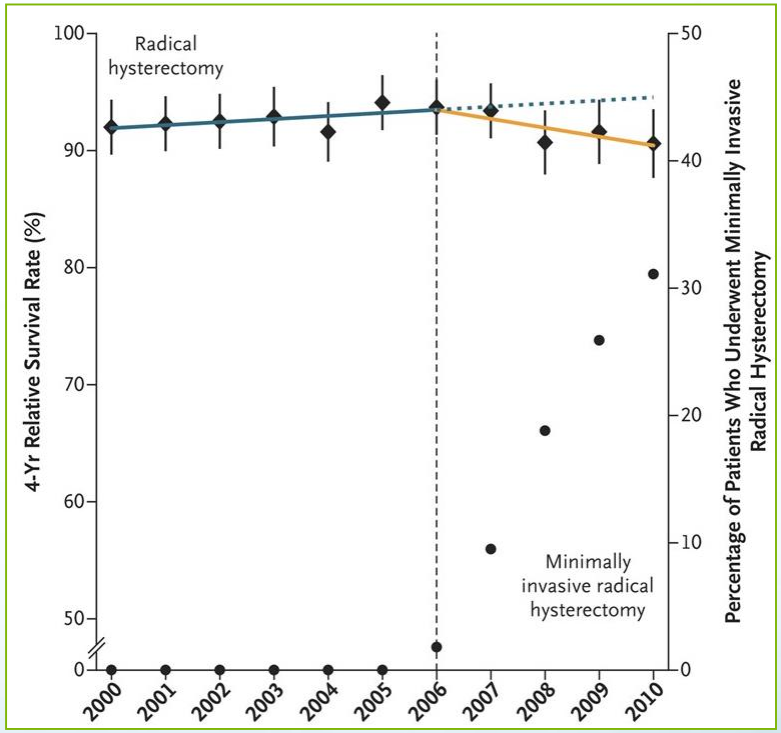
- Difference seen in all subgroups
- SEER interrupted time series analysis
  - Decrement in survival as MIS starts

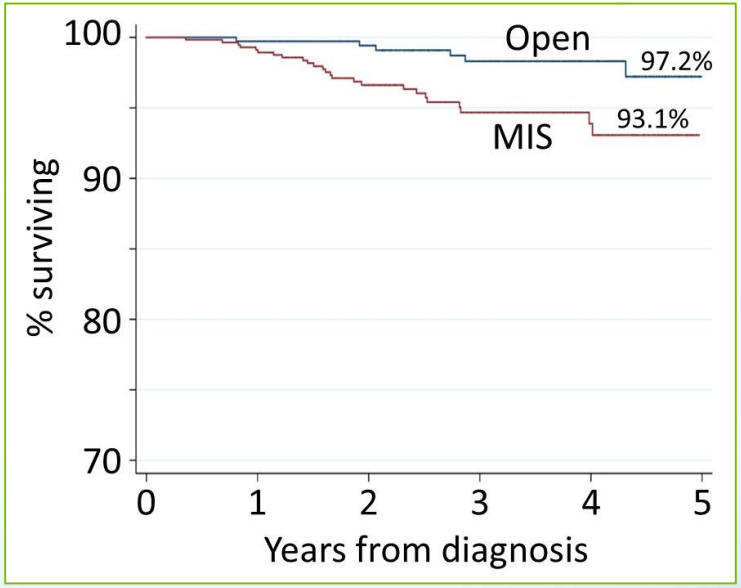


Melamed NEJM 379 2018

Public Health England

Population based review of MIS v open RH for early cervical cancer 2013-2016

- N=925
  - 564 MIS (61%)
  - 365 OS (49%)
- Use of MIS increased
  - 2013 48%
  - 2016 74%
- Risk factors balanced
- OS 93% v 97%
  - HR 4 (p = 0.007)



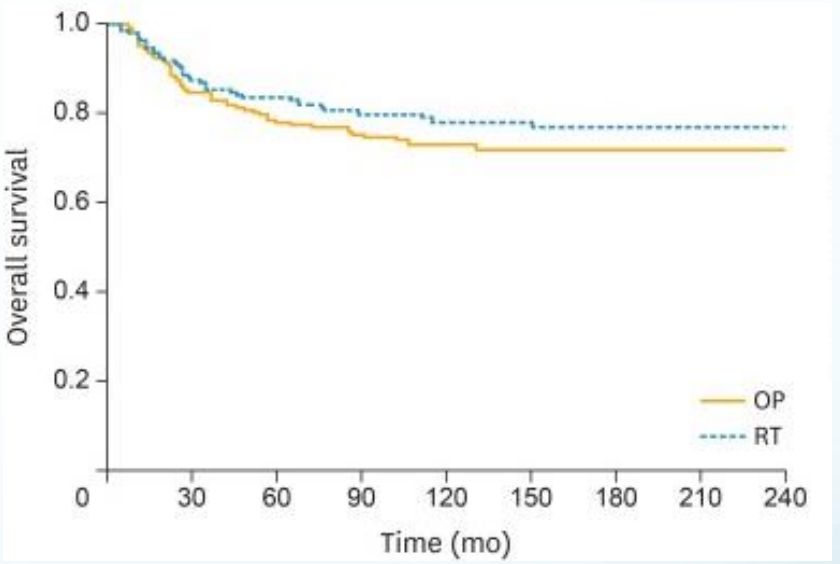
The rise and rise of minimally invasive surgery

Does a reduction in operative morbidity lead to a better outcome for patients?

Early Cervix Cancer Surgery v Radiotherapy

N=343 Stage 1B 2A

	Surgery	Radiotherapy
20 year OS	72%	78%
Relapse	28%	27%
Toxicity	51%	29%



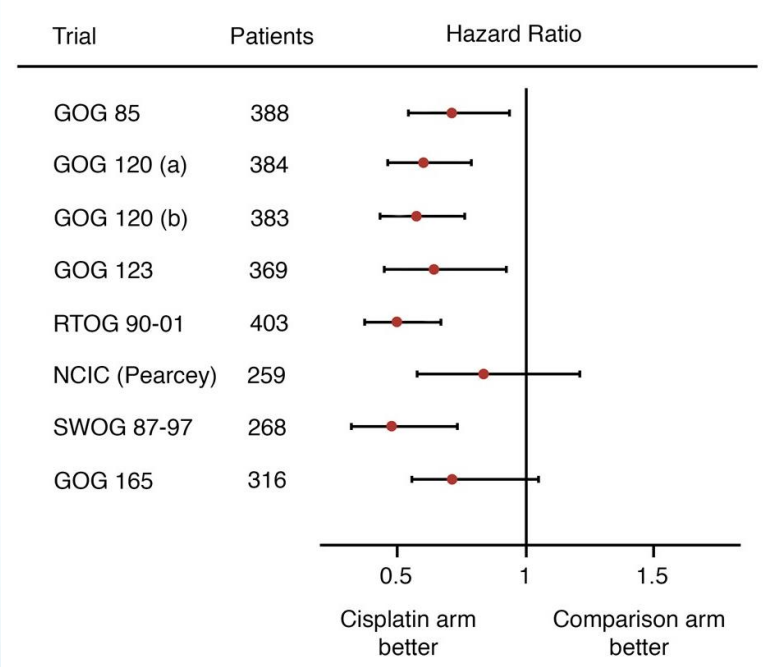
Risk factors for relapse

- Tumour size >3cm
- Histology
- Lymph node status

Landoni JGO 2017, Lancet 1997

Chemo Radiotherapy v Radiotherapy

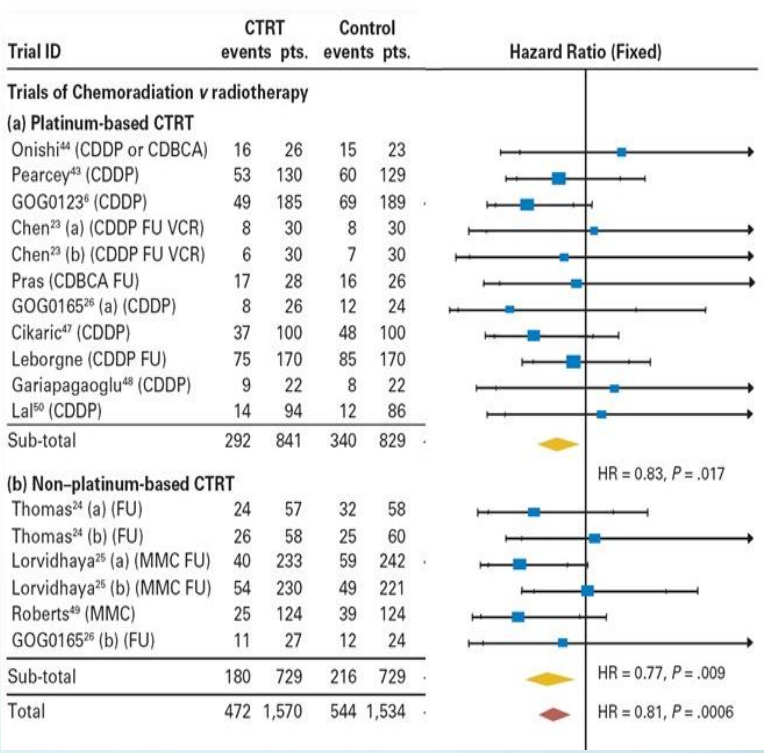
- 1999 5 trials of cisplatin based CRT are positive
  - NCI alert
  - New standard of care



Meta-analysis using individual patient data from randomized trials
Chemoradiotherapy for Cervical cancer Meta-analysis Collaboration (CCCMAC); J Clin Oncol 26:5802, 2009

Chemo Radiotherapy v Radiotherapy

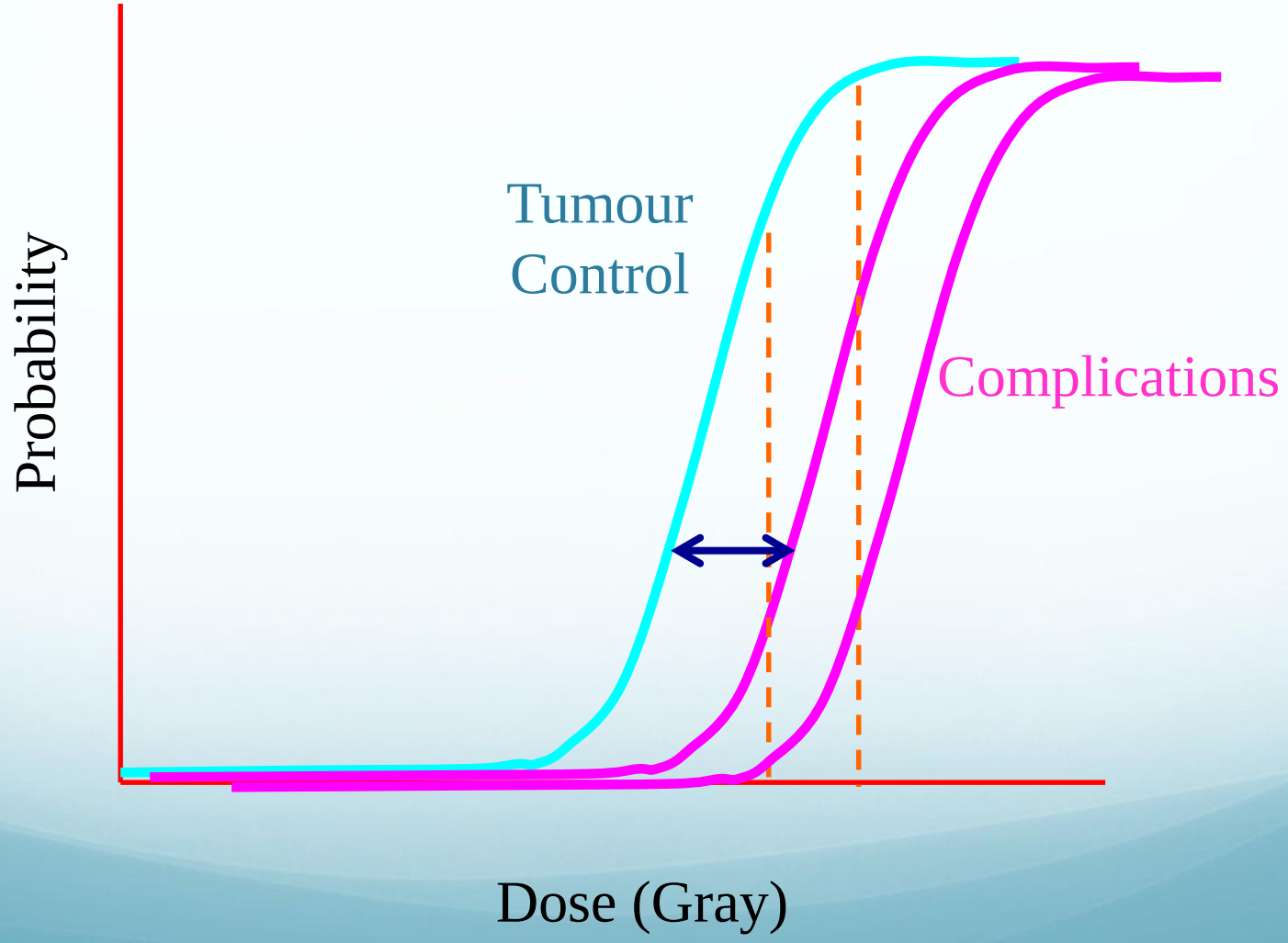
- 1999 5 trials of cisplatin based CRT are positive
  - NCI alert
  - New standard of care
- 2009 Confirmatory Meta-anlaysis
- Absolute benefit of 6% in overall survival
  - 10% in stage 1B/2a
  - 7% stage 2b
  - 3% stage 3 to 4A
- Similar benefit for platinum or non platinum treatment



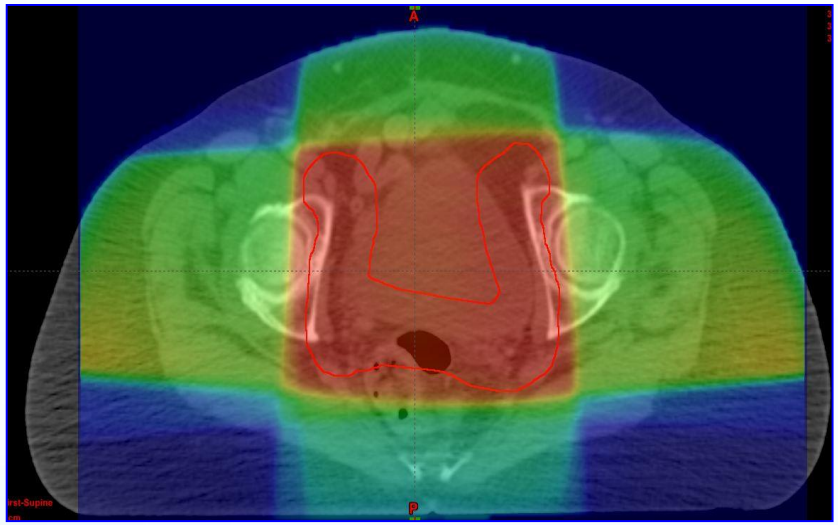
Trial ID	CTRT events	CTRT pts.	Control events	Control pts.
Trials of Chemoradiation *v* radiotherapy				
(a) Platinum-based CTRT				
Onishi[44] (CDDP or CDBCA)	16	26	15	23
Pearcey[43] (CDDP)	53	130	60	129
GOG0123[6] (CDDP)	49	185	69	189
Chen[23] (a) (CDDP FU VCR)	8	30	8	30
Chen[23] (b) (CDDP FU VCR)	6	30	7	30
Pras (CDBCA FU)	17	28	16	26
GOG0165[26] (a) (CDDP)	8	26	12	24
Cikaric[47] (CDDP)	37	100	48	100
Leborgne (CDDP FU)	75	170	85	170
Gariapagaoglu[48] (CDDP)	9	22	8	22
Lal[50] (CDDP)	14	94	12	86
Sub-total	292	841	340	829
(b) Non–platinum-based CTRT				
Thomas[24] (a) (FU)	24	57	32	58
Thomas[24] (b) (FU)	26	58	25	60
Lorvidhaya[25] (a) (MMC FU)	40	233	59	242
Lorvidhaya[25] (b) (MMC FU)	54	230	49	221
Roberts[49] (MMC)	25	124	39	124
GOG0165[26] (b) (FU)	11	27	12	24
Sub-total	180	729	216	729
Total	472	1,570	544	1,534

Meta-analysis using individual patient data from randomized trials
Chemoradiotherapy for Cervical cancer Meta-analysis Collaboration (CCCMAC); J Clin Oncol 26:5802, 2009

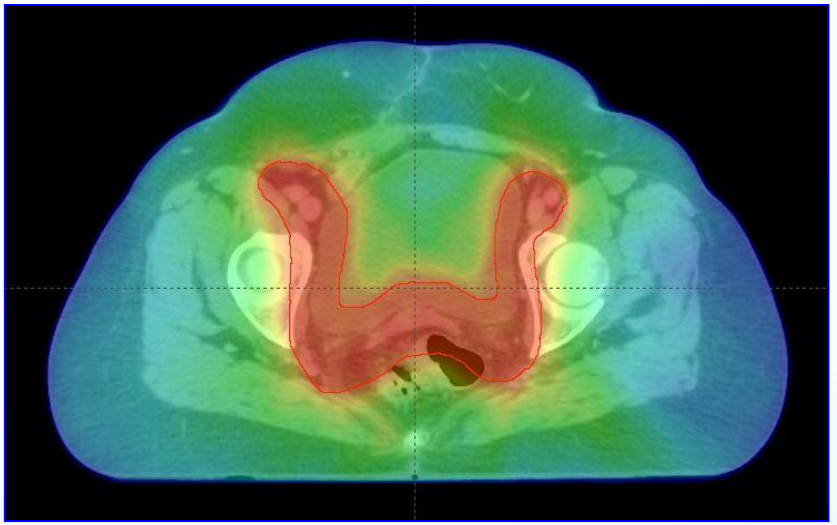
Improving outcomes: therapeutic index



IMPROVING OUTCOME



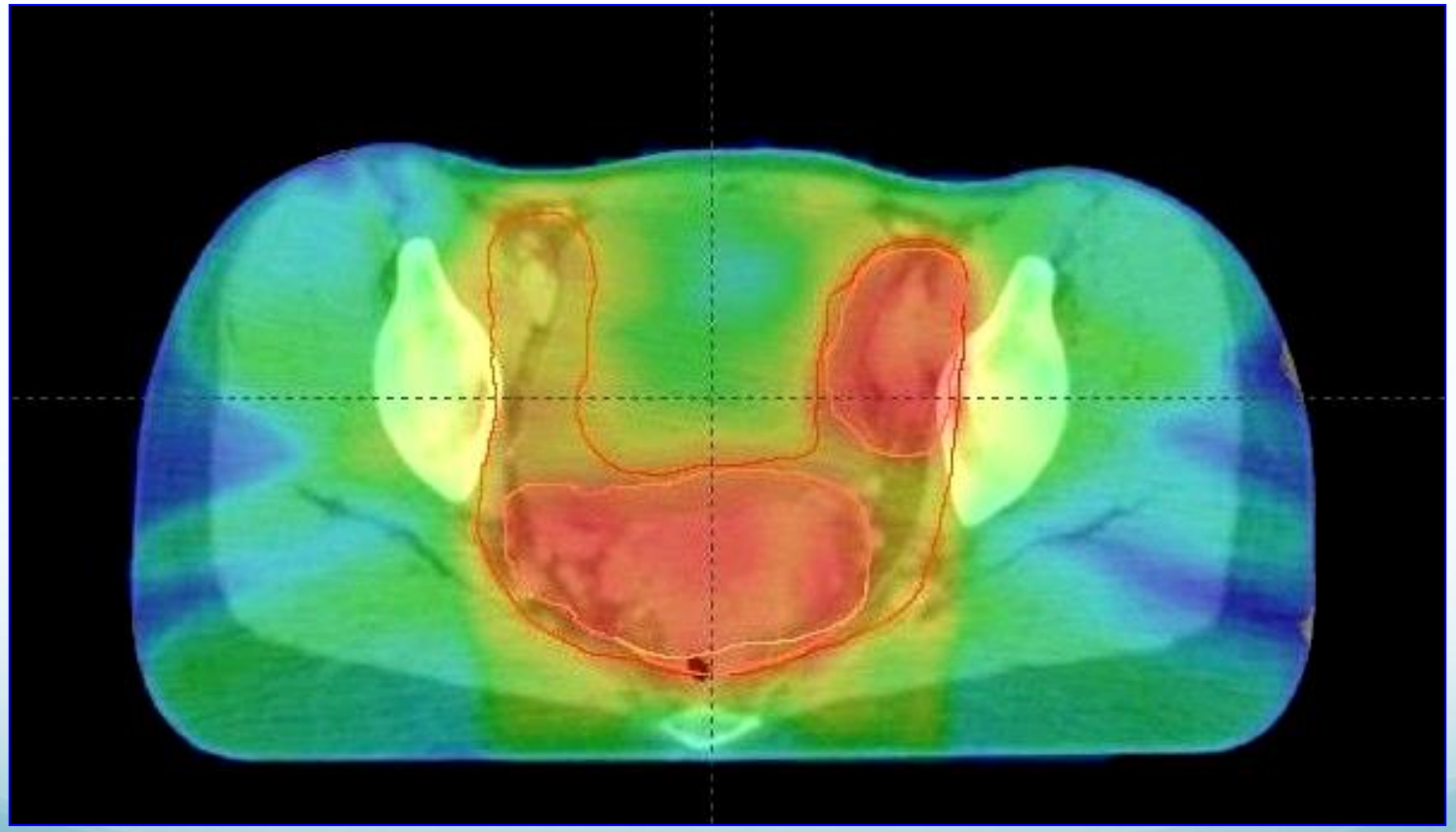
CONFORMAL



IMRT

Improving Target Delineation

PET – CT Registration



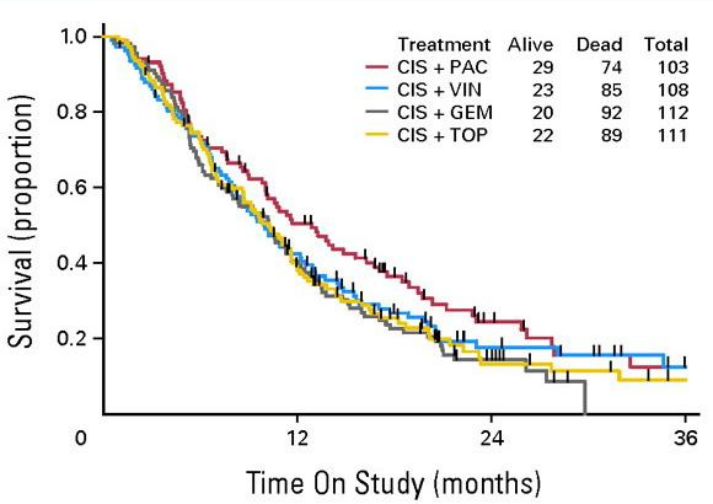
Cervix Cancer

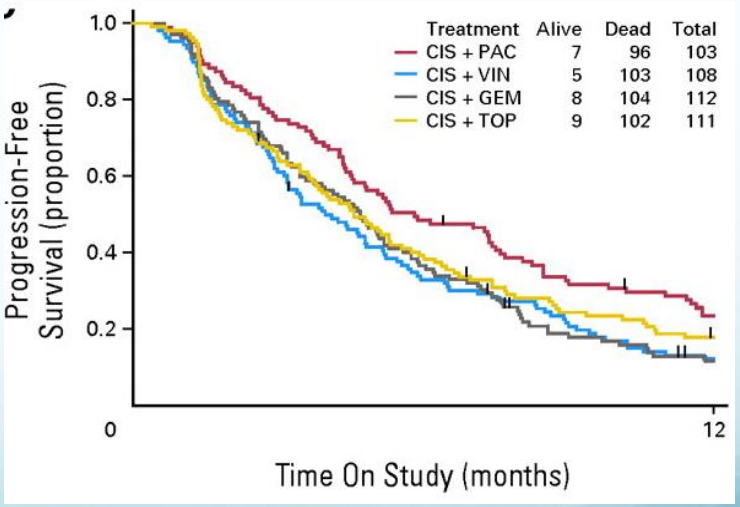




Recurrent /Persistent Metastatic Disease; How Good is chemotherapy?

	Cisplatin Paclitaxel	Cisplatin Vinorelbine	Cisplatin Gemcitabine	Cisplatin Topotecan
Response	29%	25%	22%	23%
Median PFS	5.8m	4m	4.7m	4.6m
Median OS	12.9m	10m	10m	10.2m

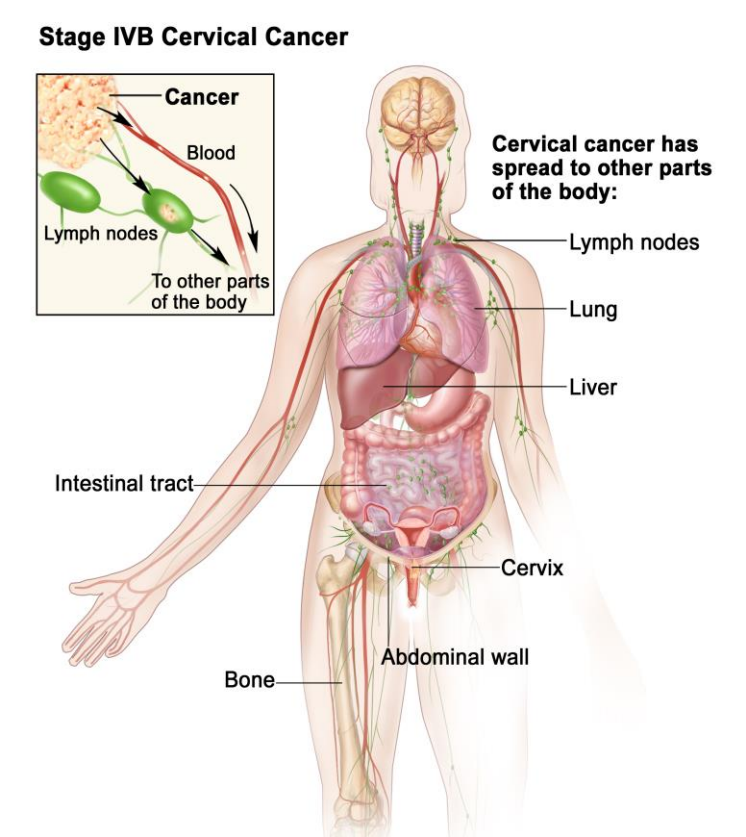




Bradley J. Monk; *JCO* **2009,** 27, 4649-4655.

Recurrent /Persistent Metastatic Disease

Unmet clinical need





Targeted Therapy – Tumour Angiogenesis

Rationale

- Clinical visible aberrant vascularity on colposcopy
- Molecular – viral integration of protein E6 and E7 up regulates VEGF expression
- Pathological – high tumour microvessel density associated with worse prognosis

Targeted Therapy: Angiogenesis

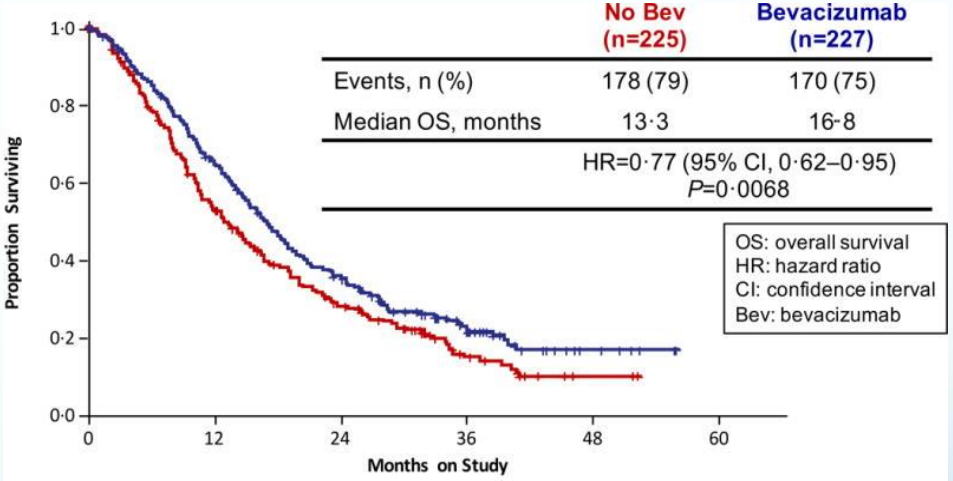
Bevacizumab in Cervical Cancer

GOG 240

N=452

Cis-paclitaxel ± Bevacizumab Topotecan Paclitaxel ± Bevacizumab

	No Bev	+Bev
RR	46%	51%
OS (months)	13.3	16.8
Progression free survival	6	8.2



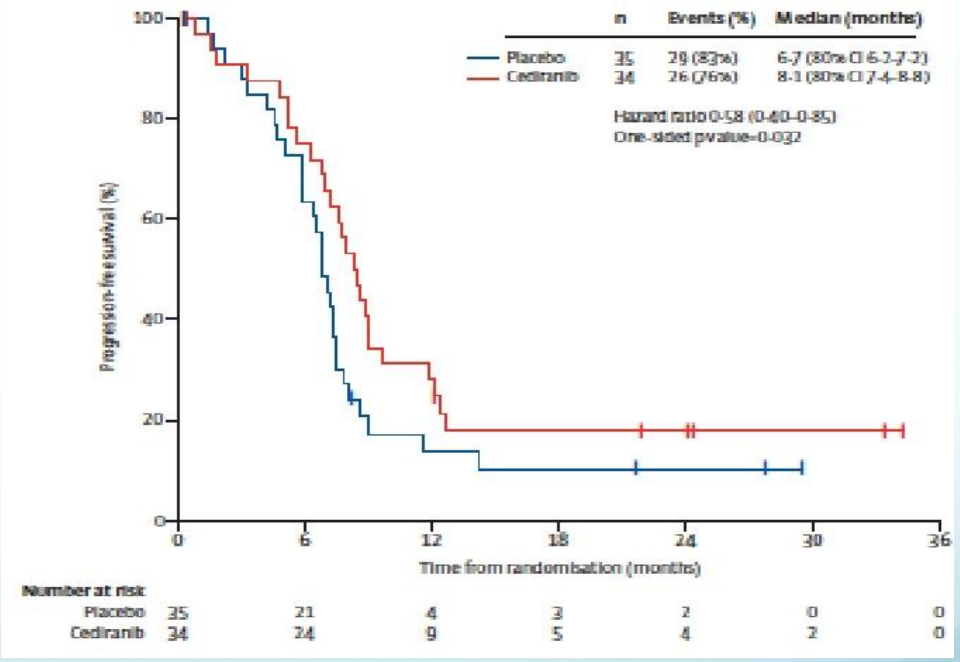
Tewari KS et al Lancet2017390 1654-63

Targeted therapy:angiogenesis

Cediranib in cervix cancer
CIRCCA

N=69
Cediranib + Carbo taxol v Placebo + Carbo Taxol

	Cediranib	Placebo
CR	9%	0
PR	56%	42%
PFS	8.1	6.1



Symonds RP, et al. *Lancet Oncol.* 2015;16(15):1515-1524.

Immunotherapy: Vaccination

- Rely on cell mediated immunity against HPV infected cells
- Onco proteins E6 and E7 are the selected antigens
- Can also target pre invasive disease
- Most are live attenuated vaccines

Targeted Therapy Immunotherapy: Vaccination

GOG/NRG 265 ASXS11-001 (axal) Phase 2
N=50

- Listeria monocytogenes as vector for targeted immunotherapy
- Relapsed or metastatic
- ≥1 line previous therapy

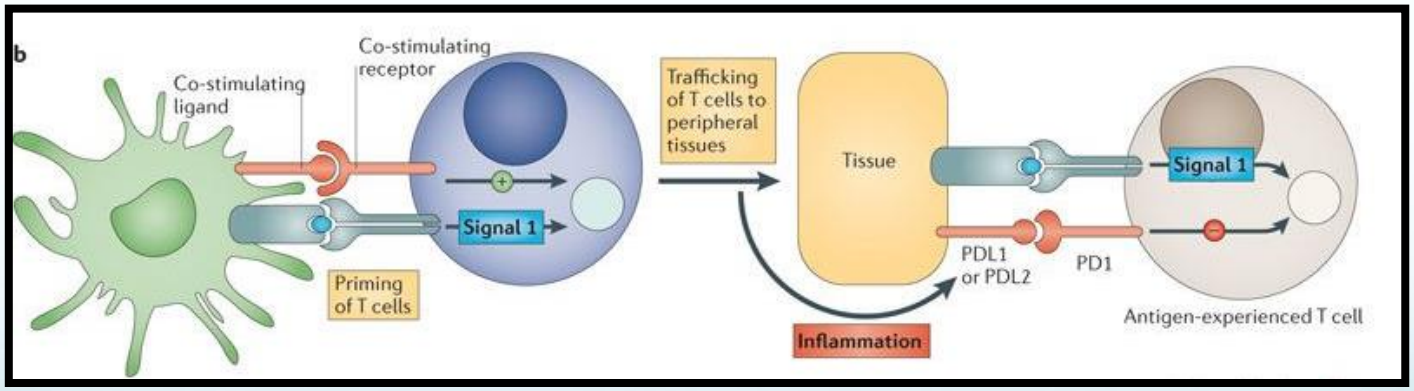
	N=50
Med OS	6.2m
OS rate	38%
Range	12-40 m

Response	**N=50**
Complete response	1(2%)
Partial Response	0
Stable disease	15 (30%)
Progressive disease	22 (44%)
Not evaluable	10
Toxicity grade 3/4	40%

Immunotherapy: Checkpoint inhibition 2

- Targets Programmed cell death pathway (PD1)
- PD1 is upregulated by activated T cells
- Acts in tissues
- Blockade induces anti-tumour immunity

Eg pembrozulimab, nivolumab



News >

FDA Approves Pembrolizumab for PD-L1+ Cervical Cancer

Jason M. Broderick @jasoncology
Published: Tuesday, Jun 12, 2018



The FDA has granted pembrolizumab (Keytruda) an accelerated approval for the treatment of patients with advanced, PD-L1–positive cervical cancer with disease progression on or after chemotherapy.

Jean-Sebastien Frenel;et al; *JCO* **2017,** 35, 4035-4041.



