REVIEW OF HPV-RELATED ANAL CANCER

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June 18, 2015

THE UNIVERSITY OF TEXAS
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Department of GI Medical Oncology

SEER FAST FACTS

SEER Stat Fact Sheets: Anal Cancer

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Statistics at a Glance

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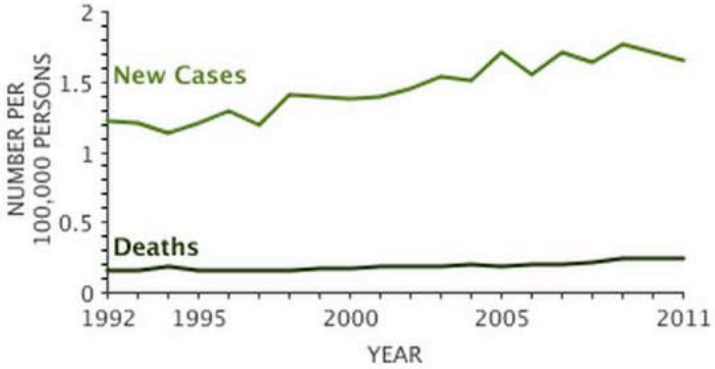
At a Glance

Estimated New Cases in 2014	7,210
% of All New Cancer Cases	0.4%
Estimated Deaths in 2014	950
% of All Cancer Deaths	0.2%



Percent Surviving 5 Years

65.5%

2004–2010

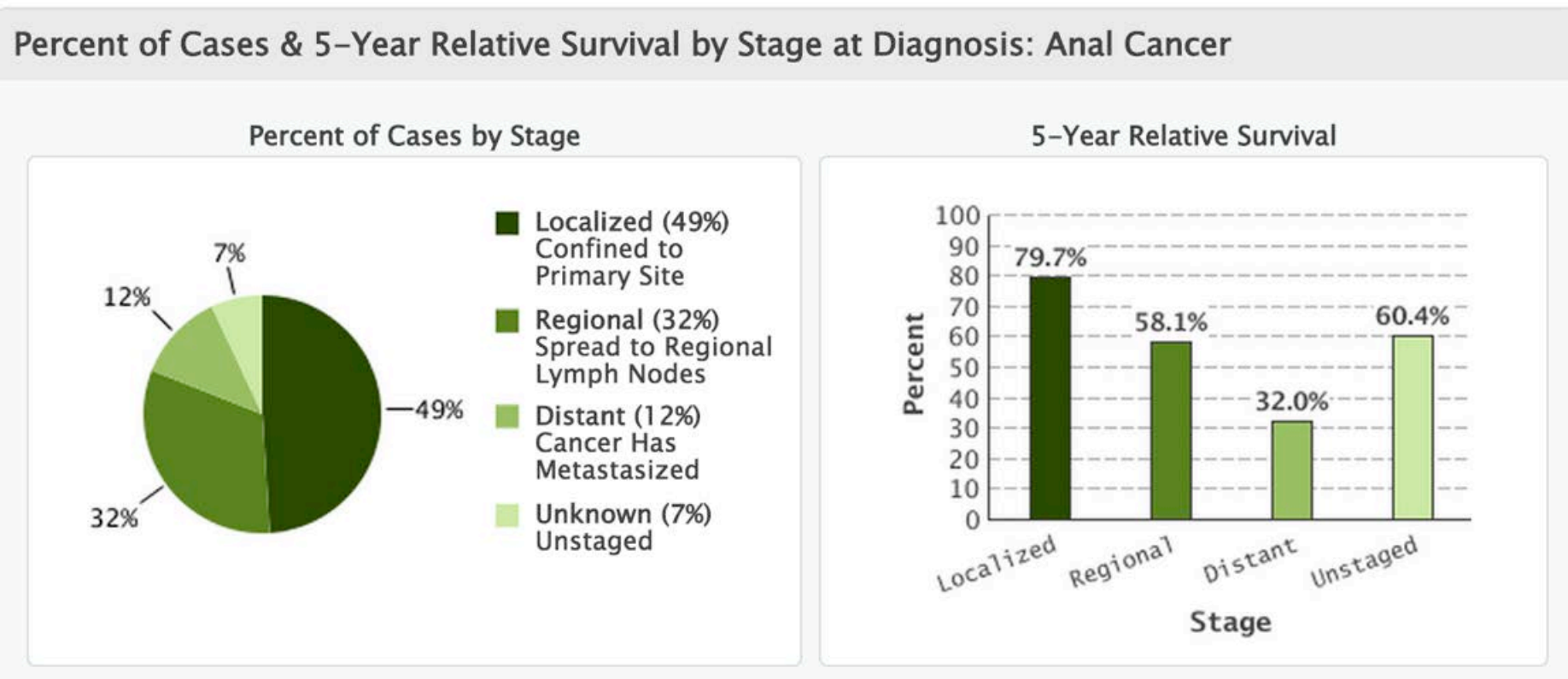
Globally, there are an estimated 27,000 new cases every year

Number of New Cases and Deaths per 100,000: The number of new cases of anal cancer was 1.8 per 100,000 men and women per year. The number of deaths was 0.2 per 100,000 men and women per year. These rates are age-adjusted and based on 2007–2011 cases and deaths.

Lifetime Risk of Developing Cancer: Approximately 0.2 percent of men and women will be diagnosed with anal cancer at some point during their lifetime, based on 2009–2011 data.

www.seer.gov; de Martel C et al. Lancet Oncol 2012;13(6):607-15).

SEER Data: 2004-2010



http://seer.cancer.gov/statfacts/html/anus.html, accessed 3/8/15

Risk Factors for Anal Canal Cancer

- > 50 years of age
- > 10 sexual partners
- Human papilloma virus (HPV)
- Chronic immunosuppressed states
  - Organ transplant pts
  - HIV/AIDS
    - *Not considered an AIDS-defining illness
- Receptive anal intercourse
- History of gynecological malignancy
- Tobacco use

C. Eng: MD Anderson Manual of Clinical Oncology, 2006;
Frisch et al: J Natl Cancer Inst 92:1500-10, 2000;
Frisch M, et al: J Natl Cancer Inst 91:708-15, 1999.

HPV in Rare Anogenital Cancers

- Incidence:
  - US: 18,310 cases per year
  - Globally: 89,000 cases per year
- Though penile cancer represents < 1% of all cancers in the US, but in Asia, Africa, and South America, penile cancer represents 10% of all malignancies diagnosed in men.
- Each of these rare cancers have been clearly linked to HPV in variable degrees of association:
  - 90% of anal and vaginal carcinomas
  - 70% of all vulvar cancers
  - 50% of penile cancers.

HIV+ and Anal Cancer

- 2-6 times likely to have HPV regardless of sexual practices and have a persistent infection
- Incidence rate for anal cancer in men who have sex with men (MSM):
  - 5.1 cases per 100,000
    - HIV^+: 45.9 cases/100,000
    - HIV^-: 12.5 cases/100,000
- Younger age of presentation if HIV^+
- No reduction in incidence despite the use of HAART medications

D'Souza G et al., J Acquir Immune Defic Syndr 2008 48(4):491
Chiao EY et al., J Clin Oncol 2008 26(3):474

Cancer Burden in HIV+ Patients

Cancer	Estimated number of cancers in people living with AIDS in 50 U.S. states and DC			P_{trend}↑	Estimated number of cancers in people in 34 U.S. states living with AIDS or HIV-only	
	1991 – 1995	1996 – 2000	2001 – 2005		AIDS	HIV-only
					2004 – 2007	2004 – 2007
AIDS-defining cancers	21,483	5727	3827	<.001	2941	---------
Kaposi Sarcoma						
Non-Hodgkin Lymphoma	12,778	7292	5968	<.001	4584	---------
Cervix	327	419	530	.003	383	---------
All AIDS-defining Cancers	34,587	13,439	10,325	<.001	7869	---------
Non-AIDS-defining cancers	181	341	503	<.001	297	103
Oral Cavity and Pharynx						
Esophagus	41	62	254	.002	86	25
Stomach	50	78	118	.06	67	41
Small Intestine	13	25	24	.48	12	13
Colorectum	108	230	438	<.001	237	135
Anus	206	770	1,564	<.001	751	154
Liver	116	261	583	<.001	269	91
Pancreas	25	62	188	<.001	76	63
Larynx	70	192	317	<.001	161	50
Lung	875	1383	1882	<.001	1143	454
Bone	5	9	2	.15	2	9
Soft Tissue including Heart	33	43	112	.06	40	6
Melanoma	76	154	264	.001	120	25

Shiels MS et al., J Natl Cancer Inst 2011 103(9):753

Pivotal Historical Trials

Study	Arms	N	Dose	3- yr	3-yr OS
Nigro	5-FU/MMC/ XRT	28 pts	MMC (single 15 mg/m^2 bolus) + 30 Gy	-	-
UKCCCR	RT	200	45 Gy + boost	61% LF	58%
	RT/ 5FU/MMC	295	MMC **12** mg/m^2 day 1, 3) 45 Gy + boost	**39% LF** (*P<.001*)	65% (*P=.25*)
EORTC	RT	52	45 Gy + boost	39% LRC	72%
	RT/ 5FU/MMC	51	MMC **15** mg/m^2 day 1, 3) 45 Gy + boost	58% LRC (*P=.02*)	65% (*P=.17*)

Nigro et al: Cancer, 1983; UKCCCR: Lancet 348:1049-54, 1996; Bartelink et al: JCO, 1997

RTOG 87-04/ECOG: 5-FU + Radiation Therapy +/- MMC

Arms	N	Dose	4-yr CFS	4-yr DFS
5-FU/RT	145	45 Gy 5-FU (1000 mg/m^2/day, D1-D4)	59%	51%
5-FU/ MMC/RT	146	1) 5-FU (1000 mg/m^2, during 1st and last week of RT, 2) MMC 10 mg/m^2 Day 1 and 29 3) 45-50.4 Gy	71% (*P*=.014)	73% (*P=.01*)

Flam et al: JCO 14:1527-39, 1996

Treatment Standard for Locally Advanced Disease

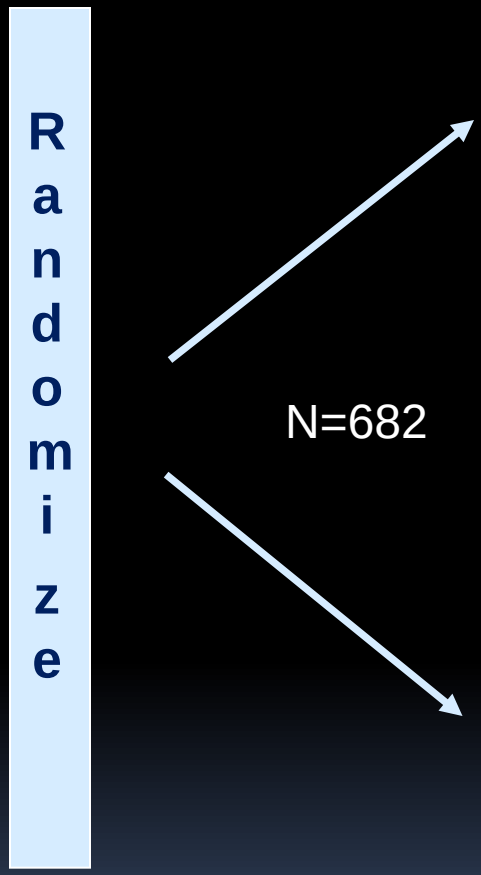
- SCCA of the anal canal is a very chemoradiosensitive cancer.
  - ChemoXRT is curative.
    - Surgery is not necessary
    - Risk factors for radioresistance: T4 or N2/N3 disease
- Salvage surgery (APR) is reserved in the setting of recurrent or refractory disease.
  - Results in a permanent colostomy

Mitomycin C vs. Cisplatin

- Myelosuppression
- Pulmonary fibrosis
- Hemolytic-uremic syndrome
- Therapy–related myelodysplastic (MDS) syndrome

- Nausea/vomiting
- Electrolyte imbalance
- Nephrotoxic
- Ototoxic
- Neuropathy

Intergroup RTOG 98-11



***Arm A*: Mitomycin-C 10 mg/m² IV bolus on day 1 & 29**

+

5-FU 1000 mg/m²/ day by CI on days 1-4 & 29-32 with RT

***Arm B* (Induction): Cisplatin 75 mg/m² over 1 hr Days 1 & 29, CIFU 1000 mg/m² Days 1-4, 29-32**

Repeat Days 57-60 and Days 85-88 with RT

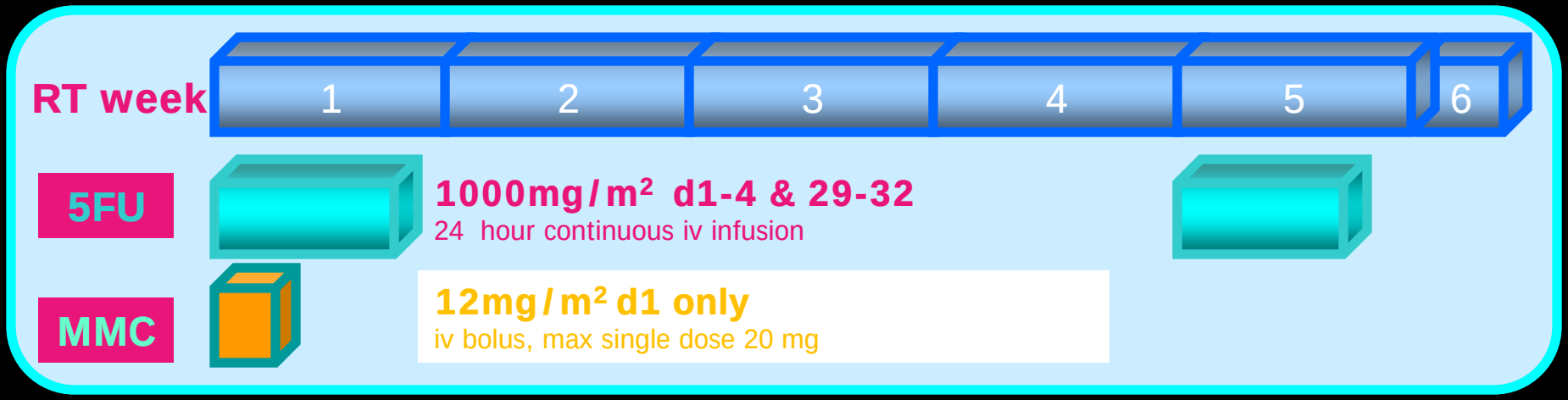
*HIV pts ineligible

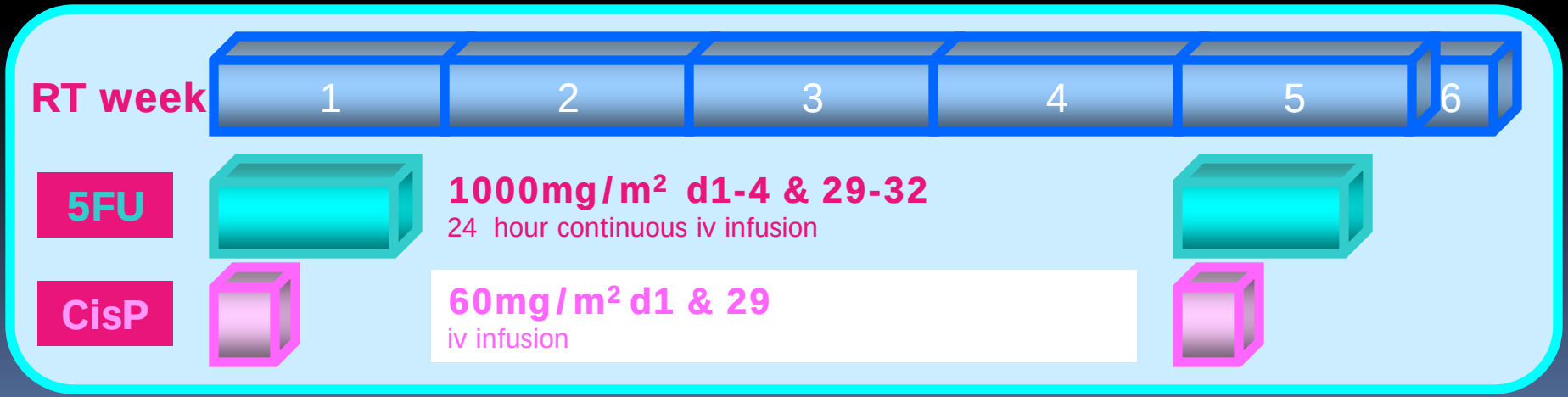
Primary endpoint: DFS (n=682)

Ajani et al: Jama 299 (16), 1914-21, 2008

ACT II: Chemoradiation Treatment

50.4 Gy in 28 fractions over 5 ½ weeks (no gap)



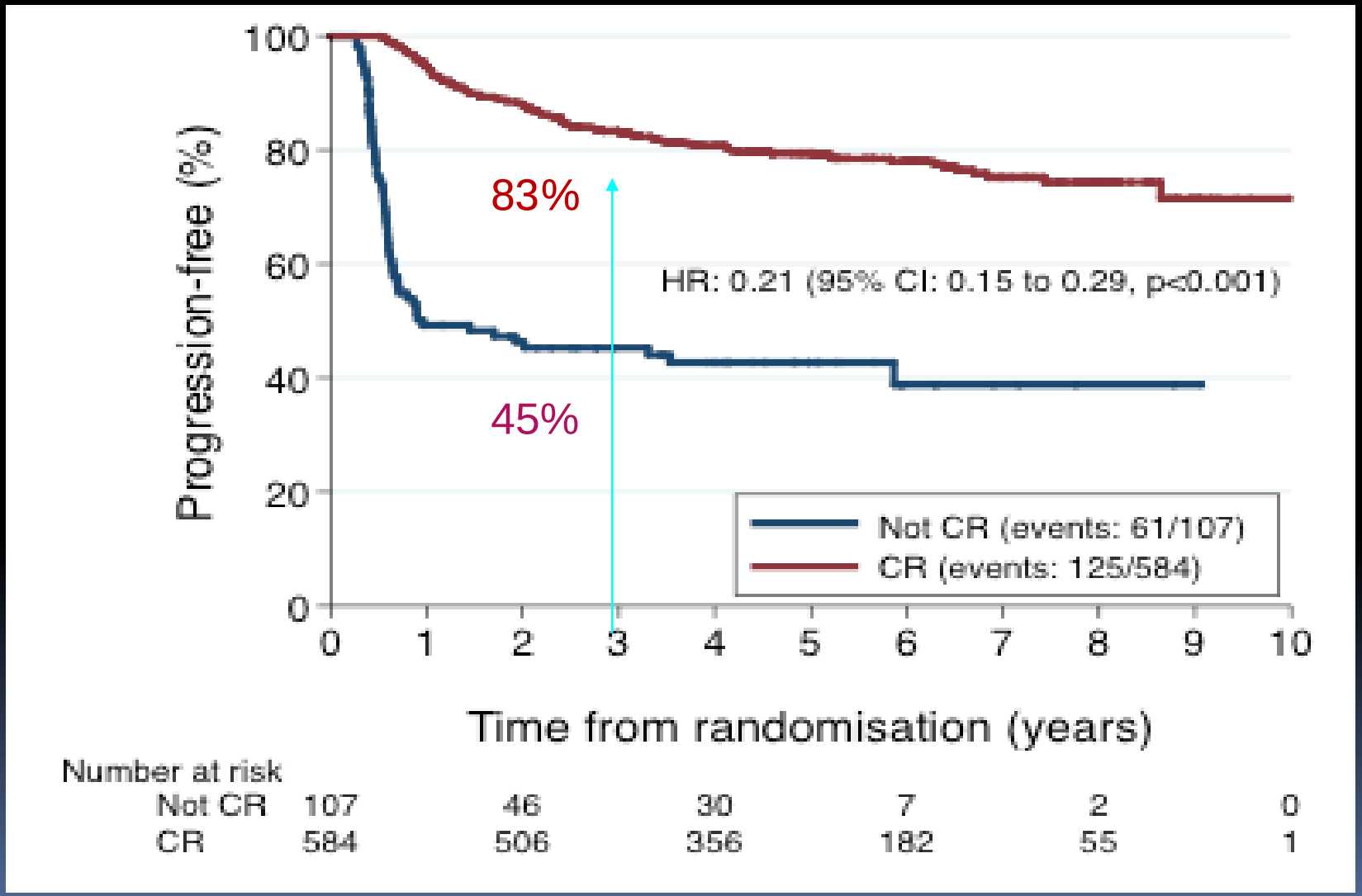


Comparison of Recent RTOG vs. ACT II Phase III Anal Ca trials

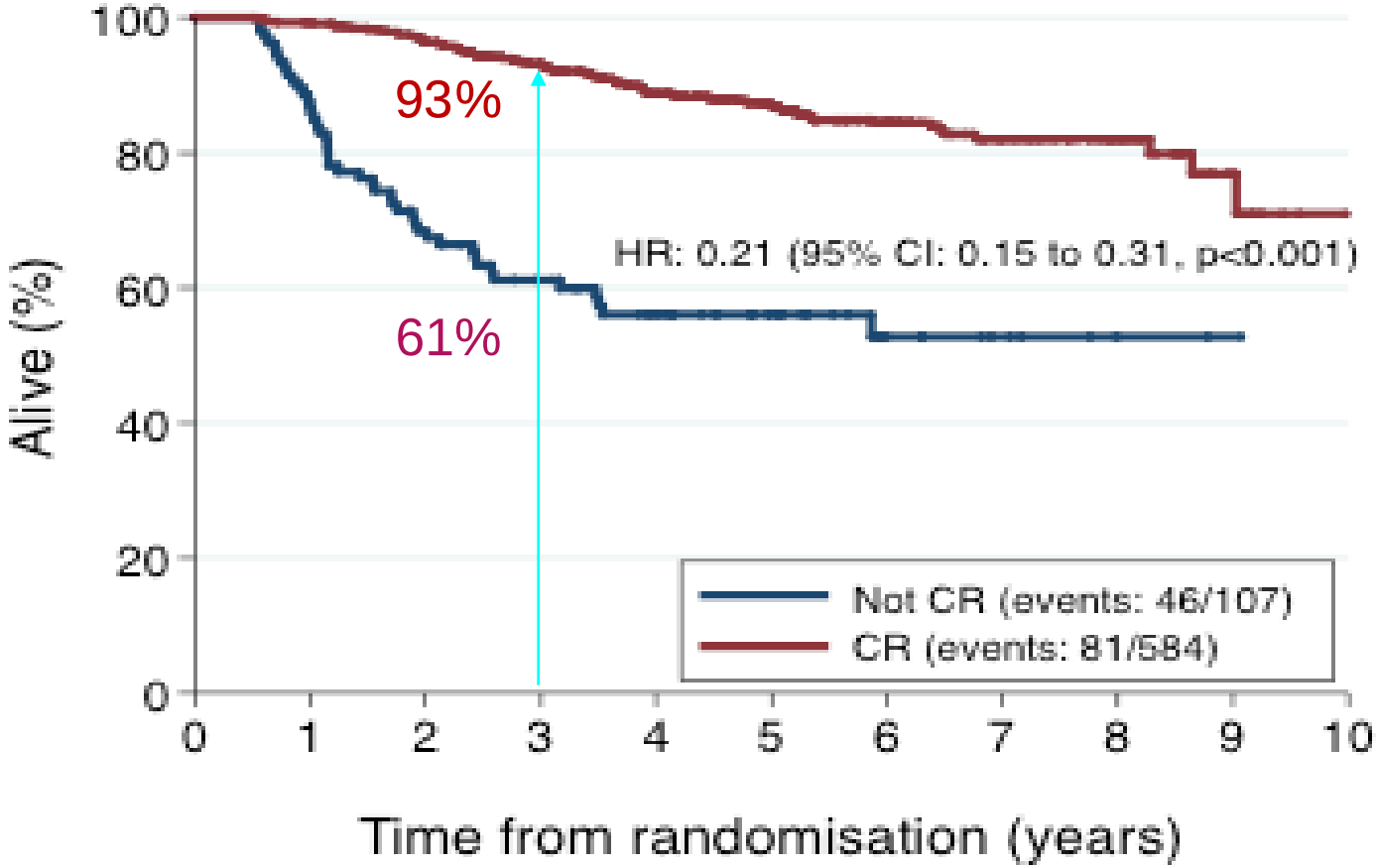
	RTOG 98-11 (N=644)	ACT II (N=940)
Induction	Yes (no benefit)	n/a
Treatment	MMC: 10 mg/m^2, Cisplatin 75 mg/m^2 D1 and 29	MMC: 12 mg/m^2, D1 Cisplatin 60 mg/m^2, D 1 and 29
Maintenance (adjuvant)	n/a	Yes (early - but unlikely benefit)
Time to Colostomy	P= 0.075	13.7% vs. 11.3%

ACT II Update ASCO 2012

PFS free-survival
CR vs No CR @ week 26



Overall Survival
CR vs No CR @ week 26



Number at risk

Not CR	107	68	39	11	3	1
CR	584	555	392	192	59	1

ACT II – ASCO 2012 Conclusions

- Excellent CR rate at 6 months - 83% v 84%
- 60% of pts not in CR at 11 weeks achieved CR at 26 weeks.
- It is recommended assessment may be completed up to 26 weeks

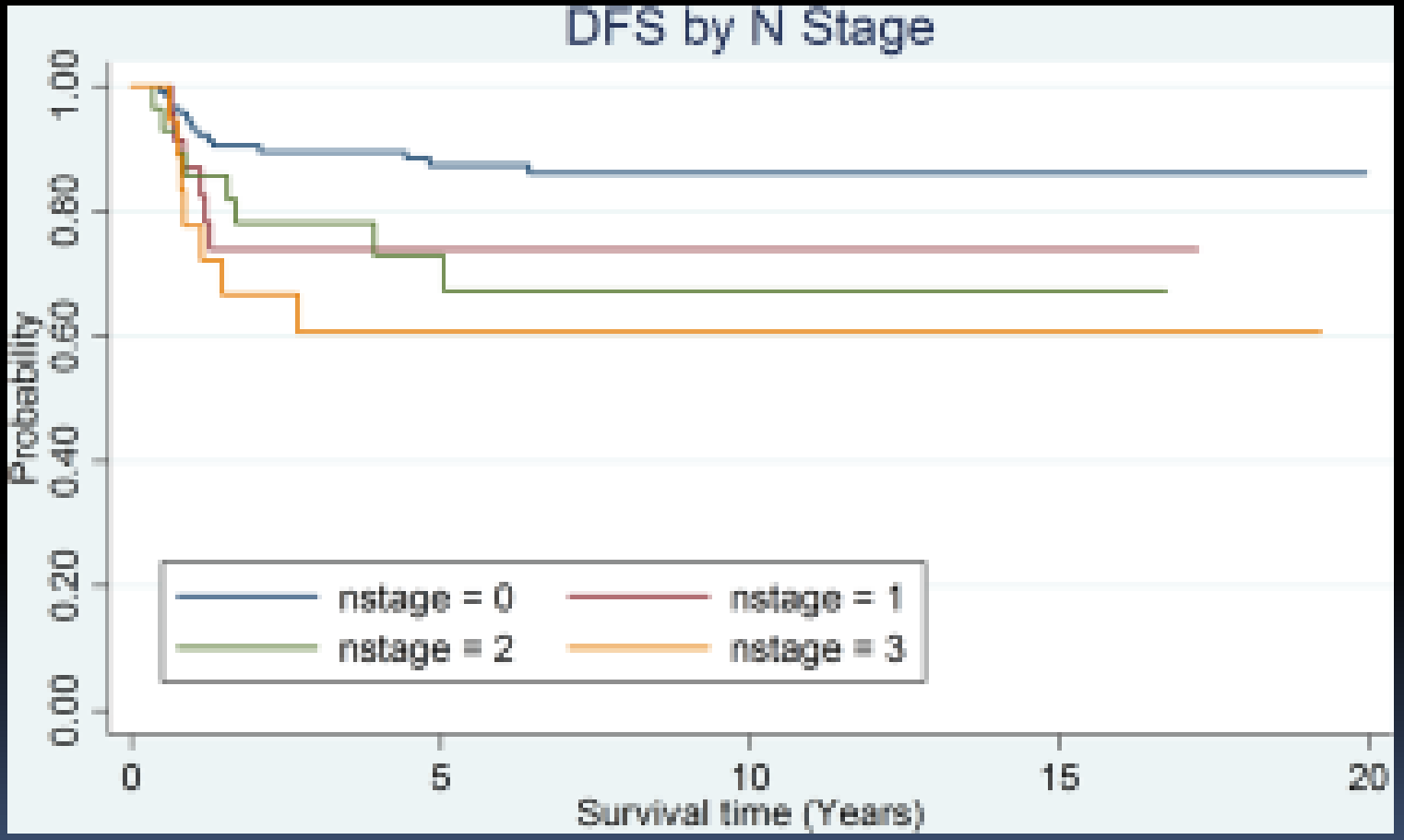
MDACC Approach to Locally Advanced Anal Cancer

MDACC - 20 yrs Experience of 5-FU/CDDP

- Median follow up: 8.6 years
- Local recurrence in 15 pts (8%)
- Distant metastasis (DM) in 16 pts (9%)
- Salvage surgery performed in 13 pts (7%)
- 5-yr DFS = 81%; 5-yr OS = 86%; and 5-yr CFS =88%.

Eng et al: Cancer. 2013 Nov 1;119(21):3769-75

MDACC: Long-term results of weekly/daily cisplatin-based chemoradiation



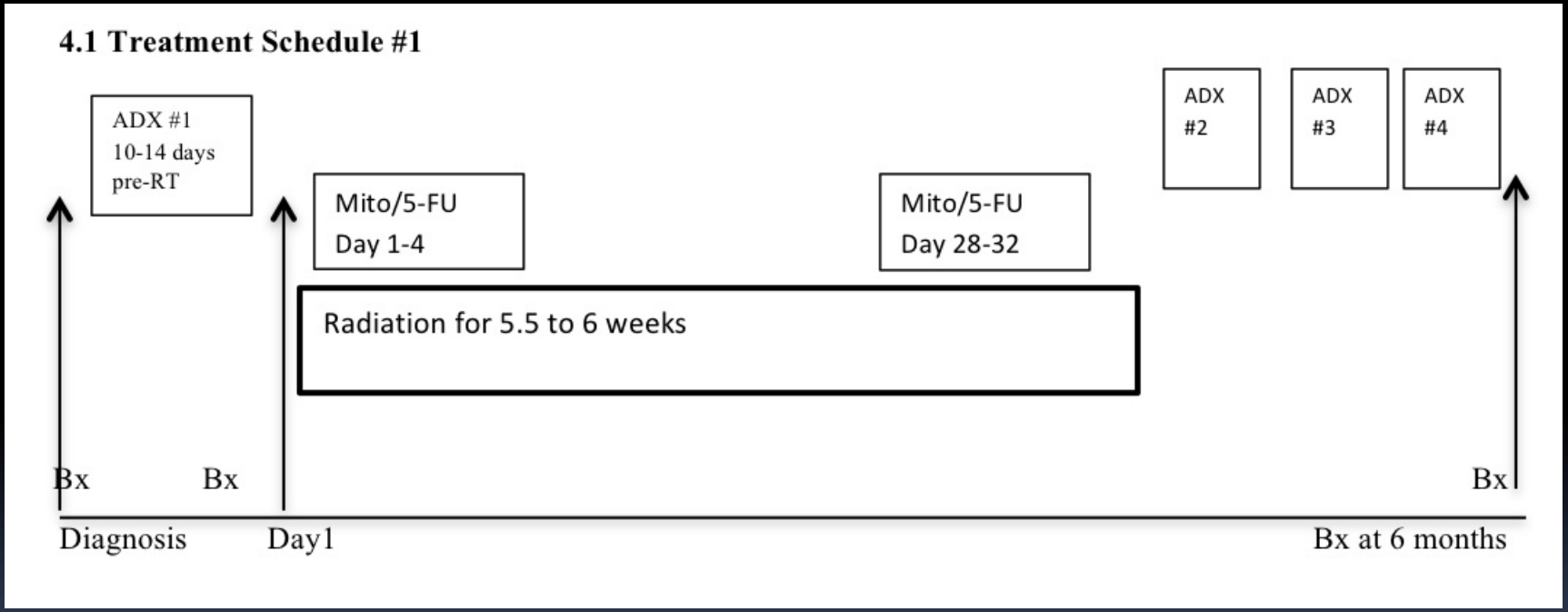
Eng etl al: Cancer
Volume 119, Issue 21, pages 3769-3775, 20 AUG 2013 DOI: 10.1002/cncr.28296
http://onlinelibrary.wiley.com/doi/10.1002/cncr.28296/full#cncr28296-fig-0001

Current Clinical Trials & the Incorporation of Novel Agents

A Phase I/II Evaluation of ADXS11-001, MMC, 5-FU and IMRT for Anal Cancer
PI: Howard Safran, Brown University

- ADXS11-001 is an attenuated listeria based vaccine carrying a plasmid for HPV-7.
- ADXS11-001 is given IV and enters antigen presenting cells (APCs). This stimulates an immune response against HPV infected tumor cells.
- Phase II studies demonstrate single agent activity of ADXS11-001 in metastatic cervical cancer.
- ADXS11-001 is being evaluated by the GOG in refractory cervical cancer and in an industry sponsored study in cervical intraepithelial neoplasia.

Multi-institutional phase I/II pilot for patients with anal cancer.



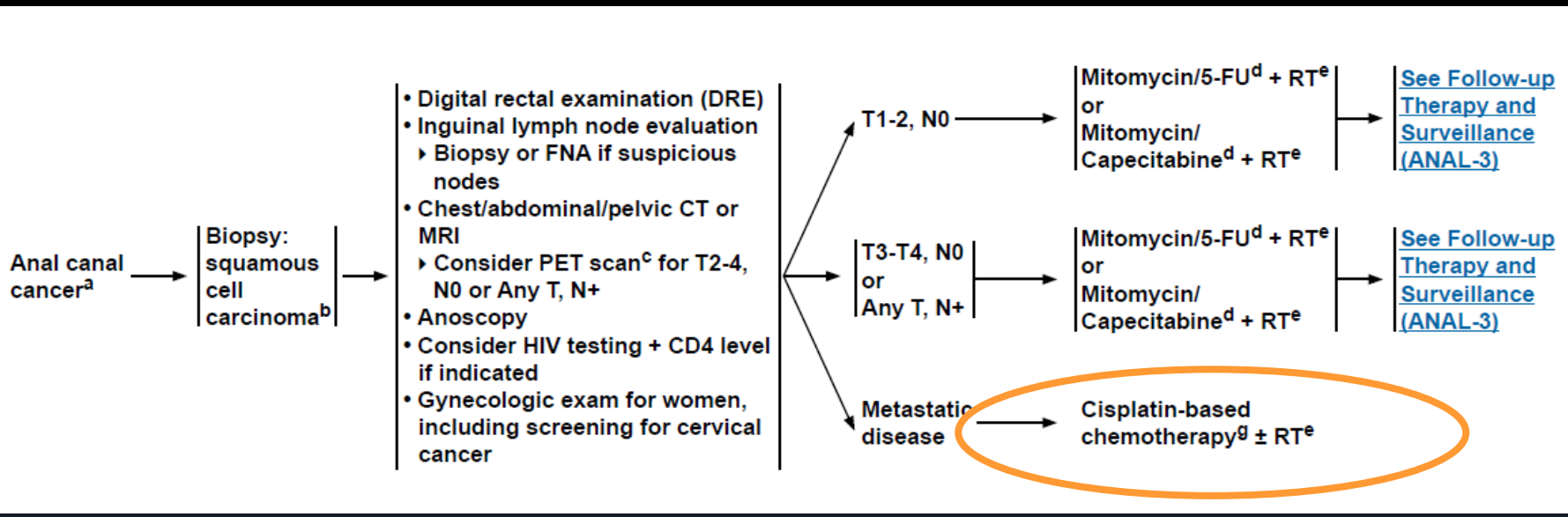
PI: Howard Safran, Brown University

Preliminary Results: Oct 2014

- 10 patients completed vaccine (all locally advanced)
  - Goal N=25
- SAE's included temporary rigors with fever and myalgia related to infusion of ADXS11-001
    - All due to ADXS administration (< 24 hrs)
- No evidence of bacterial infection
- No overlapping toxicities with chemoradiation
- Thus far, all in CR

Metastatic Anal Cancer

NCCN Guidelines for Anal Cancer



"5-FU/cisplatin is recommended for metastatic disease. No other therapy has been found to be effective."

Treatment of Metastatic Disease

- Develops in < 15% of patients
- Common site of metastases
  - Bone, liver and lung
- No standard chemotherapy regimen
- Little published data
- Review of the literature reveals:
  - Small, retrospective studies
  - Case studies
- Expected 5-yr OS: 31%

http://seer.cancer.gov/statfacts/html/anus.html#survival

Published Regimens for Met Anal SCCA

Author	N	Agents	ORR	Med PFS (months)	Med OS (months)
Wilking 1985	15	Vincristine, bleomycin & High-dose methotrexate	3/12 (25%)	2M	NR
Ajani 1989	3	5-FU/CDDP	NA	17M (2 of 3)	NA
Faivre 1999	18	5-FU/CDDP	65% (CR=15%)	4M	NA
Hainsworth 2001	60 (4 with anal cancer)	TPF (max = 4 cycles)	65% (CR = 25%)	26M	NR
Jhawer 2006	20	Mitomycin C, adriamycin, cisplatin, bleomycin-CCNU	12/20 (60%)	8M	15
Alcindor 2008	5	Taxol (1st and 2nd line)	60%	Range: 3-8M	Range: 4-20M
Abbas 2011	7	Taxol (2nd line)	57%	Range: 2-8M	Range: 5-14M
Kim 2013	8	DCF	CR: 50% (3/4 resected)	19-88M	1 yr: 62.5%

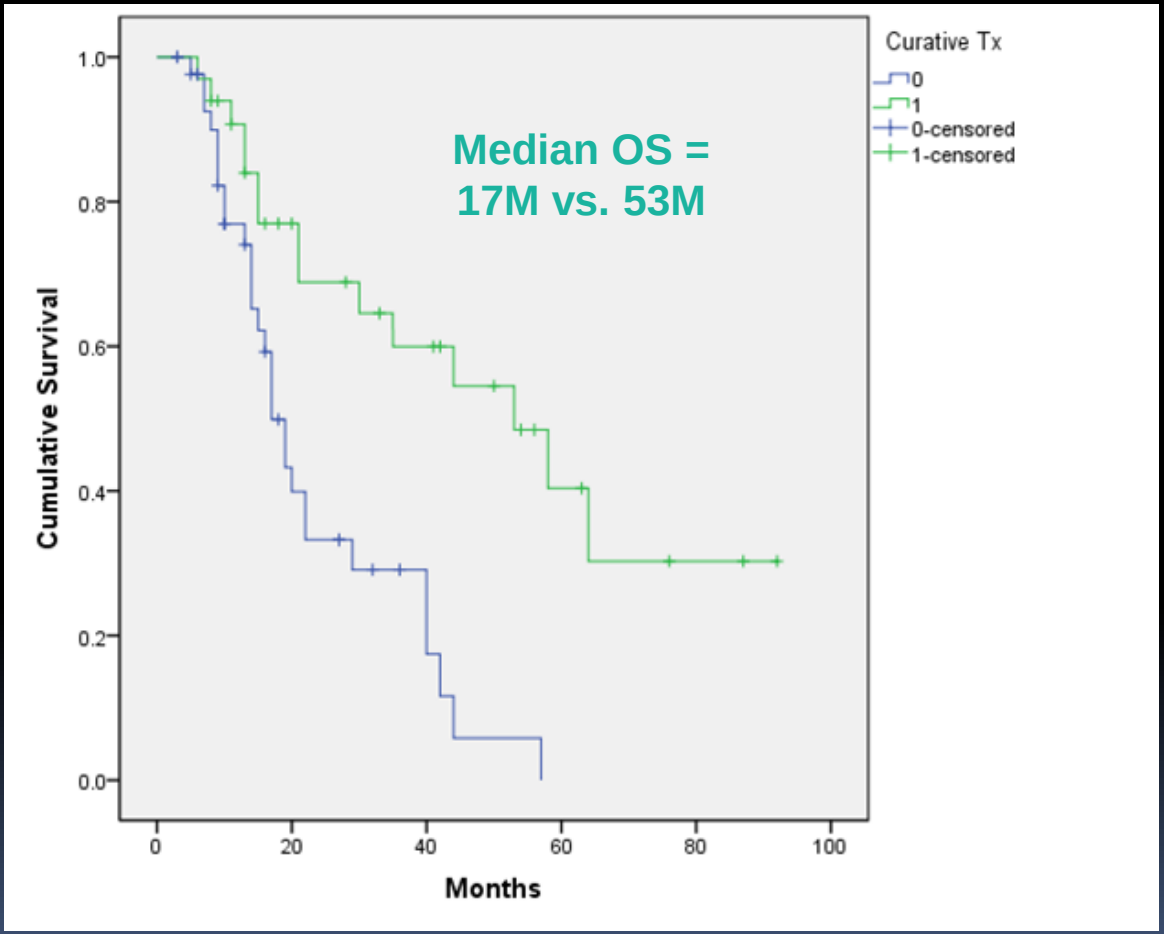
Eng et al, OncoTarget, 2014 Nov 30;5(22):11133-42.

Treatment Naïve Patients with Met SCCA of the Anal Canal: The MDACC Experience

- N=77
- 5-FU/cisplatin (PF, N=42) vs. carbo/paclitaxel (CP, N=24)
- Median follow-up = 42M
- Median PFS = 7M
- Median OS = 22M
- Patients that received PF were twice as likely to discontinue treatment due to toxicity rather than progression vs. CP (17% vs. 8%).

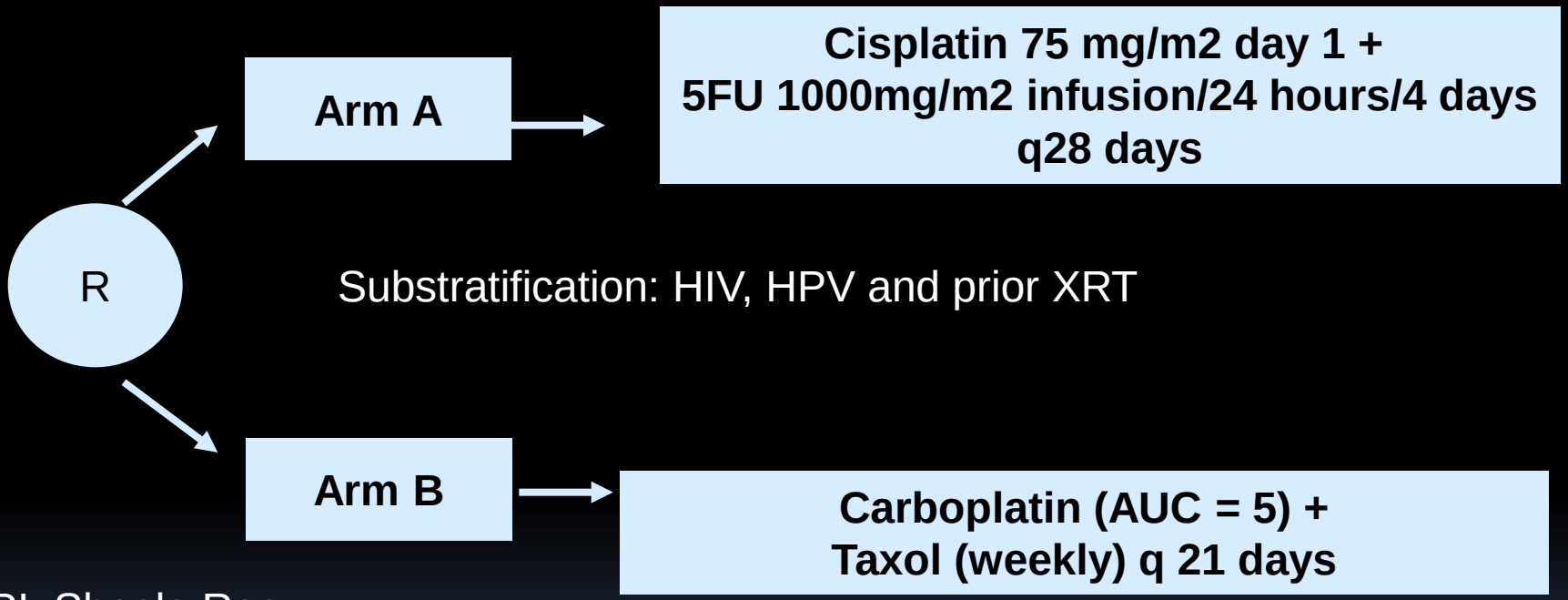
Eng et al, OncoTarget 2014

OS of Treatment Naïve Met Anal Patients:



Eng et al: OncoTarget 2014

IRCI/NCI/ECOG #EA2133 Trial : 1st line Met SCCA of the Anal Canal

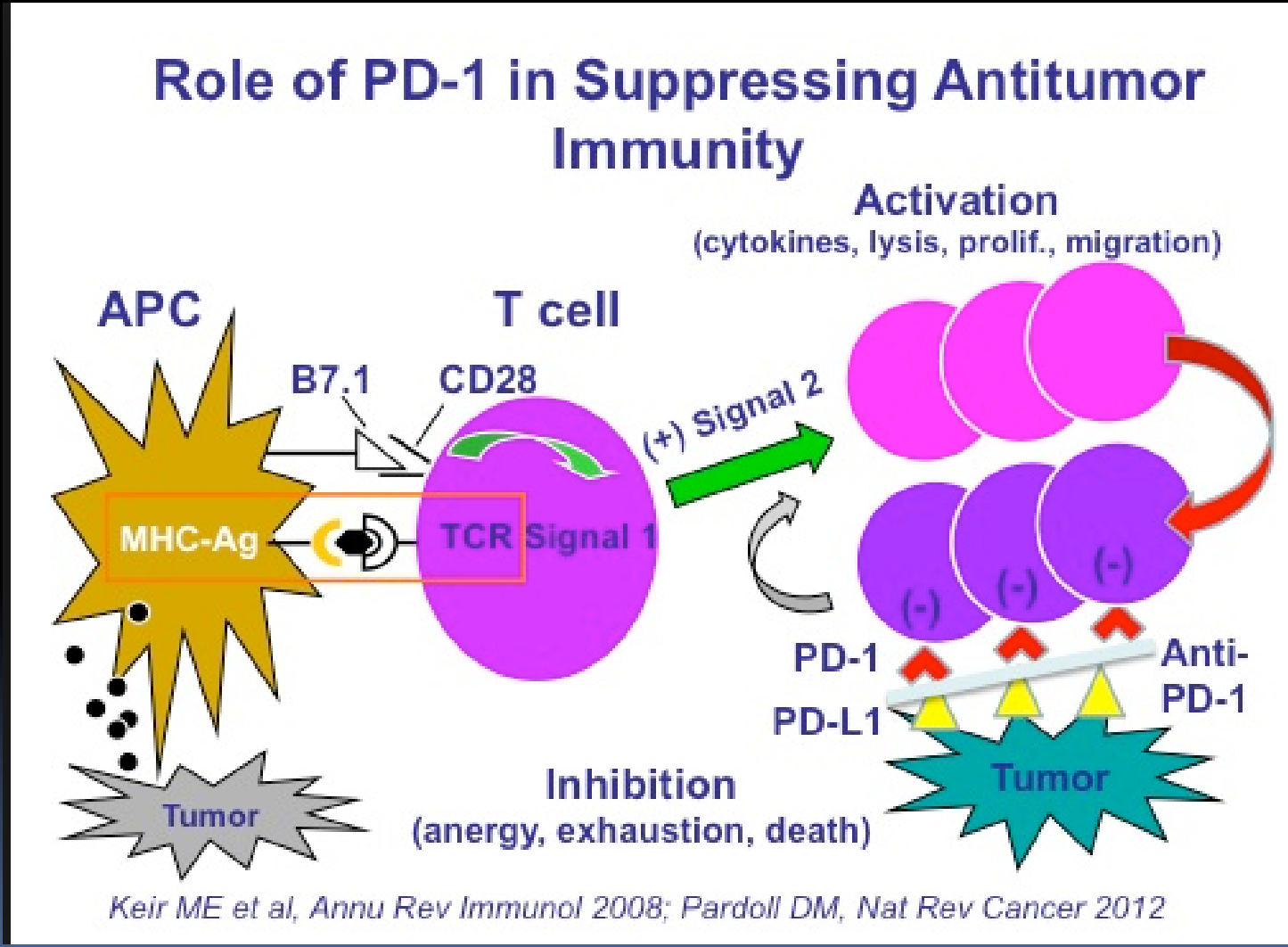


PI: Sheela Rao
ECOG US PI: C Eng

Objective: Identify best chemotherapy backbone to build for biologic development

1) **Primary endpoint: RR**
2) **Secondary endpoints: RR, OS, correlatives, and QOL, etc.**

The Potential of Immunotherapy

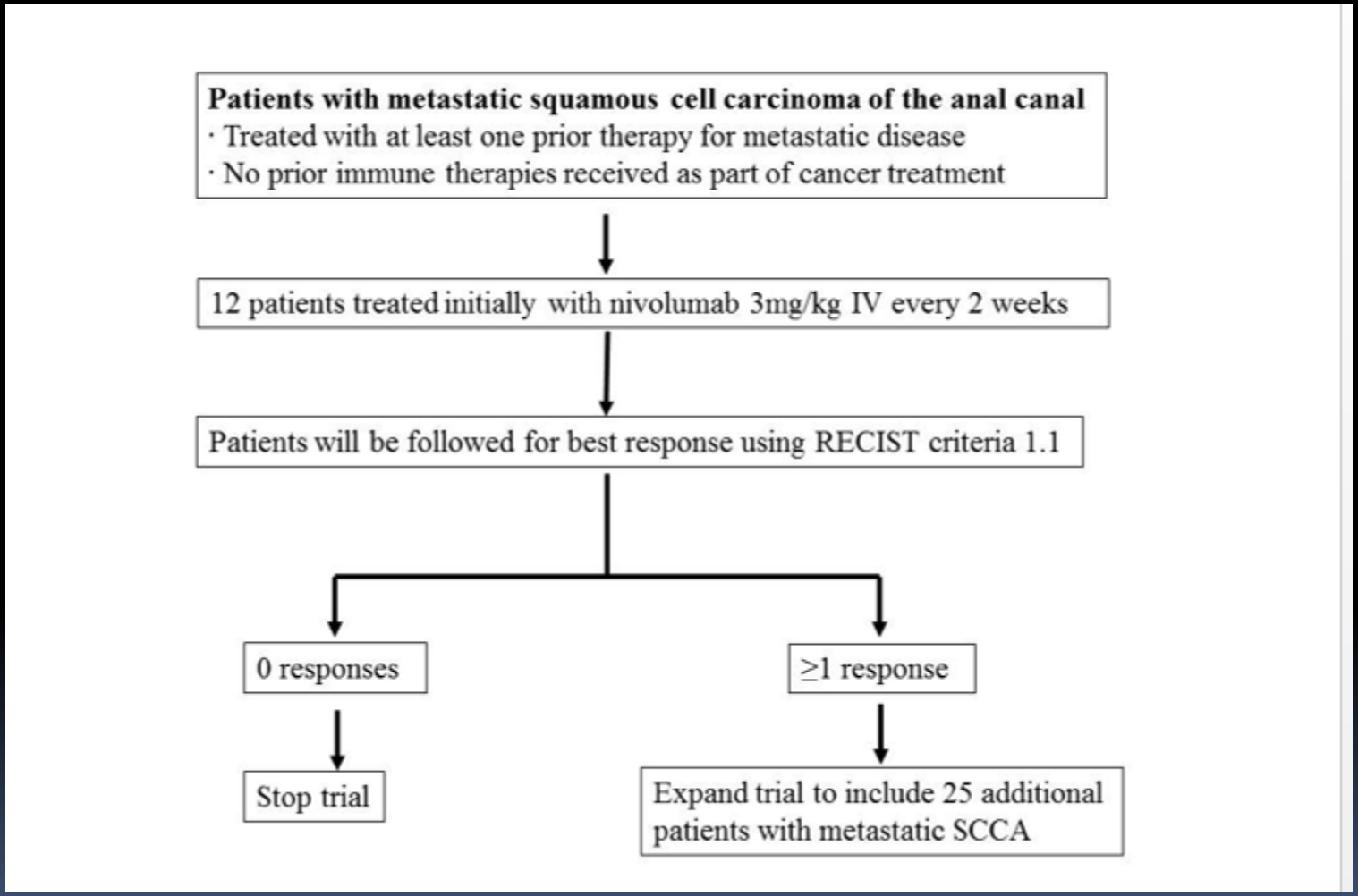


Nivolumab (Opdivo)

- PD-1 is a protein on the surface of activated T cells
- PD-1 usually binds ligands PD-L1 and PD-L2: Inactivating T cells
- Nivo is a fully human Ig anti PD-1 blocking Ab[1]
  - High affinity for PD-1 (K_D ~ 3 nM), blocks binding of both ligands PD-L1 (B7-H1) and PD-L2 (B7-DC)
  - Thereby, allowing the T-cell to develop an immunoregulatory response to the tumor.
- Manageable safety profile in a first-in-human, single-dose, dose-escalation study[1]
- FDA approved: melanoma and squamous cell (NSCLC)
  - Increased activity in pts with PD-1 expression

Brahmer J et al, ASCO 2012 Abst 7509; [1]Brahmer J, et al. J Clin Oncol 2010;28:3167-75

NCI Trial #9673: Nivolumab



PI: C. Eng, co-PI: V. Morris

NCI #9673: Eligibility Criteria

- ≥ 2 lines of therapy allowed
- HIV+ pts allowed; CD4 count ≥ 300
  - Requires ID physician for follow up
- Hepatitis B/C virus: WNL LFT's (hepatology to follow).
- PD-1 expression is not required.
- Patients will be excluded if they have systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration
- No prior chemo or XRT ≤ 28 days of drug administration

Conclusions:

- HPV associated malignancies have a large global impact
- Rising incidence of HPV associated malignancies notably in oropharyngeal and anal CA.
- Remaining challenges:
  - Identifying a new treatment paradigm
  - Treatment of metastatic patients
  - Prevention in high-risk populations: HIV + and high- risk HPV subtypes