Oncology Pharmacy Specialty Sessions, Part I

Tuesday, October 18
1:30 p.m.–4:30 p.m.
Convention Center: Rooms 306 & 307

Part of the professional development program for the recertification of board-certified oncology pharmacists, approved by the Board of Pharmacy Specialties and cosponsored by ACCP, the American Society of Health-System Pharmacists (ASHP), and the Hematology/Oncology Pharmacy Association (HOPA). Part II will be presented on Wednesday, October 19, from 9 a.m. to noon. Participants must attend all 6 hours of programming to be eligible to complete the Web-based posttest for oncology recertification credit (the posttest must be completed by December 31, 2011). Partial BCOP recertification credit is not available. The posttest fee is $45. After the Annual Meeting, program participants will receive e-mail instructions for accessing the BCOP recertification posttest. Program participants wishing to receive continuing pharmacy education credit will receive an e-mail after the Annual Meeting with instructions about how to claim continuing education credit for these sessions.

Moderator: Christy S Harris, Pharm.D., BCPS, BCOP
Assistant Professor of Pharmacy Practice, School of Pharmacy-Boston
Massachusetts College of Pharmacy and Health Sciences, Boston, Massachusetts

1:30 p.m.	The Heart of the Matter: When Targeted Cancer Therapies Cause Off-Target Toxicities Activity No. 0465-9999-11-302-L01-P *Courtney L. Bickford, Pharm.D., BCPS* Cardiology Pharmacy Clinical Specialist, University of Texas M.D. Anderson Cancer Center, Houston, Texas
2:30 p.m.	Castration-Resistant Prostate Cancer Activity No. 0465-9999-11-401-L01-P *Rebecca E. Greene, Pharm.D., BCOP* Clinical Pharmacy Specialist, Oncology, South Texas Veterans Health Care System, San Antonio, Texas
3:30 p.m.	Vaccinations in Cancer Activity No. 0465-9999-11-402-L01-P *Kamakshi V. Rao, Pharm.D., BCOP* Oncology/BMT Clinical Specialist, University of North Carolina Hospital, Chapel Hill, North Carolina

Faculty Conflict of Interest Disclosures

Courtney L. Bickford: no conflicts to disclose.
Rebecca E. Greene: no conflicts to disclose.
Kamakshi V. Rao: no conflicts to disclose.

Learning Objectives

1. Distinguish cardiac toxicities (heart failure, hypertension, QT prolongation) attributable to targeted cancer therapies.
2. Summarize the evidence regarding the pathophysiology of cardiotoxicities induced by targeted cancer therapies.
3. Develop evidence-based plans for monitoring and treating cardiovascular adverse reactions associated with targeted cancer therapies.
4. Develop a treatment algorithm for castration-resistant prostate cancer (CRPC) based on the efficacy of the therapies.
5. Analyze patient specific information to determine when a change in management is indicated in patients with CRPC.
6. Construct a treatment plan for a patient with CRPC based on prior therapy, comorbid illness and concomitant medications.
7. Differentiate the toxicities associated with various treatments for CRPC about which patients and caregivers should be educated.
8. Differentiate the changes in immune function and immunity that occur in patients undergoing therapy for cancer based on age, disease, and chemotherapy regimen.
9. Summarize the recommendations for vaccinations in oncology patients based on data and guidelines from the Centers for Disease Control, Infectious Disease Society of America, and the American Society for Blood and Marrow Transplantation.
10. Analyze limitations in the current available data and gaps in the current recommendations for vaccination in oncology patients.

Self-Assessment Questions

Self-assessment questions are available online at *www.accp.com/am*

The heart of the matter: when targeted cancer therapies cause off-target toxicities

Courtney L. Bickford, Pharm.D., BCPS
Pharmacy Clinical Specialist, Cardiology
MDAnderson Cancer Center, Houston, TX

Hematology/Oncology Pharmacy Association

Disclosures

- Courtney Bickford has no areas of conflict to disclose

Objectives

- Distinguish cardiac toxicities (heart failure, hypertension, QT prolongation) attributable to targeted cancer therapies
- Summarize the evidence regarding the pathophysiology of cardiotoxicities induced by targeted cancer therapies
- Develop evidence-based plans for monitoring and treating cardiovascular adverse reactions associated with targeted cancer therapies

Introduction

- Increased use of targeted anticancer agents
  - Prolong survival and decrease cancer recurrence
- Targeted therapies aimed at molecules overexpressed in tumor cells
  - Receptor tyrosine kinases expressed in normal tissues → Cardiotoxicity

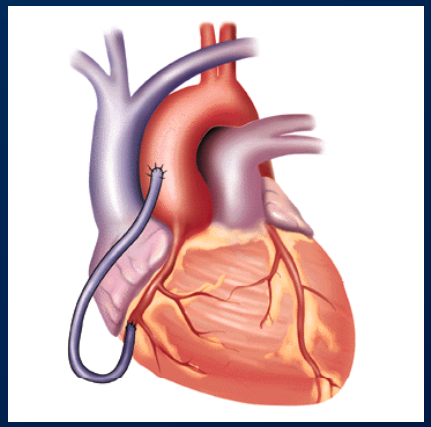
Cancer and Cardiotoxicity

- Patients with cancer often excluded from studies of cardiovascular (CV) disease
- Patients with clinically significant CV disease excluded from studies of new cancer therapies
- Definitions of cardiotoxicity vary across studies
- Study durations variable
- Determining incidence/prevalence of cardiovascular side effects and their management limited

Types of Cardiotoxicity

Arrhythmias

Left ventricular dysfunction (LVD) / Heart failure (HF)



Myocardial ischemia

Thromboembolism

Hypertension

ARS

- Inhibiting which of the following targets is implicated as a potential cause for the development of heart failure?

1. VEGF
2. ABL
3. HER2
4. All of the above

Classification of Chemotherapy-Related LVD

	Type I: myocardial damage (Anthracycline)	Type II: myocardial dysfunction (Trastuzumab)
Structural damage	Irreversible myocyte damage	Reversible myocyte dysfunction
Response to HF therapy	Permanent; Some cases may improve	Typically recovers to baseline in 2-4 months
Dose related	Yes	No
Effect of rechallenge	High probability of recurrent dysfunction	Increasing evidence for the relative safety of rechallenge

Adapted from Jones RL and Ewer MS. Expert Rev Anticancer Ther. 2006;6(9):1249-1269.

Targeted Therapies Associated with LVD

Agent	Incidence (%)
Trastuzumab	2-28
Lapatinib	1.5-2.2
Imatinib	0.5-1.7
Dasatinib	2
Sunitinib	2.7-11
Bevacizumab	1-3.8

Yeh ETH and Bickford CL. J Am Coll Cardiol. 2009;53(24):2231-47.; Chen MH, et al. Circulation. 2008;118:84-95.

New York Heart Association (NYHA) Classification of Heart Failure

NYHA Class	Symptoms
I	No symptoms No limitation in ordinary physical activity
II	Mild symptoms Slight limitation during ordinary activity Comfortable at rest
III	Marked limitation in activity due to symptoms during less than ordinary activity Patient comfortable only at rest
IV	Severe limitations Symptoms even while at rest

Hunt et al. Circulation. 2005 ;112(12):e154.

Trastuzumab and LVD

Treatment Arms	LVD (%)	NYHA Grade III/IV HF (%)
ACH	27	16
AC alone	8	3
TH	13	2
T alone	1	1

AC = Anthracycline + cyclophosphamide; H = Trastuzumab; T = Taxanes

Slamon DJ, et al. N Engl J Med. 2001;344:783-792.

Adjuvant Trastuzumab and LVD

Study	Treatment Arm	> 10% ↓ in LVEF*	NYHA Grade III/IV	Trastuzumab Timing
NSABP-31	AC → T	34%	0.8%	Post 21 days
	AC → TH	17%	4.1%	
NCCTG N9831	AC → T		0.3%	Post 21 days
	AC → T → H		2.8%	
	AC → TH → H		3.3%	
HERA	Observation	2.1%	0%	Post 89 days
	H	7%	0.6%	
BCIRG 006	AC → T	11%	0.7%	Post 21 days
	AC → TH	19%	1.9%	
	TCH	9%	0.4%	
FinHER	T , TH, V, or VH → FEC	No trastuzumab: 6% Trastuzumab: 3.5%		Pre-anthracycline

*FinHER reported incidence of LVEF decline ≥ 15% ;LVEF = left ventricular ejection fraction; V = Vinorelbine; FEC = fluorouracil, etoposide, cyclophosphamide

Tan-Chiu E, et al. J Clin Oncol.2005;23(31):7811-7819; Perez EA, et al. J Clin Oncol. .2008;26(8):1231-1238. Suter TM, et al. J Clin Oncol.2007;25(25):3859-3865. Slamon DJ, et al. Breast Cancer Res Treat 2005;94(suppl 1):S5. Joensuu H, et al. N Engl J Med.2006;354:809-20.

Adjuvant Trastuzumab with Chemotherapy

- Lower incidence of trastuzumab-induced LVD in the adjuvant setting
- Factors affecting incidence in adjuvant trials
  - Prospective monitoring of cardiac function
  - Exclusion criteria
    - HERA: LVEF < 55%
    - Other trials: LVEF < 50%
  - Chemotherapy regimen
  - Time between anthracycline and trastuzumab

Trastuzumab and Cardiotoxicity

- Long-term cardiac tolerability of trastuzumab in HER2(+) metastatic breast cancer patients (n=173)
  - Overall incidence cardiac toxicity= 28%
  - Risk factors:
    - Age >50
    - Borderline LVEF prior to treatment
    - History of CV disease
    - Sequence of chemotherapy administration
    - Prior treatment with anthracyclines
      - Cumulative dose >300 mg/m^2

Guarneri V, et al. J Clin Oncol 2006;24:4107-15.

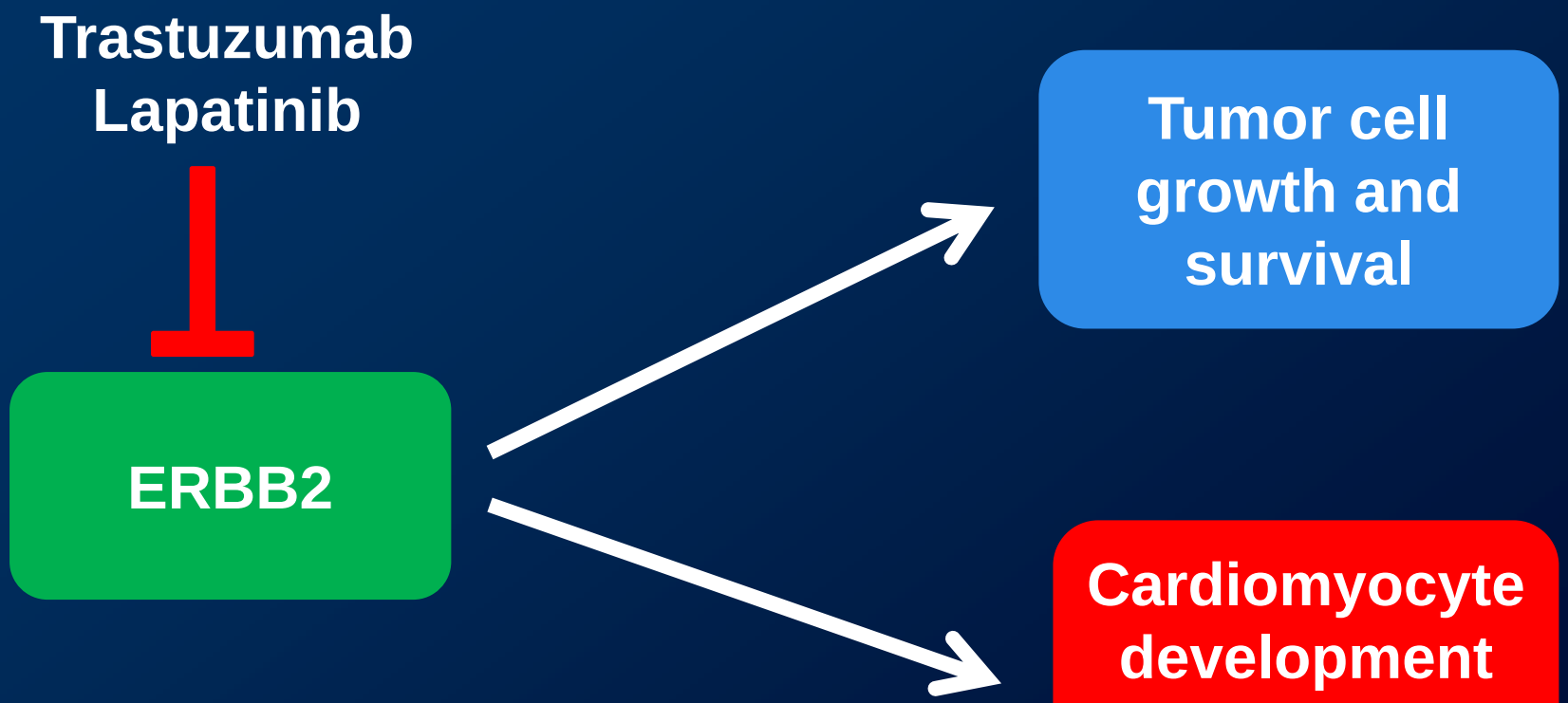
Lapatinib and Incidence of Cardiac Events

Previous Cardiotoxic Therapy	Decreased LVEF (%)	Asymptomatic LVEF Decline (%)[a]	Symptomatic LVEF Decline (%)[b]
Anthracycline (n=552)	2.2	1.6	0.5
Trastuzumab (n=826)	1.7	1.6	0.1
Neither (n=2311)	1.5	1.3	0.1
Total (n=3689)	1.6	1.4	0.2

[a]Defined as LVEF decrease ≥20% relative to baseline and below lower limit of normal
[b]Defined as Defined as National Cancer Insititute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or 4 left ventricular dysfunction

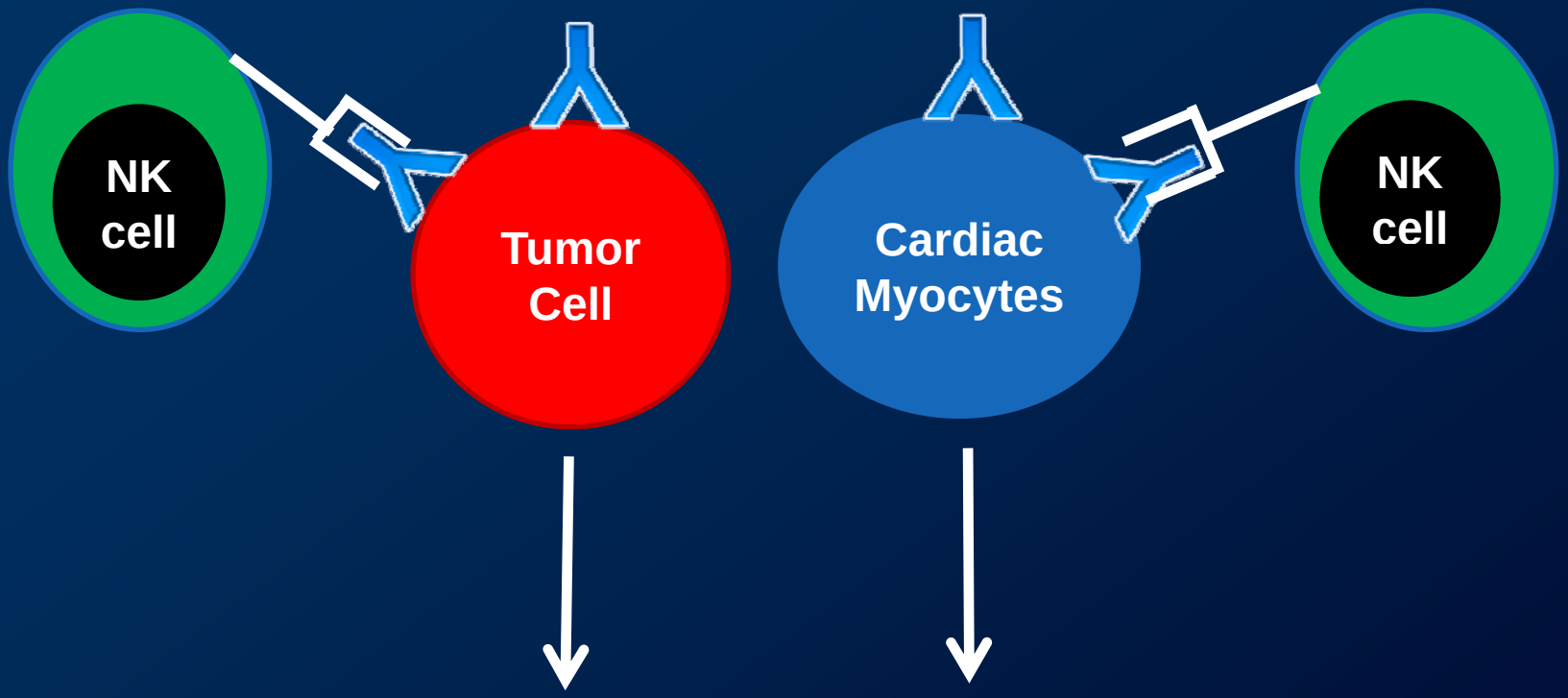
Perez EA, et al. Mayo Clin Proc. 2008;83:679-86.

Mechanisms of Trastuzumab and Lapatinib-Induced LVD



ERBB2 = v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)
Adapted from Force T, et al. Nat Rev Cancer 2007;7:332.

Trastuzumab and Antibody-Dependent Cell-Mediated Cytotoxicity



NK = natural killer cell

Adapted from Force T, et al. Nat Rev Cancer 2007;7:332.

Package Insert Guidelines for Monitoring LVEF

Targeted Therapy	Baseline	During Treatment	After Treatment
Trastuzumab	√	Every 3 months and upon completion	Every 6 months ≥ 2 years
Lapatinib	√	Periodically	

Herceptin [Package Insert]. Genentech, San Francisco, CA, 2010.; Tykerb [Package Insert]. GlaxoSmithKline, Research Triangle Park, NC, 2010.

Monitoring and Management of Trastuzumab in Asymptomatic Metastatic Breast Cancer

LVEF	Trastuzumab	LVEF monitoring	Management
↓ but normal	Continue	Repeat in 4 weeks	None
↓ >10 points but normal	Continue	Repeat in 4 weeks	Consider beta-blockers
↓ 10-20 points and LVEF >40%	Continue	Repeat in 2-4 weeks; if improved, then monitor, if not improved, then stop trastuzumab	Treat for LVD
↓ >20 points to <40% or LVEF <30%	Hold	Repeat in 2 weeks; if improved to >45%, then restart, if not improved then stop trastuzumab	Treat for LVD

Keefe DL, et al. Cancer 2002;95:1592-1600.

Monitoring and Management of Trastuzumab in Symptomatic Metastatic Breast Cancer

LVEF	Trastuzumab	LVEF monitoring	Management
↓ <10 points	Continue	Repeat in 2-4 wk; if stable or improved, then monitor, if worsened, then stop trastuzumab	Search for noncardiac pathology (eg, anemia)
↓ >10 points and LVEF >50%	Continue	Same as above	Treat for HF
↓ >30 points	Stop	Same as above	Treat for HF

Keefe DL, et al. Cancer 2002;95:1592-1600.

Guidelines for Monitoring and Management of Trastuzumab in Adjuvant Breast Cancer

Physical Status	LVEF	Trastuzumab	LVEF monitoring	Management
Asymptomatic	Normal	Continue	As scheduled	None
	↓ <16 % but normal	Continue	As scheduled	If LVEF<40% treat with ACEI
	↓ ≥16 % or subnormal (regardless of the amount of reduction)	Hold temporarily	Repeat in 4 wk; if improved, then restart T, if not improved, then stop trastuzumab	If LVEF <40% treat with ACEI
Symptomatic	<Normal	Hold permanently	Per cardiologist's discretion	Treat for HF

ACEI = Angiotensin Converting Enzyme Inhibitor

Saad A and Abraham J. Community Oncology. 2007;4(12):739-744.

Monitoring and Management of Lapatinib and LVD

- Confirm normal LVEF before starting lapatinib
- Continue LVEF evaluations during treatment
- Discontinue lapatinib:
  - ↓ LVEF that is ≥ Grade 2 (NCI CTCAE) or
  - ↓ LVEF below institution's lower limit of normal
- Recheck LVEF in minimum of 2 weeks
  - LVEF normal and patient asymptomatic:
    - Lapatinib + capecitabine: restart ↓ dose of 1,000 mg/day
    - Lapatinib + letrozole: restart ↓ dose of 1,250 mg/day

Tykerb [package insert]. GlaxoSmithKline, Research Triangle Park, NC, 2010.

Imatinib and Heart Failure

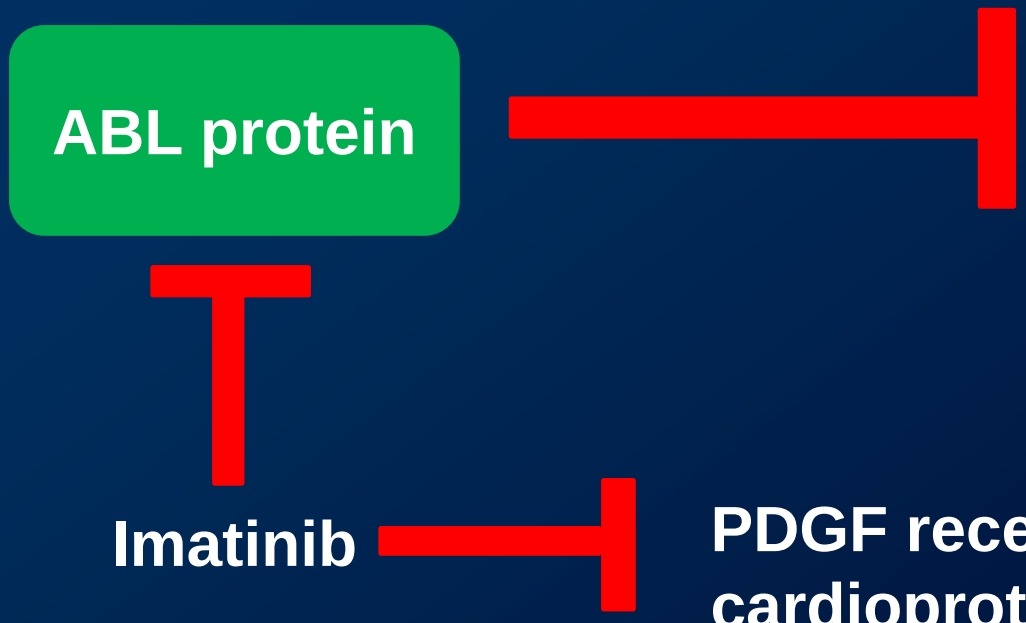
Case Series	N	HF
Kerkela (case series)	10	10

Trial	N	HF
Atallah*	1276	1.7%
Hatfield*	2327	0.5%
Trent*	219	0.4%
IRIS trial	553	1%
Verweij	942	0.2%

*Retrospective studies

Kerkela R, et al. Nat Med 2006;12:908-16.; Hatfield A, et al. Nat Med 2007;13:13; author reply 15-6.; O'Brien SG, et al. N Engl J Med.2003;348(11):994-1004; Trent JC, et al. Cancer. 2010;116:184-192; Verweij J, et al. Eur J Canc.2007;43:974-978; Atallah E, et al. Blood. 2007;110(4):1233-1237

Mechanisms of Imatinib-Induced LVD



PDGF = platelet-derived growth factor

Adapted from Kerkela R, et al. Nat Med 2006;12:908-16.; Force T, et al. Nat Rev Cancer 2007;7:332-44.

Dasatinib

- Mechanism of dasatinib-induced cardiotoxicity:
  - Inhibition of ABL
  - Inhibits Src family kinases (SFK) and a number of other kinases, which may be involved in the development of cardiotoxicity as well

- Leukemia patients (n=2182) across all dasatinib studies:
  - HF or LVD (all grades) occurred in 2%
  - Grade 3 or 4 HF: <1%

Sprycel [package insert]. Bristol-Myers Squibb, Princeton, NJ, 2010.; Chen MH, et al. Circulation 2008;118:84-95.

Sunitinib and LVD

Disease	MRCC		GIST	
Treatment Group	Sunitinib-treated (n=375)	Interferon-alpha-treated (n=360)	Sunitinib-treated (n=209)	Placebo (n=102)
Frequency of LVD	27%	15%	11%	3%

MRCC = metastatic renal cell carcinoma; GIST = Gastrointestinal stromal tumor

Sutent [package insert]. Pfizer, Inc., New York, NY, 2010.

Sunitinib and HF

Author	N	Trial Design	Decrease in LVEF	Incidence of HF
Motzer	750	Prospective	LVEF < 40%: 2%	0%
Demetri	207	Prospective	0%	0%
Chu	75	Retrospective	LVEF < 50%: 20%	8%
Telli	48	Retrospective	NR	15%
DiLorenzo	175	Retrospective	Grade 1-3: 18.9%	6.9%
Khakoo	224	Retrospective	NR	2.7%

Chu TF, et al.Lancet.2007;370:2011. Motzer RJ, et al. NEJM.2007;356:115-124. Demetri GD, et al. Lancet. 2006;368:1329-1338. ; Telli ML, et al. Ann of Oncol.2008;19:1613-1618. Khakoo AY, et al. Cancer 2008;112:2500-2508. Di Lorenzo G et al. Ann Oncol. 2009 Sep;20(9):1535-42.

Sunitinib: Mechanisms of cardiotoxicity

- Animal studies → Mitochondrial damage in cardiomyocytes
- VEGF inhibition → Hypertension → HF
- Ribosomal S6 kinase (RSK) inhibition
  - Activation of intrinsic apoptotic pathway and ATP depletion
- Platelet-derived growth factor receptor (PDGFR)-β inhibition
  - PDGFR-β signaling - essential component of the mouse cardiac response to load-induced stress
- Hypothyroidism
  - 4-16% in sunitinib-treated patients
  - Hypothyroidism associated with an increased risk of HF

Khakoo AY, et al. Cancer. 2008;112(11):2500-8.; Chu TF, et al. Lancet 2007;370:2011-9.; Force T,et al. Nat Rev Cancer 2007;7:332-44.; Chintalgattu V, et al. J Clin Invest 2010;120(2)472-484.

Guidelines for Monitoring and Management of Sunitinib

- Monitoring
  - Monitor for clinical signs and symptoms of HF
  - Baseline and periodic evaluations of LVEF
- Management
  - Discontinue sunitinib in presence of clinical HF
  - Asymptomatic LVEF <50% and >20% below baseline
    - Sunitinib dose should be interrupted and/or reduced

Sutent [package insert]. Pfizer, Inc., New York, NY, 2010.

Bevacizumab and HF

	Bevacizumab	Placebo
Overall incidence (%)	1.6	0.4
Low dose bevacizumab 2.5 mg/kg/wk	1.2	0.2
High dose bevacizumab 5 mg/kg/wk	1.9	0.4
Taxanes	1.7	0.3
Capecitabine	1.9	0.8
Anthracycline	2.8	0.5

Choueiri TK, et al. J Clin Oncol. 2011 Jan 4. [Epub ahead of print].

Mechanism of Bevacizumab Cardiotoxicity

- Uncontrolled hypertension and inhibition of VEGF/VEGFR signaling
- Animal studies → angiogenesis plays key role in normal adaptive response to pressure load
- Pressure overload → reduction of myocardial capillary density, global contractile dysfunction, cardiac fibrosis and decompensated HF

Chen MH, et al. Circulation 2008;118:84-95.

Methods for Evaluating LVD

- Endomyocardial biopsy
  - Traditionally viewed as gold standard for determining chemotherapy induced cardiac damage; Invasive
- Echocardiogram (ECHO) & Multi-Gated Acquisition (MUGA)
  - Most common methods used to monitor LV function
  - Non-invasive, cost-effective, high reproducibility
- Serial monitoring
  - Use the same method to facilitate comparison of LVEF

Raschi E, et al. Pharmacology & Therapeutics 2010;125:196-218.

Biomarkers as a Monitoring Tool

- Biomarkers
  - Early identification, assessment and monitoring of cardiotoxicity
  - Minimally invasive and less expensive than ECHO and MUGA
  - Avoid interobserver variability
- Troponin
  - Predict future development of ↓ LVEF after chemotherapy
  - Identify patients at different risks of future cardiac events
- B-type natriuretic peptide
  - Positive correlation with cardiac events & subclinical cardiotoxicity
  - Correlates more with diastolic vs. systolic dysfunction

Cardinale D, et al. Ann of Oncology 2002; 13:710.; Cardinale D, et al. Circulation. 2004; 109: 2749-54.; Nousiainen T, et al. J Intern Med. 2002; 251: 228 – 34.; Meinardi MT, et al. J Clin Oncol. 2001; 19(10): 2746-53.

Troponin and Trastuzumab-Induced LVD

- 251 breast cancer patients
  - Adjuvant and metastatic
- Primary end point: occurrence of cardiotoxicity
  - ↓ LVEF of >10 units from baseline and LVEF<50%
- Results
  - Cardiotoxicity more frequent in patients with troponin increase
  - LVEF recovery occurred less frequently
  - ↑ troponin only independent predictor of trastuzumab-induced cardiomyopathy and lack of LVEF recovery

Cardinale D, et al. J Clin Oncol 2010;28:3910-3916.

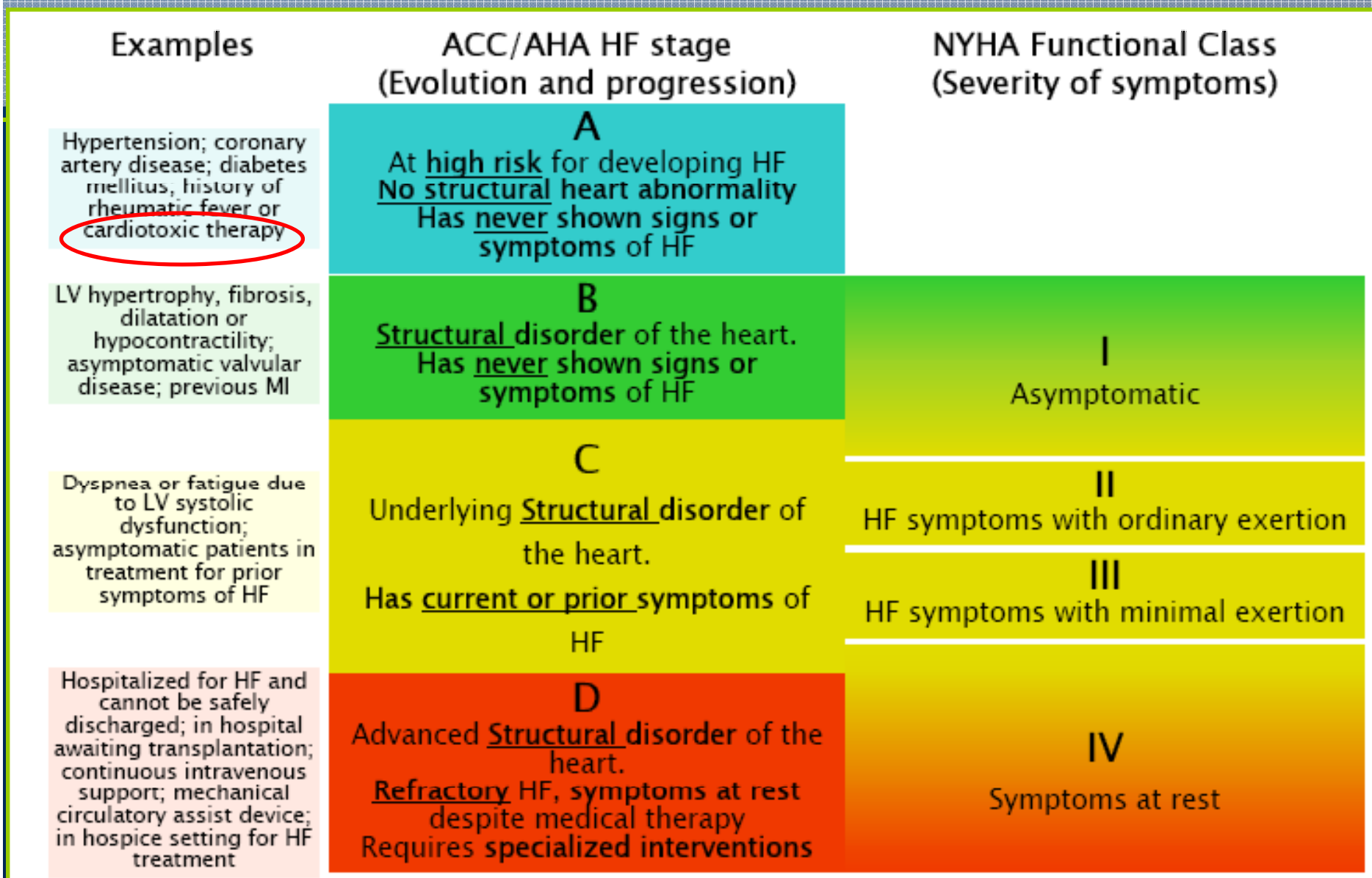
Guidelines for Monitoring LVEF

- Guidelines* suggest regular cardiac assessment by evaluation of LVEF by either ECHO or MUGA
  - > 1/3 of patients with HF have a normal EF
  - LVEF not sensitive or specific enough to predict late declines
  - Does not allow for early preventative strategy
- Symptoms are the mainstay of the diagnosis of HF
- No recommendation for biomarker testing or preventive therapy

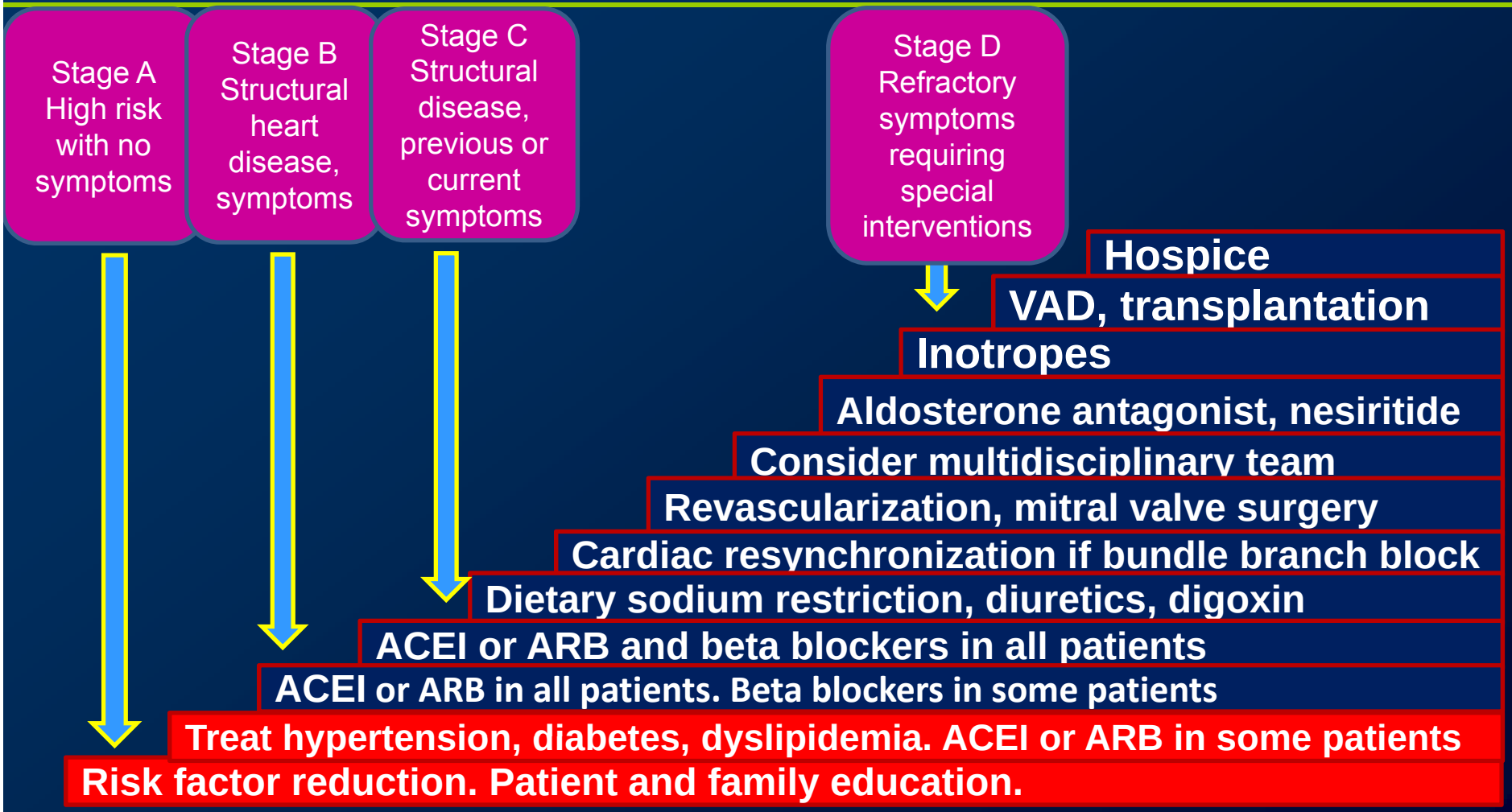
*American Heart Association (AHA), American College of Cardiology (ACC),Heart Failure Society of America (HFSA), and ASCO websites

Cardinale D and Sandri MT. Progress in Cardiovascular Diseases 2010;53:121-129.

Classification of Heart Failure



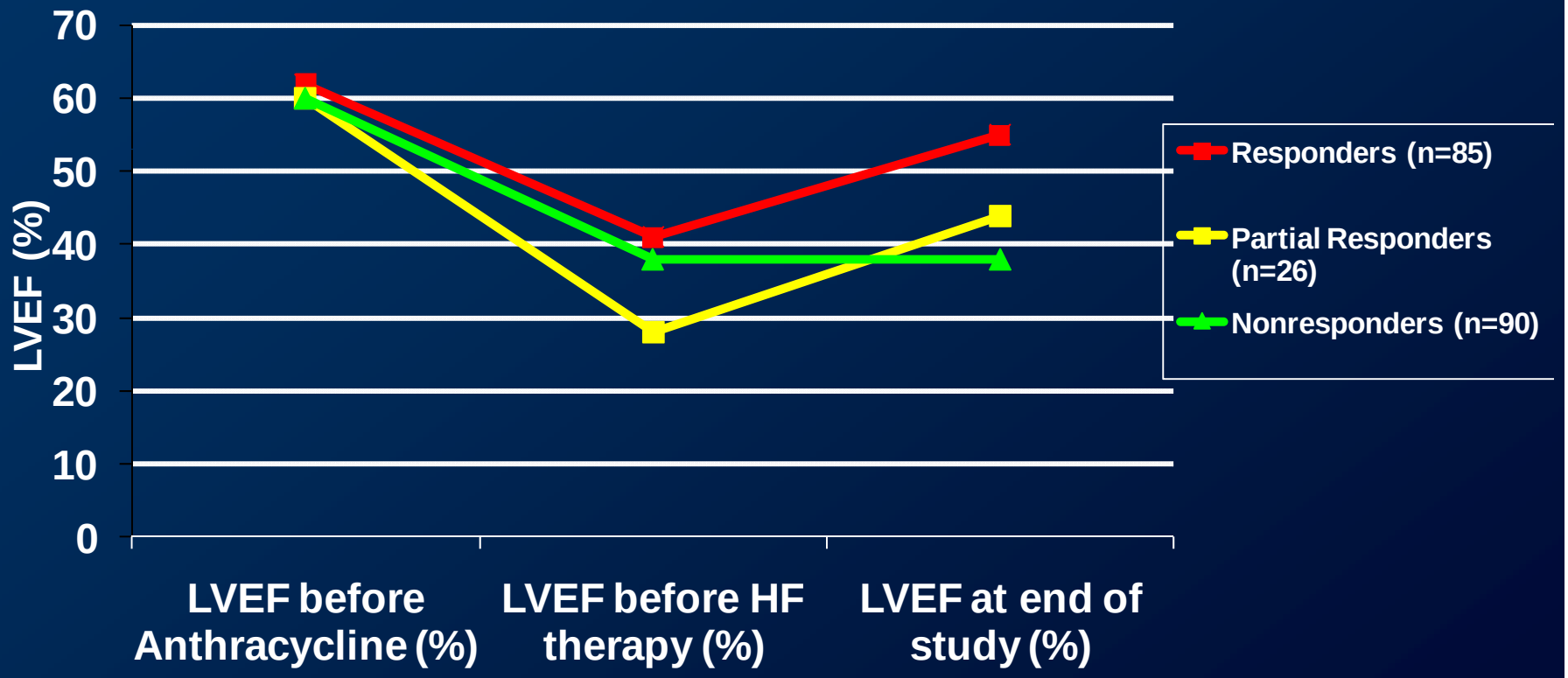
ACC/AHA Treatment Guidelines For Heart Failure



ARB = Angiotensin Receptor Blocker; VAD = ventricular assist device

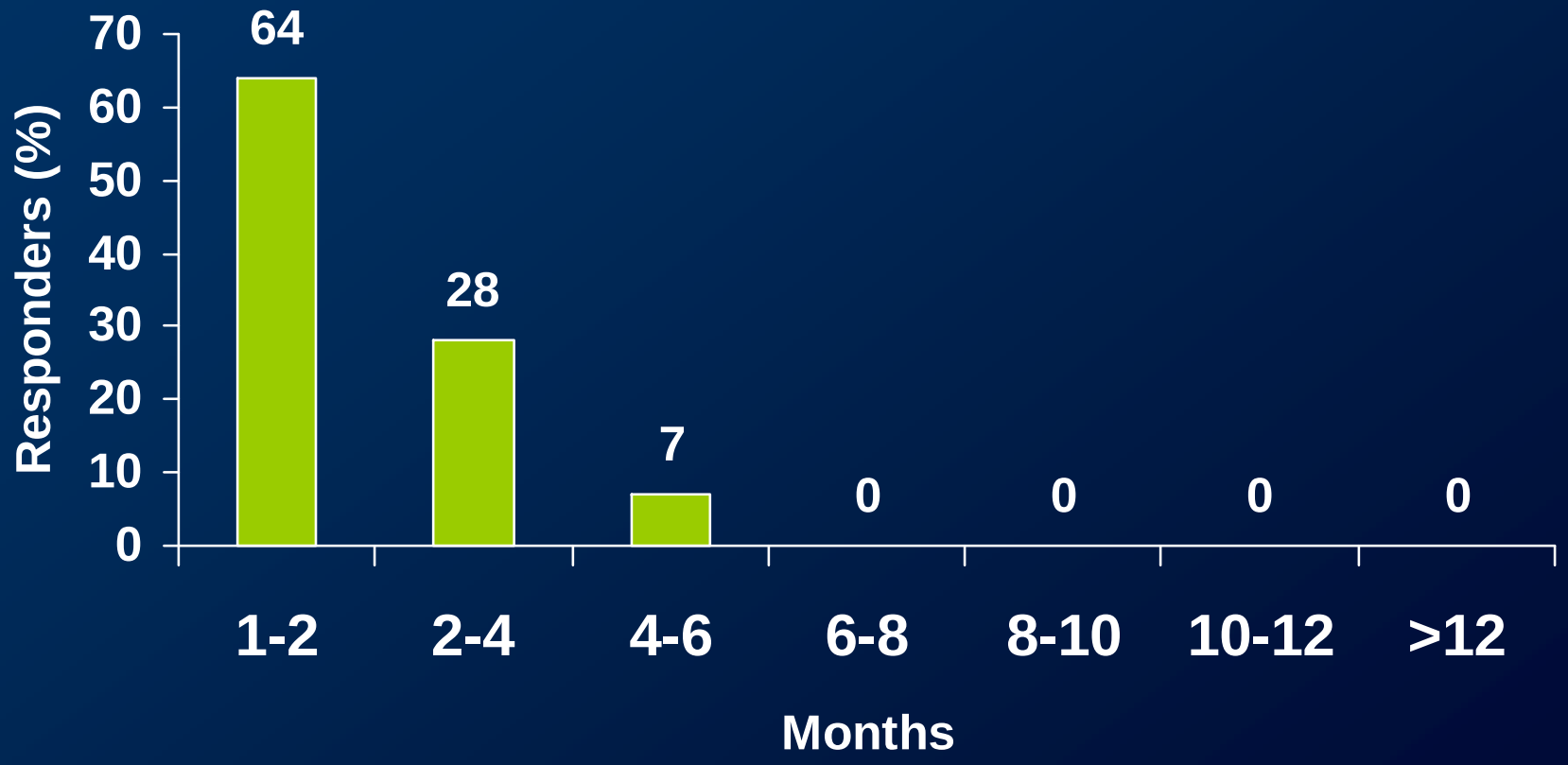
 Jessup M et al. N Engl J Med;348(20):2007-18

Anthracycline-Induced Cardiomyopathy Response to ACEI/BB



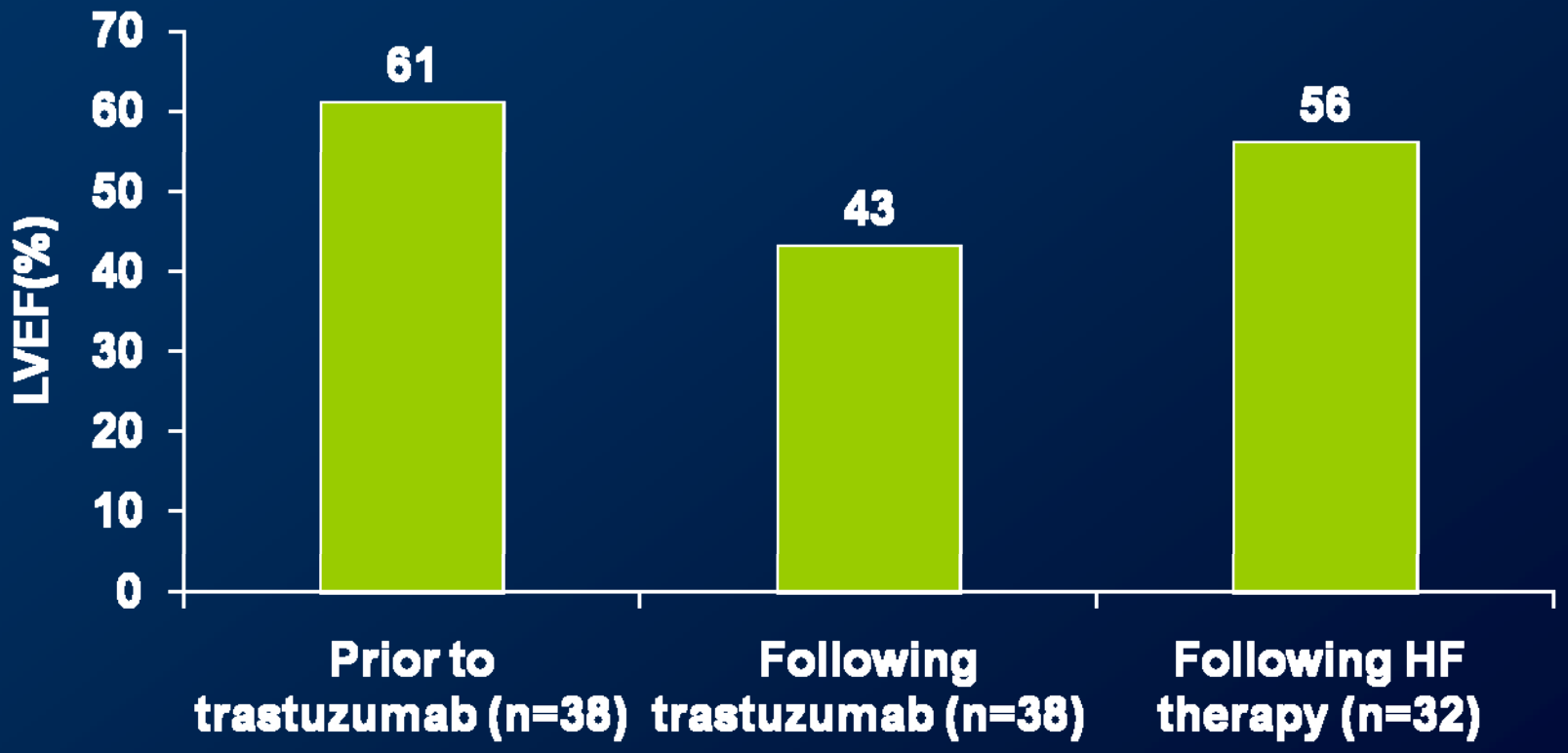
BB = beta blocker

Percentage of Responders According to Time Elapsed from Anthracycline Administration and Start of HF Therapy



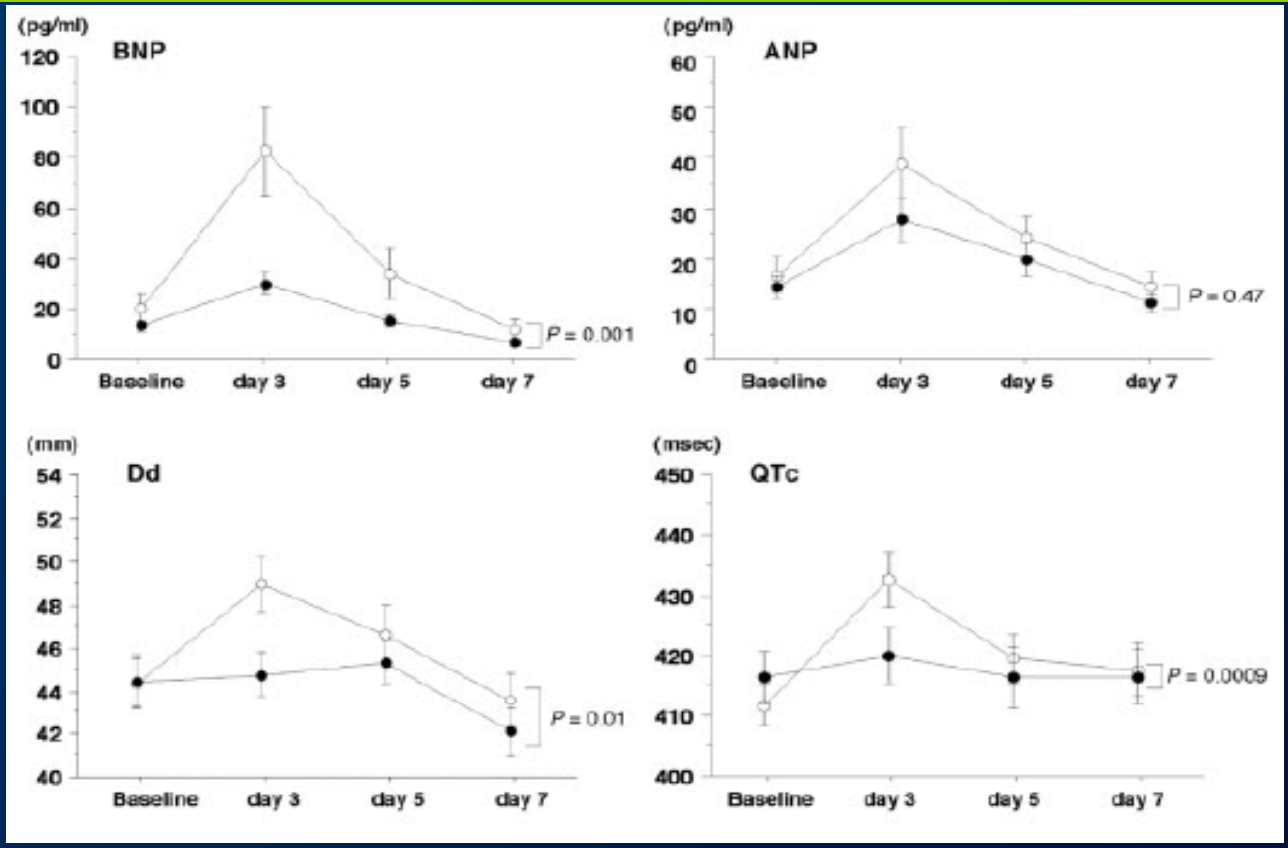
Cardinale, D. J Am Coll Cardiol, 2010; 55:213-220.

Reversibility of Trastuzumab following HF Therapy



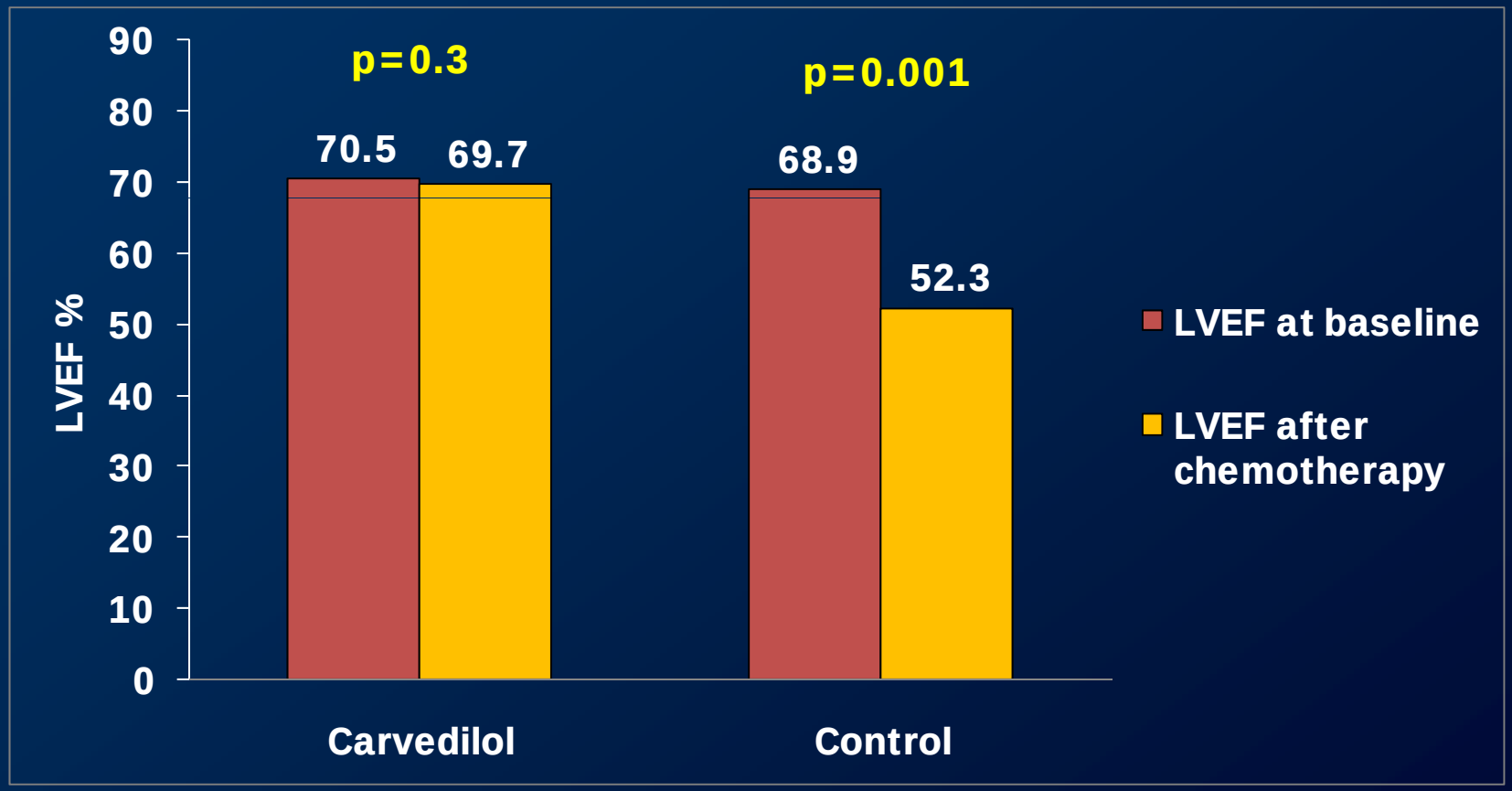
Reprinted with permission from the American Society of Clinical Oncology. Ewer MS, et al. J CLin Oncol 2005;23(31):7820-7826.

Effects of Valsartan on Acute Cardiotoxicity after CHOP Chemotherapy



The effects of valsartan on acute cardiotoxicity after chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP). Patients with non-Hodgkin lymphoma were treated with CHOP with (closed circle) or without (open circle) 80 mg of valsartan. BNP: brain natriuretic peptide; Dd: end diastolic diameter of left ventricle; QTcD: corrected QT dispersion; ANP: atrial natriuretic peptide. Values are shown as the mean and the standard error of the mean.

Protective Effects of Carvedilol Against Anthracycline-Induced Cardiomyopathy



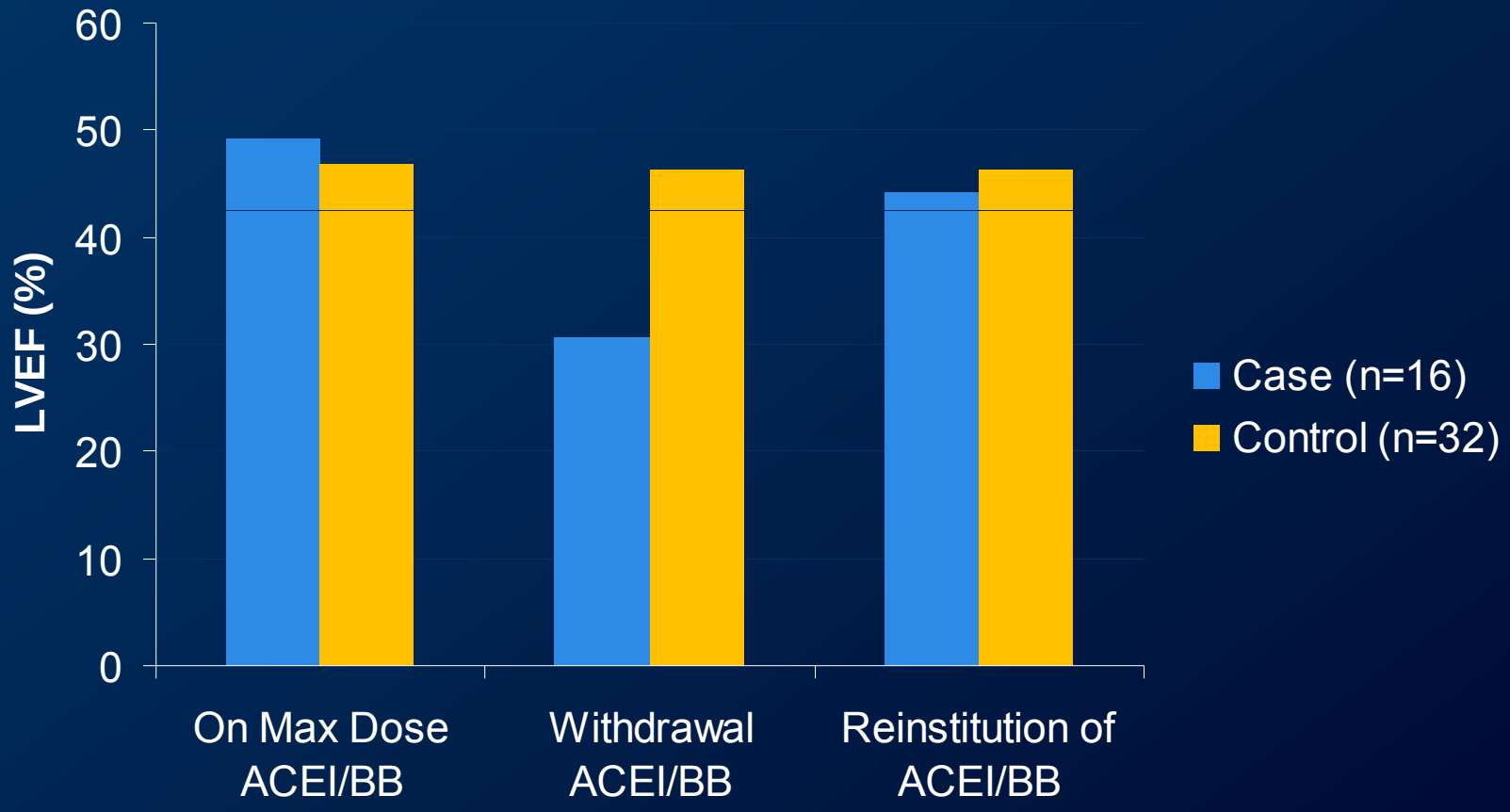
Reprinted with permission from Elsevier.
Kalay N et al. J Am Coll Cardiol. 2006; 48: 2258-62.

ARS

- A 59 year old female with a history of breast cancer treated with anthracycline-based chemotherapy as well as trastuzumab developed HF (EF 35-40%) during chemotherapy. She was managed with carvedilol and enalapril. She returns for follow-up and her EF on ECHO is now 50-55%. Would you discontinue her cardiac medications now that her EF is normal?

1. Yes
2. No

LVEF Changes After HF Therapy Withdrawal

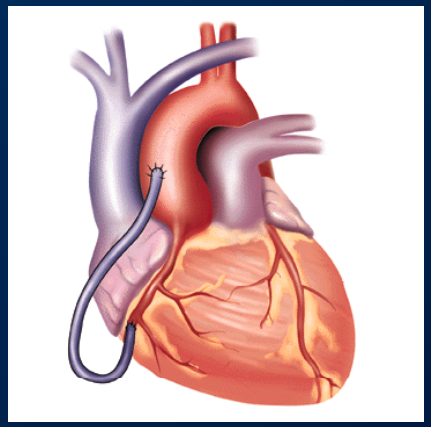


Shukla A, et al. Circulation 118 (2008), p. S797.

Types of Cardiotoxicity

Arrhythmias

Left ventricular dysfunction (LVD)/ Heart failure (HF)



Myocardial ischemia

Thromboembolism

Hypertension

Hypertension

- Hypertension (HTN) - one of the most frequent comorbid conditions found in cancer registry patients as well as observed side-effects of inhibiting VEGF signaling
- Risk factor for coronary heart disease, stroke, HF, and end-stage renal disease
  - CV risk doubles for every 20/10 mmHg increase over 115/75 mmHg
- Higher incidence of intracerebral hemorrhage reported in patients with mRCC treated with agents targeting VEGF

Maitland ML, et al. J Natl Cancer Inst 2010;102:596–604

Definition of Hypertension CTCAE v4.02

- Grade 1: Prehypertension (systolic blood pressure (SBP) 120-139 or diastolic blood pressure (DBP) 80-89 mmHg)
- Grade 2: Stage 1 HTN (SBP 140-159 or DBP 90-99 mmHg); medical intervention indicated; recurrent or persistent (≥ 24 hours); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated
- Grade 3: Stage 2 HTN (SBP ≥ 160 or diastolic blood pressure ≥ 100 mmHg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated
- Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated
- Grade 5: death

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension.* 2003 Dec;42(6):1206-52.; http://rulesworld.corticon.com/files/ctcaev4.pdf Accessed 2/20/2011

WNL=within normal limits

Incidence of Hypertension

Agent	Overall Incidence (%)	Grade 3 or 4 (%)
Bevacizumab	4-35	5-18
Pazopanib	40-47	0-4
Sunitinib	5-47	4-13
Sorafenib	17-43	1.4-38

Maitland ML, et al. J Natl Cancer Inst 2010;102:596–604 Chen MH, et al. Circulation 2008;117:84-95. Votrient [package insert]. GlaxoSmithKline, Research Triangle Park, NC, 200.

Mechanism of Hypertension

- Effects of VEGF binding VEGFR2:
  - Increase capillary permeability
  - Production of nitric oxide (NO) and prostaglandin I2 → smooth muscle relaxation
  - Endothelial cell proliferation, migration, and survival under stress
- Effects of VEGF inhibition on vasculature → ↑BP
  - Decreased NO and prostaglandin I2 → Vasoconstriction
  - Rarefaction (decreased arteriole and capillary densities)

Chen HX, Cleck JN. Nat Rev Clin Oncol. 2009 Aug;6(8):465-77.

Increased Risk of High-Grade HTN with Bevacizumab in Cancer Patients

Tumor type	B (events/SS)	Control (event/SS)	Incidence % (95% CI)	RR (95%CI)
Overall	588/6754	75/5902	7.9 (6.1-10.2)	5.28 (4.15-6.71)
Colorectal	278/3028	50/2969	8.6 (5.7-12.8)	5.24 (3.89-7.05)
NSCLC	108/1230	9/841	9.0 (6.1-13.2)	7.06 (3.66-13.62
RCC	55/779	2/693	7.1 (3.4-14.1)	8.99 (2.72-29.72)
Breast	103/1091	4/794	8.5 (3.1-21.2)	14.8 (0.92-238.51)
Pancreatic	32/563	5/550	5.5 (2.2-12.7)	5.52 (2.12-14.35)
Mesothelioma	21/268	5/258	22.6 (13.3-35.8)	2.49 (0.94-6.59)

NSCLC = non-small-cell lung cancer; SS = sample size; B= bevacizumab

Ranpura V, et al. Am J Hypertension 2010;23:460-468.

Hypertension as a biomarker of efficacy in patients with mRCC treated with sunitinib

	Max SBP ≥ 140 mmHg (n = 441)	Max SBP < 140 mmHg (n = 93)	p-value
OR, n (%)	241 (54.6)	9 (9.7)	< 0.0001
PFS, months	12.5	2.5	< 0.0001
OS, months	30.5	7.8	< 0.0001
	Max DBP ≥ 90 mmHg (n = 362)	**Max DBP < 90 mmHg (n = 172)**	**p-value**
OR, n (%)	207 (57.2)	43 (25.0)	< 0.0001
PFS, months	13.4	5.3	< 0.0001
OS, months	32.1	15	< 0.0001

Max = maximum

Rini BI, et al. American Society of Clinical Oncology Genitourinary Cancers Symposium 2010; San Francisco, CA. Abstract 312.

Angiogenesis Task Force of the National Cancer Institute Investigational Drug Steering Committee Recommendations

- Conduct formal risk assessment
- Identify preexisting HTN and address before initiation
- Monitor blood pressure throughout treatment
  - Weekly during the first cycle of treatment
  - Then at least every 2–3 weeks for the duration of treatment
- Target blood pressure: <140/90 mmHg
  - Try to reach this goal before initiation of therapy
  - Adjust lower for patients with multiple preexisting risk factors
- Manage blood pressure elevations aggressively
  - Consult hypertension specialist if difficulty maintaining goal

Maitland ML, et al. J Natl Cancer Inst 2010;102:596-604.

Management per Package Insert

Agent	Recommendations
Bevacizumab	Monitor blood pressure (BP) and treat HTN. Temporarily suspend bevacizumab if not medically controlled. Discontinue if hypertensive crisis or hypertensive encephalopathy
Pazopanib	BP should be well-controlled prior to initiating pazopanib Monitor for HTN and treat as needed
Sorafenib	Monitor BP weekly during the first 6 weeks and periodically thereafter and treat, as required In cases of severe or persistent HTN consider temporary or permanent discontinuation of sorafenib
Sunitinib	Patients should be monitored for HTN and treated as needed with standard anti hypertensive therapy. In cases of severe hypertension, temporary suspension of sunitinib is recommended until HTN controlled

Avastin [Package Insert]. Genentech Inc, San Francisco, CA. 2010.; Votrient [Package Insert]. GlaxoSmithKline, Research Triangle Park, NC, 2009.; Nexavar [Package Insert]. Bayer HealthCare Pharmaceuticals Inc., Wayne, NJ, 2010.;Sutent [Package Insert]. Pfizer, Inc., New York, NY, 2010.

Compelling Indications and Recommended HTN Treatment

Compelling Indication	Diuretic	BB	ACEI	ARB	CCB	AA
HF	*	*	*	*		*
Post MI		*	*			*
Diabetes			*	*		
CKD			*	*		
Recurrent stroke prevention	*		*			

MI = myocardial infarction; CKD = chronic kidney disease; BB = beta blocker; ARB = angiotension II receptor blocker; CCB = calcium channel blocker; AA = aldosterone antagonist

Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003 Dec;42(6):1206-52.

Other Considerations for Management of HTN

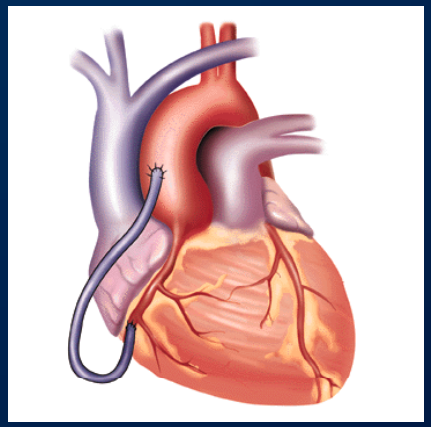
- Mechanism of HTN associated with targeted therapy
  - ACEI – ↓ microcirculatory changes, ↑ release of endothelial NO
  - Calcium channel blockers – vasodilation, ↓ rarefaction
  - Nitrates – ↑ NO levels
  - Nebivolol – vasodilation through NO pathway
- Drug interactions – Avoid diltiazem and verapamil
- Prevention of HF – ACEI and BB
- Dose reduction/temporary cessation of targeted therapy

Maitland ML, et al. J Natl Cancer Inst 2010;102:596-604.; Yeh ETH and Bickford CL. J Am Coll Cardiol. 2009 Jun 16;53(24):2231-47.

Types of Cardiotoxicity

Arrhythmias

Left ventricular dysfunction (LVD)/ Heart failure (HF)



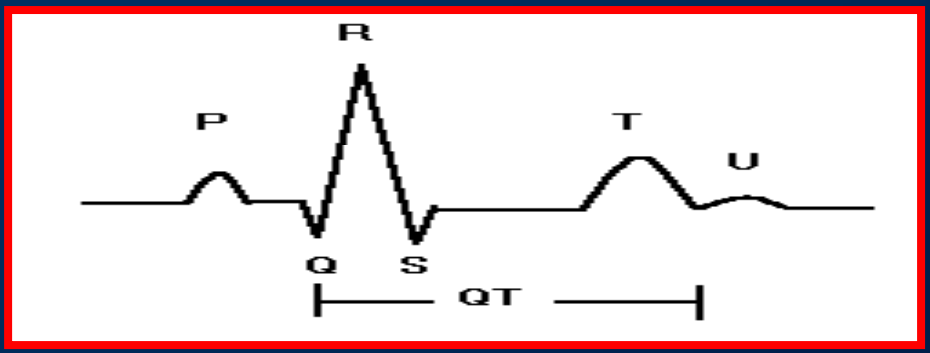
Myocardial ischemia

Thromboembolism

Hypertension

QT Prolongation

- QT interval: represents duration of ventricular action potential measured from the beginning of depolarization (Q wave) until the end of repolarization (T wave)



Normal QTc ≤440 msec

<u>QTc prolongation:</u>

Men: QTc > 450 msec

Women: QTc > 460 msec

Increases of ≥ 60 msec from baseline or >500 msec after administration of a medication

Vorchheimer DA. J Fam Pract. 2005 Jun;Suppl:S4-7.; Brell JM. Prog Cardiovasc Dis. 2010 Sep-Oct;53(2):164-72.

Risk Factors for QT Prolongation

- Female sex*
  - 2/3 of all cases
- Elderly age*
- Hypokalemia (< 3.5 mEq/L)
- Severe hypomagnesemia (< 1.4 mEq/L)
- Congestive heart failure*
- Myocardial ischemia or infarction*
- Bradycardia
- Recent conversion from atrial fibrillation, especially with a QT-prolonging drug
- High drug concentrations
- Rapid rate of infusion of QT-prolonging medication
- Congenital long -QT syndrome*
- Baseline QT interval prolongation
- Ion-channel polymorphisms

*Prominent risk factors
~70% of patients who experience QT prolongation have 2 or more risk factors

Vorchheimer DA. J Fam Pract. 2005 Jun;Suppl:S4-7.

Risk Factors in Cancer Patients

- Patients with cancer predisposed to QT prolongation
  - 36% have ECG abnormality at screening
  - ~15% patients have prolonged QT
    - High prevalence of comorbid diseases
    - Renal and hepatic dysfunction
    - Concomitant medications
      - Antiemetics, antihistamines, antibiotics, antifungals, antidepressants, antipsychotics, methadone, antiarrhythmics
    - Electrolyte disturbances

Brell JM. Prog Cardiovasc Dis. 2010 Sep-Oct;53(2):164-72. ; Strevel EL, et al. J Clin Oncol 2007;25:3362-3371.; Yusuf SW, et al. Curr Probl Cardiol 2008;33:163-196.

Targeted Therapies and QT Prolongation

Medication	Incidence (%)
Dasatinib	<1
Lapatinib	16
Nilotinib	1-10
Pazopanib	<2
Sunitinib	<0.1
Vorinostat	3.5-6

The mechanism underlying QT prolongation: UNKNOWN

When discussing drug-induced QT prolongation, it is now understood that the blockade of delayed rectifier potassium (IKr) current by medications is at least in part responsible for their pro-arrhythmic effect

Yeh ETH and Bickford CL. J Am Coll Cardiol. 2009 Jun 16;53(24):2231-47.; Votrient [package insert]. GlaxoSmithKline, Research Triangle Park, NC, 2009.

Nilotinib Black Box Warning: QT Prolongation and Sudden Death

- Hypokalemia or hypomagnesemia must be corrected prior to nilotinib administration and should be periodically monitored
- Drugs known to prolong the QT interval and strong CYP3A4 inhibitors should be avoided
- Avoid food 2 hours before and 1 hour after nilotinib
- Use with caution in patients with hepatic impairment
- ECGs should be obtained to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, as well as following any dose adjustments.

Tasigna [package insert] Novartis, East Hanover, NJ, 2007.

Nilotinib Dose Adjustment for QTc>480 msec

1. Withhold nilotinib, assess & supplement potassium / magnesium; review concomitant medications
2. Resume within 2 weeks at prior dose if QTc returns to <450 msec and to within 20 msec of baseline
3. If QTc 450-480 msec after 2 weeks reduce dose to 400 mg once daily
4. If QTc returns to >480 msec on 400 mg daily, nilotinib should be discontinued
5. ECG should be repeated 7 days after any dose adjustment

Tasigna [package insert] Novartis, East Hanover, NJ, 2007.

Monitoring Recommendations for QT Prolongation

Agent	Package Insert Recommendation
Nilotinib	ECG at baseline, 7 days after initiation, periodically thereafter, and following any dose adjustments Avoid strong CYP3A4 inhibitors Use caution in patients with hepatic impairment
Dasatinib	None
Lapatinib	Baseline and on-treatment ECGs; electrolyte monitoring
Pazopanib	Baseline and periodic ECGs; maintain normal electrolytes
Sunitinib	No ECG monitoring recommendations Avoid strong CYP3A4 inhibitors; consider dose reduction of sunitinib
Vorinostat	None

Votrient [Package Insert]. GlaxoSmithKline, Research Triangle Park, NC, 2009.;Sutent [Package Insert]. Pfizer, Inc., New York, NY, 2010. Tasigna [package insert] Novartis, East Hanover, NJ, 2007 ; Tykerb [package insert]. GlaxoSmithKline, Research Triangle Park, NC, 2010; Sprycel [package insert]. Bristol-Myers Squibb, Princeton, NJ, 2010.; Zolinza [Package Insert]. Merck &Co, Whitehouse Station, NJ, 2009.

QT Prolongation Summary

- Identify risk factors
- Recognize drug-drug interactions
  - Pharmacodynamic
    - Other QT-prolonging medications
    - www.torsades.org
  - Pharmacokinetic
    - Strong 3A4 inhibitors + nilotinib
- Obtain baseline ECG in patients receiving QT-prolonging drugs and follow periodically

ARS

- Which of the following targeted therapies causes hypertension, heart failure, and QT prolongation?

1. Bevacizumab
2. Dasatinib
3. Pazopanib
4. Sunitinib

Summary of Cardiotoxicities Associated with Targeted Therapies

Bevacizumab	Hypertension, Heart failure
Dasatinib	Heart failure, QT prolongation
Imatinib	Heart failure
Nilotinib	QT prolongation
Pazopanib	Hypertension, QT prolongation
Sorafenib	Hypertension, Heart failure
Sunitinib	Hypertension, Heart failure, QT Prolongation
Trastuzumab	Heart failure

Conclusion

- Targeted therapies have made tremendous advances in oncology, but there is still inadequate understanding in regards to predicting, preventing, and reducing the occurrence of cardiotoxicity
- From a pharmacological perspective, eventual understanding of primary mechanisms responsible for cardiotoxicity is essential
- From a clinical perspective, there is a need to define clinical endpoints of cardiotoxicity and harmonize cardiac monitoring
- Case-by-case: therapeutic gain vs. cardiovascular risks
- Multidisciplinary approach encompassing basic science and oncology/cardiology expertise in order to minimize CV risks associated with targeted therapy

The heart of the matter: when targeted cancer therapies cause off-target toxicities

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MDAnderson Cancer Center, Houston, TX

Hematology/Oncology Pharmacy Association

Castration Resistant Prostate Cancer

Rebecca E. Greene, Pharm.D., BCOP
Clinical Pharmacy Specialist, Oncology
South Texas Veterans Health Care System

Hematology/Oncology Pharmacy Association

Faculty Disclosure

- Rebecca Greene has no areas of conflict to disclose

Learning Objectives

At the completion of this presentation, the participant should be able to:

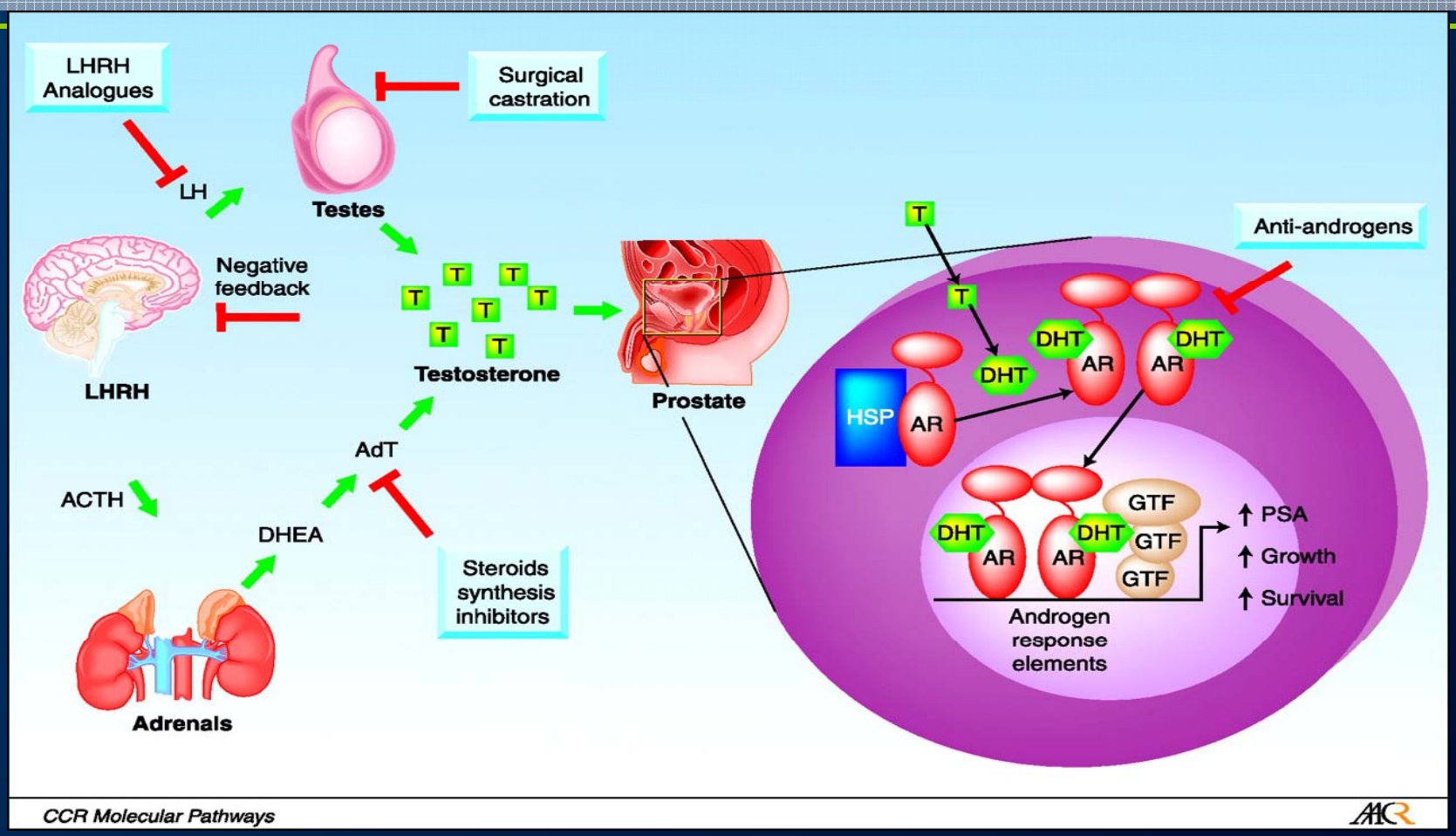
- Develop a treatment algorithm for castration-resistant prostate cancer (CRPC) based on the efficacy of the therapies
- Analyze patient specific information to determine when a change in management is indicated in patients with CRPC
- Construct a treatment plan for a patient with CRPC based on prior therapy, comorbid illness and concomitant medications
- Differentiate the toxicities associated with various treatments for CRPC about which patients and caregivers should be educated

Prostate Cancer (PCa)

- Most common cancer in men in US
- 2010 estimates
  - Cases: 217,730 (28%)
  - Deaths: 32,050 (11%)
- Hormone dependent

American Cancer Society. *Cancer Facts & Figures 2010.* Atlanta: American Cancer Society; 2010

Points of intervention utilized by androgen deprivation therapies



T: testosterone; LH: luteinizing hormone; LHRH: luteinizing hormone releasing hormone; HSP: heat shock protein; DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; ACTH: adrenocorticotropic hormone; AR: androgen receptor

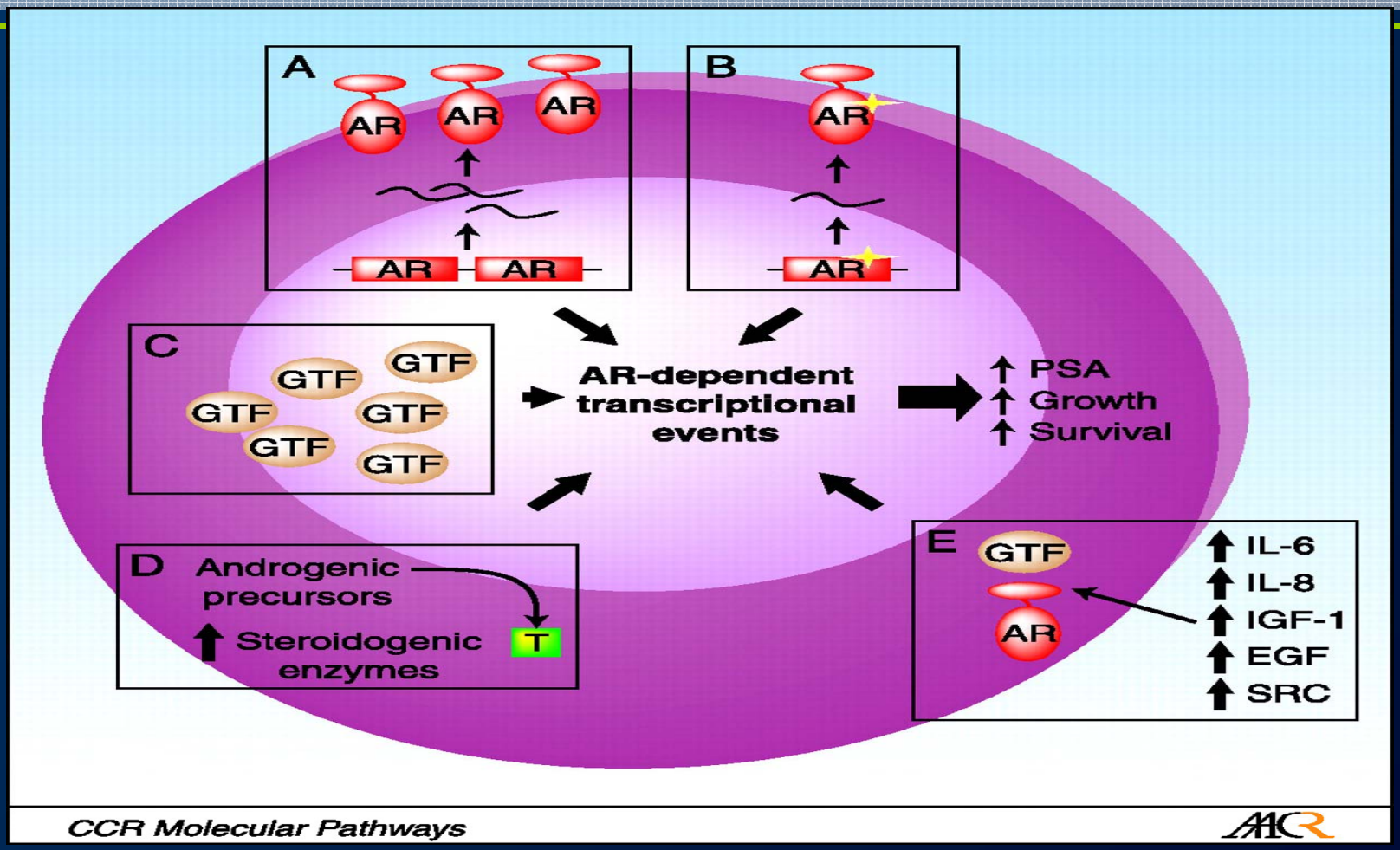
Attar R M et al. Clin Cancer Res 2009;15:3251-3255

Clinical Cancer Research

Initial Therapy of Advanced PCa

- Deprive cancer cell of androgen
  - Castration (Serum testosterone < 50 ng/dL)
    - Surgical
    - Chemical
- CRPC
  - Serum testosterone < 50 ng/dL
  - Rising PSA
  - Metastatic disease

Mechanisms involved in castration resistant prostate cancer

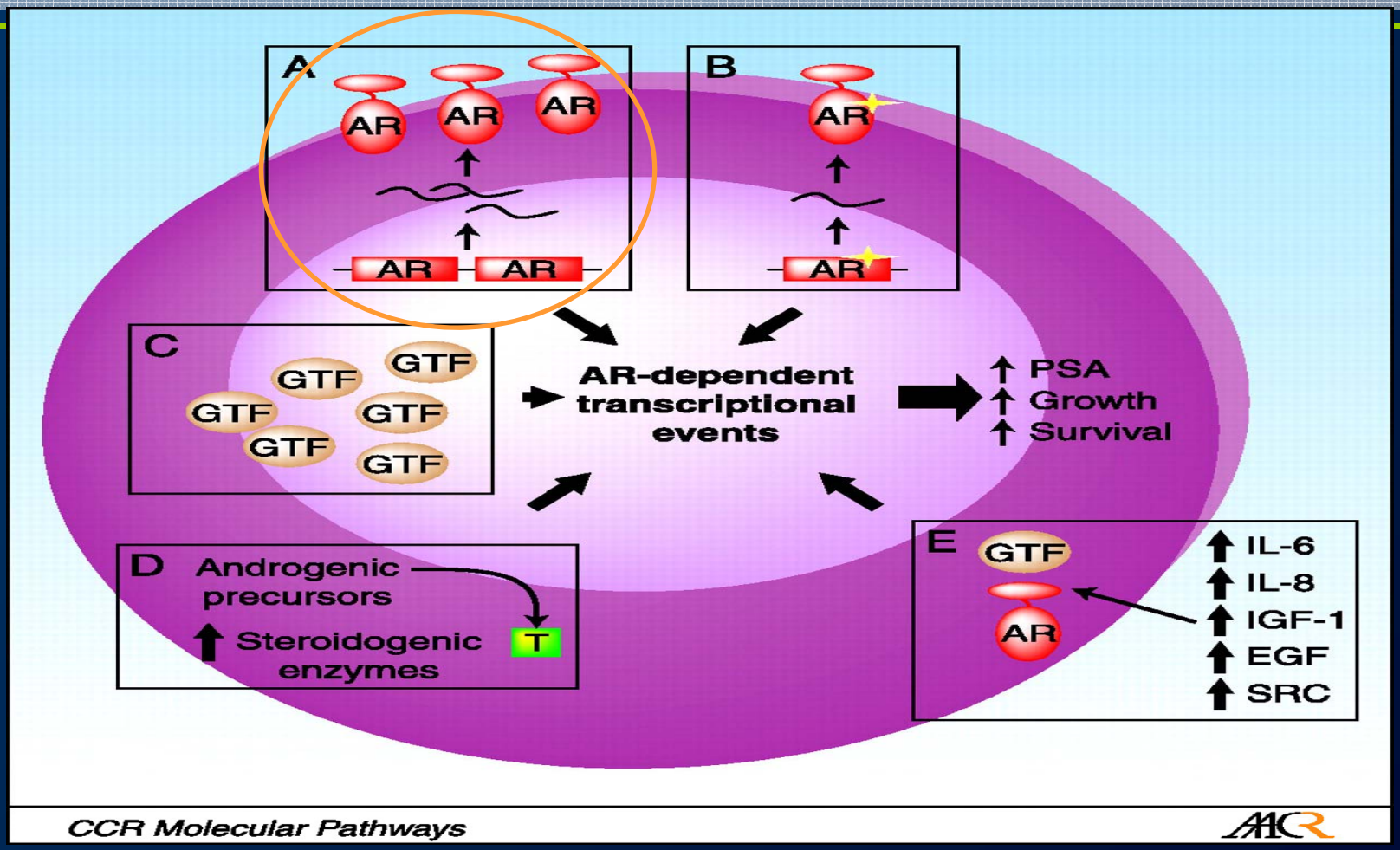


GTF: general transcription factor; AR: androgen receptor; T: testosterone; IL: interleukin; IGF: insulin-like growth factor; EGF: epidermal growth factor; SCR: sarcoma

Attar R M et al. Clin Cancer Res 2009;15:3251-3255

Clinical Cancer Research

Mechanisms involved in castration resistant prostate cancer



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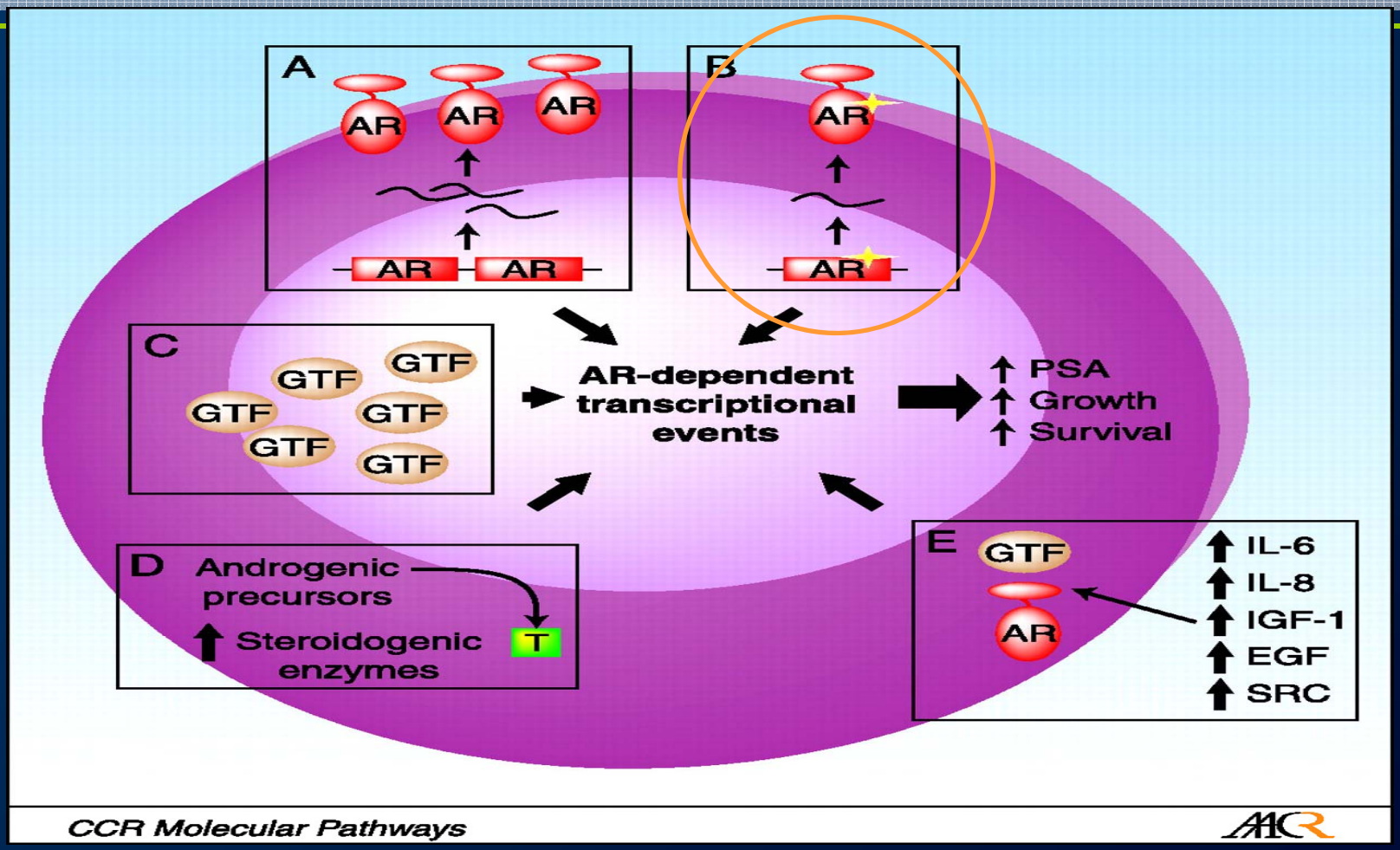
Mechanisms involved in castration resistant prostate cancer



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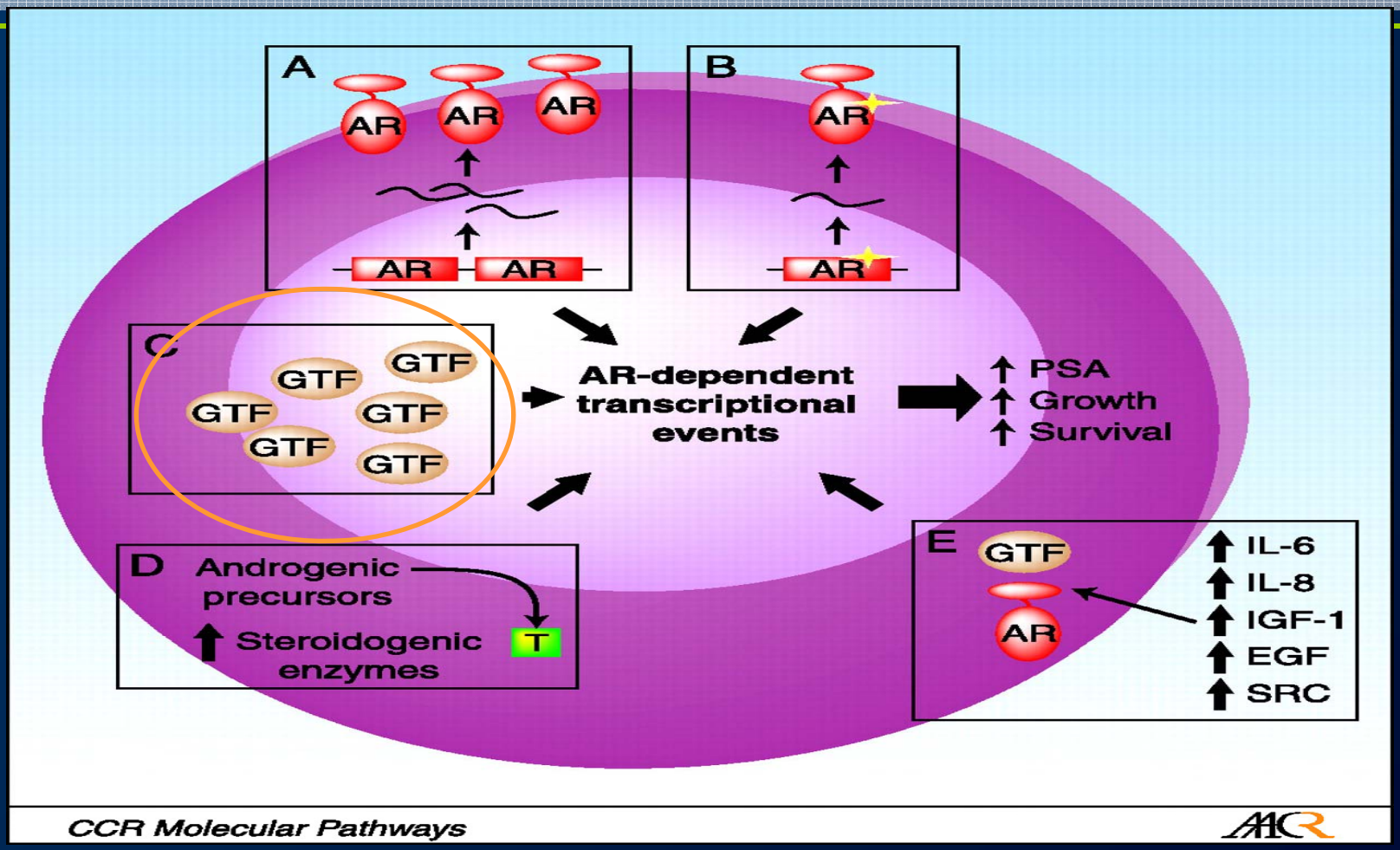
Clinical Cancer Research

Mechanisms involved in castration resistant prostate cancer



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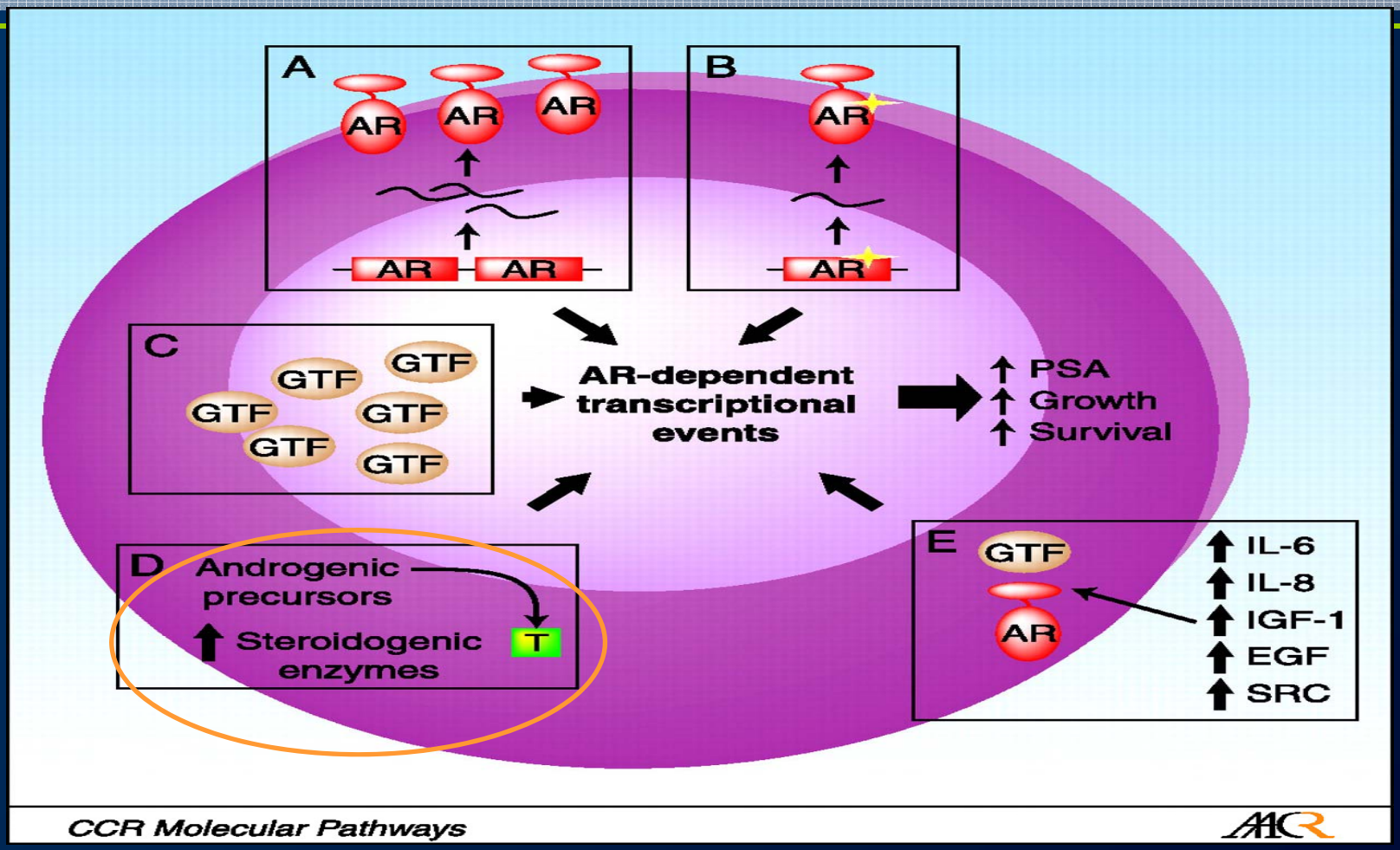
Mechanisms involved in castration resistant prostate cancer



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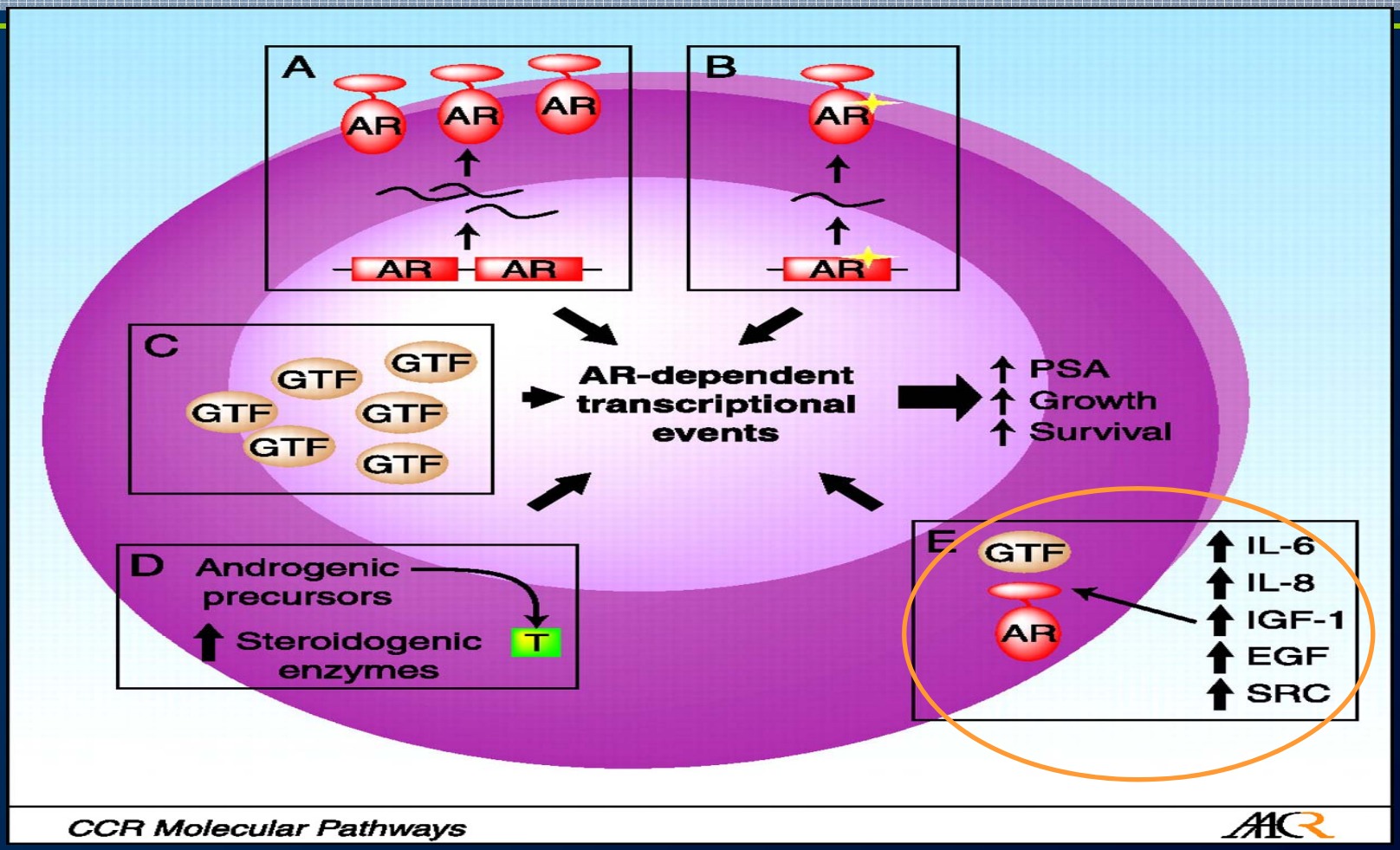
Attar R M et al. Clin Cancer Res 2009;15:3251-3255

Clinical Cancer Research

Mechanisms involved in castration resistant prostate cancer



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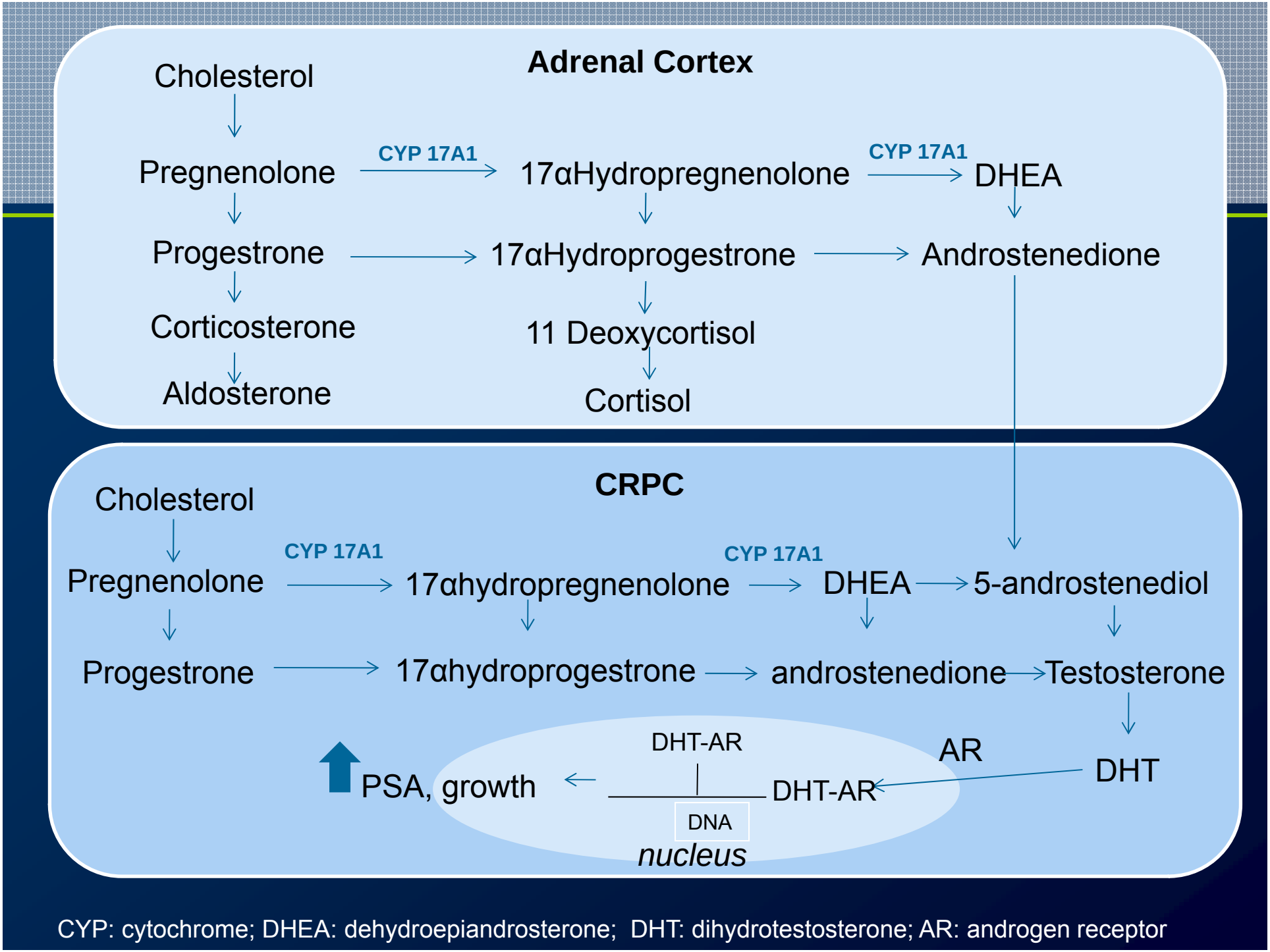
Clinical Cancer Research



CYP: cytochrome; DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; AR: androgen receptor

Therapy for CRPC in 2009

- Ensure castration (testosterone < 50 ng/dL)
- Add antiandrogen
- Antiandrogen withdrawal
- First line chemotherapy
  - Docetaxel based
- Second line chemotherapy
  - Mitoxantrone/prednisone
  - Ketoconazole/hydrocortisone
  - Clinical trial

Audience Response Question #1

WG is a 63 yo male with metastatic prostate cancer. WG has been receiving leuprolide IM Q3 months for the past 2 years. WG returns to clinic today for follow up and it is noted that PSA has increased from 3.5 ng/mL to 5 ng/mL to 9 ng/mL over the past 6 months. Testosterone is < 50 ng/dL and CTs confirm new bone lesions. Which therapy would you recommend?

A. Docetaxel 75 mg/m^2 q 3 weeks + prednisone 5 mg po bid
B. Sipuleucel-T infused every 2 weeks x 3 treatments
C. Cabazitaxel 25 mg/m^2 q 3 weeks + prednisone 10 mg po daily
D. Mitoxantrone 12 mg/m^2 q 3 weeks + prednisone 5 mg po bid

Docetaxel Based Therapy

	SWOG 9916 N=770		TAX 327 N=1006			TAX 327 Update		
	DE (n=386)	MP (n=384)	D3P (n=335)	D1P (n=334)	MP (n=337)	D3P	D1P	MP
Median survival (months)	**17.5***	**15.6***	**18.9***	17.4	**16.5***	**19.2***	17.8	**16.3***
TTP (months)	6.3	3.2	NR	NR	NR	NR	NR	NR
50% decrease in PSA	50%	27%	45%	48%	32%	NR	NR	NR

* p<0.05; DE: docetaxel/estramustine; MP: mitoxantrone/prednisone; D3P: Q3week docetaxel/prednisone; D1P: Q1week docetaxel/prednisone; NR: not reported

Tannock IF, et al. *N Engl J Med.* 2004;351:1502-12.; Petrylak D, et al. *N Engl J Med.* 2004;351:1513-20.

Phase III Trial of Bevacizumab with Docetaxel/Prednisone in First Line Treatment of CRPC (CALGB 90401)

PCa

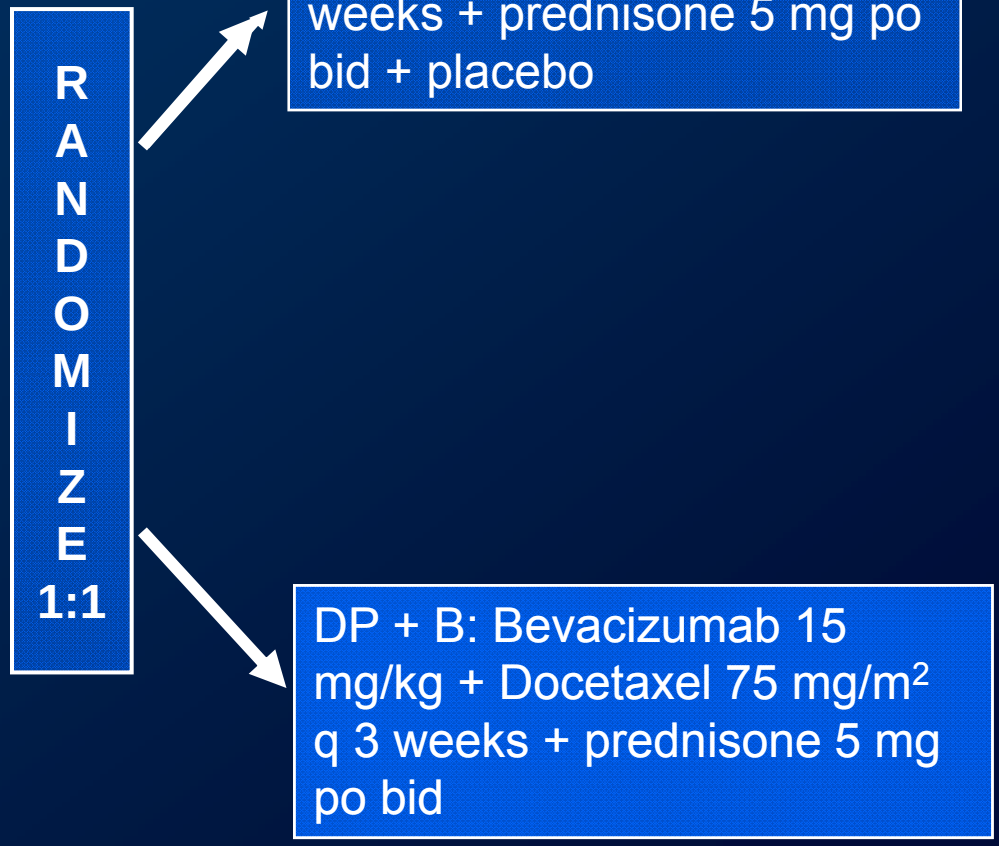
- mCRPC
- Chemotherapy naïve
- ECOG PS $\leq$ 2

Primary endpoint

- OS

Stratification

- 24 month survival probability
- Age
- Prior arterial thrombotic event



ECOG = Eastern Cooperative Oncology Group

Kelly WK, et al. ASCO abstract LBA4511, 2010

Phase III Trial of Bevacizumab with Docetaxel/Prednisone in First Line Treatment of CRPC (CALGB 90401)

	DP (n=526)	DP + B (n=524)	P value
Median OS, months	21.5	22.6	**0.181**
Median PFS, months	7.5	9.9	<0.0001
≥ Grade 3 adverse events	55.3%	**74.8%**	<0.001
Treatment related deaths	1.1%	**4.4%**	0.0014

Kelly WK, et al. ASCO abstract LBA4511, 2010

Bevacizumab Summary

- Not approved for first line therapy
- OS in control group was longer than seen in previous studies
- Several phase II trials evaluating bevacizumab with docetaxel/prednisone after progression on docetaxel/prednisone

Treatment of CRPC in 2011

- Asymptomatic
  - Sipuleucel-T
- First line
  - Docetaxel
- Second line
  - Cabazitaxel
  - Satraplatin
- Third line
  - Clinical trial

Sipuleucel-T

- Active cellular immunotherapy
- Stimulate T-cell immunity against prostatic acid phosphatase (PAP)
- Preparation
  - 1.5-2 blood volume mononuclear cell leukapheresis
  - Antigen presenting cells (APCs) isolated
  - APCs cultured with fusion protein of PAP-GMCSF (PA2024)

Prescribing Information, Provenge ™ , Dendreon Corporations 2010

Integrated Data of 2 Phase III Trials of Sipuleuclel-T (D9901 + D9902A)

Inclusion

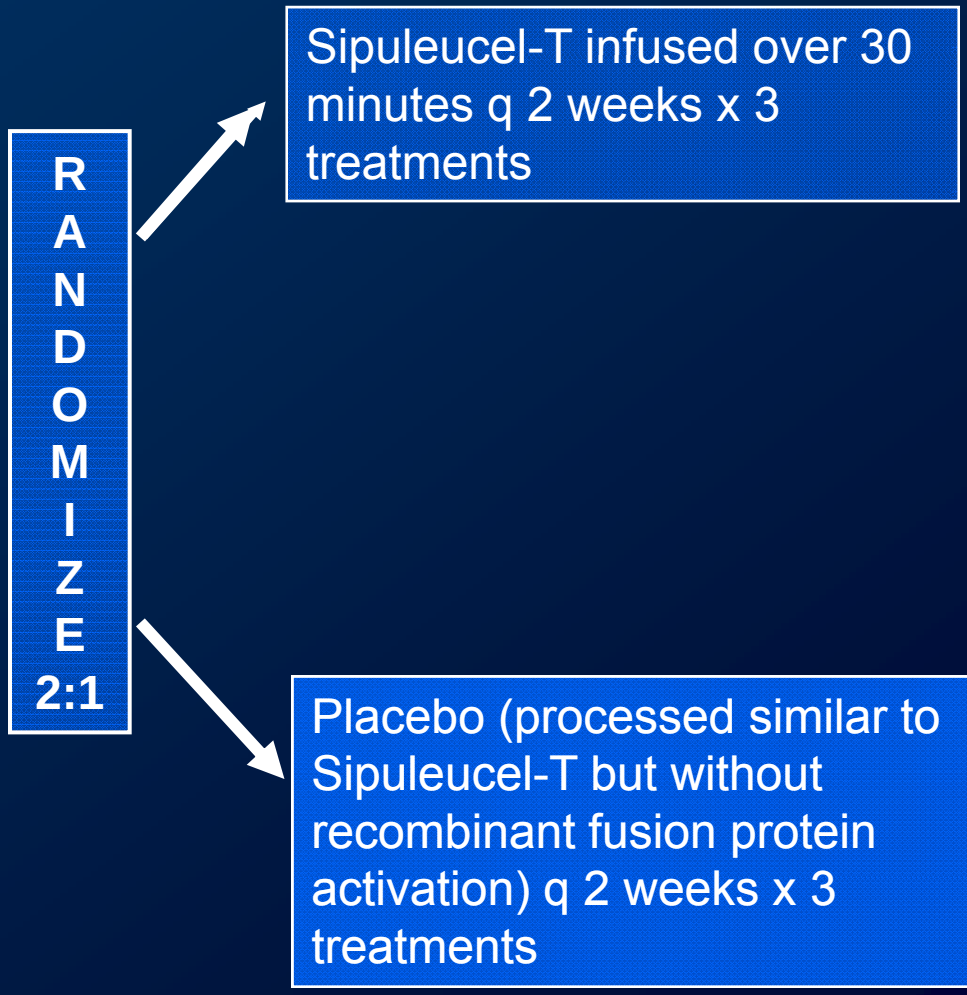
- mCRPC
- Progressive disease
- ECOG PS 0-1
- + PAP staining in 25% of cells

Exclusion

- Pain
- Visceral metastases

Primary endpoint

- TTP



Higano CS, et al. *Cancer.* 2009;115:3670-9.

Integrated data of 2 Phase III trials of Sipuleucel-T (D9901 + D9902A)

	Sipuleucel-T (n=147)	Placebo (n=78)	P value
Time to progression Hazard ratio (CI)	11.1 weeks	9.7 weeks	0.111 1.26 (0.95-1.68)
Median survival Hazard ratio (CI)	23.2 months	18.9 months	0.011 1.5 (1.10-2.05)
Cerebrovascular Events	7.5%	2.6%	NR

NR: not reported

Higano CS, et al. *Cancer* 2009;115:3670-9.

Phase III Trial of Sipuleucel-T for Asymptomatic mCRPC (IMPACT)

Inclusion

- mCRPC
- Progressive disease
- ECOG PS 0-1
- + PAP staining in 25% of cells
- Gleason ≤ 7 and asymptomatic but amended to any Gleason and minimally symptomatic

Exclusion

- Visceral metastases
- Pain
- ≥ 2 chemotherapy regimens

Primary Endpoint

- OS

RANDOMIZE 2:1

Sipuleucel-T infused every 2 weeks x 3 doses

Placebo every 2 weeks x 3 doses

Stratified

- Primary Gleason
- Number of bone metastases
- Bisphosphonate use

Kantoff PW, et al. *N Engl J Med.* 2010;363:411-22.

Phase III Trial of Sipuleucel-T for Asymptomatic mCRPC (IMPACT)

Baseline Characteristics	Sipuleucel-T (n=341)	Placebo (n=171)
Disease location - %		
Bone only	50.7	43.3
Soft tissue only	7.0	8.2
Bone and soft tissue	41.9	48.5
Previous prostate cancer therapy - %		
Androgen-deprivation therapy	100	100
Chemotherapy	19.6	15.2
Docetaxel	15.5	12.3

Kantoff PW, et al. *N Engl J Med.* 2010;363:411-22.

Phase III Trial of Sipuleucel-T for Asymptomatic mCRPC (IMPACT)

	Sipuleucel-T (n=341)	Placebo (n=171)	HR (95% CI)
Median survival	**25.8 months**	**21.7 months**	**0.78 (0.61-0.98)**
Time to objective disease progression	3.7 months	3.6 months	0.95 (0.77-1.17)
Antibody > 400 titers against PA2024 after baseline	66.2%	2.9%	NR
Antibody > 400 titers against prostatic acid phosphatase after baseline	28.5%	1.4%	NR

NR: not reported

Kantoff PW, et al. *N Engl J Med.* 2010;363:411-22.

Phase III Trial of Sipuleucel-T for Asymptomatic mCRPC (IMPACT)

Adverse Events	Sipuleucel – T (N=338) No (%)	Placebo (N=168) No (%)
Chills	183 (54.1)	21 (12.5)
Pyrexia	99 (29.3)	23 (13.7)
Headache	54 (16)	8 (4.8)
Myalgia	33 (9.8)	8 (4.8)
Influenza-like illness	33 (9.8)	6 (3.6)
Hypertension	25 (7.4)	5 (3)
Groin pain	17 (5)	4 (2.4)
Cerebrovascular events	8 (2.4)	3 (1.8)

Kantoff PW, et al. *N Engl J Med.* 2010;363:411-22.

Sipuleucel-T Summary

- Patients with antibody > 400 titers against PA2024 or PAP lived longer
- Benefit primarily in asymptomatic, docetaxel-naïve patients
- OS different despite no difference in TTP
  - Delayed onset of antitumor response
  - TTP not appropriate endpoint for immunotherapy in CRPC
- Access issues

Kantoff PW, et al. *N Engl J Med.* 2010;363:411-22.

Treatment for CRPC in 2011

- Asymptomatic
  - Sipuleucel-T
- First line
  - Docetaxel
- ***Second line***
  - ***Cabazitaxel***
  - **Satraplatin**
- Third line
  - Clinical Trial

Cabazitaxel

- Approved second line after docetaxel
- Novel taxane
- Anititumor activity in paclitaxel and docetaxel resistant models
- Low affinity for multi-drug resistance transporter, p-glycoprotein

Phase III Trial of Cabazitaxel for Second Line Treatment of CRPC (TROPIC)

Inclusion

- mCRPC
- ECOG PS 0-2
- Progression during or after docetaxel
- *Received $\geq$ 225 mg/m^2 docetaxel

Exclusion

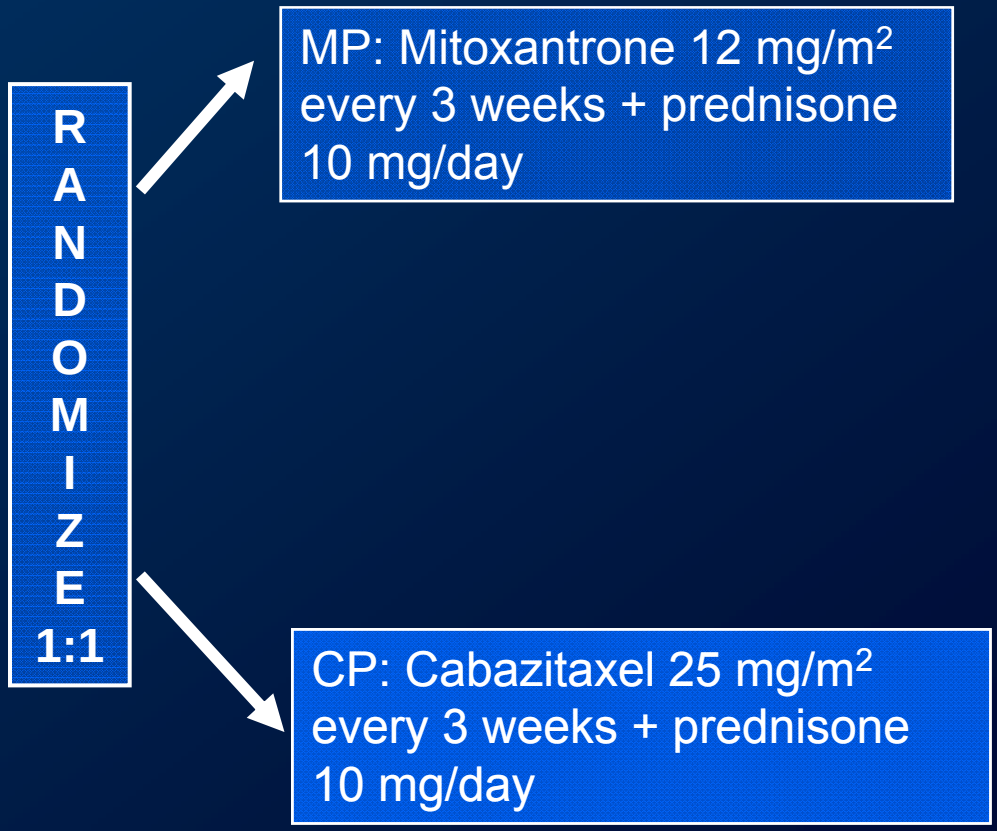
- Cardiovascular risk factors
- $\geq$ Grade 2 neuropathy or stomatitis

Primary Endpoint

- OS

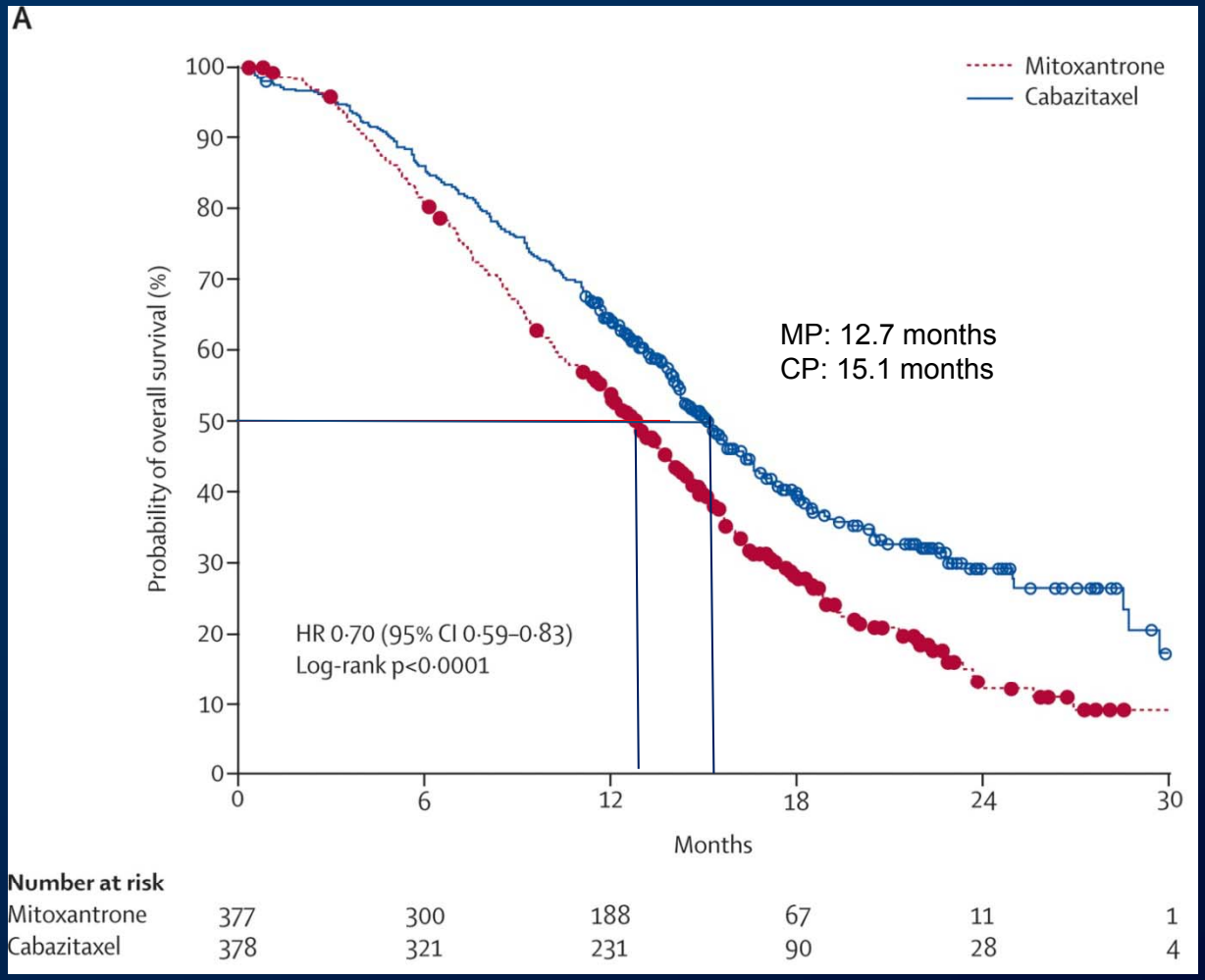
Stratified

- Disease measurability
- ECOG PS



De Bono JS, et al. *Lancet.* 2010;376:1147-54. * Amendment to protocol after 59 patients enrolled

Phase III Trial of Cabazitaxel for Second Line Treatment of CRPC (TROPIC)



Reprinted with permission from Elsevier. De Bono JS, et al. *Lancet.* 2010;376:1147-54.

Phase III Trial of Cabazitaxel for Second Line Treatment of CRPC (TROPIC)

	MP (n=377)	CP (n=378)	HR (95% CI)
Median PFS, months	1.4	2.8	0.74 (0.64-0.86)
Median TTP, months	5.4	8.8	0.61 (0.49-0.76)
Dose reductions, # patients	15 (4%)	45 (12%)	NR

OS: overall survival; PFS: progression free survival; TTP: time to progression; NR: not reported

De Bono JS, et al. *Lancet.* 2010;376:1147-54.

Phase III Trial of Cabazitaxel for Second Line Treatment of CRPC (TROPIC)

Adverse Events	MP (n=377)		CP (n=378)	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Neutropenia	325 (88)	215 (58)	347 (94)	303 (82)
Febrile neutropenia	**	5 (1)	**	28 (8)
Anemia	302 (81)	18 (5)	361 (97)	39 (11)
Diarrhea	39 (11)	1 (<1)	173 (47)	23 (6)
Peripheral neuropathy	12 (3.2)	3 (1)	52 (14)	3 (1)

De Bono JS, et al. *Lancet.* 2010;376:1147-54.

Phase III Trial of Cabazitaxel for Second Line Treatment of CRPC (TROPIC)

- Death due to causes other than disease progression within 30 days of last dose
  - 18 (5%) cabazitaxel patients
  - 3 of 131 (2%) of patients <65 years old
  - 15 of 240 (6%) of patients ≥ 65 years old
- Fatal adverse reactions
  - Infections (n=7)
  - Cardiac (n=5)
  - Renal failure (n=3)

De Bono JS, et al. *Lancet.* 2010;376:1147-54.

Cabazitaxel Summary

- First agent to show OS benefit for second line therapy of CRPC
- Majority of study patients ECOG 0 or 1
- Caution in elderly patients
- Patient education
  - Febrile neutropenia
  - Diarrhea

Satraplatin

- Oral platinum
- Activity in cell lines resistant to taxanes
- Phase II trial results - Activity in CRPC
- Not susceptible to some cisplatin mechanisms of resistance

Phase III Trial of Satraplatin for Second Line Treatment of CRPC (SPARC)

Inclusion

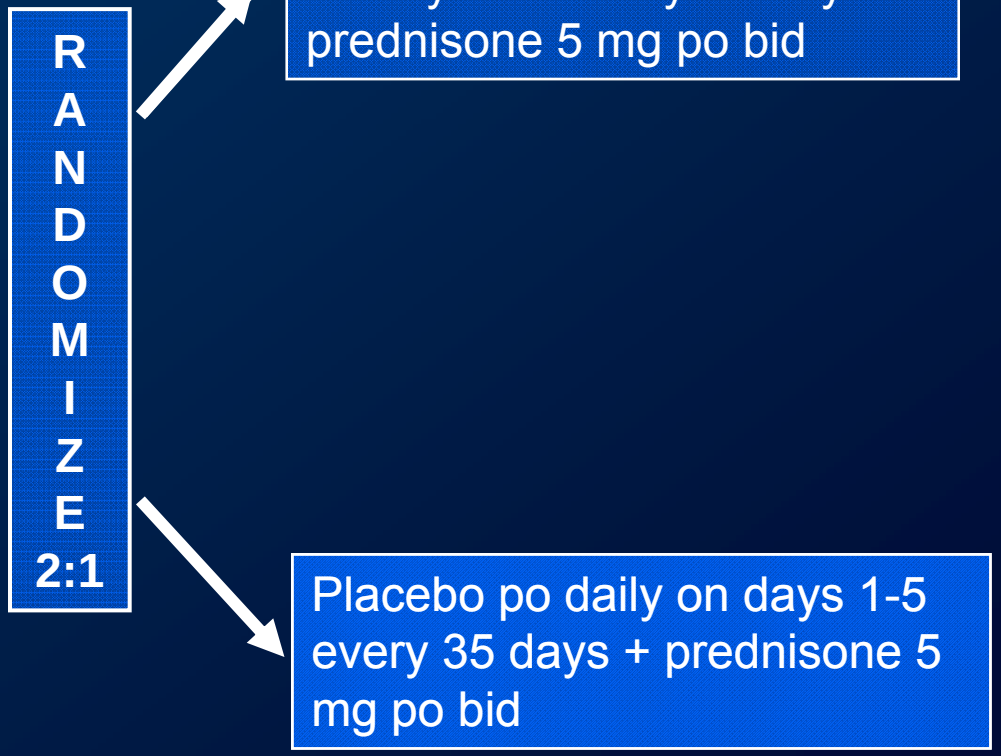
- mCRPC
- Disease progression after 1 prior chemotherapy regimen
- ECOG $\leq$ 2

Stratified

- ECOG PS
- Mean baseline Present Pain Intensity score
- Type of disease progression

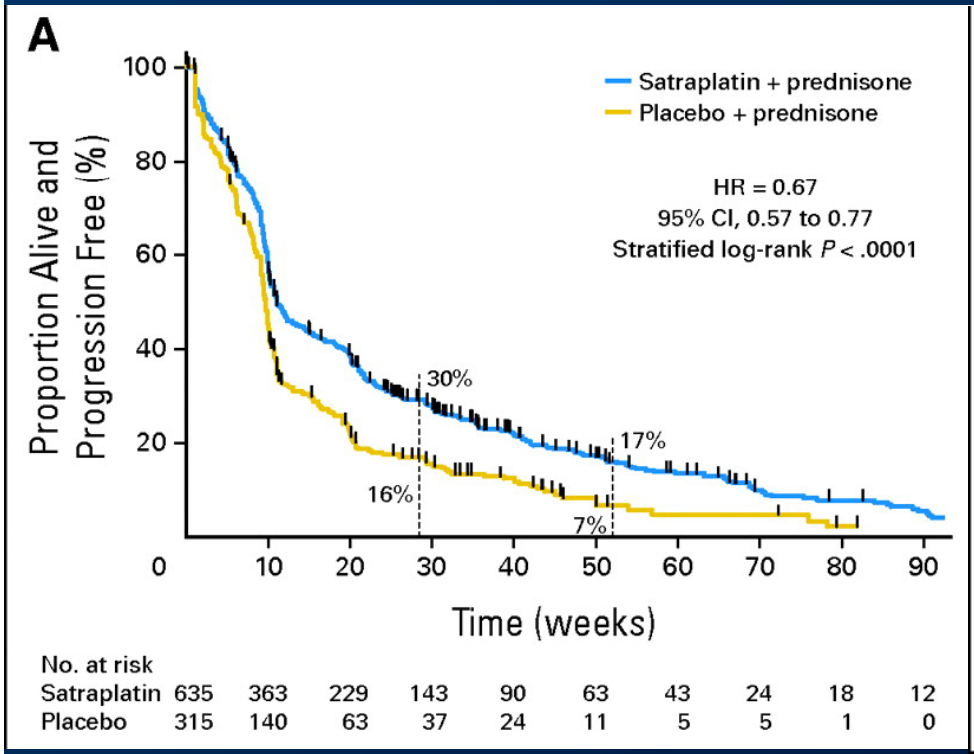
Primary Endpoints

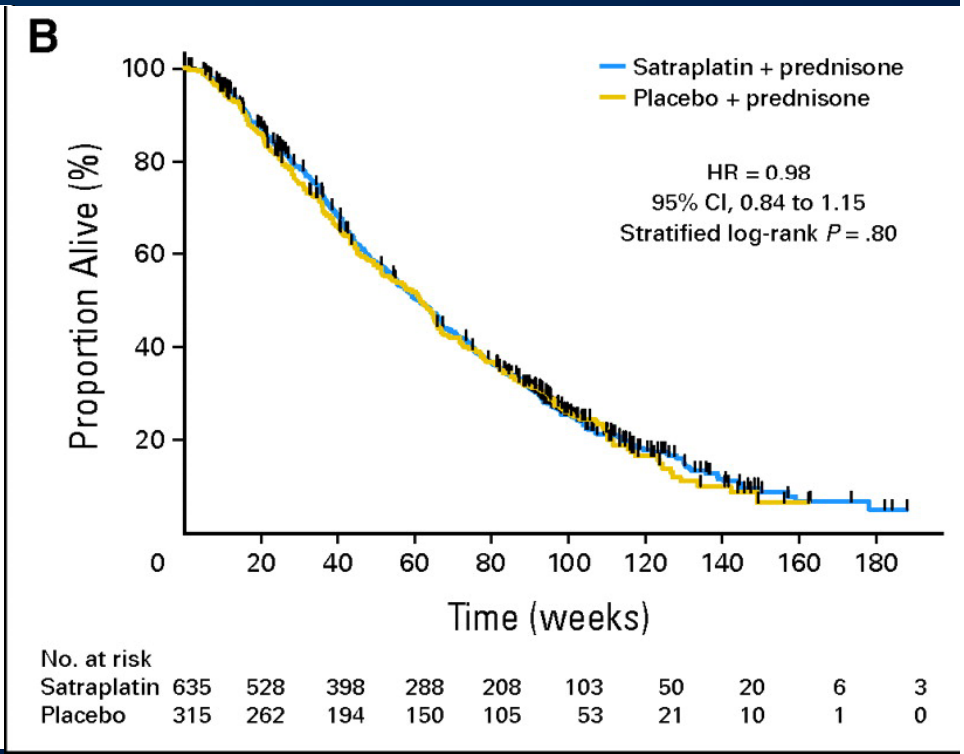
- OS
- PFS



Sternberg CN, et al. *J Clin Oncol.* 2009;27:5431-38.

Phase III Trial of Satraplatin for Second Line Treatment of CRPC (SPARC)





Phase III Trial of Satraplatin for Second Line Treatment of CRPC (SPARC)

	Satraplatin (n=635)		Placebo (n=315)	
Adverse Event	**All Grades**	**Grade 3 and 4**	**All Grades**	**Grades 3 and 4**
Neutropenia %	62.8	22.3	6.4	0.6
Thrombocytopenia %	87.4	22.6	22.4	1.9
Anemia %	96.5	11.9	92.3	4.8
Diarrhea %	24.3	1.9	6.4	0
Vomiting %	16.4	1.6	8.9	0

Sternberg CN, et al. *J Clin Oncol.* 2009;27:5431-38.

Satraplatin Summary

- Not approved due to lack of improvement in OS
- Longer than expected OS in placebo group
- Study started prior to docetaxel/prednisone becoming standard of care for first line
  - Only 50% of patients received docetaxel prior to satraplatin

Audience Response Question #2

Primary prophylaxis with colony stimulating factors should be considered in all patients receiving which chemotherapy?

A. Docetaxel
B. Cabazitaxel
C. Sipuleucel-T
D. None of the above

Toxicity Comparison of FDA Approved Agents

	Mitoxantrone	Docetaxel	Sipuleucel-T	Cabazitaxel
Nausea	38*	42*	28.1	34
Vomiting	*	*	17.8	23
Fever			29.3	12
Febrile neutropenia	2	3	NR	8
Myalgias	13	14	9.8	11
Chills	NR	NR	54.1	NR
Neutropenia	22	32	NR	82
Neuropathy	7	30	NR	14

* Combination of nausea and/or vomiting reported; NR: not reported

Tannock IF, et al. *N Engl J Med.* 2004;351:1502-12.; Petrylak D, et al. *N Engl J Med.* 2004;351:1513-20. Kantoff PW, et al. *N Engl J Med.* 2010;363:411-22. De Bono JS, et al. *Lancet.* 2010;376:1147-54.

Treatment for CRPC in 2011

- Asymptomatic
  - Sipuleucel-T
- First line
  - Docetaxel
- Second line
  - Cabazitaxel
- ***Third line***
  - ***Clinical Trial***

Audience Response Question #3

WG received docetaxel/prednisone x 8 cycles. PSA prior to cycle 9 shows an increase from 6 ng/dL to 20 ng/dL. Restaging CTs showed a new lung lesion. Which therapy is most appropriate?

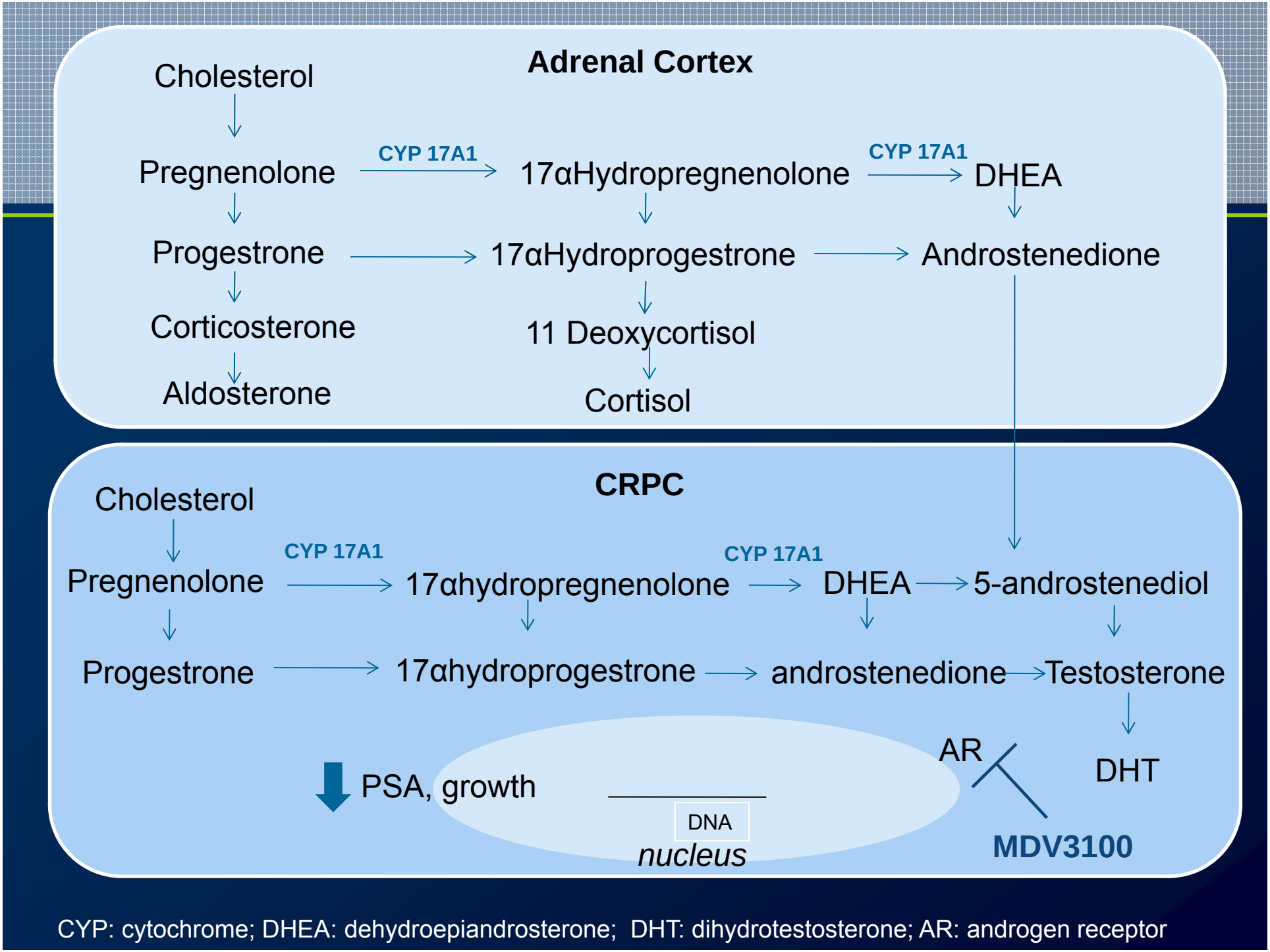
A. Sipuleucel-T
B. Mitoxantrone/prednisone
C. Cabazitaxel/prednisone
D. Ketoconazole/hydrocortisone

Novel Agents

- MDV3100
- Abiraterone

MDV3100

- AR antagonist
- Prevents nuclear translocation and DNA binding
- Higher affinity for AR than bicalutamide
- No agonist activity



CYP: cytochrome; DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; AR: androgen receptor

MDV 3100 Phase I/II Study

- CRPC with progressive disease (n = 140)
- 54% had previous chemotherapy

	Previous chemotherapy		Previous hormones		Previous ketoconazole	
	No (n=65)	Yes (n=75)	≥2 (n=74)	≥3 (n=66)	No (n=77)	Yes (n=63)
>50% PSA decrease	62%	51%	61%	50%	71%	37%
≥30-50% PSA decrease	9%	11%	5%	15%	5%	15%

Scher HI, et al. *Lancet.* 2010;375:1437-46.

MDV 3100 Toxicities

Adverse Events	Grade 3/4 No (%)
Fatigue	16 (11)
Anemia	4 (3)
Arthralgia	3 (2)
Seizure	3 (2)
Rash	2 (1)
Myocardial infarction	1 (1)

Scher HI, et al. *Lancet.* 2010;375:1437-46.

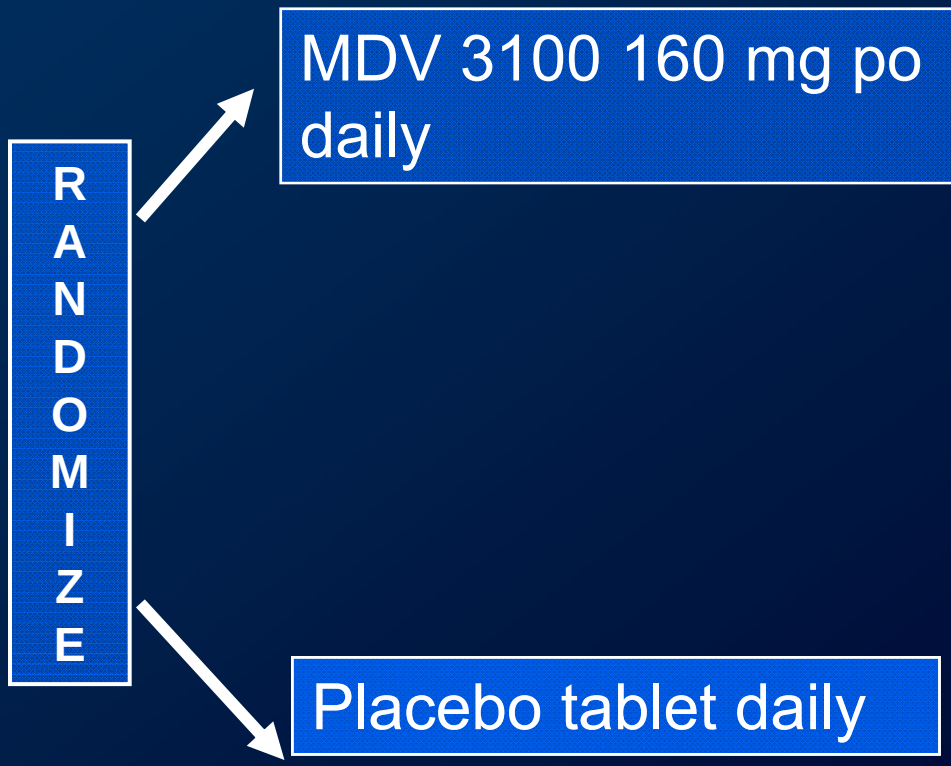
Phase III Trial of MDV 3100 in Docetaxel Refractory mCRPC (AFFIRM)

Inclusion

- mCRPC
- Disease progression after 1-2 prior chemotherapy regimens (1 regimen with docetaxel)
- ECOG PS ≤ 2

Primary Endpoint

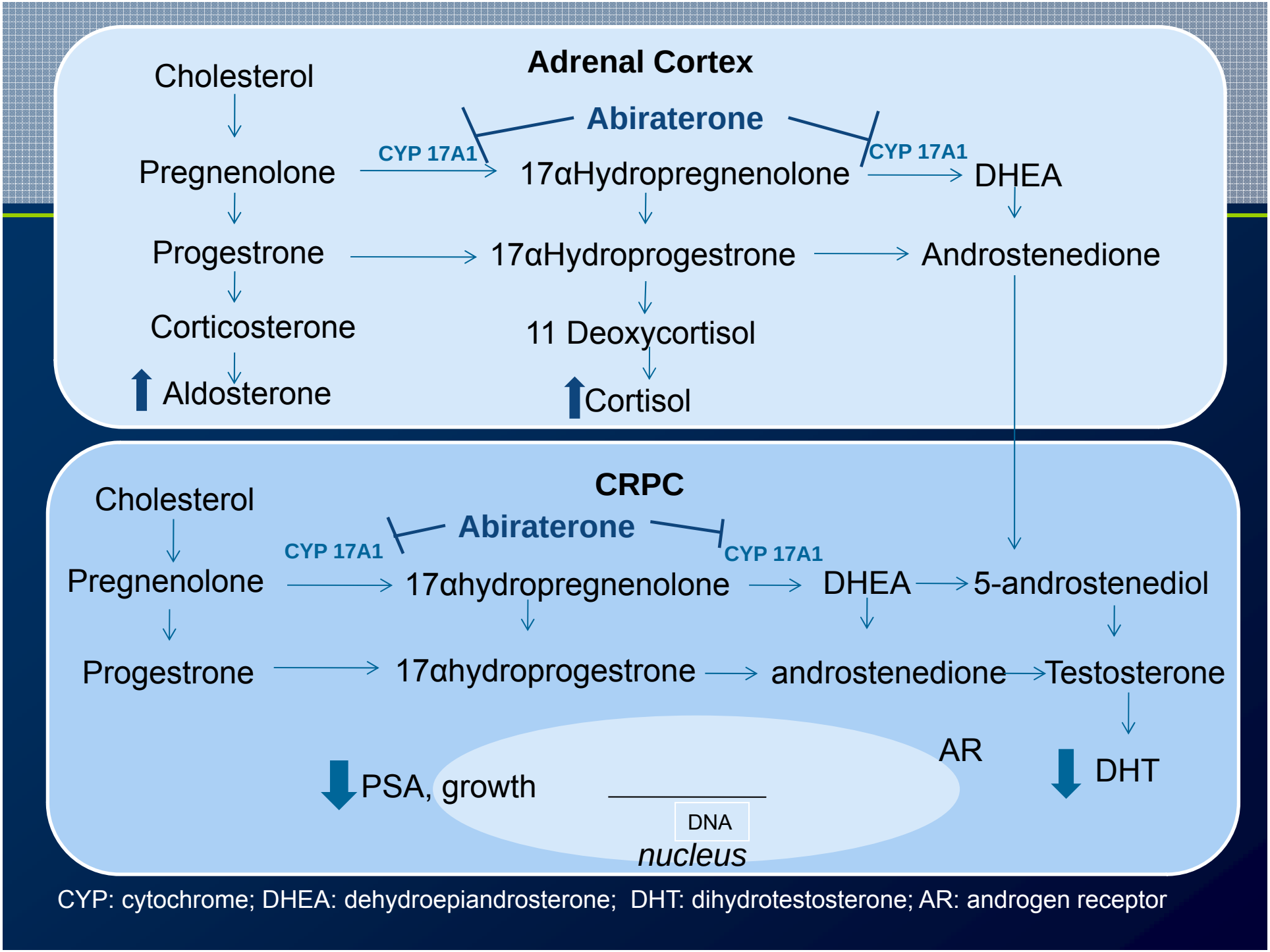
- OS



http://www.clinicaltrials.gov/ct2/show/NCT00974311?term=mdv+3100&rank=2

Abiraterone

- Oral irreversible inhibitor of CYP17A
- More selective and specific than ketoconazole



CYP: cytochrome; DHEA: dehydroepiandrosterone; DHT: dihydrotestosterone; AR: androgen receptor

Abiraterone

- Phase II data shown response in chemo-naïve and docetaxel treated patients
  - Two Phase II trials in CRPC after progression on docetaxel
  - Abiraterone 1000 mg po daily

Danila DC, et al. *J Clin Oncol.* 2010;28:1496-1501; Reid AH, et al. *J Clin Oncol.* 2010;28:1489-95.

Abiraterone

	≥ 30% PSA decrease	**≥ 50% PSA decrease**	≥ 90% PSA decrease
Danila DC, et al (n=58)			
Overall	47%	43%	16%
Previous ketoconazole	33%	30%	0
Ketoconazole-naïve	58%	55%	9%
Reid AH, et al (n=47)	68%	51%	15%

Danila DC, et al. *J Clin Oncol.* 2010;28:1496-1501; Reid AH, et al. *J Clin Oncol.* 2010;28:1489-95.

Phase III Trial of Abiraterone in Docetaxel Refractory mCRPC (COU-AA-301)

Inclusion

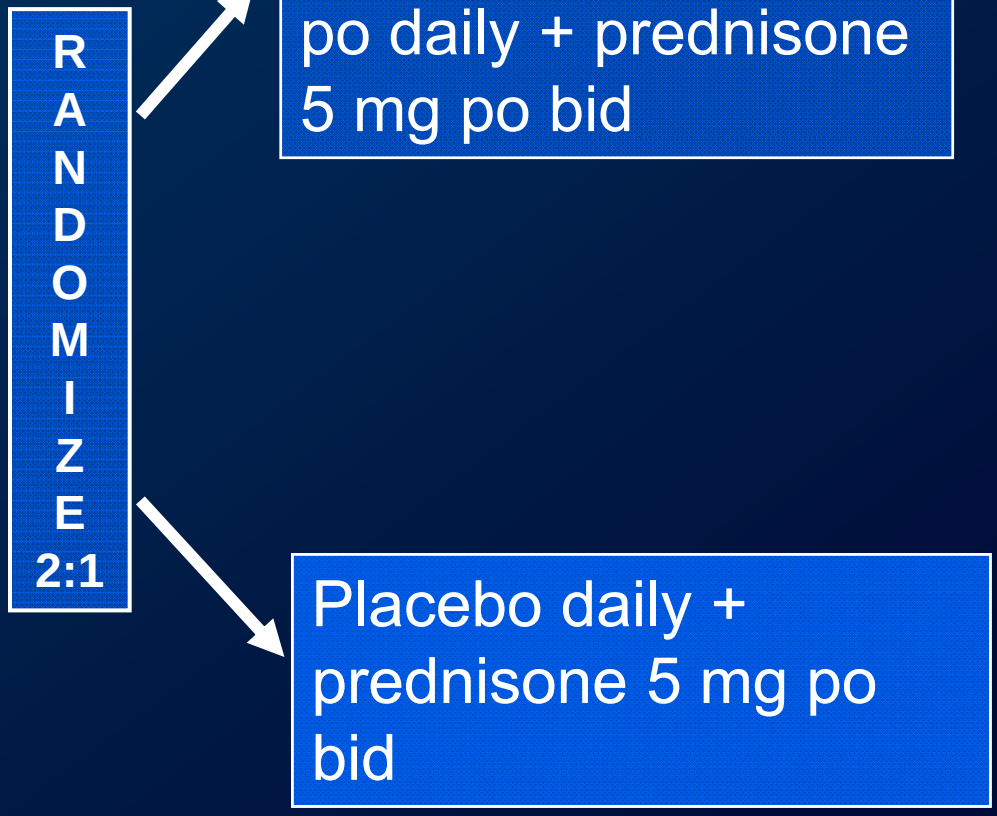
- mCRPC
- Disease progression after 1-2 prior chemotherapy regimens (1 regimen with docetaxel)
- ECOG PS $\leq$ 2

Stratified

- ECOG PS
- Number of lines of prior chemotherapy
- Pain score
- Type of disease progression

Primary Endpoint

- OS



http://www.clinicaltrials.gov/ct2/show/NCT00638690?term=abiraterone&rank=12

Phase III Trial of Abiraterone in Docetaxel Refractory mCRPC (COU-AA-301)

	Placebo + prednisone	Abiraterone + prednisone	P value
OS, months	10.4	14.8	<0.0001
Time to PSA progression, months	6.6	10.2	<0.0001
PSA response rate	5.5%	29.1%	<0.0001

Pal SK, Sartor O. *Maturitas.* 2011;68:103-05.

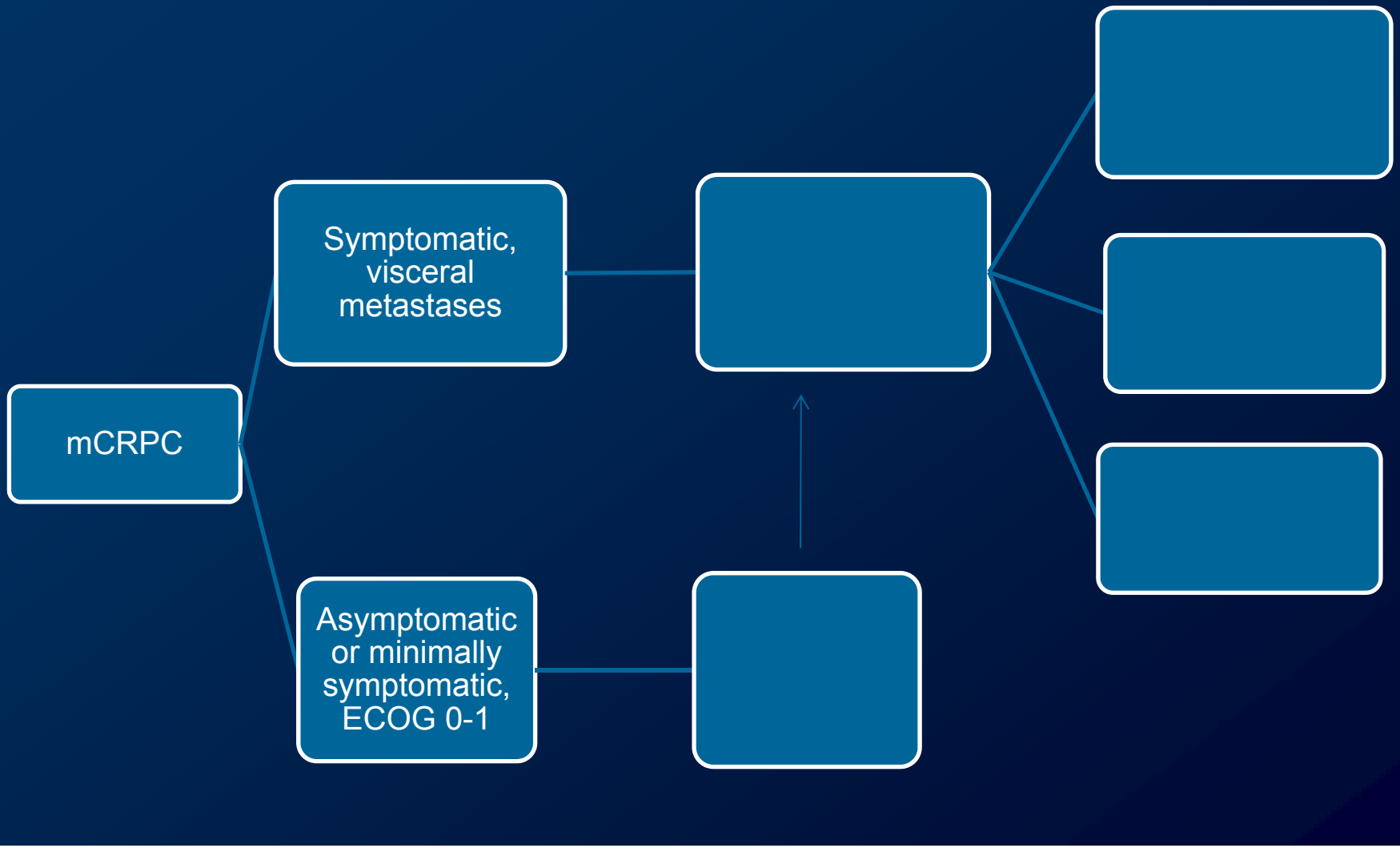
Abiraterone

Adverse Events	Danila DC, et al (n=58)	Reid AH, et al (n=47)	COU-AA-301
Hypokalemia	55%	5%	3.8%
Hypertension	17%	<5%	1.3%
Fluid retention	15%	9%	2.3%
Nausea	14%	14%	NR
Fatigue	34%	31%	NR
Cardiac disorders	NR	NR	4.1%

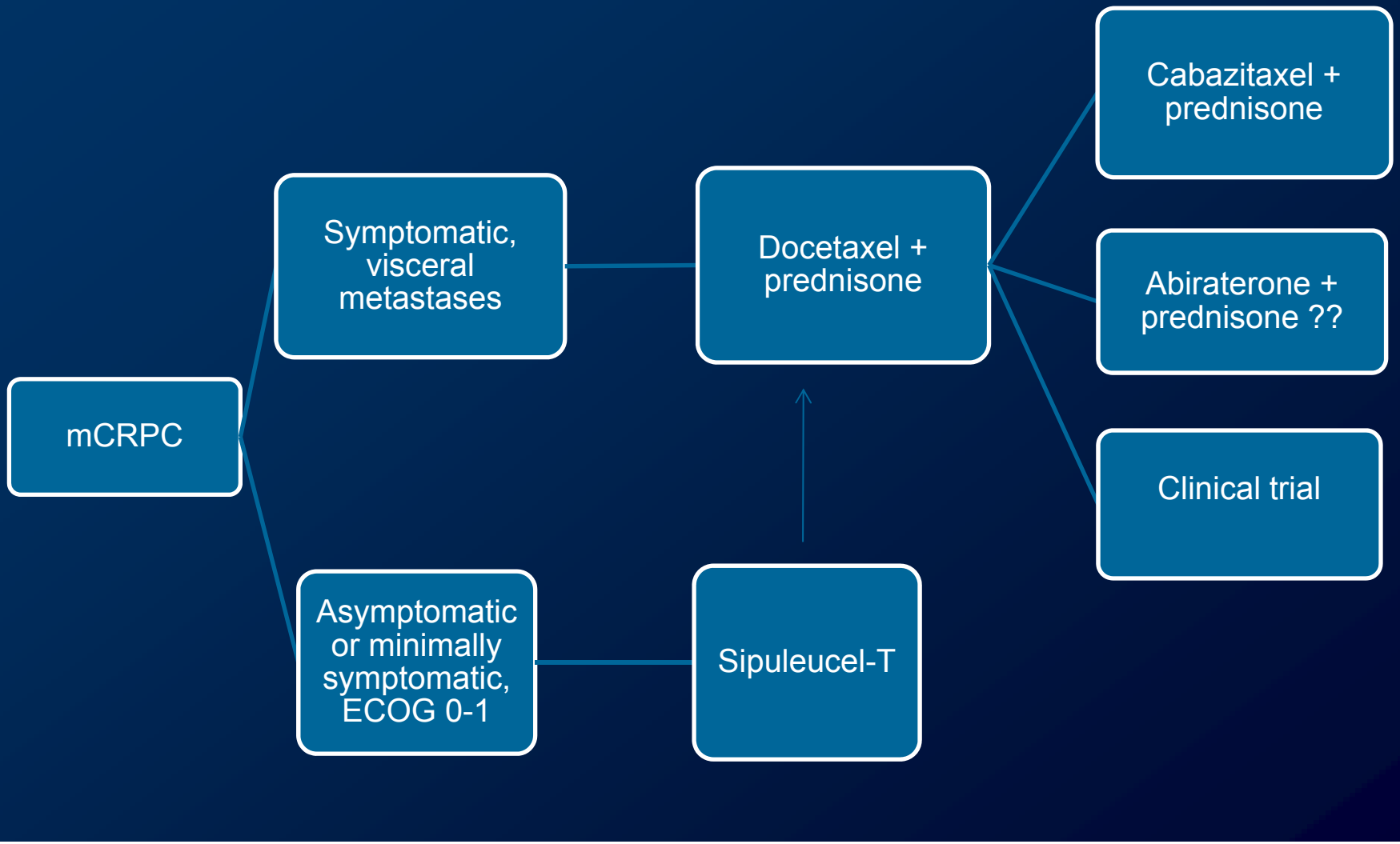
NR: not reported

Danila DC, et al. *J Clin Oncol.* 2010;28:1496-1501; Reid AH, et al. *J Clin Oncol.* 2010;28:1489-95. Pal SK, Sartor O. *Maturitas.* 2011;68:103-05.

Summary


mCRPC
Symptomatic, visceral metastases
Asymptomatic or minimally symptomatic, ECOG 0-1

Summary


mCRPC
Symptomatic, visceral metastases
Asymptomatic or minimally symptomatic, ECOG 0-1
Docetaxel + prednisone
Sipuleucel-T
Cabazitaxel + prednisone
Abiraterone + prednisone ??
Clinical trial

Summary

- New options for treatment of mCRPC
  - Docetaxel-refractory
  - Asymptomatic
- CRPC remains hormone dependent despite castrate serum levels of testosterone

Castration Resistant Prostate Cancer

Rebecca E. Greene, Pharm.D., BCOP
Clinical Pharmacy Specialist, Oncology
South Texas Veterans Health Care System

Hematology/Oncology Pharmacy Association

Vaccinations in Cancer

Kamakshi V. Rao, Pharm.D., BCOP, CPP

BMT Clinical Pharmacist Practitioner

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Chapel Hill, North Carolina

Hematology/Oncology Pharmacy Association

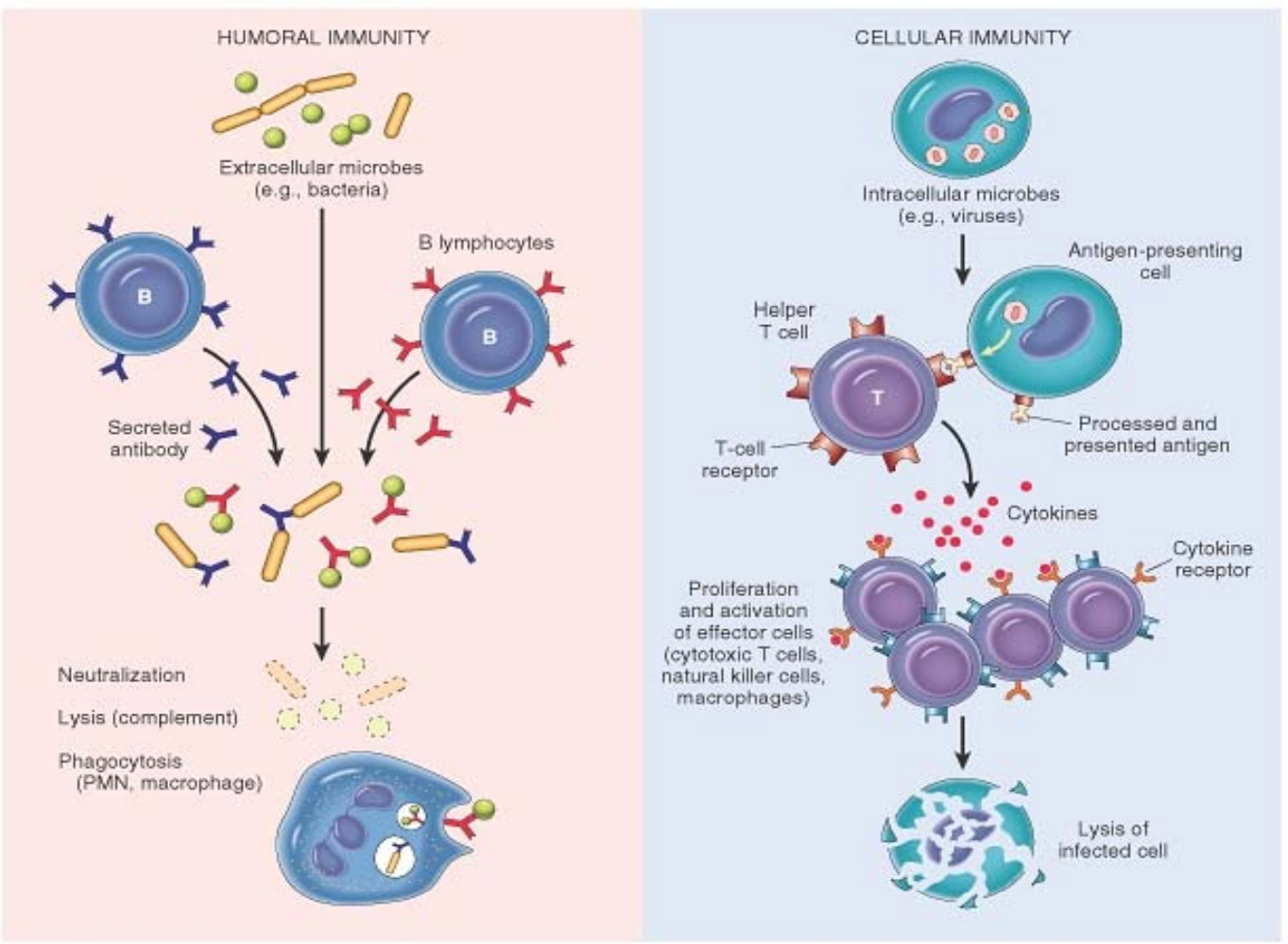
Faculty Disclosure

- Kamakshi Rao has no areas of conflict to disclose

Objectives

- Differentiate the changes in immune function and immunity that occur in patients undergoing therapy for cancer based on age, disease, and chemotherapy regimen
- Summarize the recommendations for vaccinations in oncology patients based on data and guidelines from the Centers for Disease Control, Infectious Disease Society of America, and the American Society for Blood and Marrow Transplantation
- Analyze limitations in the current available data and gaps in the current recommendations for vaccination in oncology patients

Immunity



Robbin's Basic Pathology, 8th Edition 2007

Cancer and the Immune System

- Historically, theory suggested that the presence of cancer itself depletes immunity
  - Numerous studies have demonstrated that children with cancer have normal levels of immunoglobulins and antibodies at the time of disease presentation
- Specific diseases where immune function may be compromised upfront
  - Leukemias
  - Sarcomas
  - Untreated Hodgkin's lymphoma
  - Burkitt's lymphoma

Cancer Therapy and the Immune System

Numerous chemotherapy and immunotherapy agents can induce varied levels of immune suppression and dysfunction

Traditional Chemotherapy

- Cyclophosphamide
- Fludarabine
- Mercaptopurine
- Corticosteroids

Immunotherapy

- Rituximab
- Alemtuzumab
- Anti-thymocyte globulin

Mackall CL. Stem Cells 2000;18:10-8

Cancer Therapy and the Immune System

- Lymphocyte depletion is the most significant cause of immunosuppression from chemotherapy

T cells

- Profound and prolonged decrease in circulating CD3+ and CD4+ cells
- Increased susceptibility of T cells to activation-induced apoptosis

B cells

- Minor decrease in Immunoglobulin G levels
- Significant decrease in Immunoglobulin M and A levels
- Immunoglobulin levels tend to increase when therapy moves to less intensive phases of treatment

Komada Y et al. Cancer Immunol Immunother 1992;271-6
Hakim FT et al. Blood 1997;90:3789-98
Mackall CL Stem Cells 2000;18:10-18

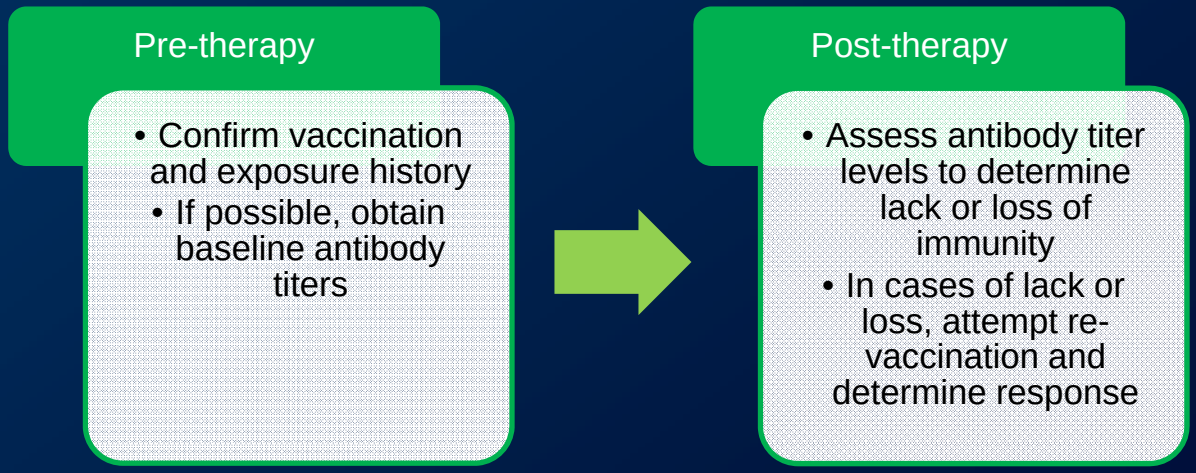
Loss of Immunity – The Data

- Numerous studies have evaluated the presence and persistence of antibody titers in patients at the end of chemotherapy
- Evidence exists with a number of vaccine preventable diseases
  - Hepatitis B (HBV), Measles-mumps-rubella (MMR), tetanus, polio, influenza, pneumococcal disease

Zignol M et al. Cancer 2004;101:635-41
Lehrnbecher T et al. BJH2009;147:700-705
Yu J et al. Pediatr Blood Cancer 2007;49:656-660

Loss of Immunity – The Data

- 192 pediatric patients completing first-line therapy for malignancy, who attained a CR
  - 70.3% hematologic malignancies
- Evaluated for immunity to Hepatitis B, measles, mumps, rubella, tetanus, and polio



Zignol M et al. Cancer 2004;101:635-41

Loss of Immunity – The Data

"Lack of Immunity"

Hepatitis B	53/116 (46%)
Measles	35/138 (25%)
Mumps	35/127 (28%)
Rubella	31/131 (24%)
Tetanus	22/162 (14%)
Polio	10/137 (7%)

"Loss of Immunity"

Hepatitis B	35/67 (52%)
Measles	23/92 (25%)
Mumps	16/77 (21%)
Rubella	14/76 (18%)
Tetanus	13/102 (13%)
Polio	6/77 (8%)

Zignol M et al. Cancer 2004;101:635-41

Loss of Immunity – The Data

- Success of booster vaccinations

	Successful revaccination
Hepatitis B	29/32 (91%)
Measles	4/5 (80%)
Mumps	1/1 (100%)
Rubella	5/5 (100%)
Tetanus	10/10 (100%)
Polio	6/6 (100%)

Zignol M et al. Cancer 2004;101:635-41

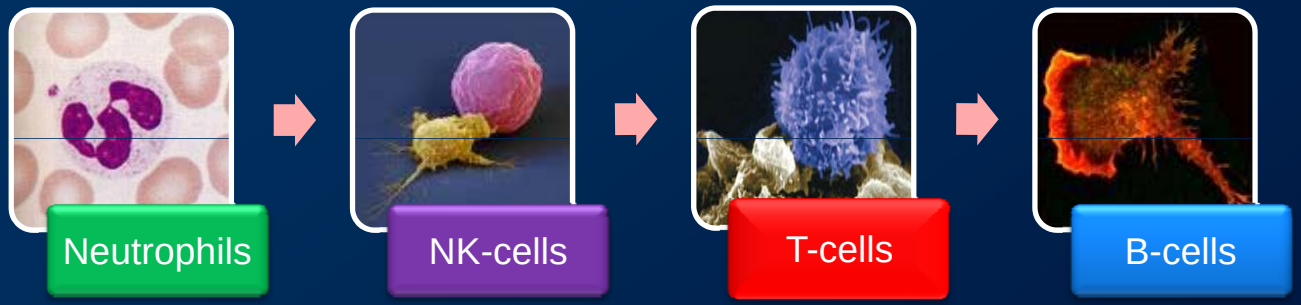
Loss of Immunity – The Data

- Predictive factors for loss of immunity
  - Against mumps, rubella, and tetanus
    - younger age (p=0.021)
  - Against measles
    - female gender and younger age
  - Underlying disease not predictive

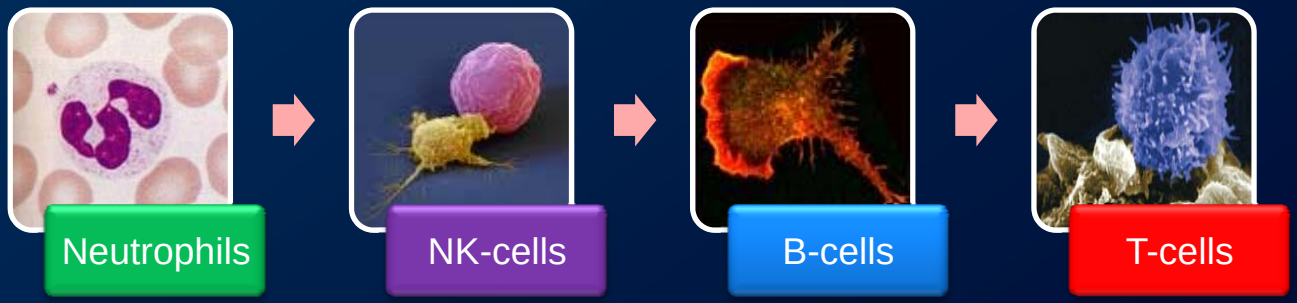
Zignol M et al. Cancer 2004;101:635-41

Immune Reconstitution following Therapy

- In children



- In adults



Alanko S et al. Cancer 1992;69:1481-6
Alanko S et al. Med Pediatr Oncol 1995;24:373-8

Affected Populations

- Pediatric oncology patients
  - Greatest likelihood of cancer diagnosis and chemotherapy interrupting routine childhood vaccination schedules
  - Younger children are at even greater risk because of chemotherapy effects on B-cell development and bone marrow plasma cell development

Nisson et al. Pediatrics 2002;109:e91-6

Affected Populations

- Adult oncology patients
  - Lack data to determine utility of re-vaccination for childhood immunizations
    - Efficacy of immunization is difficult to quantify because most studies use surrogate endpoints
      - does antibody titer = clinical prevention?
  - Variable immunocompetence
    - Tumor type, therapy type, duration of therapy, and response to therapy

Affected Populations

- Stem cell transplant recipients
  - More data for re-vaccination with childhood immunizations
  - Wide variability in time to immune reconstitution
    - transplant type (autologous vs. allogeneic)
    - duration of immunosuppressive therapy
    - need for further immunosuppression for graft versus host disease

Affected Populations

- Stem Cell Transplant recipients
  - Vaccine effectiveness depends on adequate adaptive immunity
    - B cell counts nadir for 1-3 months post transplant
      - recovery by 12 months
      - EXCEPTION: post-SCT rituximab
    - T cell counts nadir at 1-3 months post transplant
      - recovery affected by age, T-cell depletion, acute and chronic GVHD
  - Differences between autologous, allogeneic, cord blood, haploidentical, and nonmyeloablative transplants exist
    - Guidelines make uniform recommendations for ALL transplant patients

Ljungman P et al J Infec Dis 1989;159:610-615
Storek J et al. Clinical Bone Marrow and Blood Stem Cell Transplantation. Cambridge Press 2004;194-226
Horwitz SM et al. Blood 2004;103:777-83
Nordoy T et al. BMT 2001;28:681-7

ARS Question #1

- Which of the following patients is likely the most immunosuppressed?
  - A. A 54 year old female with locally advanced breast cancer, receiving cycle #2 of doxorubicin + cyclophosphamide
  - B. An 16 year old male with osteosarcoma, currently undergoing cycle #6 with doxorubicin and cisplatin
  - C. A 2 year old with ALL 4 months into maintenance therapy with methotrexate/vincristine
  - D. A 62 year old male with CLL, undergoing cycle # 4 of therapy with fludarabine, cyclophosphamide, and rituximab

Guidelines

- Recommendations regarding immunizations can be found from
  - CDC
  - IDSA

  } General concepts regarding immunosuppressed patients
  - ASBMT – provides specific recommendations
- Outside of the SCT population, most data regarding pediatric and adult oncology patients comes from small trials, anecdotal experience, and evaluations of antibody titers in these populations

CDC-Center for Disease Control, IDSA-Infectious Disease Society of America, ASBMT-American Society for Blood and Marrow Transplantation

CDC guidelines

- Provide all indicated vaccines to all persons before initiation of therapy
- No Live-attenuated vaccines administered until 3 months after therapy
- Re-immunization may be required for inactivated vaccines
  - ALL > AML, lymphoma, other malignancies, or radiation
- Revaccination of a person after chemotherapy or radiation therapy is not necessary if the vaccination occurred before therapy
  - exception = SCT
- Determination of the level of immune memory and the need for revaccination should be made by the treating physician.

www.cdc.gov

IDSA guidelines

- Full guidelines for vaccination in immunocompromised hosts due to be published in spring 2011
  - Will address specific considerations to be made in administration of immunizations to immunocompromised patients, including cancer patients

IDSA Guidelines

- 2009 Immunization Programs for Infants, Children, Adolescents, and Adults – comprehensive immunization recommendations
  - Immunosuppressed individuals can safely receive inactivated vaccines
    - response may be suboptimal
    - higher doses or additional doses may be needed
  - Live, attenuated vaccines are not recommended
    - known or theoretical risks of disseminated infection due to the vaccine virus

Pickering L et al. CID 2009;49:817-40

ASBMT Guidelines

- Specifically address vaccinations in patients after stem cell transplantation
- Guidelines divide recommendations into 3 parts
  - Vaccinations with good evidence for safety and immunogenicity, recommended in all SCT patients
  - Vaccinations in special situations (i.e., exposure, travel), lacking or limited data available
  - Vaccination of family members, household contacts and healthcare workers to minimize exposure

Tomblyn M et al. BBMT 2009;15:1143-1238

Individual Vaccinations

	Inactivated vaccines	Live attenuated vaccines	Conjugate vaccines	Polysaccharide vaccines
Influenza	X	X		
Hepatitis B	X			
MMR		X		
Tdap/DTaP	X			
Varicella		X		
Polio	X	X		
Pneumococcal			X	X
Hib			X	
Meningococcal			X	X

Influenza

- Consequence of susceptibility
  - Upper/lower respiratory tract symptoms
  - Secondary bacterial pneumonia, sinusitis, otitis media
  - Infection can lead to delays in therapy
  - Mortality rate = 9% in oncology patients

Pollyea DA et al. J Clin Oncol 2010;28:2481-90

Influenza

- Since the early 1970's, >20 studies have evaluated the utility and effectiveness of influenza vaccination in a variety of oncology populations
  - Pediatrics
  - Adult hematologic malignancy
  - Adult solid tumors
  - Stem cell transplantation

Pollyea DA et al. J Clin Oncol 2010;28:2481-90

Influenza - Pediatrics

- 2009 Cochrane review evaluated 9 trials
  - 1 RCT, 8 case-controlled trials
  - N=708
  - Clinical outcomes were not reported in any studies
  - All reported on immunity to influenza
    - Variability in measurement of immunity
- Results
  - % of patients with adequate immune response to influenza vaccination
    - Current chemotherapy = 25-52%
    - Completed chemotherapy = 50-86%
    - Healthy children = 71-89%

Goossen GM et al. Cochrane Review 2009

Influenza - Adults

- Solid Tumors
  - Most data in patients not currently receiving chemotherapy
    - Detectable, albeit diminished response to vaccination
  - 1225 colorectal cancer patients[1]
    - 40% received influenza vaccination
    - Decreased rates of influenza, pneumonia and trend towards decreased morbidity and mortality
- Hematologic Malignancies
  - Respond more poorly to vaccine than solid tumor patients
    - Use of immunosuppressive agents and/or rituximab
  - 34 patients with lymphoproliferative diseases
    - >60% response, compared to 80% in normal healthy controls

[1]Earle CC. J.Clin Oncol 2003;21:1161-66
[2]Rapezzi D et al. Eur J Haematol 2003;70:225-30

Influenza - Adults

- Vaccination during chemotherapy
  - Solid and hematologic malignancies
    - Vaccinated patients
      - Concurrently with administration of chemotherapy or
      - Between cycles, at the nadir of blood counts
    - Immunologic response seen in
      - 50% for concurrent administration
      - 93% for in between cycle administration
  - Consider administration of vaccination in between chemotherapy cycles if possible

Ortbals DW et al. Ann Intern Med 1977;87:552-7

Influenza - Stem Cell Transplant

- Data not uniform in relation to time from transplant for vaccination
  - No benefit from immunization within the first 6 months of SCT
  - Longer interval between SCT and immunization correlates with improved responses
  - Two-shot series may be recommended in times of high risk

Ljungman P et al. BMT 2009;44:521-6

Recommendation - Influenza

Population	Recommendation	Evidence
Pediatrics	Inactivated virus vaccination upon completion of chemotherapy or between chemotherapy cycles	Strong
Adult	*Solid Tumors:* Inactivated virus vaccination during active chemotherapy. Consider live attenuated vaccination if chemotherapy completed >4-6 months *Hematologic Malignancy:* Inactivated virus vaccination between chemotherapy cycles or after completion of chemotherapy	Strong Strong
Stem Cell Transplant	Inactivated virus vaccination no sooner than 6 months after SCT. If high risk season occurs prior to 6 months, consider 2-shot series 3 months after SCT	Strong (AII)

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

ARS Question #2

- RP is a 54 year old man with stage III colorectal cancer. He is undergoing therapy with Fluorouracil, Leucovorin, and Oxaliplatin. He arrives to clinic for cycle #3 in November, and wants to know if he can receive an influenza vaccination at his visit today
  - A. Wait until 4 months after chemotherapy ends to vaccinate
  - B. Administer inactivated vaccine now
  - C. Administer live attenuated vaccine now
  - D. Administer inactivated vaccine between cycles 3 and 4

Hepatitis B

- Infection is associated with serious consequences in immunosuppressed patients, including liver failure and death
- Risk of reactivation or infection in cancer patients is highest in those with hematologic malignancies
  - Greater need for transfused blood products
  - Greater degree of immunosuppression to allow reactivation
- Stem cell transplantation often leads to reactivation
  - Lack of surface antibody in donor
  - Graft versus host disease requiring immunosuppression

Lalazar G et al. BJH 2007;136:699-712

Hepatitis B

- Chemotherapy associated with HBV reactivation
  - Corticosteroids
    - HBV DNA contains a glucocorticoid responsive element that facilitates replication
    - Propos steroid free chemotherapy to minimize risk
  - Anthracyclines
    - in vitro models indicate they may stimulate HBV DNA secretion
  - Others
    - Immunsuppressive agents (rituximab, alemtuzumab, infliximab)

Tur-Kaspa et al . PNAS 1986; 83:1627-31
Hsu et al. Anticancer Res 2004;24:3035-40

Hepatitis B

- Vaccination typically consists of a 3-shot series at 0, 1, and 6 months
  - Safety/efficacy of 2-shot series if needed, separated by 3-4 weeks

Recommendation - Hepatitis B

Population	Recommendation	Evidence
Pediatrics	Data demonstrates positive response to vaccination during and after chemotherapy -Children who **have not** started or completed ~~standard series at diagnosis: standard vaccination at~~ 0, 1, and 6 months -Children who **have** completed vaccination schedule at diagnosis: 2 booster doses 3 months apart after the completion of chemotherapy	Moderate
Adult	Immunize with at least 2 doses within a 3-4 week interval Third dose can be given after chemotherapy is completed	Moderate
Stem Cell Transplant	-3 dose series beginning 6-12 months after transplant	Moderate (BII)

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

Measles, Mumps, and Rubella (MMR)

- Measles in immunocompromised patients may have atypical presentation with prolonged viral shedding
  - Pneumonitis, encephalitis
- Vaccine details
  - In combination MMR, as a live attenuated vaccine
  - 1- 2 doses
  - Should not be administered while patient is heavily immunosuppressed

Recommendation - MMR

Population	Recommendation	Evidence
Pediatrics	**Not vaccinated:** 2 doses separated by 3 months in patients off therapy for 6 months **Prior vaccination**: single booster dose in patients off therapy for 6 months	Moderate
Adult	Insufficient data to recommend routine reimmunization. Consider checking serostatus and vaccinating if negative. For leukemia patients, consider booster vaccination >3 months after end of chemotherapy	Poor
Stem Cell Transplant	Pediatrics: 2 doses, starting 24 months post transplant Seronegative adults: 1 dose 24 months post transplant	Moderate (BII)

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

DTaP/Tdap

- Pertussis: gram negative coccobacillus can cause acute respiratory illness
  - Vaccination typically provides protection for approximately 5 years, necessitating booster vaccination in healthy adolescents and adults
- Vaccine details
  - DTaP: 3-dose series recommended in children through age 6
  - Tdap: recommended single dose post therapy, then Q10 year dose in adolescents and adults

Small TN et al. BBMT 2009;15:1538-42

Dtap (age <7): Diphtheria, Tetanus, acellular Pertusis
Tdap (Age ≥7): Tetanus, diptheria (reduced), acellular pertussis (reduced)

DTaP/Tdap in Pediatric / Adult

- Data on immunity
  - Pediatric data: response to DTP booster vaccine given 6, 8, and 10 months after completion of chemotherapy
    - Low rates of seronegativity at baseline
      - 16.4%, 3.9% and 3.5% for D, P, and T, respectively
    - 100% were able to respond adequately to immunization
  - Adult data: adult cancer patients, especially hematologic malignancies, have been shown to have a higher rate of tetanus seronegativity than healthy controls
    - Greater in lymphoid malignancies than myeloid malignancies

Hammarstrom V et al. BMT 1998;22:67-81

DTaP/Tdap in SCT

- Response to Tdap following auto-SCT
  - Median of 3 years post transplant
    - 86.5% of patients had suboptimal anti-P and anti-T titers
    - >50% had undetectable titers
  - 28/57 patients were re-vaccinated
    - 26 failed to attain adequate anti-P titers
    - Slightly better response to tetanus and diphtheria, but still high rate of failure
  - Patients receiving post-transplant rituximab uniformly failed to respond to re-vaccination, regardless of time after transplant

Small TN et al. BBMT 2009;15:1538-42

Recommendation – DTaP/Tdap

Population	Recommendation	Evidence
Pediatrics	**Not vaccinated:** standard 3-dose schedule DTaP starting 3 months after completion of therapy **Prior vaccination**: administer booster dose after off therapy for 3 months (less data re: pertussis)	Moderate
Adult	Same schedule as healthy persons. Limited data on loss of immunity, but good data to show response to vaccination	Moderate
Stem Cell Transplant	-3-dose DTaP series for all SCT recipients beginning 6-12 months after transplant - if DTaP unavailable, can administer Tdap x 2 annual doses beginning 6-12 months after transplant	Moderate (BII)

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

Varicella

- Varicella zoster and herpes zoster infections pose serious and life-threatening risks to immunocompromised hosts
  - Dermatologic complications, pneumonitis, encephalitis, hepatitis
- Vaccine details
  - Varivax: prevention of chickenpox, live attenuated vaccine with low viral titers
    - Dose recommendations for children, adolescents, and adults
  - Zostavax: prevention of shingles, live attenuated vaccine with high viral titers
    - Recommended only for those >60 years of age

Varicella

- Efficacy/safety
  - Pediatrics: 437 VZV seronegative children with ALL received 2 doses of varicella vaccine (Varivax®) separated by 3 months
    - Patients with CRx1 year, ALC>700/uL, platelet >100,000/uL, with all maintenance therapy held for 1 week before and 1 week after vaccination
    - 85% developed antibody response
    - 75% of nonresponders responded to second dose.
    - Long term follow up showed 36 cases of varicella
      - 35 were mild/moderate, indicating attenuation by vaccine

Gershon AA. JAMA 1984;252:355-62
Gershon AA. N Eng J Med 1989; 320:892-7

Varicella

- Efficacy/Safety
  - Adults: case reports of patients developing disseminated zoster infections following administration of VZV (Zostavax) vaccine
    - Reports in solid tumors and hematologic malignancies
  - SCT: high viral titers in VZV vaccines (Zostavax) pose high risk of disease activation
    - Consideration for use of chickenpox vaccine (Varivax) if benefit outweighs risk

Curtis KK et al. JGIM 2008;23(5):648-9

Recommendation - Varicella

Population	Recommendation	Evidence
Pediatrics	**Not vaccinated**: 2 doses separated by 3 months in patients meeting criteria for ability to receive live attenuated vaccines **Prior vaccination**: single booster dose in patients meeting same criteria above	Moderate
Adult	**Not recommended** in immunocompromised patients (lymphoma, receiving immunosuppression). *Solid Tumors: C*onsider allowing a minimum of 3 months from last chemotherapy *Hematologic Malignancy: C*onsider allowing a minimum of 3 months from last chemotherapy, given disease in remission	Moderate
Stem Cell Transplant	In general, not recommended until at least 24 months, off immunosuppression -Consider using Varivax over Zostavax because of lower varicella titer, decreasing risk of activation	Strong (CIII/EIII)

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

Pneumococcal, Meningococcal, and Hib vaccines

- Risks from infection with Streptococcus pneumoniae, Neisseria meningitides, and Haemophilus influenza is highest in asplenic patients due to reduced capacity to clear encapsulated bacteria from bloodstream

Vaccine details

- Pneumococcal (3 types)
  - Conjugate 7-valent (PCV7) - now unavailable
  - Conjugate 13-valent (PCV13) – 3 shot series recommended in children < 5 years old, has replaced PCV7
  - Polysaccharide 23-valent (PPSV23) – 1-2 shot series recommended in adults >65 and in all ages at high risk for disease
- Meningococcal
  - Conjugate vaccine (MCV4) – recommended for adults <55 years old
  - Polysaccharide vaccine (MPSV4) – recommended for adults >56 years old
  - MCV4 booster dose recommended 3-5 years after initial dose
- Hib
  - Conjugate polysaccharide vaccine – not generally recommended for those > 5 years old
  - In children < 5 years old, 3-shot series recommended

Pneumococcal vaccine

- Adults
  - Patients with solid tumors typically respond similar to healthy adults
  - Patients with lymphoma and myeloma respond at much lower rates than healthy controls
- SCT
  - PCV7 shown to elicit better responses than PPSV23 despite narrower spectrum of protection
    - Little to no benefit seen when PPSV23 administered within one year of SCT

Schildt RA et al. Med Pediatr Oncol 1983;11;305
Schildt RA et al. J Infect Dis 1981;143:590

Pneumococcal vaccine

- Timing of vaccination in relation to SCT
  - Multicenter, randomized noninferiority study in allogeneic transplant recipients

  - Vaccination consisted of 3 doses of PCV7 at one month intervals, followed by a single dose of PPSV23 7 months after last PCV7

Cordonnier C et al. CID 2009;48:1392

Pneumococcal vaccine

Arm	Response	Antibody titer 0.15 mcg/ml		
		Prevaccination	1 month post dose 3	24 months post SCT
Early	45/57 (79%)	33/74 (45%)	45/57(79%)	26/44 (59%)
Late	47/57 (82%)	6/64 (9%)	47/57(82%)	35/42 (83%)
P	NS	<.001	0.64	0.013

- Prior to PPV23 vaccination, % of patients with adequate titers was similar between groups (59% vs 66%). One month after administration, % of patients with adequate response was significantly higher in the late group (88% vs 69%, p=0.02)
- Differences between study and nationally accepted definitions of adequate titer

Cordonnier C et al. CID 2009;48:1392

Recommendation – Pneumococcal vaccine

Population	Recommendation	Evidence
Pediatrics	**Not vaccinated**: primary schedule once patient is off therapy for 3 months **Prior vaccination**: consider booster dose in patients off therapy for 3 months	Poor
Adult	Administer 23-valent vaccination to any nonimmune cancer patient, especially lymphoma or myeloma -Administer prior to splenectomy, >10d before start of chemotherapy, or 3 months after completion of chemotherapy -Administer booster dose 3-5 years later because of high rate of antibody titer loss	Poor
Stem Cell Transplant	Administer 4 shot series (3xPCV13 followed by 1xPPSV23), beginning 3-6 months after SCT	Moderate (BI)

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

Recommendation – Meningococcal Vaccine

Population	Recommendation
Pediatrics	**Not vaccinated**: primary schedule once patient is off therapy for 3 months
	Prior vaccination: *booster dose in patients off therapy for 3 months
Adult	- Vaccination is recommended prior to splenectomy, especially in lymphoma patients - Consider reimmunization 3-5 years after initial dose because of frequency of loss of adequate titers
Stem Cell Transplant	Single dose 6-12 months after SCT

* - more studies required to validate this recommendation

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

Recommendation – Hib vaccine

Population	Recommendation
Pediatric	**Not vaccinated**: 3 shot series after patient off therapy for 3 months **Prior vaccination**: booster dose in patients off therapy for 3 months
Adult	Recommended in lymphoma patients undergoing staging splenectomy - prior to splenectomy, >10 days prior to start of chemotherapy, or 3 months after completion of chemotherapy
Stem Cell Transplant	3-shot series starting 6-12 months after SCT

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

BMT Specific Recommendations

- Household contact and healthcare worker vaccinations
- Donor vaccination
- Optional vaccinations/Contraindicated vaccinations

Household Contact and HCW Vaccinations

Vaccine	Recommendations	Evidence
Hepatitis A	Recommended for children>12yo and those at risk for Hepatitis A	BIII
Inactivated influenza	Annual vaccination is strongly recommended *Intranasal vaccination is contraindication	AII
Polio	If necessary, should use inactivated polio vaccine	AII
MMR (live)	Recommended for all ≥12 months old who are not pregnant or immunocompromised. No evidence to show transmission from person to person	AIII
Pertussis	DTaP for children <7years old, Tdap for adolescents and adults	BIII
Varicella(live)	Recommended for all ≥12 months old who are not pregnant or immunocompromised. Minimal risk of transmission person to person	AIII

Ljungman P et al. BMT 2009;44:521-6

Donor Vaccinations

- Vaccination of stem cell donors has been shown to improve the post-transplant immunity of the recipient in certain situations
  - Tetanus toxoid, PCV-7, Hib vaccines
- No current recommendations given practical and ethical issues surrounding vaccination in patients who do not need them

Ljungman P et al. BMT 2009;44:521-6

Optional and Contraindicated Vaccines in SCT Patients

- Data is largely lacking for many immunizations

Table 1. Evidence-Based Rating System Used in the Hematopoietic Cell Transplantation (HCT) Guidelines [2]

Strength of Recommendation

Category	Definition
A	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. *Should always be offered.*
B	Moderate evidence for efficacy—or strong evidence for efficacy, but only limited clinical benefit—supports recommendation for use. *Should generally be offered.*
C	Evidence for efficacy is insufficient to support a recommendation for or against use, or evidence for efficacy might not outweigh adverse consequences (eg, drug toxicity, drug interactions), or cost of the chemoprophylaxis or alternative approaches. *Optional.*
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. *Should generally not be offered.*
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. *Should never be offered.*

Quality of Evidence Supporting the Recommendation

Category	Definition
I	Evidence from at least one well-executed randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization; cohort or case-controlled analytic studies (preferably from more than one center); multiple time-series studies; or dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Optional and Contraindicated Vaccinations in SCT Patients

Optional

- Hepatitis A (CIII)
- HPV (CIII)
- Yellow fever (EIII<24 months, CIII>24 months)
- Rabies (CIII)

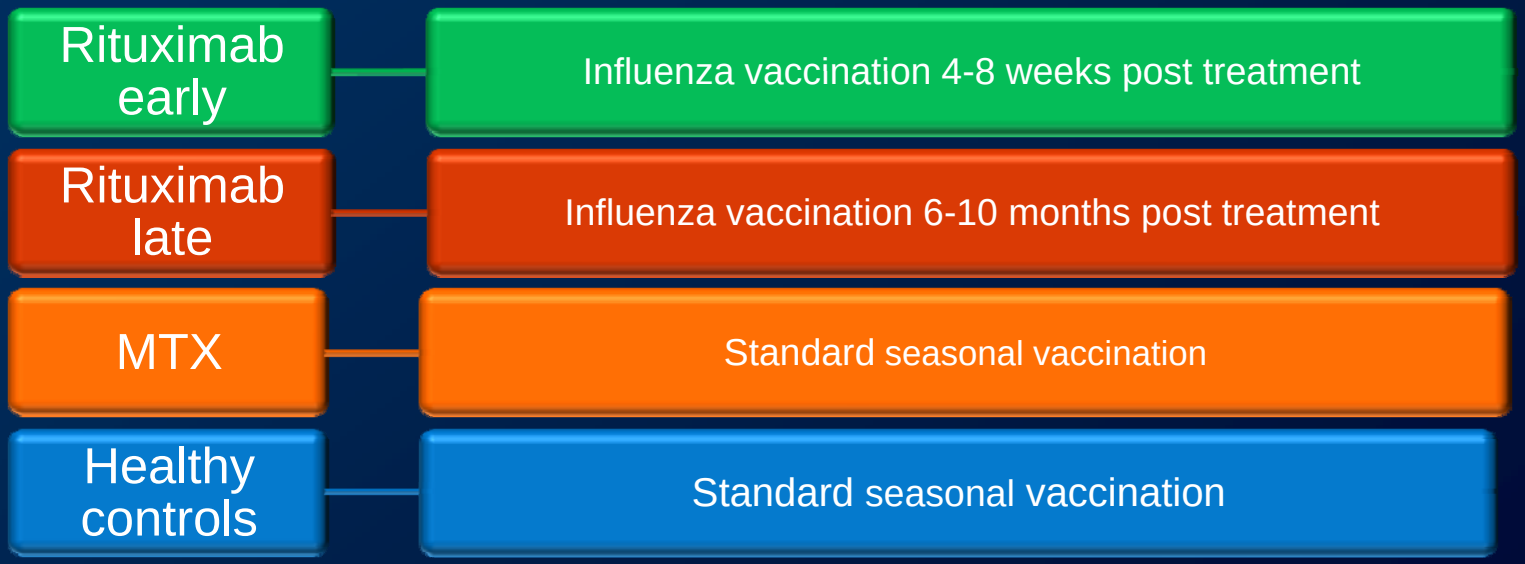
Contraindicated

- BCG (EII)
- OPV (EIII)
- Intranasal influenza (EIII)
- Cholera (DIII)
- Typhoid (PO/IM) (EIII/DIII)
- Rotavirus (EIII)
- Zoster vaccine (EIII)

Ljungman P et al. BMT 2009;44:521-6

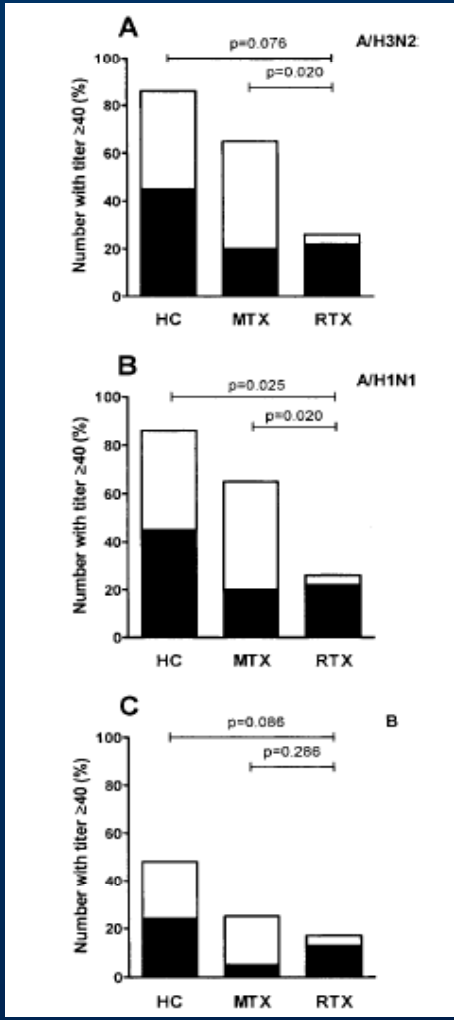
Drug-Based Recommendation Rituximab

- Results in B-cell depletion for at least 6-9 months, during which time humoral response to antigens is reduced significantly
- Evaluation of effect of rituximab on humoral immunity in RA patients



Van Assen S et al. Arthritis and Rheumatism 2010; 62(1):75-81

Drug-Based Recommendation Rituximab



- Results showed markedly decreased response to immunizations in both rituximab arms
- Between early and late rituximab arms, late arm showed consistently higher geometric mean titers of antibody ($p<0.05$ for all influenza strains)
- Based on these results, consider delaying immunizations in patients receiving rituximab therapy to at least 6 months after the completion of therapy rather than the typically recommended 3 months

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ARS Question #3

- Limitations of data regarding vaccination include
  - A. Recommendations are many times based on expert opinion or case reports
  - B. Evidence of efficacy or lack thereof is often not conclusive
  - C. Populations studied sometimes do not match actual patient populations
  - D. All of the above

Limitations to Recommendations

- Extremely limited data for children who have received partial immunization series at time of cancer diagnosis
- Questions regarding timing of administration
- Limited or lacking data regarding newer vaccinations (e.g. HPV)
- Variable definitions of immunity
- Largely retrospective data
- Lack of reporting of incidence of some vaccine preventable diseases

Esposito S et al. Vaccine 2010;28:3278-84, Arrowood JR et al. Ann Pharmacother 2002;36:1219-20, Ljungman P et al. BMT 2009;44:521-6

Conclusions

- Alterations in immunity are highly variable among the wide spectrum of oncology patients
- Current guidelines provide some basis to determine the need for vaccination in specific patients
- Research still needed to more clearly define time to vaccination, real need for booster therapy, and appropriate ways to assess immunity

Vaccinations in Cancer

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