Dendreon

Targeting Cancer, Transforming Lives™

Dendritic Cell Based Cancer Vaccine Development

November 10, 2005 CVCWG Meeting

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Meeting the challenges of developing cancer vaccines-- APC8015 (Provenge™) as a case study

- Immunogenicity and Breaking Tolerance
- Appropriate endpoints and patient populations
- Survival as an achievable endpoint for active immunotherapy
- Extending to earlier disease and to combination therapy

The challenge of generating a ‘functional’ immune response against a cancer antigen

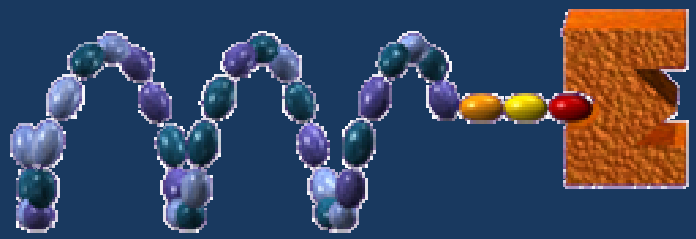
Immunogenicity and Breaking Tolerance--
Tumor antigens are ignored by the immune system

- What is a good “tumor antigen”?
  - Often selected based on a pattern of over-expression relative to normal tissue
  - Typically not expressed in a uniform pattern and not in 100% of cells in a particular tumor
  - Selection of antigen negative variants?
  - Need for cross-priming and/or ‘epitope-spreading’?
- T cell tolerance and cancer
  - Central tolerance to tumor antigens
  - Peripheral tolerance and/or Anergy
  - Regulatory T cells
- Tumor specific effects
  - Local production of inhibitory cytokines [e.g. TGFβ]

A strong priming response is fundamental to break immune tolerance in cancer

Dendreon's Cancer Vaccine Platform

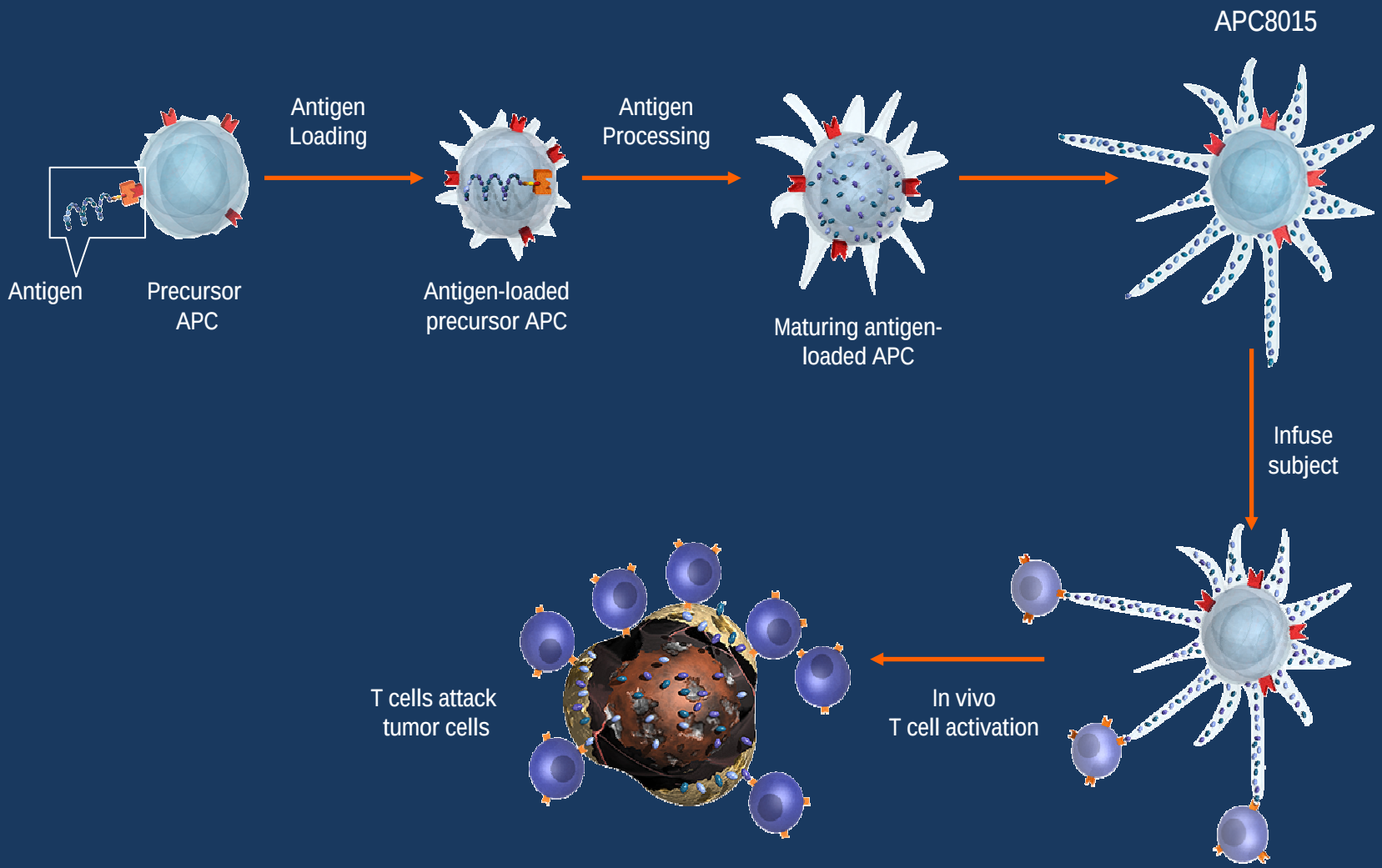
- Select well validated and well characterized antigen targets
- Well characterized recombinant protein
- Proprietary Antigen Delivery Cassette™ technology



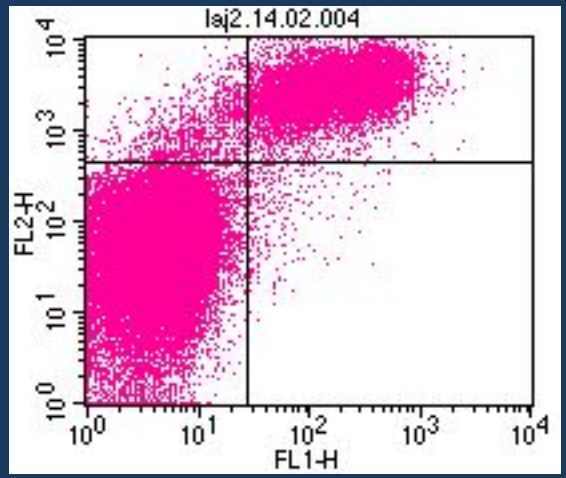
Prostatic Acid Phosphatase (PAP)

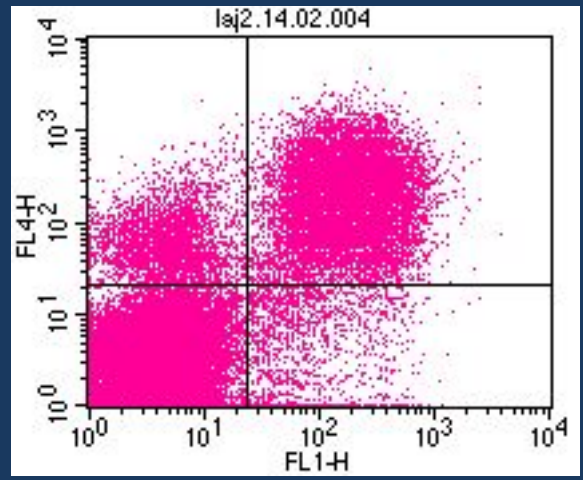
GM-CSF

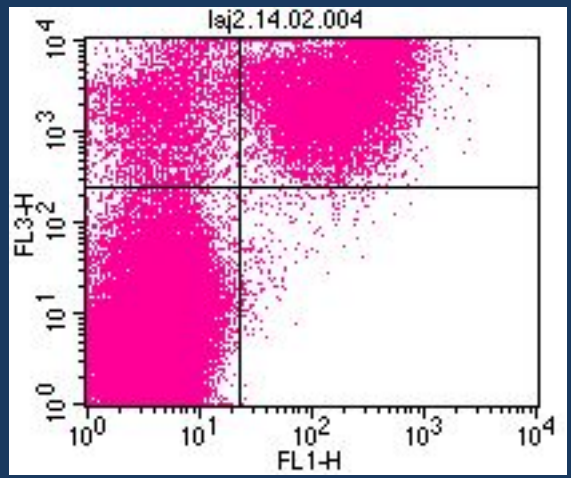
APC8015 (Provenge™)

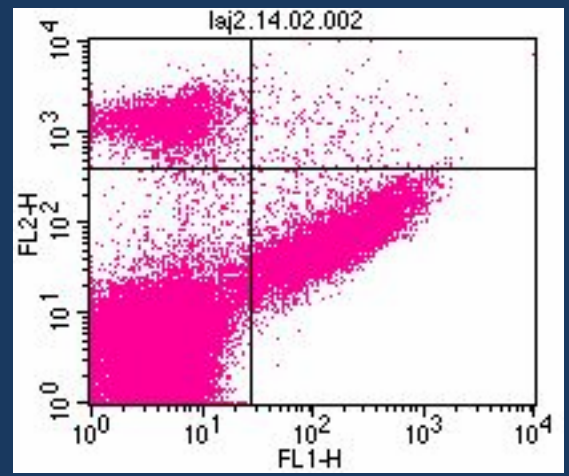


PA2024-FITC Binds to Antigen Presenting Cells

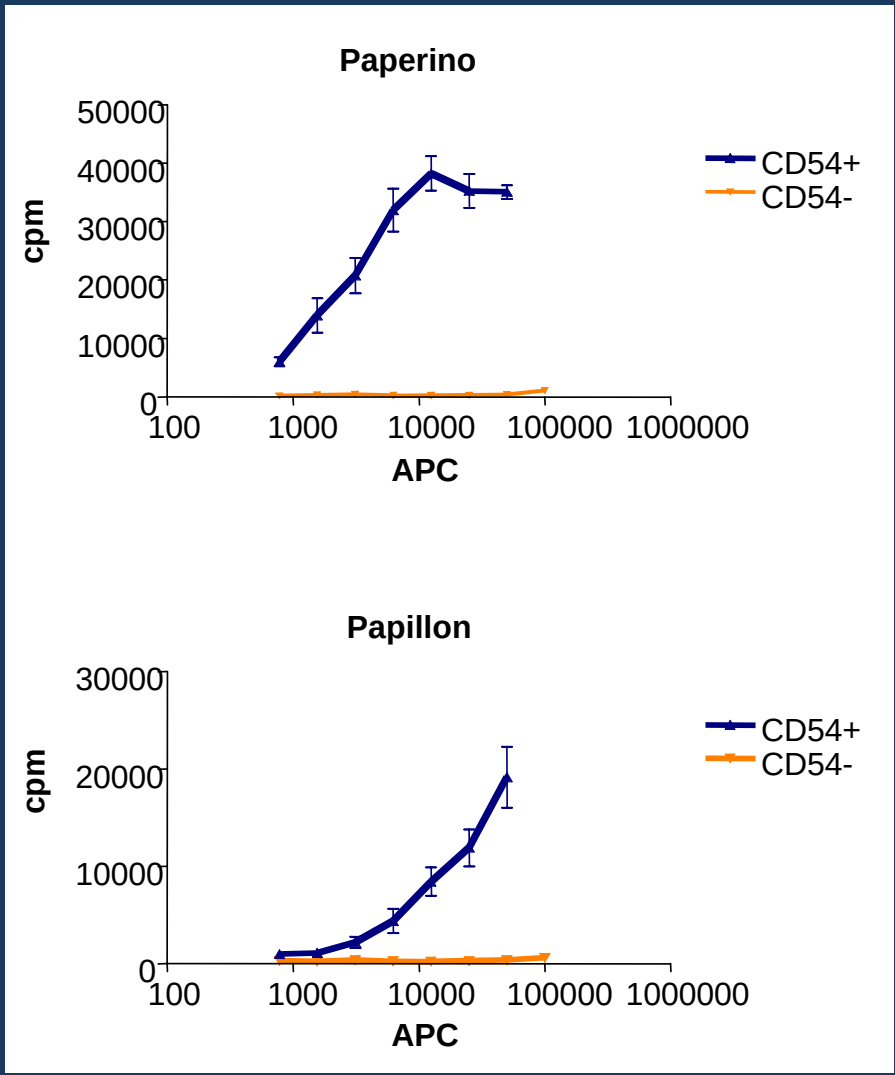




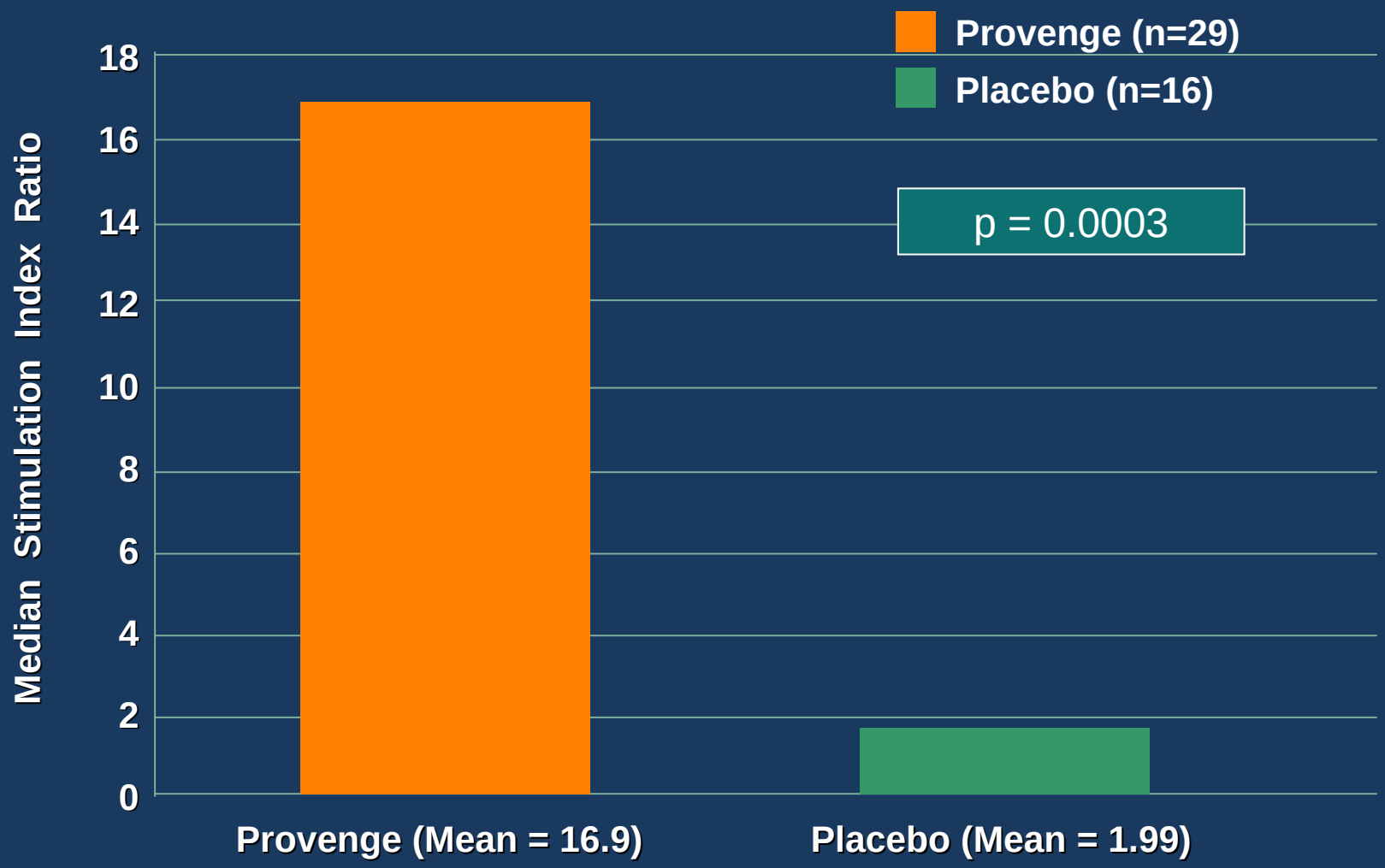




PAP Antigen Presenting Activity is found in CD54+ Cells



Provenge (APC8015) Induces Significant T-cell Mediated Immune Response (Week 0 to Week 8)



Additional immunological data to support mechanism of action

- From Phase 1 and 2 Studies
  - T cell response is specific to PA2024 antigen (KLH data)
  - T cell response is associated with IFNγ production (ELISA, ELISPOT)
  - T cell precursor frequency increases from undetectable background
- From Ongoing Studies
  - The T cell response is associated with IFNγ production
  - Boosting appears to augment T cell response
  - Intriguing data consistent with ‘epitope spreading’

The Role of Immune Monitoring

- Critical role in early phase clinical studies of cancer vaccines
- Need better definition of tools (CD4, CD8, cytokine response)
- Need to better define whether immune responses are true ‘surrogates’ for clinical activity

The challenge of defining appropriate endpoints in a relevant and meaningful patient population

Dogma of Clinical Development of Cancer Vaccines

- Cancer vaccines would be expected to have more benefit in the context of micro-metastatic and/or ‘minimal residual disease’
- Bulky, metastatic disease might provide a hurdle too high for active immunotherapy
- Not all tumor types would be expected to respond to active immunotherapy (e.g. melanoma/renal better than other solid tumors)
- Long term endpoints such as survival can be prohibitive from a trial perspective

Prostate Cancer offers unique challenges and opportunities for Cancer Vaccines

Early Stage → **Advanced Stage**

Androgen Dependent PCa

Primary Therapy

- Radical Prostatectomy
- Brachytherapy
- Radiation Therapy
- Cryotherapy
- Watchful Waiting

Androgen Deprivation

- Lupron
- Zoladex
- Casodex
- Eulexin
- Ketoconazole

Androgen Independent PCa

Asymptomatic

PROVENGE®

- Taxotere

Symptomatic

- Palliative Interventions
- Bisphosphonates
- Novantrone
- Emcyt

Phase I and 2 Clinical Development in Androgen-Independent, Metastatic Prostate Cancer

Results
APC8015 (Provenge™) Phases 1 & 2 Studies

Safety:

- No dose limiting toxicities
- Treatment well tolerated

Immunogenicity:

- Regimen: maximum immune responses reached after 3 infusions
- Dose response: giving more cells (> 100 million) associated with increased immunogenicity

Effectiveness:

- Some PSA responses
- One striking objective response
- Immune responses to PAP correlated with Time-to-Progression

Small EJ, et al., J Clin Onc 2000;18:3894-3903

What did we know about APC8015 at the end of Phase 2?

- Safe and well tolerated
- Highly immunogenic resulting in antigen-specific T cell responses
- 3 dose regimen sufficient
- A statistically significant effect on PSA or objective response rate would be unlikely
- Early signal in delaying time to disease progression
- Unmet clinical need in metastatic AIPC
- Long term effect on survival not assessed

Goal:

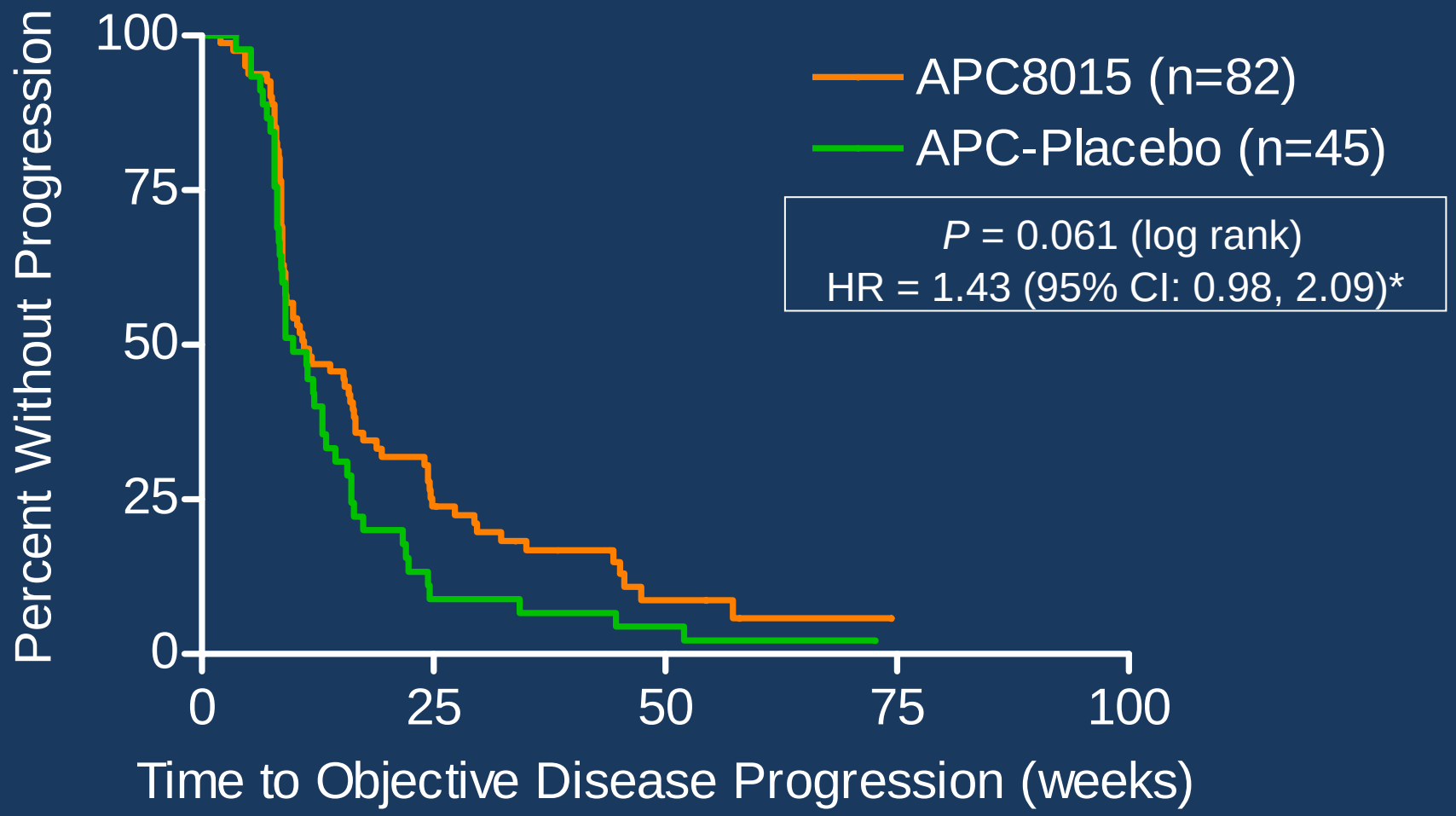
To develop an active immuno-therapeutic agent with evidence of clinical benefit in men with metastatic, AIPC with a favorable toxicity profile

Provenge® Phase 3 Development Program (c.1999)

Two identical Phase 3 studies (D9901 & D9902)

- 2:1 randomization (active vs. placebo)
- Open-label salvage protocol available for those who progress on placebo
- Population: asymptomatic, metastatic, hormone refractory
- Primary Endpoint: Time to Progression
  - Each study of n=120 powered for TTP
  - Assumed Asymptomatic men progress more slowly than Symptomatic men
  - First scan at 8 weeks
- Secondary Endpoint: Delay in onset of cancer related pain
  - Both studies to be pooled (n=240) for pain endpoint
- 36 month follow-up for survival on every subject explicitly stated in protocol and statistical analysis plan

D9901 Time to Objective Progression
Intent-to-Treat Population



* HR and CI are based on proportional hazards model.

Time-to-Progression (TTP) as a Primary Endpoint—Hindsight is 20:20

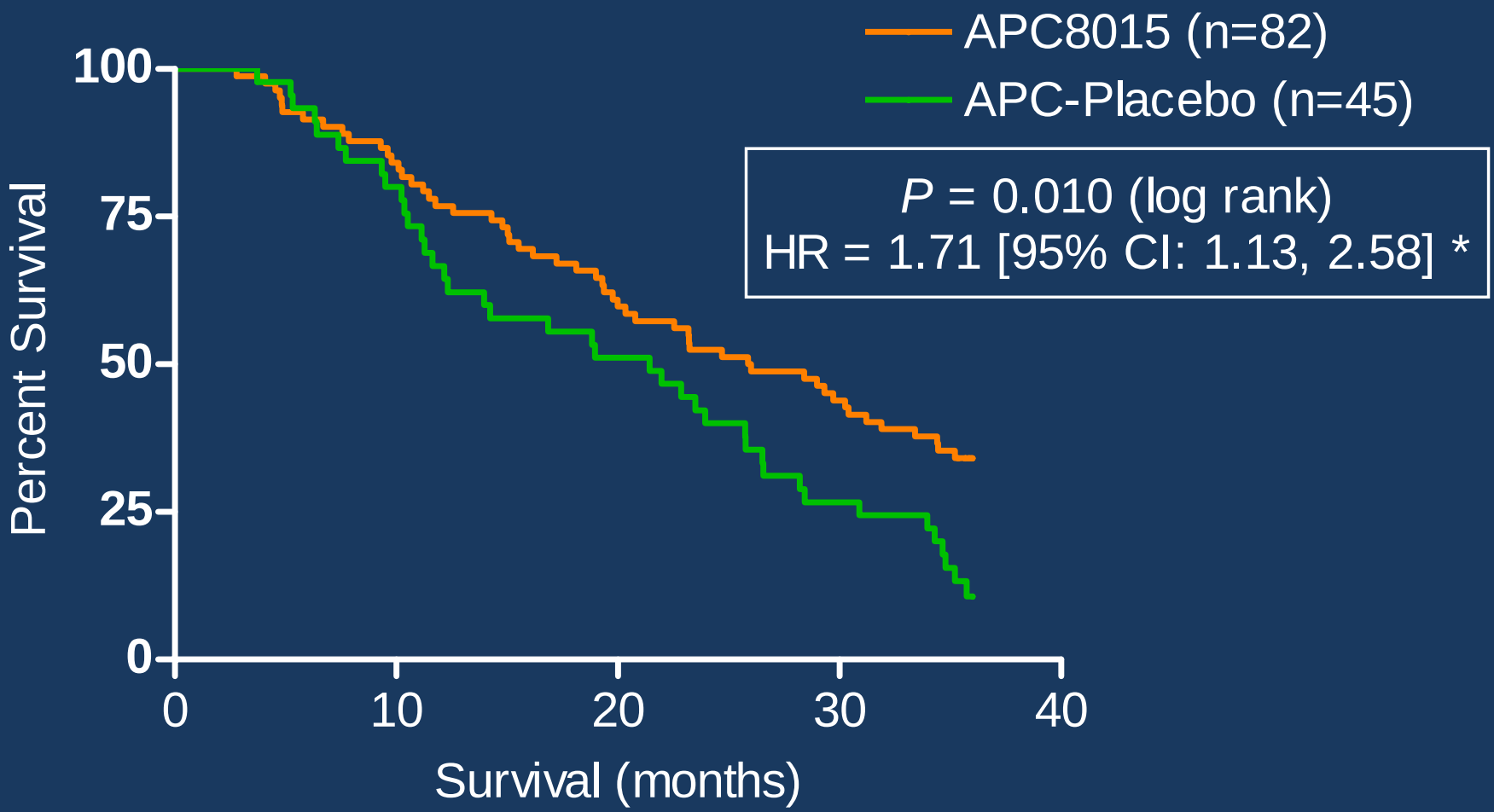
- Kinetics of immune induction make delaying TTP difficult
- Need alternate approaches/definitions for TTP/PFS for active immunotherapy products (subject of subsequent Workstreams)
- TTP is particularly challenging in a rapidly progressive disease in the context of clinical heterogeneity

Why is Survival the “Gold Standard”?

- Survival offers a clear, meaningful benefit that can be appreciated by both the physician and the patient
- Assessment of survival is not subject to significant bias

Is demonstration of a statistically significant survival benefit with a cancer vaccine possible in late-stage cancer?!?

D9901 Overall Survival
Intent-to-Treat Population



* HR and CI are based on proportional hazards model.

D9901 Overall Survival
Intent-to-Treat Population

Treatment	Number of Subjects	Deaths	Alive at 36 months	Median Survival (months)
APC8015	82	54	28 (34%)	25.9
APC-Placebo	45	40	5 (11%)	21.4

Various factors can influence a survival analysis including imbalances and the effect of concurrent or subsequent therapy

D9901 Chemotherapy Use Following Treatment

Intent-to-Treat Population

Chemotherapy	APC8015 (n = 78)	APC-Placebo (n = 41)	p-value (Fisher's Exact)
Docetaxel	29 (37.2%)	20 (48.8%)	0.244
Chemotherapy other than taxanes	36 (46.2%)	13 (31.7%)	0.170
Taxane-based chemotherapy	34 (43.6%)	22 (53.7%)	0.337
Any chemotherapy[a]	44 (55.7%)	27 (62.8%)	0.565

[a] For any chemotherapy, APC8015 (n=79) and APC-Placebo (n=43)

Adjustments for Prognostic Factors – Methodology

- 20 prognostic factors considered
- Evaluated the significance of each of the 20 prognostic factors by use of a Cox regression model using a single prognostic factor as a covariate
- Used all significant prognostic factors as simultaneous covariates in a Cox regression model
- Determined the treatment effect adjusted for the covariates in the final model

D9901 Proportional Hazards Regression Model for Survival
Intent-to-Treat Population

	HR	95.0% CI for HR		p-value
		Lower	Upper	
Treatment with APC8015	2.122	1.310	3.438	0.0022
Baseline PSA (ln)	1.320	1.094	1.594	0.0039
Lesion count (0-5 lesions, 6-10 lesions, >10 lesions)				0.0101
Lesion count: 0-5 lesions versus 6-10 lesions	1.695	0.907	3.167	0.0979
Lesion count: 0-5 lesions versus >10 lesions	2.161	1.289	3.623	0.0035
Localization of Disease (bone and soft only versus both)	1.539	0.962	2.461	0.0720
LDH (ln)	4.880	2.011	11.844	0.0005
Weight (lbs)	0.992	0.985	0.999	0.0315

N = 127: Events =85, Censored = 32, and Cases with Missing Values = 10

Cancer Vaccines are well tolerated

D9901 Safety: Adverse Events Occurring at a Significantly Higher Frequency with APC8015 Compared with APC-Placebo

Events	APC8015		APC-Placebo	
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4
Any Adverse Event, n (%)	**59 (72.0)**	**23 (28.0)**	**32 (71.1)**	**12 (26.7)**
Events More Frequent with APC8015:				
Chills	47 (57.3)	4 (4.9)	4 (8.9)	0 (0.0)
Pyrexia	26 (31.7)	2 (2.4)	2 (4.4)	0 (0.0)
Tremor	8 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	14 (17.1)	0 (0.0)	2 (4.4)	0 (0.0)

Percent of subjects with adverse events: APC8015 (n=82) and APC-Placebo (n=45)

Dendreon is filing a Biologics License Application (BLA) for APC8015 in Metastatic AIPC

- **Significant, unmet medical need**
  - Only one available therapy shown to prolong survival in metastatic AIPC and it is associated with significant toxicity
- **D9901 demonstrates survival advantage in asymptomatic metastatic AIPC**
  - 25.9 months vs 21.4 months [unadj. HR 1.71; P=0.01 log rank]
  - 28 subjects (APC8015) vs 5 subjects (placebo) remaining alive at the 36 month cutoff
  - Delay in development of objective disease progression
- **D9902A provides supportive evidence of clinical benefit**
- **Highly favorable safety profile**
  - Most common AEs in Provenge treated subjects are chills, fever, tremor, asthenia and headache

APC8015

Expanding the study of APC8015 (Provenge™) to earlier stage Prostate Cancer and to combination therapy

The Prostate Cancer Continuum

Early Stage → **Advanced Stage**

Androgen Dependent PCa

Primary Therapy

- Radical Prostatectomy
- Brachytherapy
- Radiation Therapy
- Cryotherapy
- Watchful Waiting

Androgen Deprivation

- Lupron
- Zoladex
- Casodex
- Eulexin
- Ketoconazole

Androgen Independent PCa

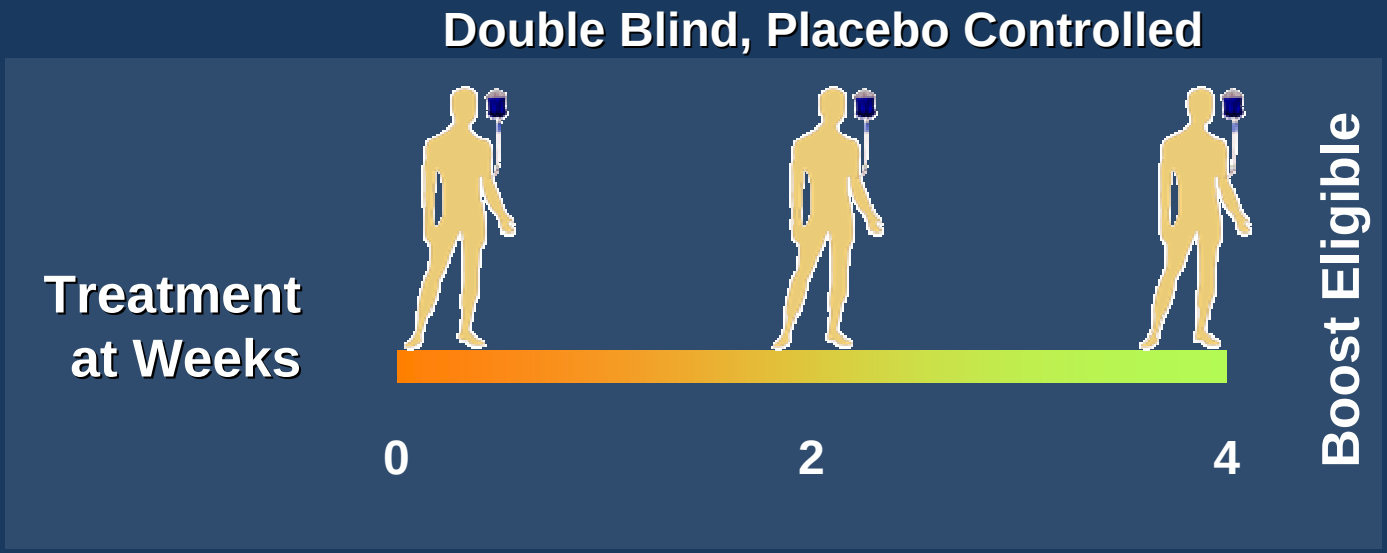
Asymptomatic

PROVENGE®

Symptomatic

- Palliative Interventions
- Bisphosphonates
- Taxotere
- Novantrone
- Emcyt

APC8015 Provenge: P-11 (PROTECT)
Phase 3 Study in Early Stage Prostate Cancer

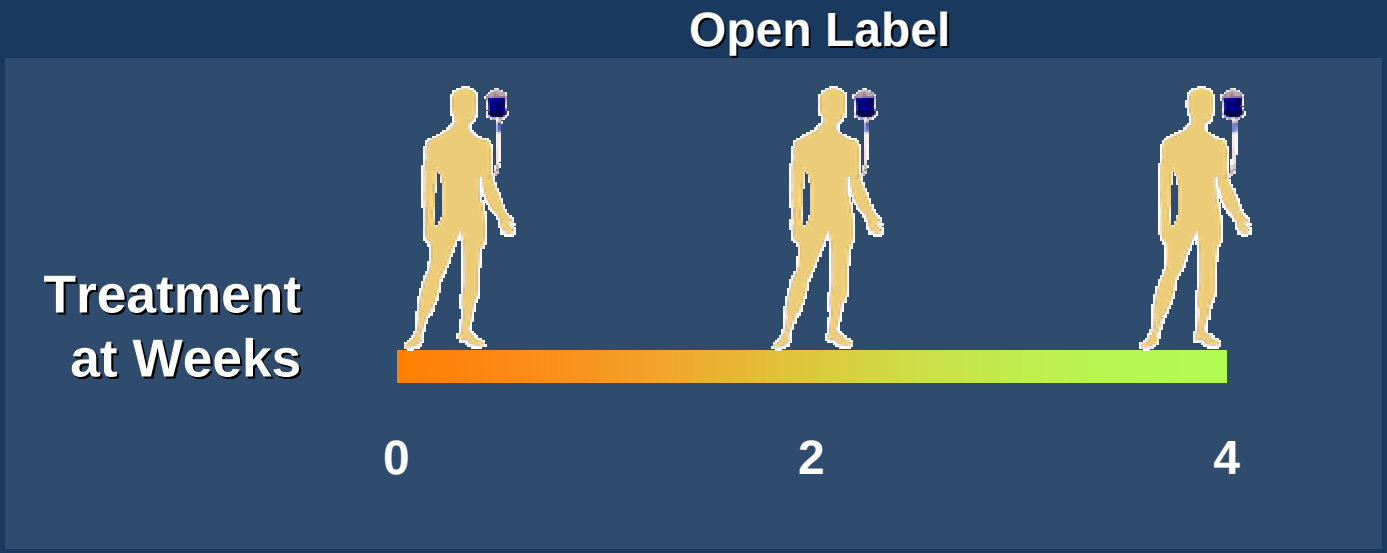


- Trial in androgen dependent prostate cancer
- Evaluating men with biochemical recurrence following prostatectomy
- Over 170 patients enrolled at 19 sites in the U.S.
- Composite endpoints of biochemical and clinical progression
- Enrollment completed; data available in 1H 2006

Possible Combinations with APC8015 (Provenge™)

- Modulators of APC function
  - Toll-like receptor agonists
  - Anti-VEGF
- Modulators of T regulatory cell activity
- Modulators of T cell activation
- Chemotherapy
- Hormonal Therapy

APC8015 Provenge: P-16*
Phase 2 Study in Early Stage Prostate Cancer



- APC8015 combined with bevacizumab in androgen dependent prostate cancer
- Evaluating men with serologic progression after primary therapy
- 26 patients enrolled

*** NCI-sponsored study**

- Endpoints: safety, immune response, PSA response
- Results presented at 2005 Multidisciplinary Prostate Cancer Symposium

PSA Summary Data

PSA Reduction	Number of Patients (n=22)	Percent of Patients
> 50%	1	5%
> 25%	3	14%
Any	9	41%

PSADT (n=21)	
Median pre-treatment	6.7 months
Median post-treatment	12.7 months
Increase in median PSADT	6.0* months

* *P* = 0.004

Presented at 2005 Multidisciplinary Prostate Cancer Symposium

Conclusions

- We have developed an autologous active immunotherapy (APC8015, Provenge™) that is:
  - Highly immunogenic
  - Well tolerated
  - Capable of providing a meaningful, statistically significant survival benefit in men with metastatic AIPC
  - Derived from a consistent, defined manufacturing process that is scaleable
- These data support the belief that cancer vaccines will be an important and feasible treatment option in a variety of settings