Urologische Tumoren

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POST—ASCO

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Disclosure

• ASCO 2017 travelgrant Pfizer • Steering committee Pfizer	

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Onderwerpen

- Niercelcarcinoom
- Urotheelcelcarcinoom
- Prostaatcarcinoom

Niercelcarcinoom

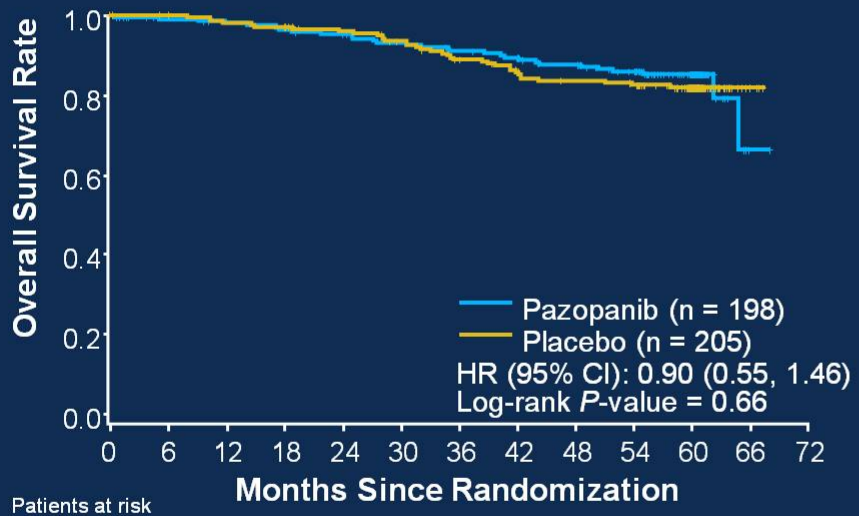
- Adjuvant studies
- Risk score
- Immuno studie: Imotion 150

Reported TKI Adjuvant Trials

Trial	Drug	DFS Benefit	OS Benefit	Patient Population
ASSURE	Sunitinib Sorafenib Placebo	No No	No No	Non clear cell included T2Gr3/4+ Starting dose lower
S-TRAC	Sunitinib Placebo	Yes (1.2 yrs) (HR 0.75)	No (immature, unpowered)	Clear cell T3+ Standard dose
PROTECT	Pazopanib Placebo	No	No	Clear cell T2Gr3/4+ Starting dose lower

PROTECT OS in ITT_{800mg} and ITT_{All}

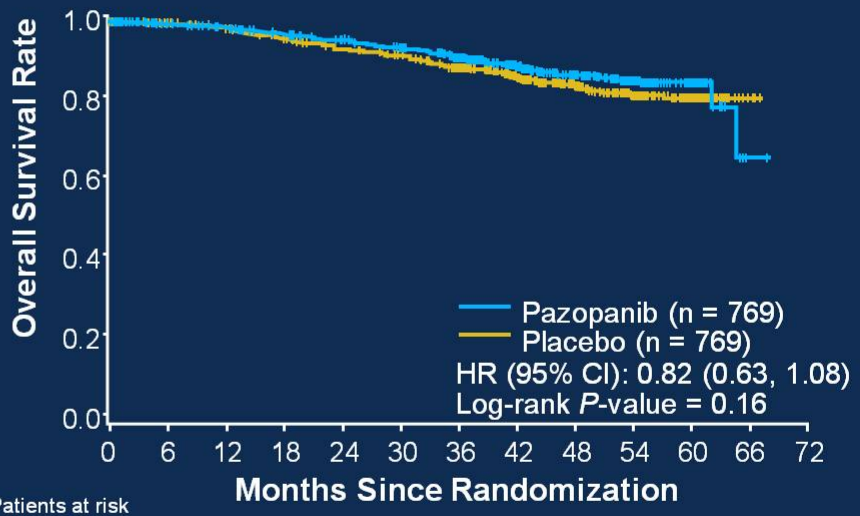
ITT_{800mg}



Patients at risk

Pazopanib	198	185	181	178	174	169	164	157	152	138	78	1	0
Placebo	205	202	197	194	187	179	167	157	153	148	92	3	0

ITT_{All}



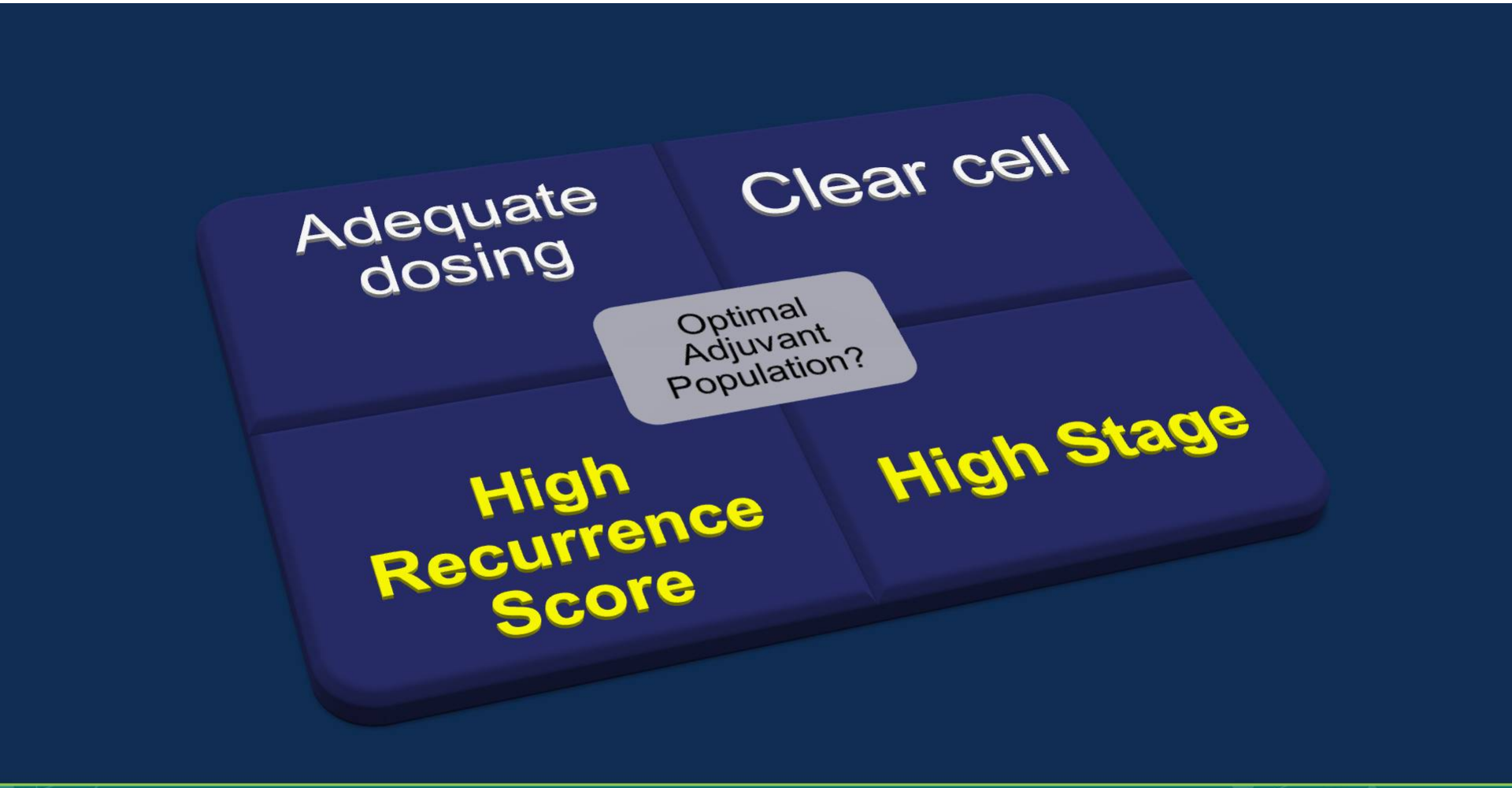
Patients at risk

Pazopanib	769	714	698	676	658	637	592	472	330	196	78	1	0
Placebo	769	741	722	698	671	655	594	467	329	211	92	3	0

Interim analysis was based on 29 and 35 events for the pazopanib and placebo arms in ITT_{800mg}, respectively and 94 and 118 events for the pazopanib and placebo arms in ITT_{All}, respectively. The analysis was performed on data cut-off, which occurred on October 15, 2016 as part of the DFS follow up.

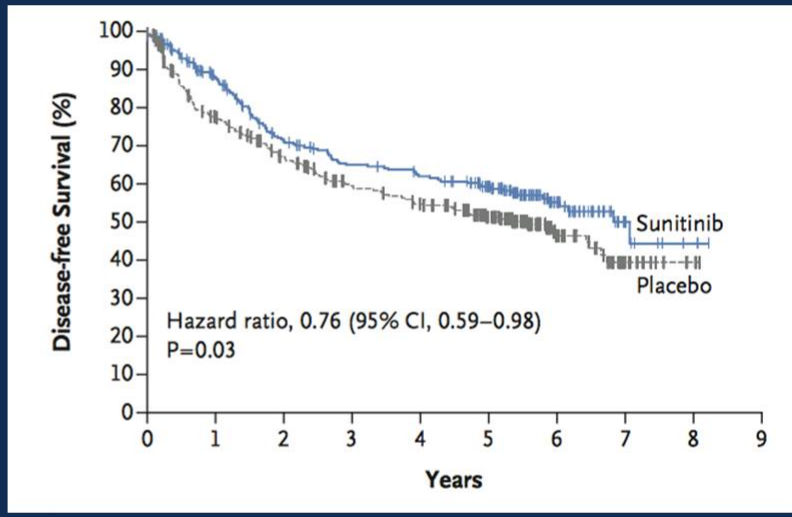
Awaited Adjuvant Trials in Targeted Therapy Era

Trial	Drug	RCC Histology	T stage
ATLAS	Axitinib vs placebo	>50% clear cell	T2+ or N+
SORCE	Sorafenib (1 vs 3 yr vs placebo)	Clear/non-clear	Leibovich 3-11
EVEREST	Everolimus vs placebo	Clear/non-clear	T1b-4 or N+



Recurrence scores helpful only if there is adjuvant therapy

- ASSURE and PROTECT data negative
- S-TRAC data positive for DFS and immature OS
  - Identify high risk group that benefits from adjuvant sunitinib?
  - Are recurrence scores better than S-TRAC selection criteria
    - Clear cell, stage III



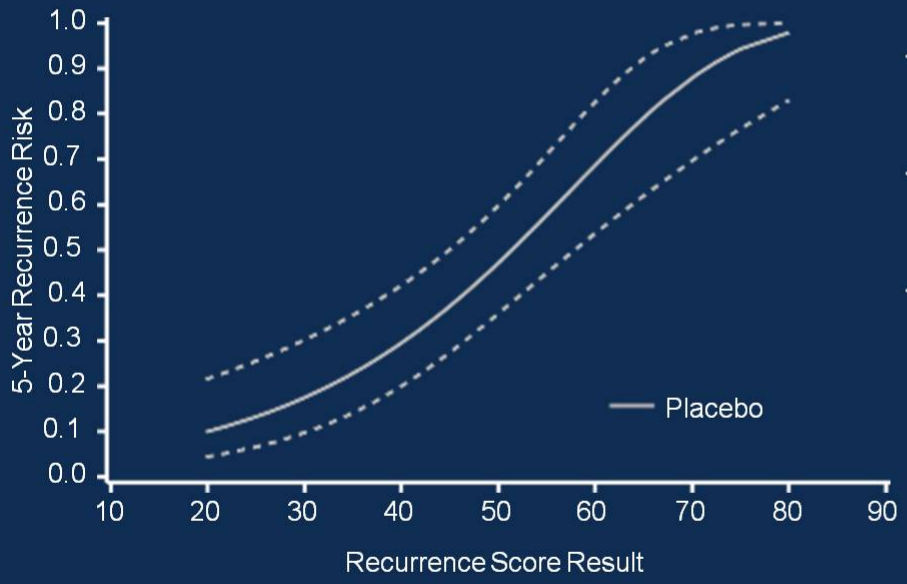
Ravaud et al NEJM 2016

POST–ASCO

Presented By Daniel Heng at 2017 ASCO Annual Meeting

Oncologisch Netwerk Zuidoost-Nederland

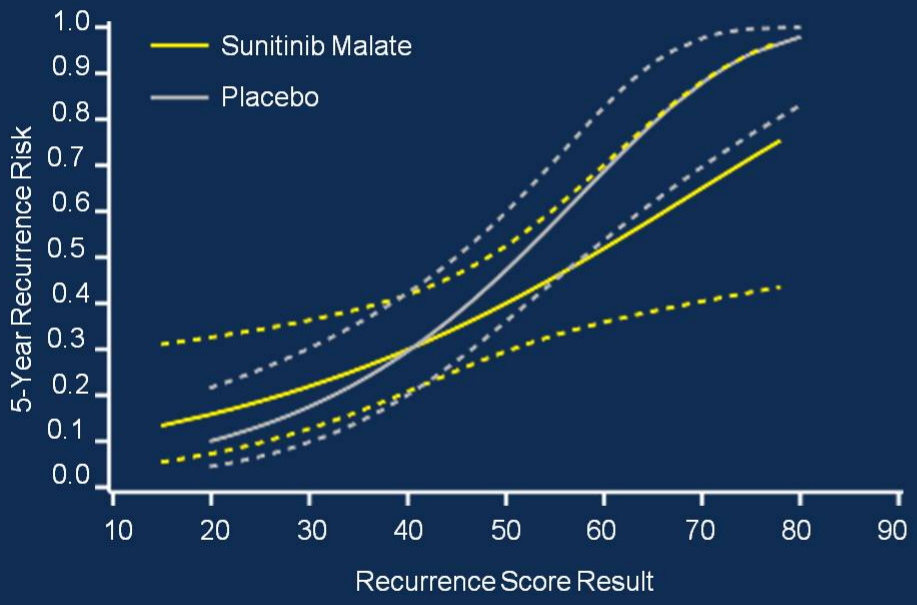
Primary Objective: Prognostic Value
Association of RS with TTR in placebo arm



Study arm	HR (95% CI) per 25-unit increase in RS	*P* Value
Placebo (n=90)	4.24 (2.31–7.80)	<0.0001

- RS strongly predicted risk of recurrence in the placebo arm

Primary Objective: Predictive Value
Association of RS with TTR in placebo vs sunitinib

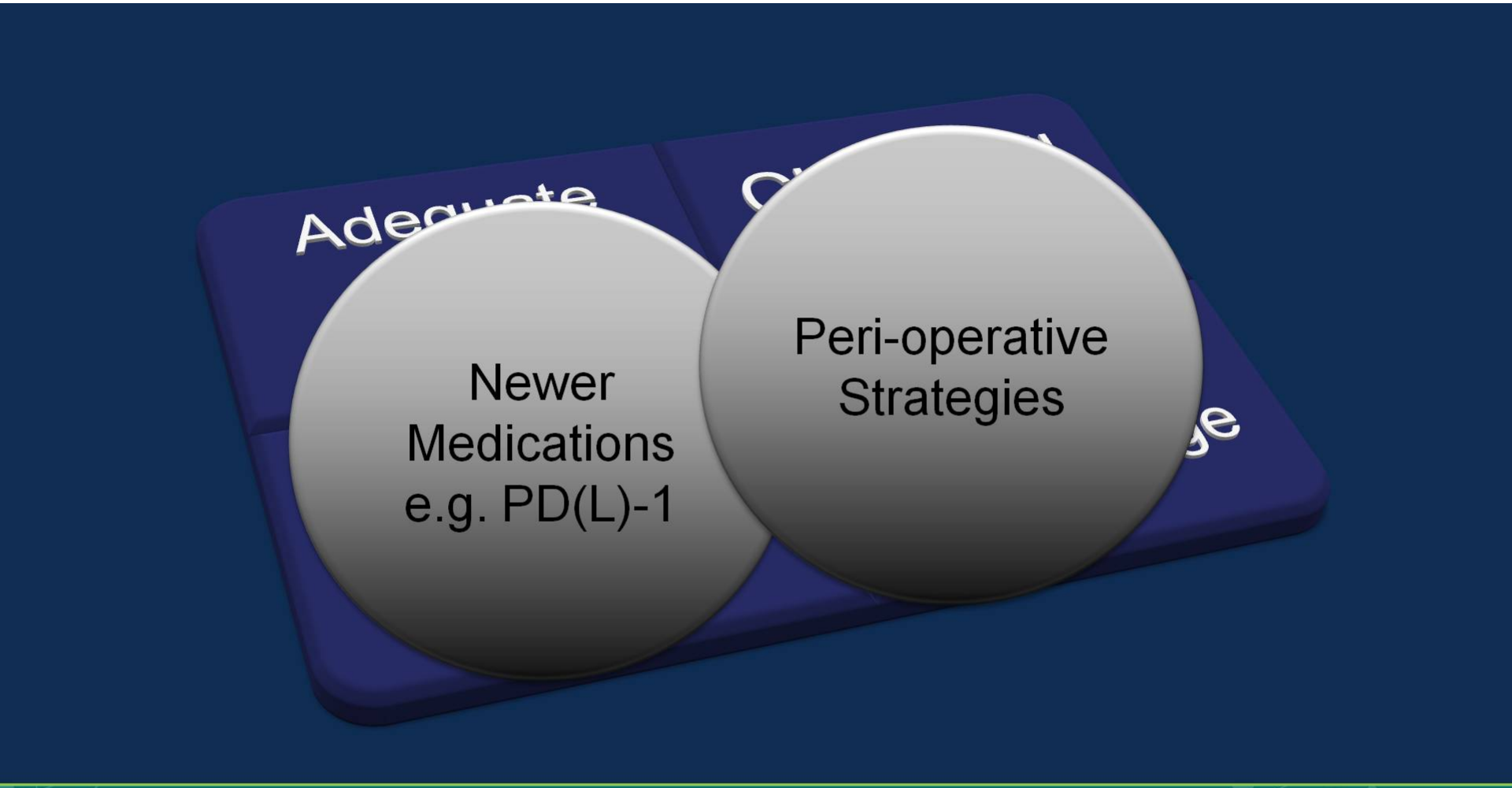


Study arm	HR (95% CI) per 25-unit increase in RS	*P* Value
Placebo (n=90)	4.24 (2.31–7.80)	<0.0001
Sunitinib (n=103)	2.53 (1.29–4.97)	0.008

- Interaction of RS with treatment did not reach significance, *P*=0.19
  - Small number of recurrences (n=63) provided low power for an interaction test

16 Gene Recurrence Score (RS)

- RS is prognostic for recurrence
- Should be investigated prospectively (PD1 trials) and retrospectively (VEGF/mTOR trials) to look for predictive ability
  - May require a meta-analysis to attain adequate power



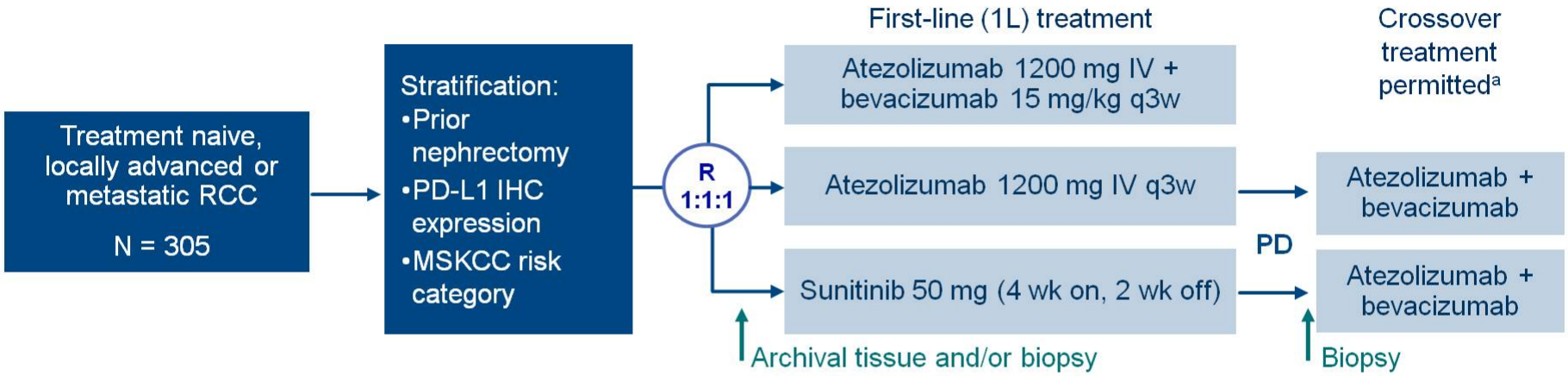
Selected Adjuvant Immunoncology Trials

Others will be activating soon

Conclusions

- Adjuvant pazopanib should not be used
- The 16 gene recurrence score is now externally validated
  - Should not be used for now to determine if will benefit from adjuvant sunitinib (not predictive)
- Optimal adjuvant patient still controversial
  - We have hints based on subgroup analyses and trial inclusion criteria only
    - Clear cell, better dose, higher stage, higher RS
- Patient participation and tissue collection critical in advancing predictive biomarkers for adjuvant therapy

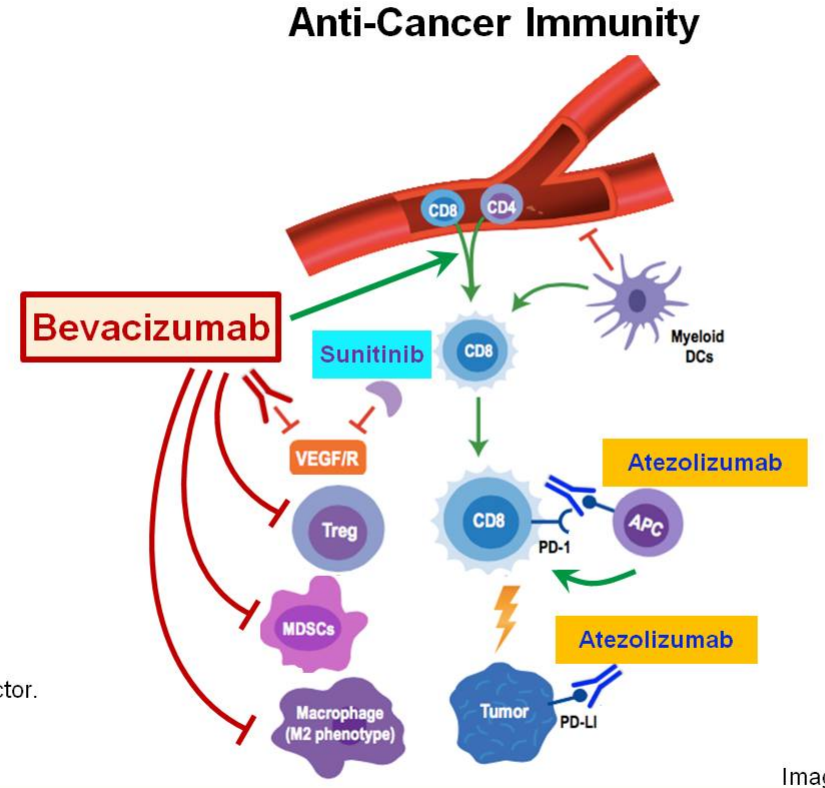
IMmotion150 (Phase II) Trial Design



- IMmotion150 was designed to be hypothesis generating and to inform the Phase III study IMmotion151
- The coprimary endpoints are PFS (RECIST v1.1 by IRF) in ITT and PD-L1+ patients
  - PD-L1 positivity is defined as ≥ 1% of tumor-infiltrating immune cells (IC) expressing PD-L1
- Secondary endpoints include INV-assessed PFS, ORR and analysis of efficacy after crossover (ORR, PFS)

INV, investigator; IRF, independent review facility; PD, progressive disease; RCC, renal cell carcinoma.
[a]Crossover from atezolizumab monotherapy not allowed in Europe.

Shifting the Balance Toward Anti-Cancer Immunity With Combined VEGF/PD-L1 Blockade



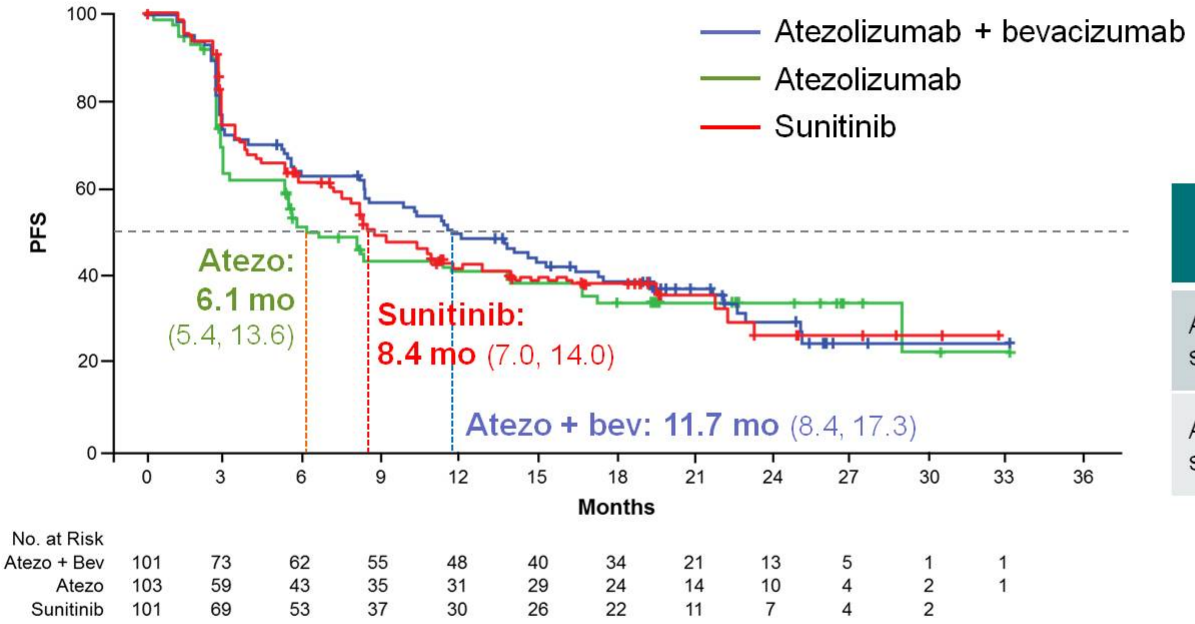
PD-L1, programmed death-ligand 1;
VEGF, vascular endothelial growth factor.

1. Finke, *Clin Cancer Res*. 2008;
2. McDermott, *J Clin Oncol*. 2016;
3. Wallin, *Nat Commun*. 2016.

Image courtesy of and adapted from Einstein and McDermott.

1L Progression-Free Survival

ITT

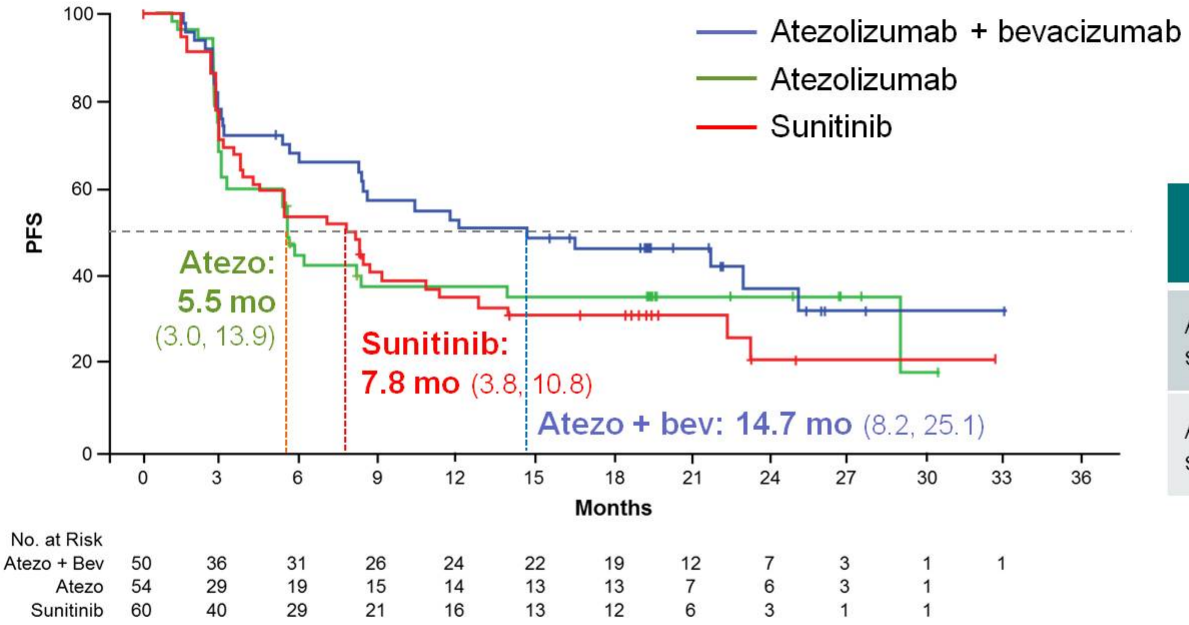


	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	1.00 (0.69, 1.45)	0.982
Atezo vs sunitinib	1.19 (0.82, 1.71)	0.358

Atezo, atezolizumab; bev, bevacizumab.
PFS measured by independent review facility.
[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.
Clinical cutoff, Oct 17, 2016. Median duration of follow-up, 20.7 mo. McDermott, ASCO GU 2017.

1L Progression-Free Survival

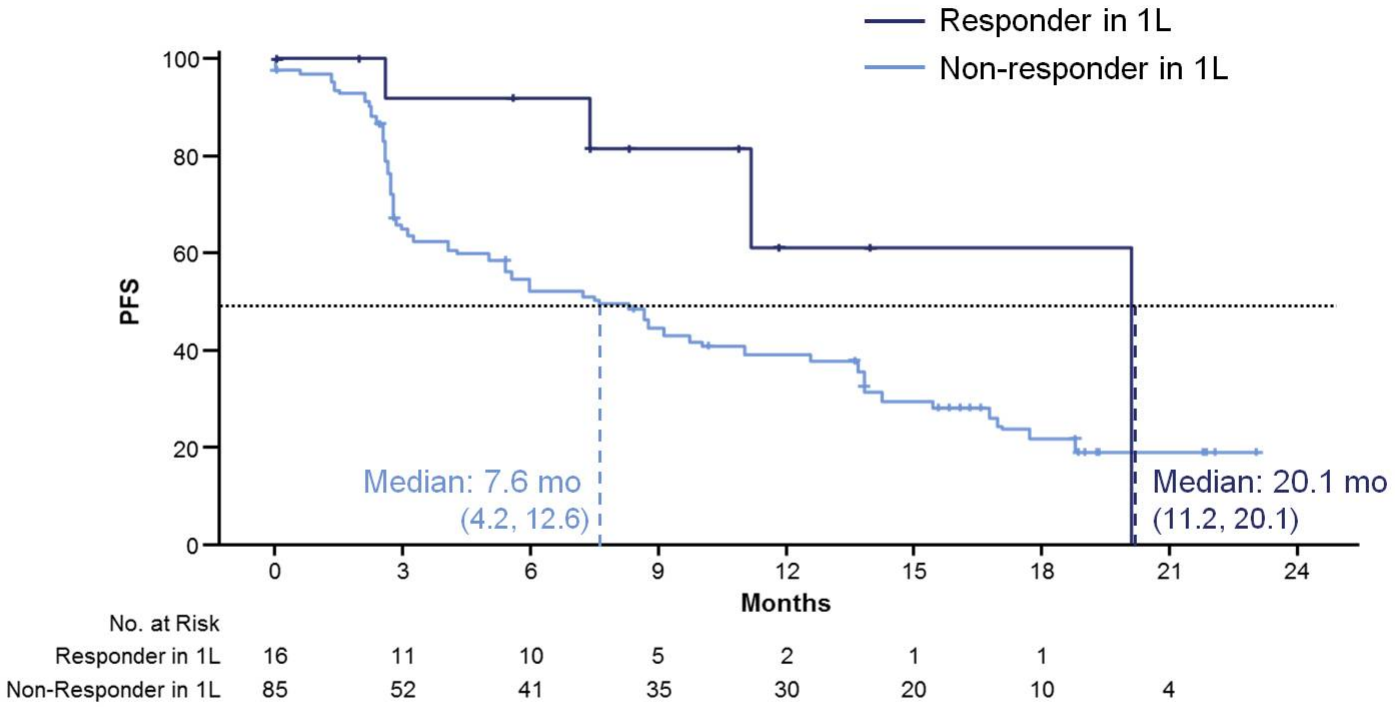
≥ 1% of IC Expressing PD-L1



	Stratified HR (95% CI)	*P* Value[a]
Atezo + bev vs sunitinib	**0.64 (0.38, 1.08)**	**0.095**
Atezo vs sunitinib	1.03 (0.63, 1.67)	0.917

Atezo, atezolizumab; bev, bevacizumab.
PFS measured by independent review facility.
[a] *P* values are for descriptive purposes only and not adjusted for multiple comparisons.
Clinical cutoff, Oct 17, 2016. Median duration of follow-up, 20.7 mo. McDermott, ASCO GU 2017.

Crossover Progression-Free Survival by 1L Response Status



PFS measured by investigator.
Clinical cutoff date, Oct 17, 2016. Median duration of follow-up: All crossover, 12.7 mo.

Conclusions

- Atezolizumab + bevacizumab resulted in encouraging efficacy vs sunitinib in PD-L1+ 1L mRCC patients
- Clinical activity of atezolizumab + bevacizumab was also seen in crossover patients regardless of prior 1L atezolizumab or sunitinib therapy and response, further supporting combination treatment
  - ORR: 26% in all crossover patients (28% in crossover post sunitinib; 24% in crossover post atezolizumab)
  - Median PFS: 8.8 mo in all crossover patients
  - In an exploratory analysis, tumor PD-L1 status modestly enriched for crossover therapy response
- Safety profile of the crossover arms was consistent with the safety profiles of individual treatment components and the 1L atezolizumab + bevacizumab arm

Urotheelcelcacinoom

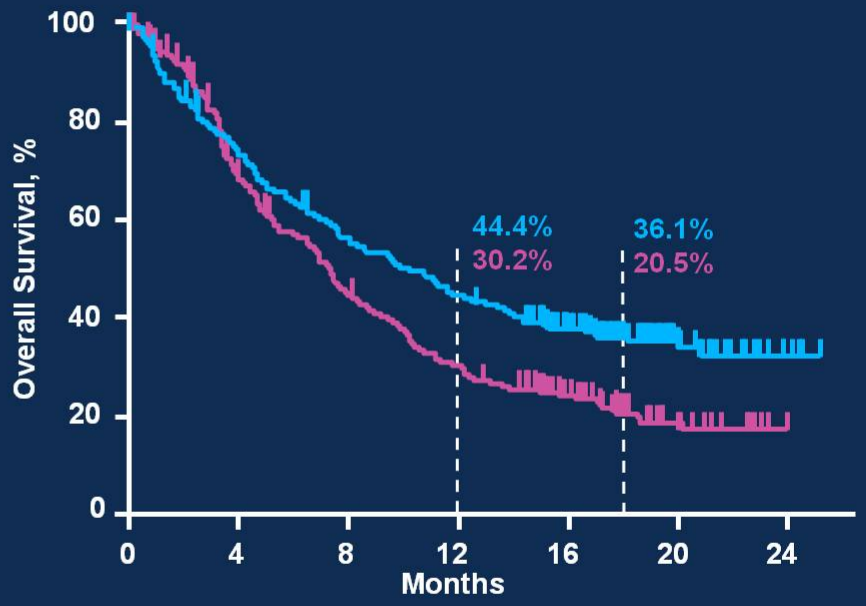
- Relatief weinig echt nieuws
- Immuun studies

Metastatic urothelial carcinoma

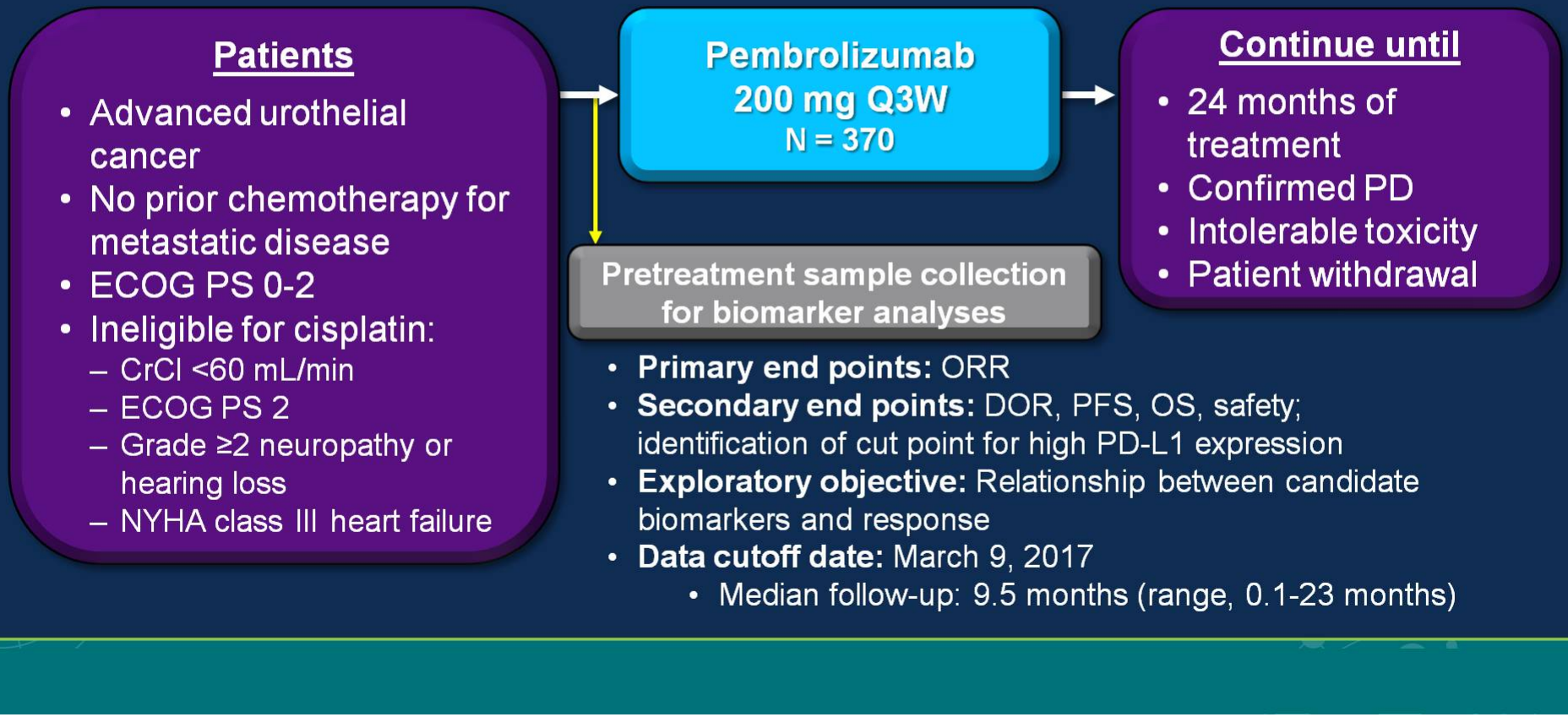
- Development of immune checkpoint blockade in urothelial carcinoma has led to significant progress and new treatment options
- Transformed the treatment of previously-treated and cisplatin-ineligible urothelial carcinoma
- 5 agents approved in US
  - Atezolizumab, nivolumab, durvalumab, avelumab, and pembrolizumab
- Despite these dramatic advances, outcomes are still suboptimal for most patients
  - Objective response rates remain between 14.8-21.1% in 2nd-line setting and the median survival remains < 1 year

Abstract 4501: Survival analysis from phase 3, open-label study of pembrolizumab versus chemotherapy in advanced UC

- Longer follow up confirms the initial data
- Objective responses occurred rapidly and were generally durable, with duration of response not yet reached
- Safety and tolerability favor pembrolizumab over 2nd and 3rd line chemotherapy



KEYNOTE-052 (NCT02335424): First-Line Pembrolizumab for Cisplatin-Ineligible Advanced Urothelial Cancer



Confirmed Objective Response Rate: Validation Set

	CPS <10% n = 185			CPS ≥10% n = 80		
	n	%	95% CI	n	%	95% CI
Objective response rate	42	**23**	17-29	41	**51**	40-63
Complete response	5	3	1-6	14	18	10-28
Partial response	37	20	15-27	27	34	24-45
Stable disease	35	19	14-25	15	19	11-29
Progressive disease	86	47	37-54	19	24	15-35

Data cutoff: March 9, 2017.

Assessed per RECIST v1.1 by central imaging vendor review. 361/370 patients had CPS and ORR data. For CPS <10%, 17 additional patients had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy, and 5 patients had ≥1 postbaseline tumor assessment, none of which were evaluable. For CPS ≥10%, 5 additional patients did not have a postbaseline imaging assessment.

Advanced Bladder Cancer Treatment Algorithm: June 2017

Disease state	Context	Level 1 evidence	Standard Options
Metastatic no prior chemotherapy	Cisplatin-eligible	Cisplatin-based combination chemotherapy	
Metastatic no prior chemotherapy	Cisplatin-ineligible		Atezolizumab Pembrolizumab Gemcitabine-carboplatin Single agent chemotherapy
Metastatic, prior platinum chemotherapy or relapse within 1 year of perioperative cisplatin		Pembrolizumab	Atezolizumab Nivolumab Durvalumab Avelumab
Metastatic, prior immunotherapy			Taxane chemotherapy Vinflunine (EU)

Clinical trial enrollment appropriate throughout disease spectrum

Prostaatcarcinoom

- Fase 2 studie Enza vs Abi laat geen verschil zien
- Doorgaan met Enza bij start Abi bij progressieve ziekte heeft geen toegevoegde waarde: PLATO studie
  - Echter wat als Radium of docetaxel toevoegen?
- Duur ADT bij hoog risico patienten
- Risk score
- Stampede en Lattidu studies

Duration of Androgen Deprivation Therapy in High Risk Prostate Cancer: Final Results of a Randomized Phase III Trial

Abdenour Nabid[1], Marie-Pierre Garant[1], André-Guy Martin[2], Jean-Paul Bahary[3], Céline Lemaire[4], Sylvie Vass[5], Boris Bahoric[6], Robert Archambault[7], François Vincent[8], Redouane Bettahar[9], Nathalie Carrier[1], Marie Duclos[10], Luis Souhami[10]*

[1]Centre Hospitalier Universitaire de Sherbrooke, CA, [2]Centre Hospitalier Universitaire de Québec, CA
[3]Centre Hospitalier Universitaire de Montréal, CA, [4]Hôpital Maisonneuve-Rosemont de Montréal, CA,
[5]Centre de Santé et Services Sociaux de Chicoutimi, CA, [6]Hôpital Général Juif de Montréal, CA
[7]Hôpital de Gatineau, CA, [8]Centre Hospitalier Régional de Trois-Rivières, CA
[9]Centre Hospitalier Régional de Rimouski, CA, [10]Centre Universitaire de Santé McGill, CA

PRESENTED AT: ASCO ANNUAL MEETING '17 | #ASCO17 Abstract ID 5008 (186877)

Inclusion Criteria

T3-T4, PSA >20 ng/ml, Gleason score >7
Age ≤80 years, Zubrod 0-1
Normal hepatic function
No regional disease
No distant metastases

Exclusion Criteria

Pre-existing medical conditions precluding use of androgen deprivation therapy (ADT) or radiotherapy (RT)

Randomization 10/2000 to 01/2008

630 Patients

Arm 1 (310) : ADT* 36 months + RT**

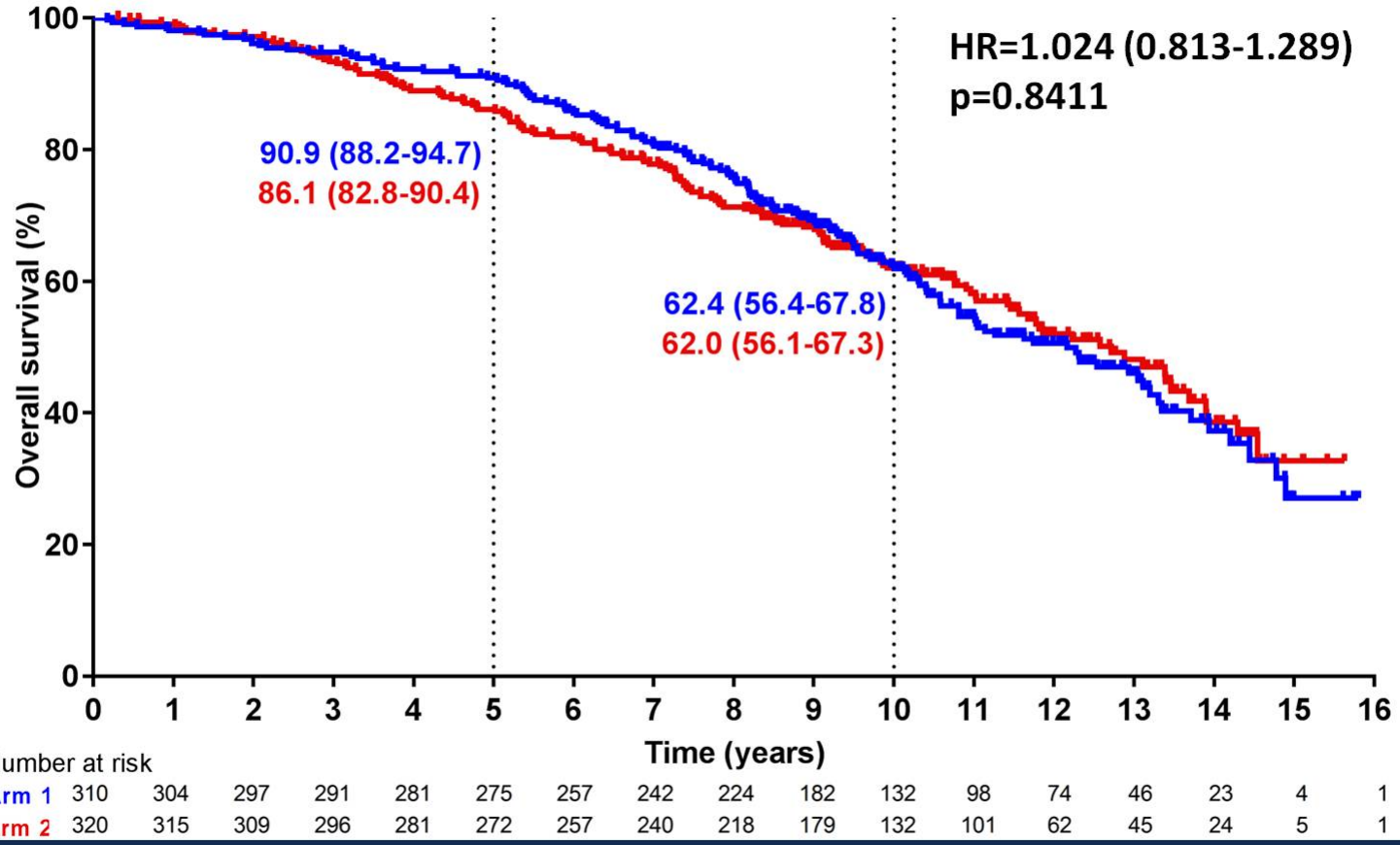
Arm 2 (320) : ADT* 18 months + RT**

*ADT: Bicalutamide 50 mg id x 1 month + Goserelin 10.8 mg q 3 months

**RT: pelvis 44 Gy - 4 ½ weeks, prostate 70 Gy - 7 weeks

Median Follow-up 9.4 years

Overall Survival



3 Studies With Genetic Testing/Correlates:

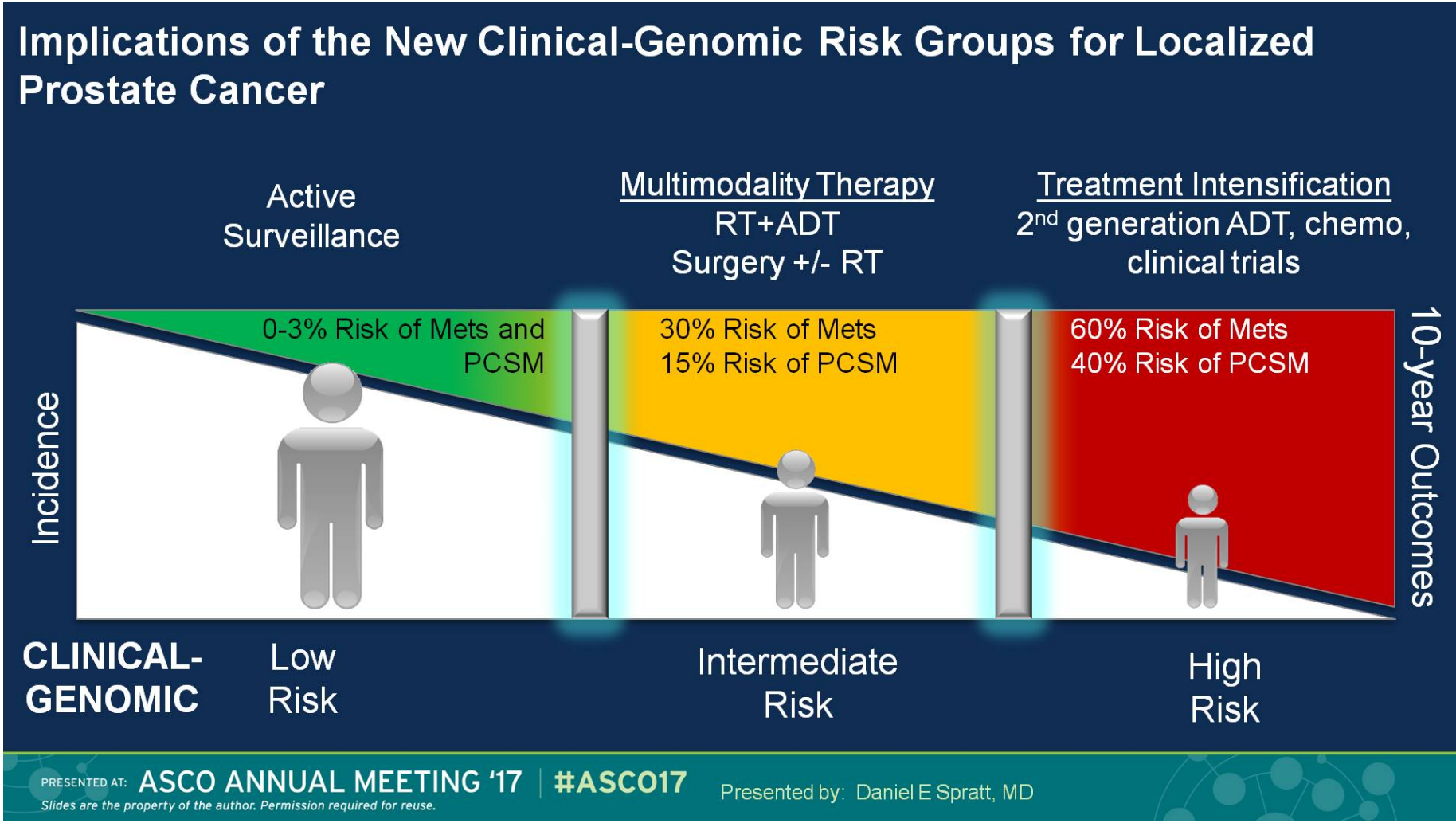
Spratt and colleagues: Development and validation of a novel clinical-genomic risk group classification for prostate cancer incorporating genomic and clinicopathologic risk

Chi and colleagues: A randomized phase II cross-over study of abiraterone + prednisone vs enzalutamide for patients with metastatic, castration-resistant prostate cancer

Hussein and colleagues: Abiraterone + Prednisone (Abi) +/- Veliparib (Vel) For Metastatic on-Resistant Prostate (CRPC pts): NCI 9012 Updated Clinical and Genomics Data

Do we know the biology behind the test ?
Do we have a validated clinical-grade assay ?
Is it cheap and is it adoptable worldwide ?
Is it prognostic or predictive ?
Does it better our clinical decision-making and change treatment ?

Risk score verlaagt in 30% de risk groep

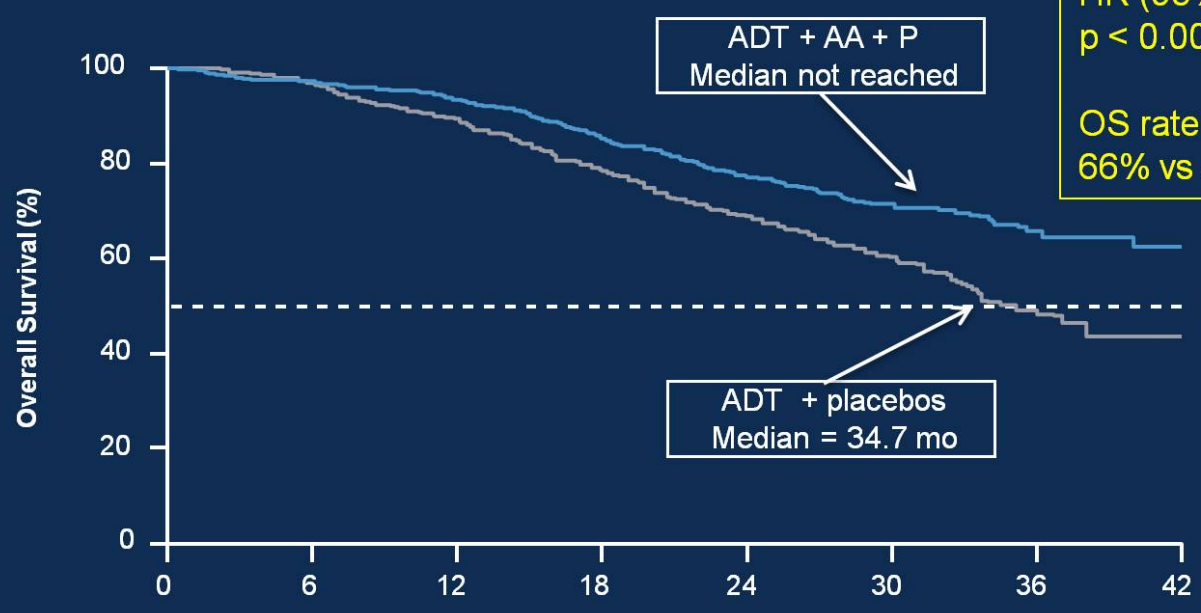


Lattitude en Stampede studies

- OS
- DFS
- PCSM
- Time to radiographic progression
- Time to PSA rise

Lattitude OS

Overall Survival as Co-Primary Endpoint: Results



HR (95% CI) = 0.62 (0.51-0.76);
p < 0.001

OS rate at 3 years:
66% vs 49%, favoring Abiraterone

No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

From Fizazi et al, ASCO 2017

Subsequent life-prolonging therapy for prostate cancer

	ADT + AA + P (enrolled; n = 597)	ADT + placebos (enrolled; n = 602)
Patients who discontinued study treatment (total = 783)	**314**	**469**
Patients who received post-study life-prolonging therapy (%) **Total**	**125 (40%)**	**246 (52%)**
Docetaxel	106 (34)	187 (40)
Enzalutamide	30 (10)	76 (16)
Abiraterone/Prednisone	10 (3)	53 (11)
Cabazitaxel	11 (4)	30 (6)
Radium-223	11 (4)	27 (6)

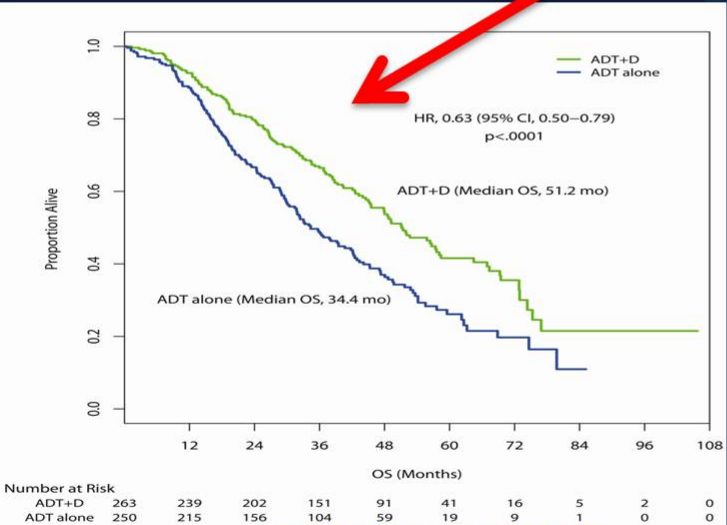
Where does chemotherapy fit in?

- The addition of docetaxel to ADT has previously been shown to prolong life in the CHAARTED and STAMPEDE trials*
- Should ADT + Docetaxel have been the control arm in Latitude?
- Latitude fully accrued before docetaxel results published

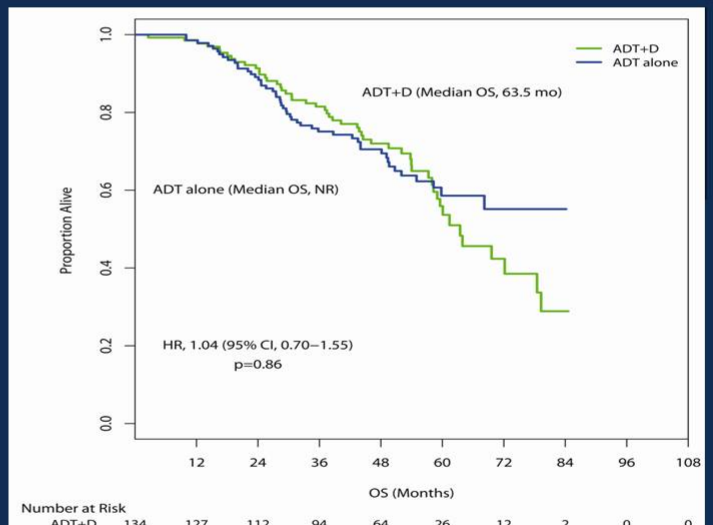
*Sweeney C, et al. *N Engl J Med*. 2015;373:737-746; James N, et al. *Lancet*. 2016;387:1163-1177.

CHAARTED: OS benefit (HR for death = 0.73) in favor of ADT + Docetaxel

Evaluation of Rx by disease volume interaction using Cox proportional hazards model		
	HR (ADT+D/ADT)	95% CI
Overall	0.73	0.59 - 0.89
High volume	0.63	0.50 - 0.79
Low volume	1.04	0.70 - 1.55



Sweeney et al. ESMO 2016



Comparing CHAARTED High Volume Patients and LATITUDE Patients

	N	Eligibility Criteria
LATITUDE All Patients	**1199**	**Meets at least 2 of 3 high-risk criteria:** • Presence of ≥ 3 lesions on bone scan • Presence of measurable visceral lesion • Gleason score of ≥ 8
CHAARTED High Volume	**513**	**Meets one or both criteria:** • Presence of ≥ 4 lesions on bone scan (with at least one lesion outside pelvis and spine) • Presence of measurable visceral lesion

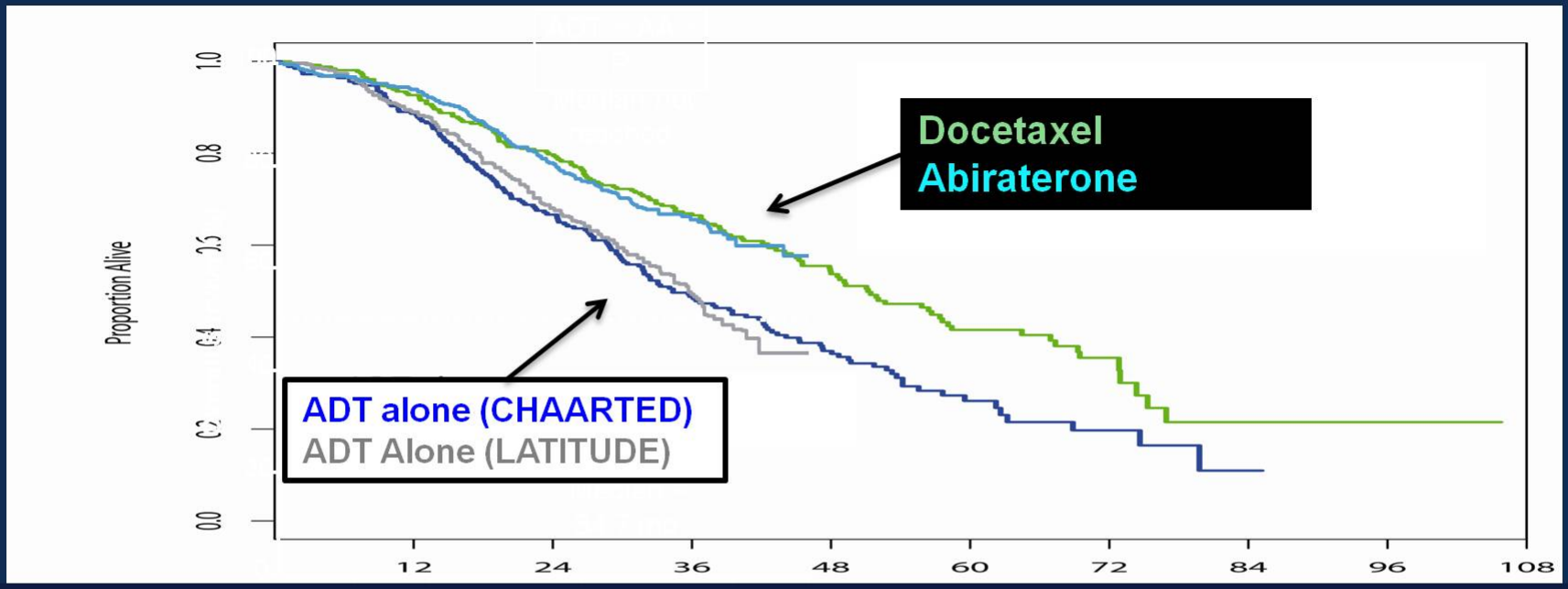
Comparing LATITUDE and CHAARTED Patients

	N	Patient Characteristics
LATITUDE	**1199**	GS≥ 8 97.5% ≥3 bone mets 97.5% Visceral mets 17% Median Age 67.5 yrs
CHAARTED	**790**	GS ≥ 8 60% "high vol" 65% ≥4 bone mets na Visceral mets 24% Median Age 63.5 yrs

Comparing Overall Survival Across Studies

	Median OS			3 yr OS rate*	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%	~65%

* Estimated from KM plots



Overlay of LATITUDE KM Plot on CHAARTED (high volume) KM Plot

Comparing r-PFS* Across Studies

	HR (95% CI)	Control Arm (months)	Treatment Arm (months)
LATITUDE	0.47 (0.39-0.55)	14.8 mo	33.O mo
CHAARTED (High Volume)	0.53 (0.42-0.67)	13.O mo	27.3 mo

*CHAARTED: Clinical Progression (sx, RECIST, clinical)
LATITUDE: r-PFS

Comparing Toxicity Across Studies

	Agent	Treatment-Associated Toxicity		Duration of experimental drug exposure
		grade 3	**grade 4**	
LATITUDE	Abi + Pred	HTN: 20% ↓K: 10% ALT: 4%	0% 0.8% 0.3%	On Rx until PD (median = 33 mos)
CHAARTED (entire cohort)	Docetaxel	Neutropenia: 12% Neutropenic fever: 6% Gr 3 or 4 infection with neutropenia: 2% 1 early death		6 cycles = 4.5 mos

CONCLUSIONS: Comparing LATITUDE and CHAARTED

Comparison across studies is fraught with hazards! Nevertheless….

In a similar risk group of metastatic prostate cancer patients, the addition of either Abiraterone or Docetaxel:

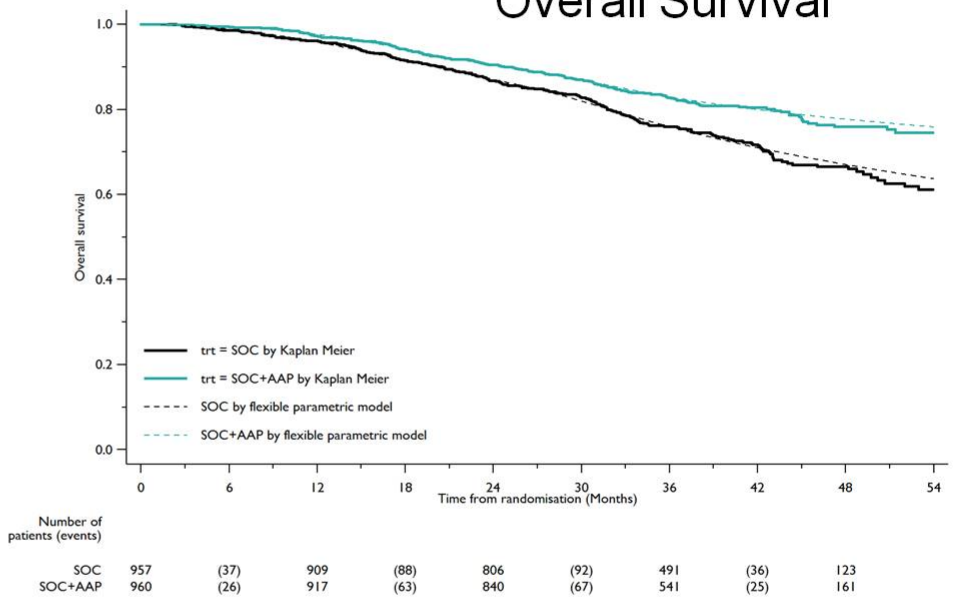
Each resulted in a HR for death of ~ 0.6

Each had similar 3 yr Δ in OS compared with control (~ 65% vs. 50%)

Each resulted in a HR for radiographic progression of ~ 0.5

Data from STAMPEDE

1%	WHO PS 2
21%	WHO PS 1
67yr	Median age (min 39, max 85)
52%	Metastatic (88% Bony mets)
20%	N+M0
28%	N0M0
99%	LHRH analogues
41%	Planned for RT (96% of N0M0 pts; 62% of N+M0 pts)
5%	Previous local therapy



HR	**0.63**
95% CI	0.52 to 0.76
P-value	0.000000115

From James et al, ASCO 2017

Comparing Overall Survival Across Studies

	Median OS			3 yr OS rate	
	HR (95% CI)	Control (months)	Rx (months)	Control	Rx
LATITUDE	0.62 (0.51-0.76)	34.7 mo	NR	49%	66%
STAMPEDE	0.63	not reached (0.52 – 0.76)			
CHAARTED High Volume	0.63 (0.50-0.79)	34.4 mo	51.2 mo	~50%*	~65%*

Unanswered Questions: Efficacy

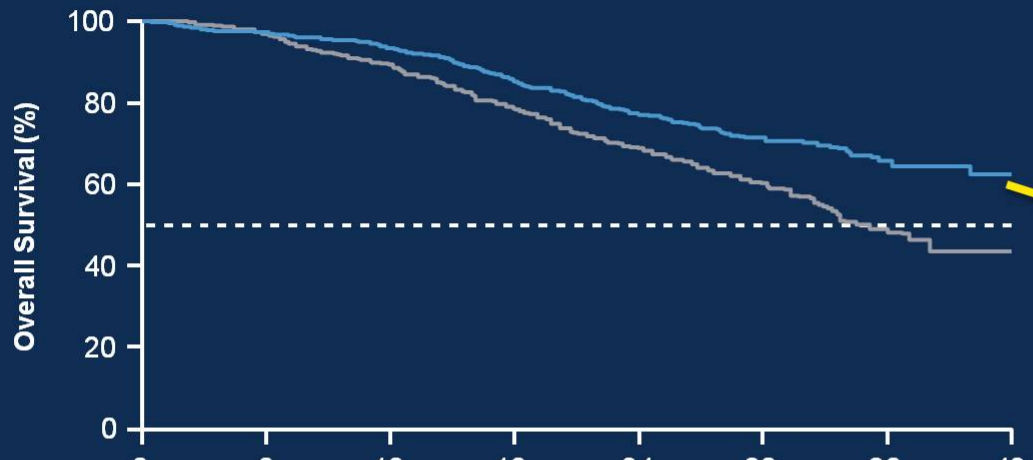
Selecting the optimal way to use Abiraterone

Can a genomic classifier be used to select patients more likely to benefit from abiraterone or docetaxel?

What about adding abiraterone in even earlier settings? e.g. with radiation, or for climbing PSA Patients?

Should abiraterone and docetaxel be combined or used sequentially?

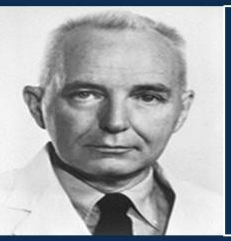
Implications: While there is much to celebrate…



No. at risk								
ADT + AA + P	597	565	529	479	388	233	93	9
ADT + placebos	602	564	504	432	332	172	57	2

Many of these patients are still likely to die from their disease

The Longitudinal Timeline of Systemic Therapy for Metastatic Hormone "Naïve" Prostate Cancer



1941: Charles Huggins publishes his observations that Androgen Deprivation Therapy is highly effective in controlling metastatic prostate cancer.

75 years!

2015: CHAARTED and STAMPEDE trials demonstrate that the addition of docetaxel to ADT prolongs life in men with (high volume) metastatic prostate cancer.

2 years

2017: LATITUDE and STAMPEDE: The addition of abiraterone to ADT prolongs life

??

Take Homes from Latitude

- The benefit obtained from adding abiraterone to ADT appears to be the same as that seen with docetaxel.
- The use of abiraterone
  - Avoids Chemotherapy
  - Avoids (rare) neutropenic complication/ treatment-associated deaths
  - Replaces short term IV treatment with long term oral treatment
  - May be more appropriate in elderly or debilitated
- Future evaluation
  - QOL and financial toxicity
  - Testing earlier (eg climbing PSA patients)
  - Combination with docetaxel