IX Congresso Internacional de Uro-Oncologia

IV SIMPÓSIO MULTIPROFISSIONAL DE URO-ONCOLOGIA

1 a 3 de Março de 2018

SHERATON SÃO PAULO WTC HOTEL

MEDICINA BASEADA EM EVIDÊNCIA

DISCUSSÃO

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EXEMPLO 1:

Cost-effectiveness of sunitinib or pazopanib for metastatic renal cell carcinoma in Brazil: A public health system perspective

Sasse A. et al; SONHE - Sasse Oncology and Hematology Group, Campinas, Brazil; UNICAMP - University of Campinas, Campinas, Brazil

- ✓ Benefício clínico relevante – ITK- mRCC
- ✓ Sistema Público Brasil- Tratamento padrão (Interferon?)
- ✓ SBOC- Incorporação de nova tecnologia- CONITEC

OBJETIVO: Estimar custo efetividade de Sunitinibe/ Pazopanibe x Interferon em pacientes do SUS tratados por mRCC

MÉTODO: Análise de custo efetividade, modelo Markov sobre tempo de vida do indíviduo e 3 estados de saude:

1ra Linha/ Progressão de doença/ Morte

- ✓ Custos de tratamento padrão, complicações e vigilância foram obtidos de hospitais públicos no Brasil.
- ✓ O preço das medicações foi negociado diretamente com a indústria
- ✓ Benefício expresso em anos de vida (Life Years) e custo em Dolares.
- ✓ A relação de custo benefício foi expressa em:

Taxa de Aumento de custo efetividade por ano de vida salvo (ICER)

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TABLE 3 Tabled and negotiated prices of Sun and Paz

Drug	Package	Tabled price (tax free)	Negotiated discount	Final price
Sun (Sutent®)	Box of 28 capsules (50 mg)	4,112.85	38.4%	2,535.52
	Daily cost*	97.93		60.32
Paz (Votrient®)	Box of 60 capsules (800 mg)	1,886.54	-	-
	Daily cost	62.88	-	-

*Sun daily cost using 4 weeks on 2 weeks off regimen (42 days cycle)

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TABLE 1 Probability of transitioning from one state to another depending on the treatment started

Treatment	Initial state	Final state	Transition probability
TKI	1st line treatment	Disease progression	6.4%
	1st line treatment	Death	3.6%
	Disease progression	Death	3.6%
IFN	1st line treatment	Disease progression	11.9%
	1st line treatment	Death	5.6%
	Disease progression	Death	5.6%

TABLE 2 TKI's efficacy in reducing the relative risk of outcomes versus IFN

Outcome	Sun or Paz (versus IFN)
Efficacy in reducing the risk of progression	HR PFS: 0.539
Efficacy in reducing the risk of death	HR OS: 0.647

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Resultados:

	Life Years	Total Cost	ICERS
Interferon	1.92	$2,000	
Sunitinibe	2.84	$19,584	$18,565/LY
Pazopanibe	2.84	$19,646	$18,634/LY

- ✓ **Conclusão:** Com a margem de desconto + Limite disponível para pagamento (Willingness-to-pay) de $25,615/ LY (3x produto interno bruto per capita) tanto Pazopanib quanto Sunitinib são estratégias econômicas em relação ao Interferon.
- ✓ Impactos dos ITK na saude publica em geral ainda para ser avaliado dentro de um orçamento específico.
- ✓ Foi encaminhada uma solicitação formal a CONITEC como incorporação de nova tecnologia

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EXEMPLO 2:

- Duration of androgen deprivation therapy in high risk prostate cancer: Final results of a randomized phase III trial.

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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)

Endpoints

Primary :	Overall survival
	Quality of life
	Disease specific survival
Secondary :	Biochemical failure
	Sites of tumor relapse
	Disease-free survival

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

Patient's Characteristics

		36 months	18 months
Age (IQR)		71 (67-74)	71 (65-74)
PSA (IQR)		16.4 (8.6-28.2)	15.4 (8.4-28.1)
Gleason Score (IQR)		8 (6-10)	8 (6-10)
Clinical Stage – n (%)	T1c	76 (24.5)	80 (25.0)
	T2a	58 (18.7)	64 (20.0)
	T2b	78 (25.2)	80 (25.0)
	T2c	18 (5.8)	24 (7.5)
	T3	80 (25.8)	70 (21.9)
	T4	0 (0.0)	2 (0.6)

Risk Factors

	36 months n=310	18 months n=320	Total n=630
T3 – T4	80 (25.8)	72 (22.5)	152 (24.1)
PSA >20	142 (45.8)	137 (42.8)	279 (44.3)
Gleason score >7	183 (59.0)	193 (60.3)	376 (59.7)

Causes of Death

Events	36 months	18 months
Second cancer	35 (23.8%)	40 (28.0%)
Prostate cancer	31 (21.1%)	33 (23.1%)
Cardiovascular	25 (17.0%)	25 (17.5%)
Pulmonary	22 (15.0%)	17 (11.9%)
Digestive	4 (2.7%)	5 (3.5%)
Other causes	20 (13.6%)	15 (10.5%)
Unknown	10 (6.8%)	8 (5.6%)
Total 290/630	147/310 (47.4%)	143/320 (44.6%)

Statistical analysis

Kaplan Meier method with log-rank test:

OS and DFS

Survival analysis with competing risks methods:

BF, DFS, DSS

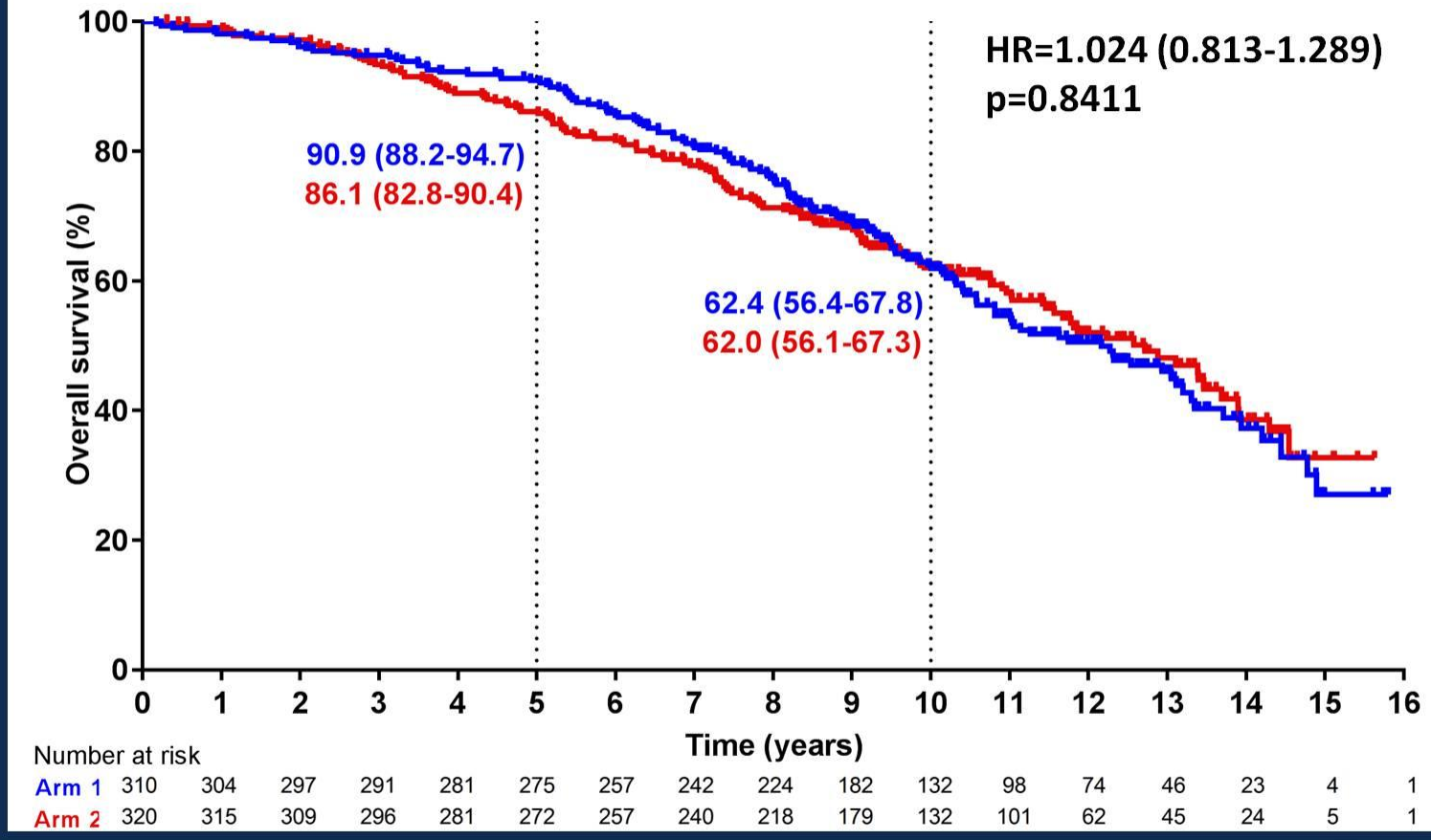
Multivariate Cox regression:

Factors associated with OS

Mixed linear models:

EORTC30 and PR25

Overall Survival



Quality of Life

In favor of 18 months of ADT:

- 13/55 items, 6/21 scales

Clinically significant: $p<0.01$

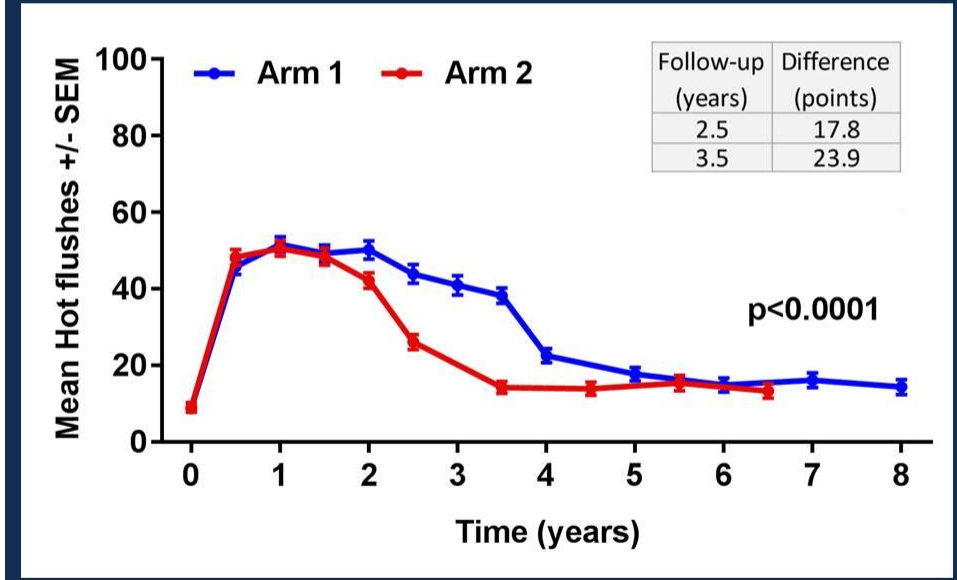
-2 items (Hot flushes, enjoyable sex)

Clinically Relevant:

difference in mean scores ≥10 points

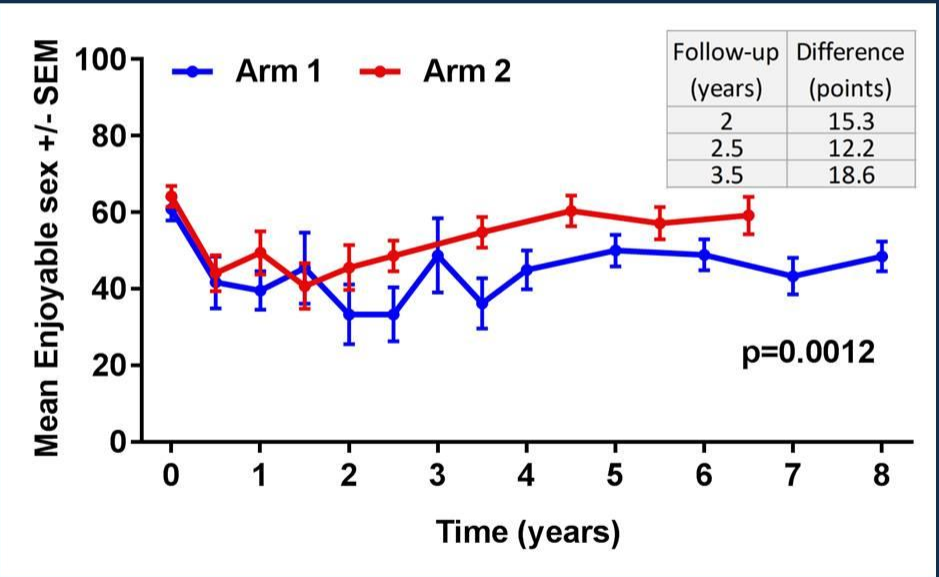
Quality of Life

Hot Flushes



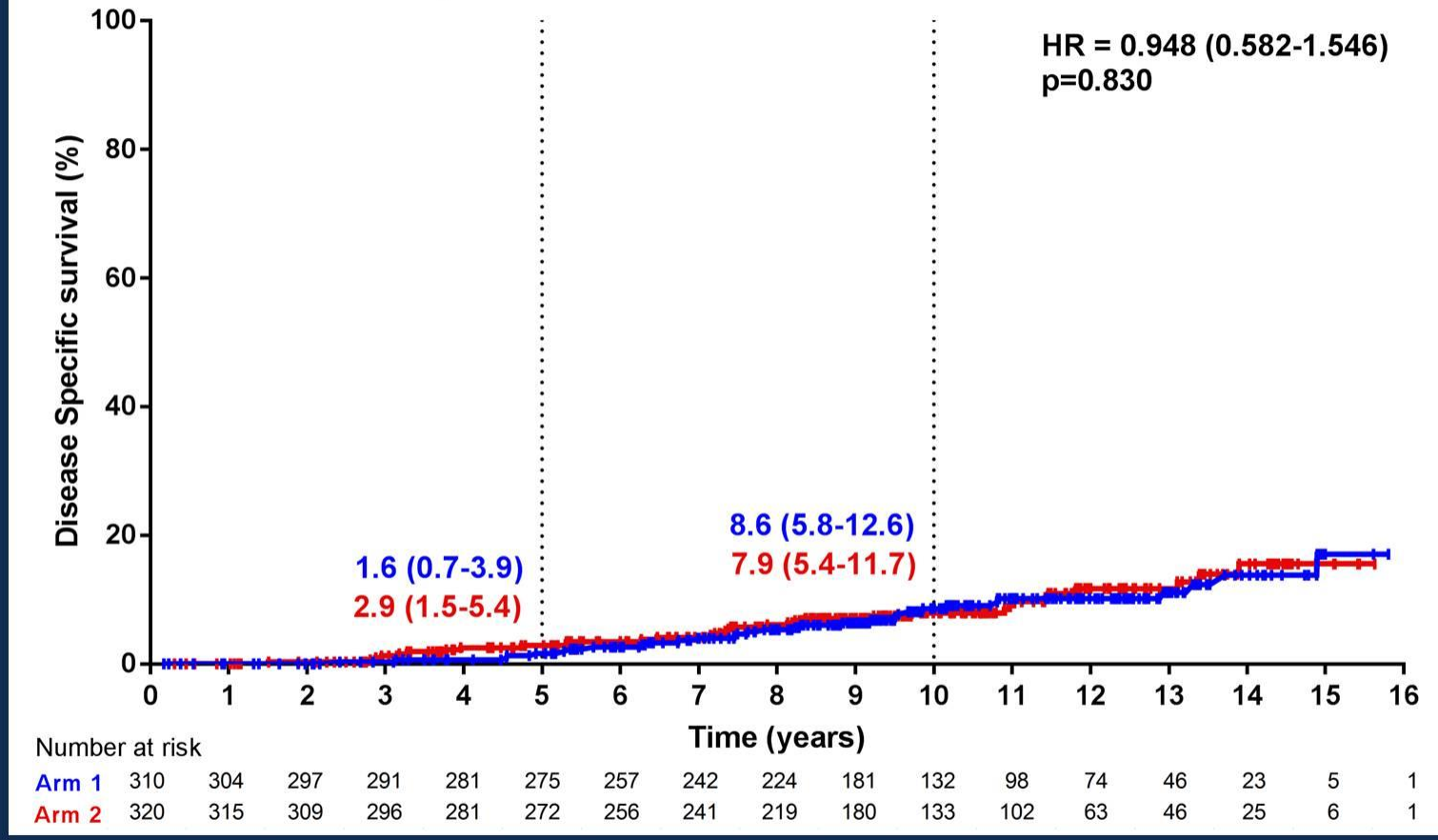
Follow-up (years)	Difference (points)
2.5	17.8
3.5	23.9

Enjoyable sex

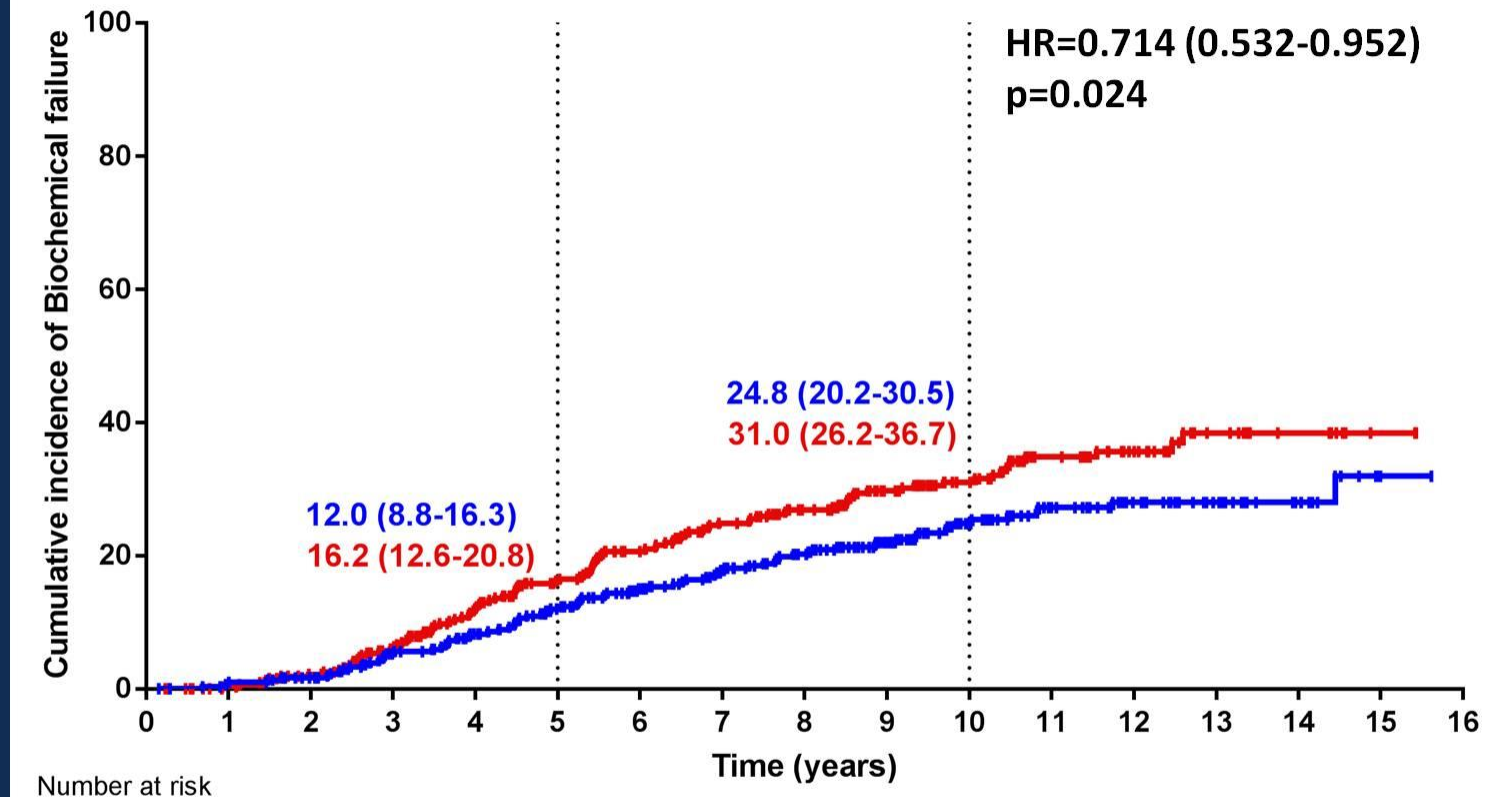


Follow-up (years)	Difference (points)
2	15.3
2.5	12.2
3.5	18.6

Disease Specific Survival



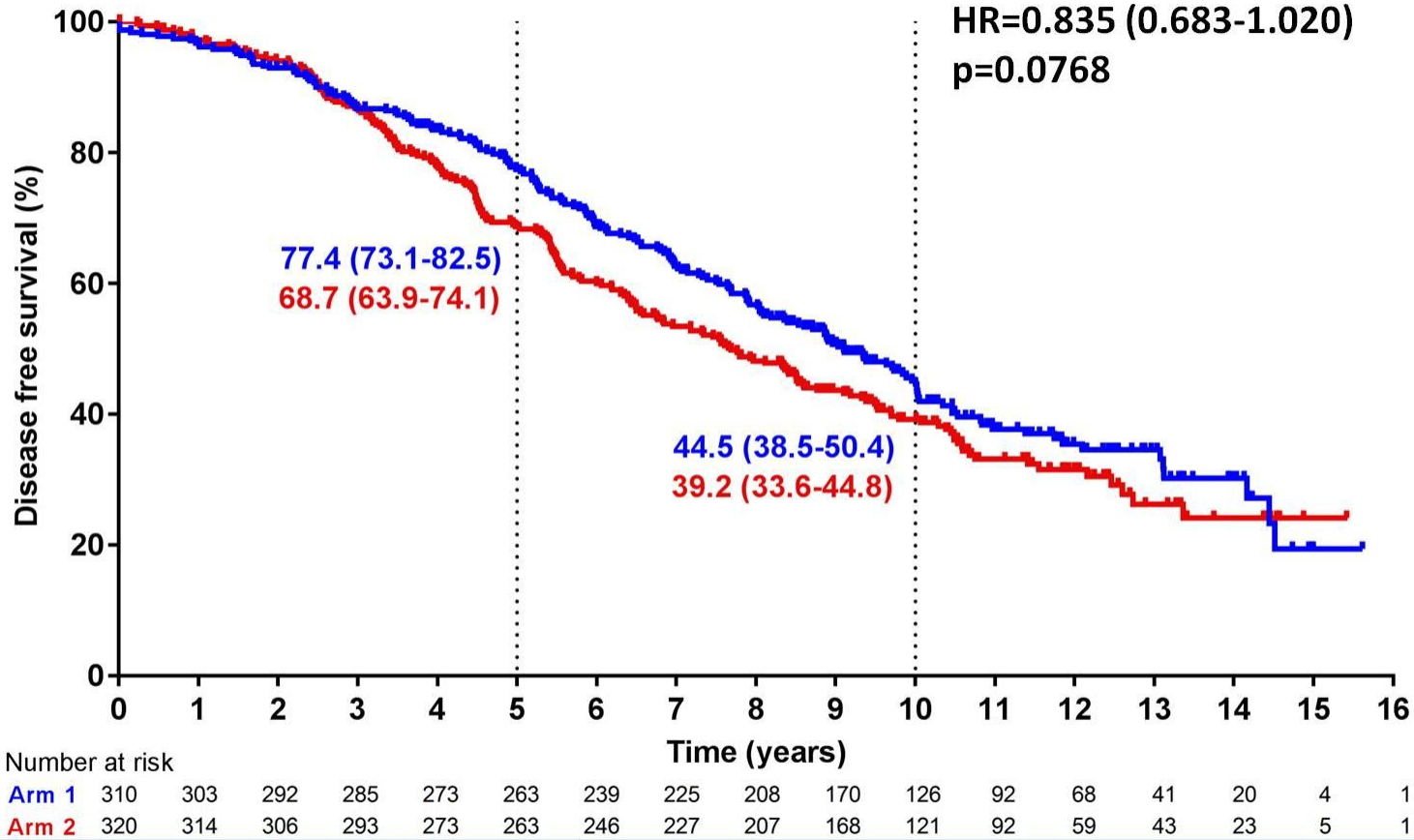
Biochemical Failure (nadir PSA+2)



Number at risk

Arm	306	301	290	269	253	233	206	185	166	129	86	58	40	26	13	2	1
Arm	319	309	298	274	245	215	186	161	144	111	79	48	32	16	9	2	1

Disease Free Survival



Univariate and Multivariate Cox Regression Analysis for Overall Survival

	Univariate		Multivariate	
	HR (95 % CI)	p-value	HR (95 % CI)	p-value
36 vs 18 months [1]	1.02 (0.81-1.29)	0.8412	1.01 (0.80-1.27)	0.9431
Age (years) [1]	1.05 (1.03-1.07)	<0.0001	1.05 (1.03-1.07)	<0.0001
PSA > 20 [1]	0.88 (0.70-1.11)	0.2830	1.12 (0.84-1.49)	0.4482
Gleason score >7 [1]	1.40 (1.10-1.78)	0.0062	1.42 (1.06-1.90)	0.0205
T3 – T4 [1]	1.04 (0.80-1.36)	0.7527	1.21 (0.92-1.60)	0.1752
Biochemical failure [2]	0.88 (0.68-1.13)	0.3126	1.03 (0.79-1.35)	0.8160

[1] At study entry [2] During follow-up

Conclusion

In localised HRPC treated with RT and ADT:

ADT duration can be safely reduced from 36 to 18 months

18 months could represent a threshold effect in ADT duration

Side effects and treatment costs can be reduced

18 months of ADT represents a new standard of care

EXEMPLO 3:

IMvigor211: A Phase III Randomized Study Examining Atezolizumab vs. Chemotherapy for Platinum-Treated Advanced Urothelial Carcinoma

Powles T. et al. EAS 2017

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IMvigor211 Study Design

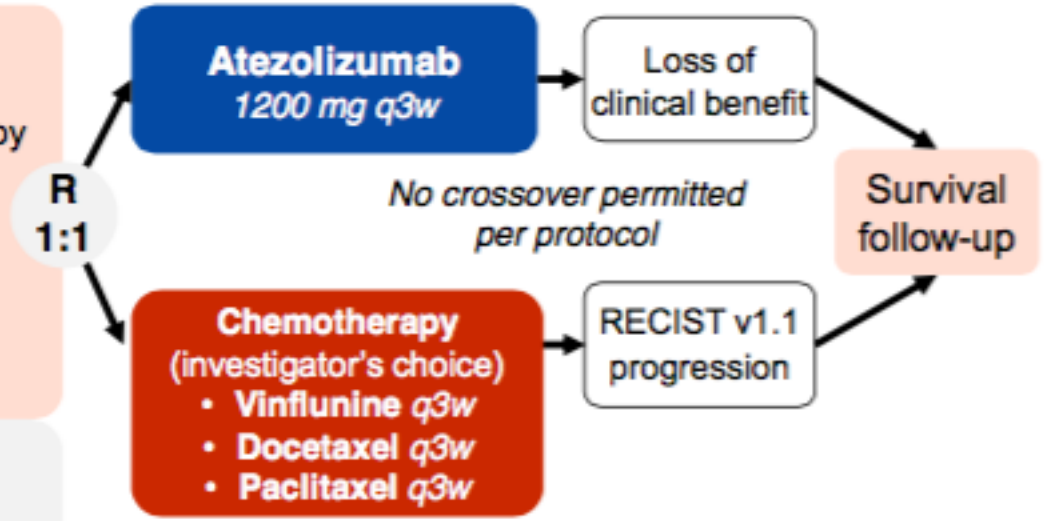
Key Eligibility Criteria[a]

- mUC with progression during or following platinum-based chemotherapy – ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(N = 931)

Stratification Factors

- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)



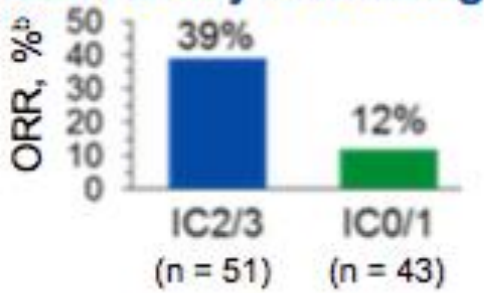
- **Primary endpoint**
  - OS, tested hierarchically in pre-specified populations
- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

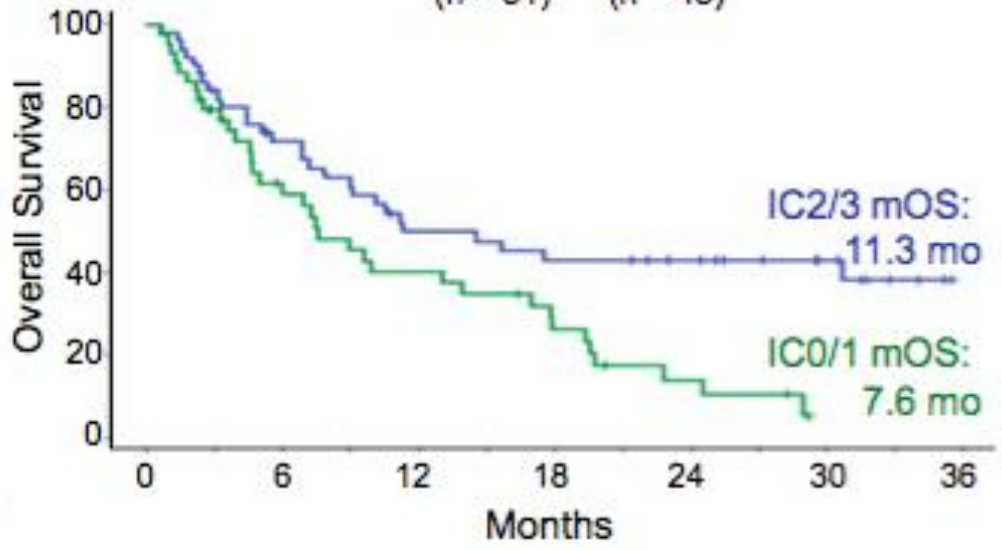
DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. [a] ClinicalTrials.gov, NCT02302807. [b] Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. [c] Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

Powles T, et al. EAS 2017, IMvigor211.

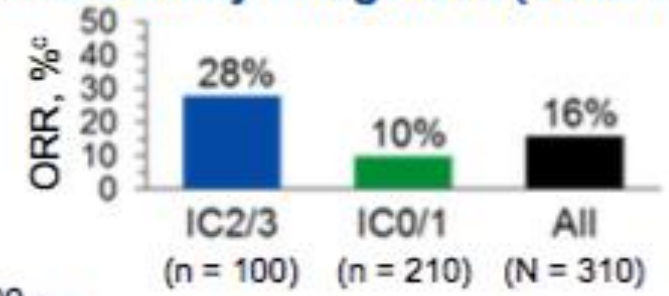
- In Phase I[1,2] and II[3,4] studies in previously treated mUC, atezolizumab demonstrated ORR and OS that were associated with PD-L1 expression on IC[a]

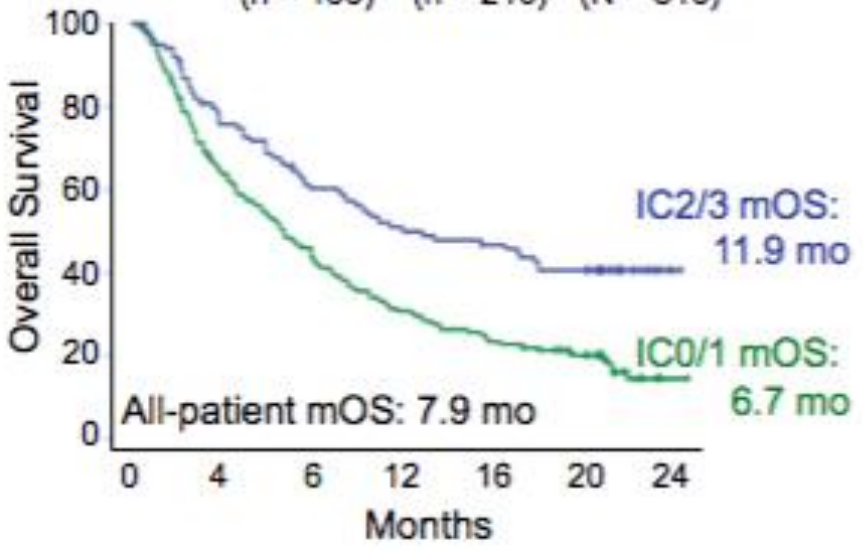
Phase I Study PCD4989g[2]





Phase II Study IMvigor210 (cohort 2)[4,5]





[a] PD-L1 evaluated by VENTANA SP142 IHC assay: IC3 (≥ 10%), IC2 (≥ 5% and < 10%), IC1 (≥ 1% and < 5%) and IC0 (< 1%). [b] Investigator assessed. 1 patient not response evaluable. [c] Per independent review facility.

1. Powles *Nature* 2014. 2. Petrylak ASCO GU 2017. 3. Rosenberg *Lancet* 2016. 4. Loriot ESMO 2016. 5. Roche/Genentech, data on file.

Powles T, et al. EAS 2017, IMvigor211.

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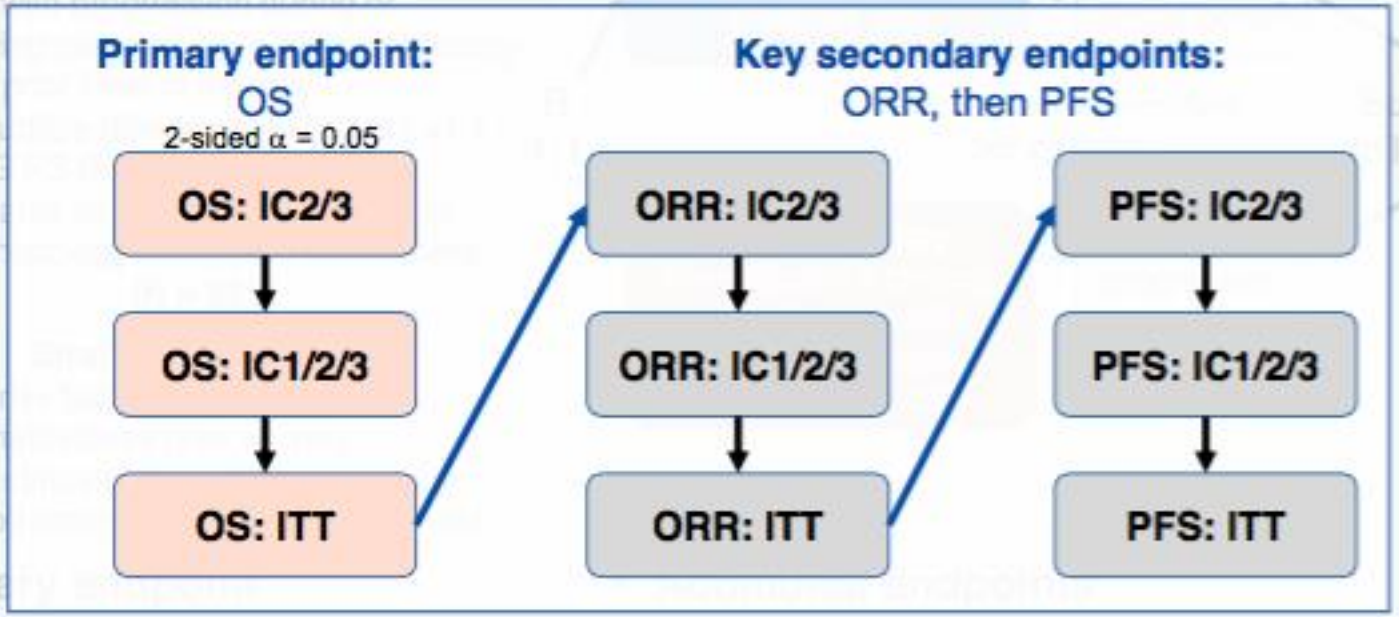
IMvigor211 Study Design



DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TCC, transitional cell carcinoma. [a] ClinicalTrials.gov, NCT02302807. [b] Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. [c] Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

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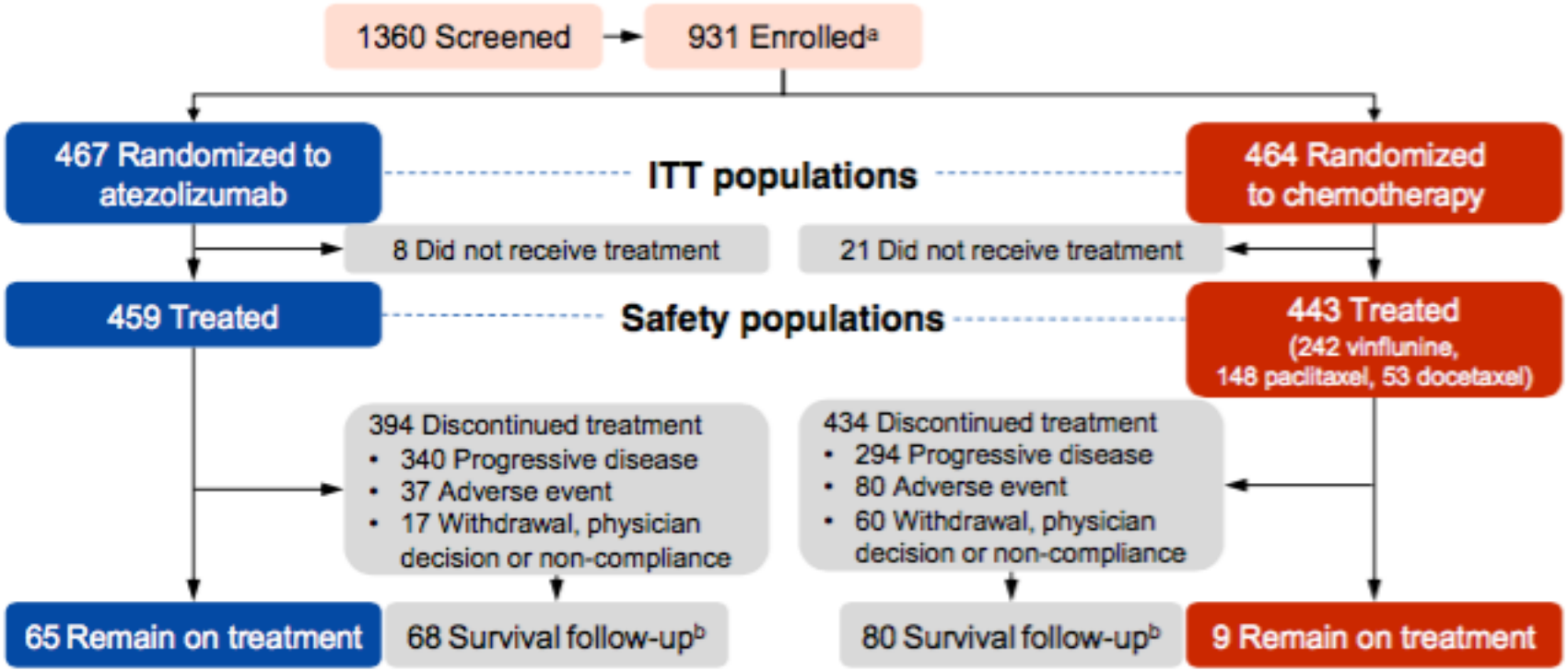
Patient Flowchart



- Enrollment took place at 198 study sites: 712 patients (77%) from Europe, 71 (8%) from North America, 132 (14%) from Asia Pacific, 16 (2%) from other regions
  - Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

[a] 1 patient was randomized to chemotherapy twice due to a randomization error but counted only once in this analysis.
[b] An additional 5 deaths (4 in the chemotherapy arm; 1 in the atezolizumab arm) were collected from public records and included as uncensored deaths in the efficacy analyses.

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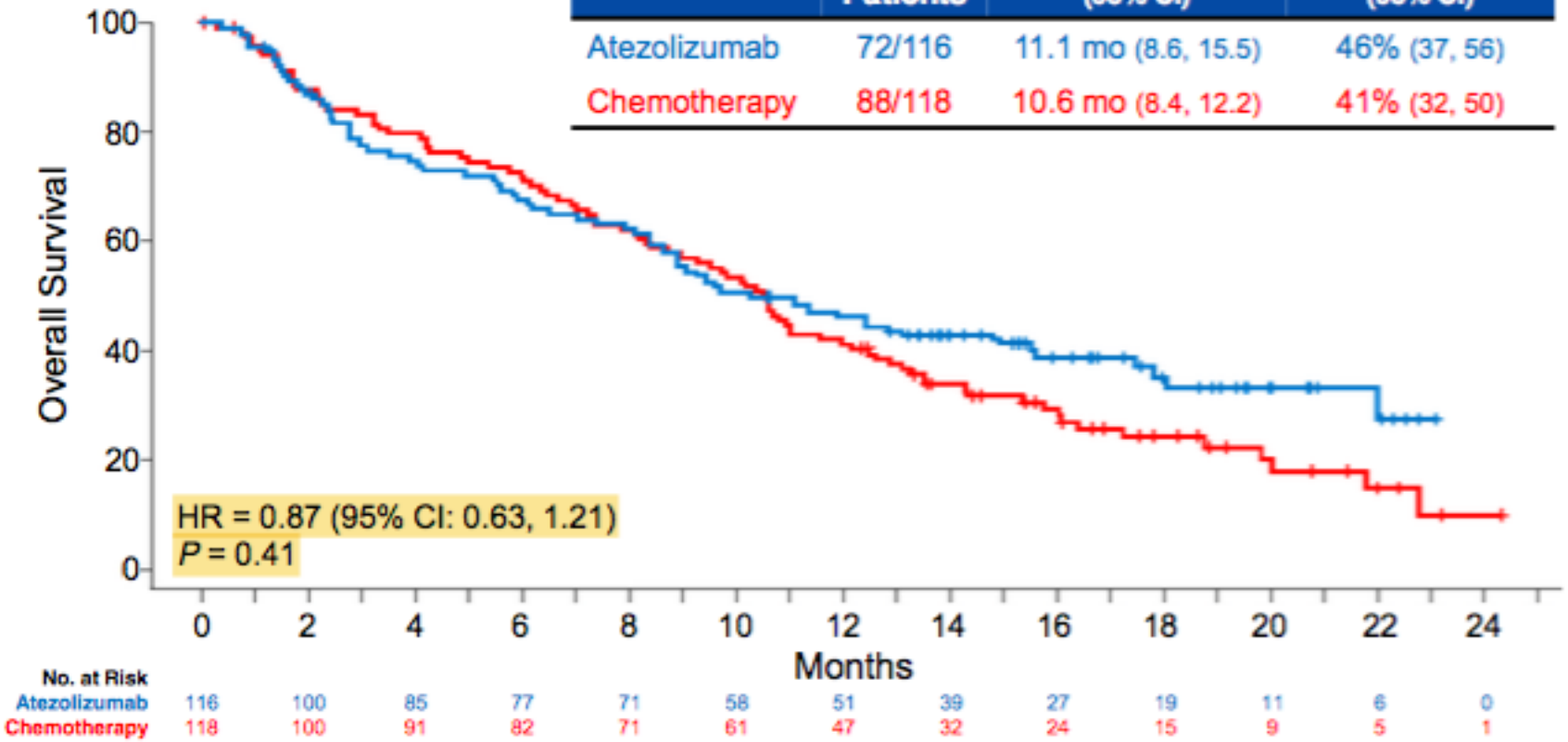
OS Analysis: IC2/3 Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)



HR, hazard ratio.

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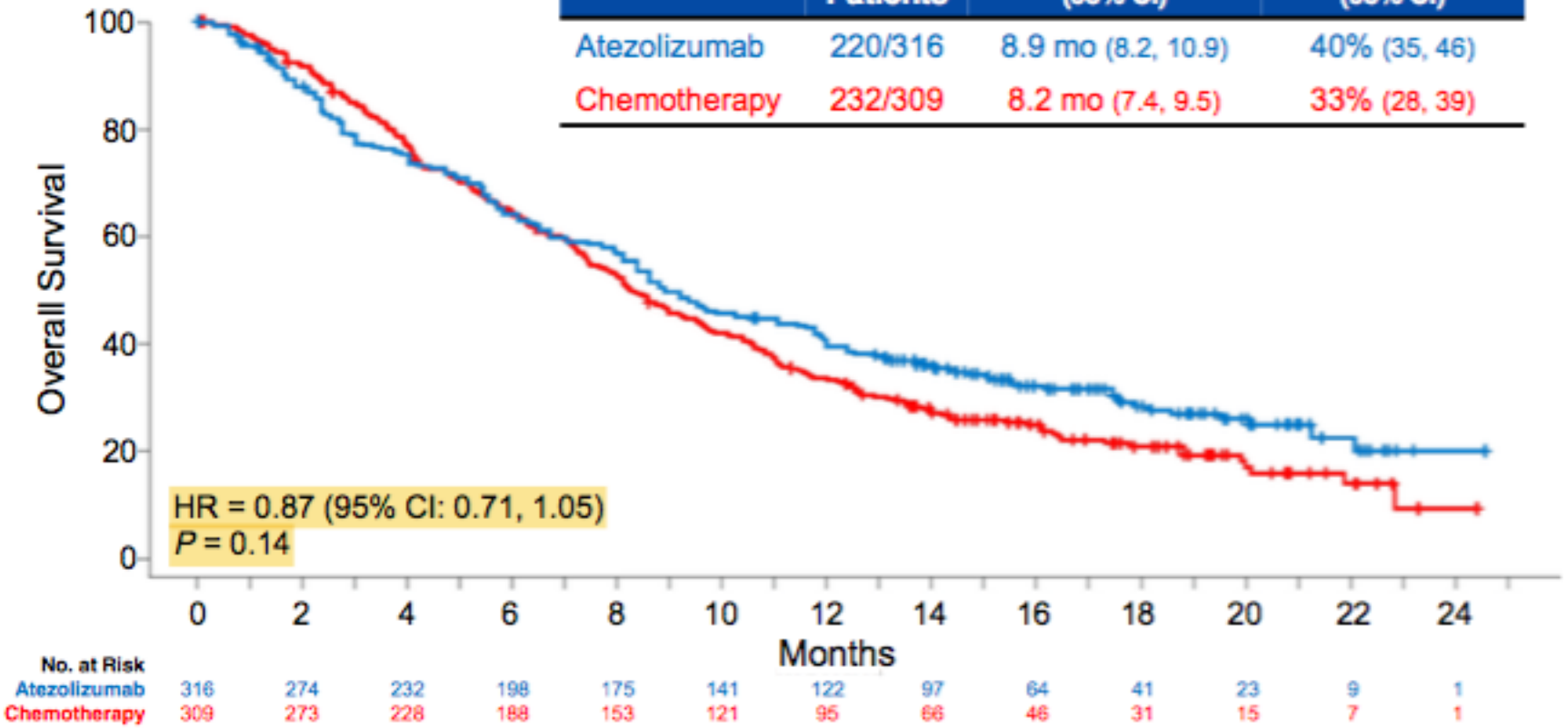
OS Analysis: IC1/2/3 Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	220/316	8.9 mo (8.2, 10.9)	40% (35, 46)
Chemotherapy	232/309	8.2 mo (7.4, 9.5)	33% (28, 39)



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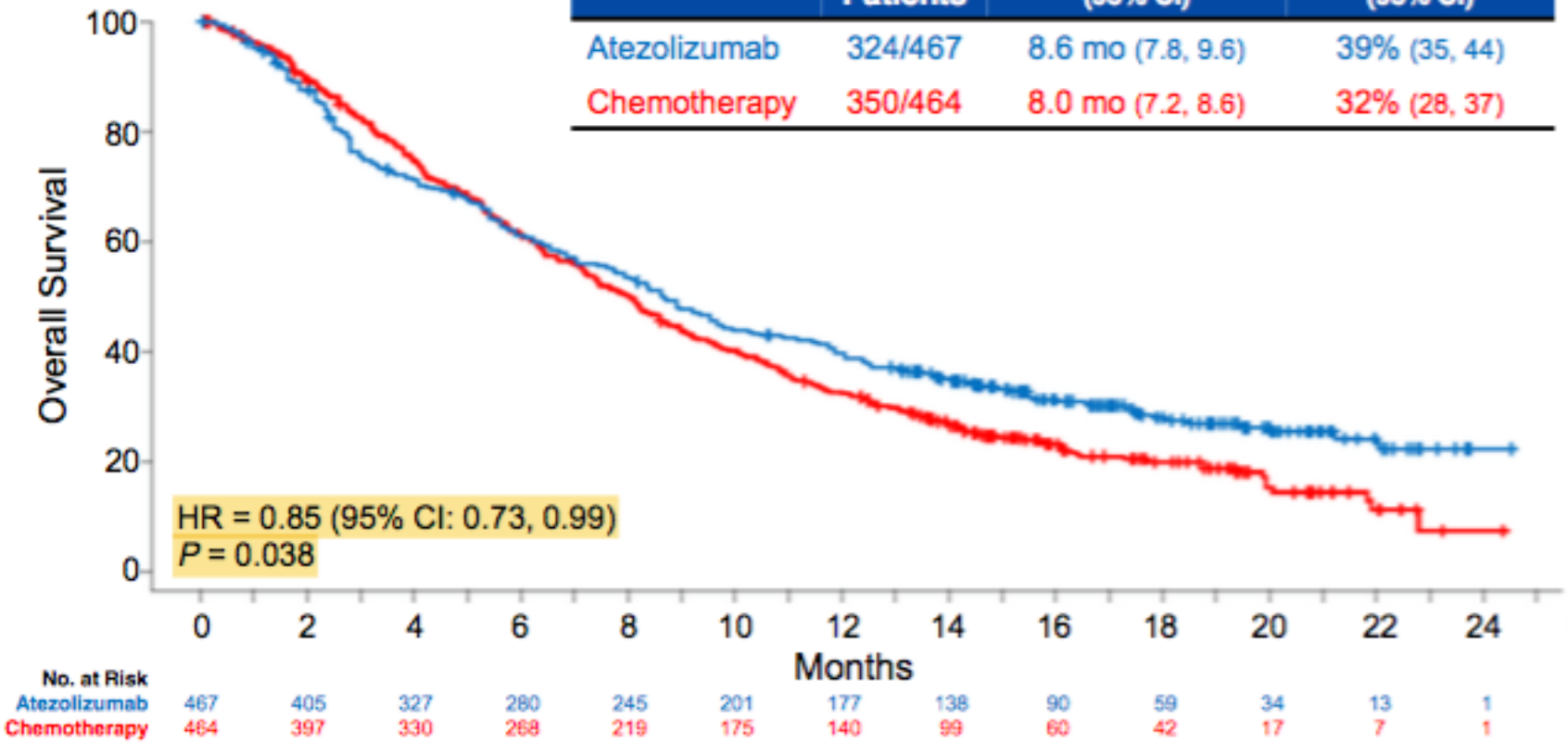
OS Analysis: ITT Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)



- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

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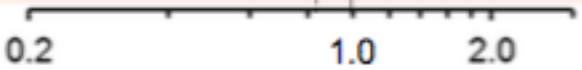
OS in Clinical and Treatment Subgroups

Subgroup		Atezolizumab mOS	Chemotherapy mOS
PD-L1 status	IC2/3	11.1 mo	10.6 mo
	IC1/2/3	8.9 mo	8.2 mo
	ITT	8.6 mo	8.0 mo
Tobacco use history	Current	9.2 mo	6.7 mo
	Previous	8.4 mo	8.2 mo
	Never	10.4 mo	8.1 mo
ECOG PS	0	12.0 mo	10.1 mo
	1	6.1 mo	6.4 mo
Primary tumor site	Bladder	8.9 mo	7.7 mo
	Urethra	NE	12.5 mo
	Renal pelvis	5.9 mo	8.5 mo
	Ureter	8.9 mo	8.1 mo
Liver metastases	Yes	4.0 mo	5.2 mo
	No	10.1 mo	9.7 mo
Lymph node–only metastases	Yes	17.4 mo	12.2 mo
	No	8.1 mo	7.2 mo
Chemotherapy stratification	Taxane	8.3 mo	7.5 mo
	Vinflunine	9.2 mo	8.3 mo



NE, not estimable. Unstratified hazard ratios are plotted. Dashed line refers to HR for ITT population.

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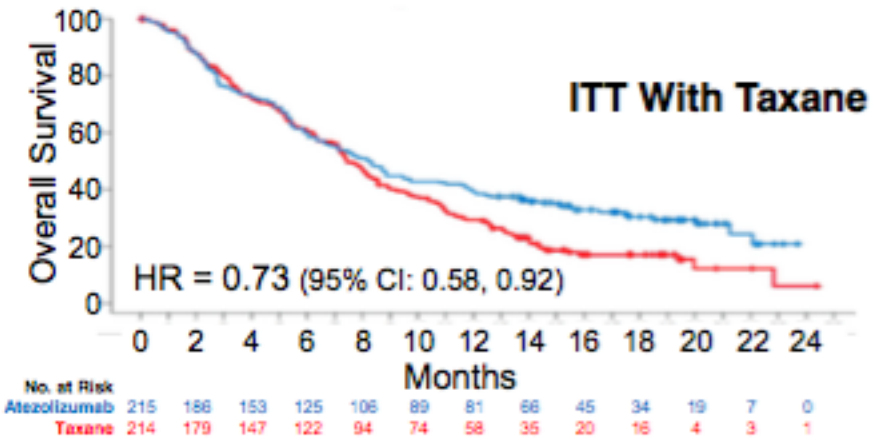
OS by Chemotherapy Type



- OS was also examined in subgroups based on chemotherapy type at randomization
  - Improved OS was observed with atezolizumab vs. taxanes

Subgroup	Median OS (95% CI)
Atezolizumab	8.3 mo (6.6, 9.8)
Taxane	7.5 mo (6.7, 8.6)

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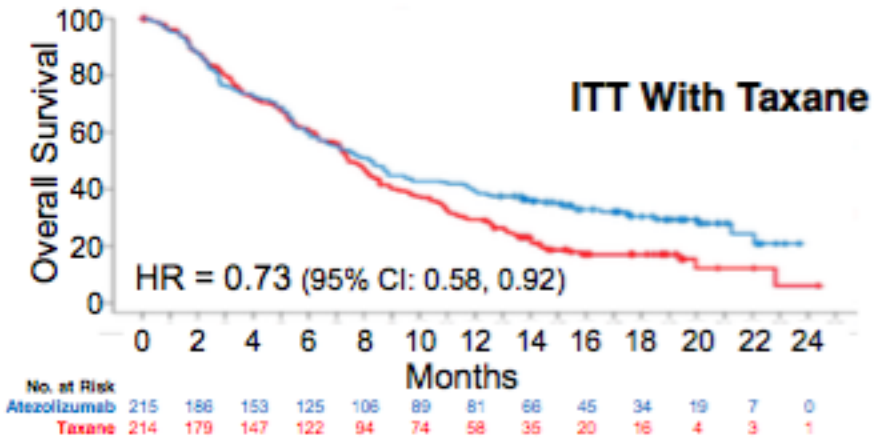
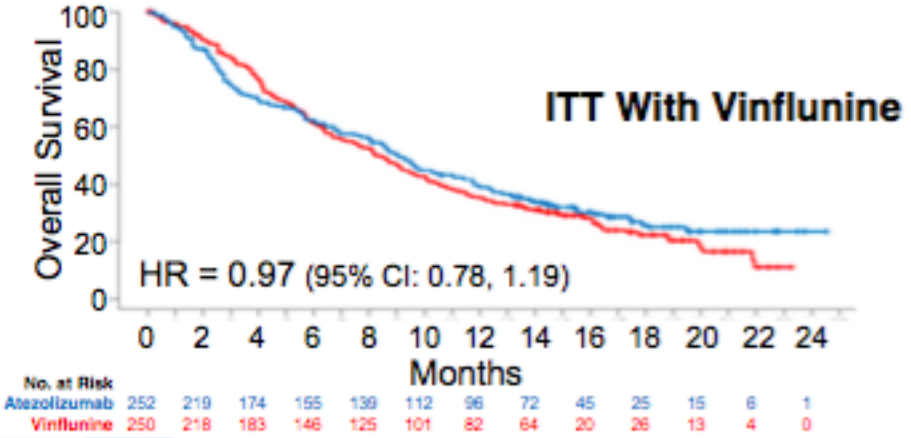
OS by Chemotherapy Type





- OS was also examined in subgroups based on chemotherapy type at randomization
  - Improved OS was observed with atezolizumab vs. taxanes

Subgroup	Median OS (95% CI)
Atezolizumab	8.3 mo (6.6, 9.8)
Taxane	7.5 mo (6.7, 8.6)

Subgroup	Median OS (95% CI)
Atezolizumab	9.2 mo (7.9, 10.4)
Vinflunine	8.3 mo (6.9, 9.6)

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Response by PD-L1 Subgroup

Confirmed ORR[a]	IC2/3		IC1/2/3		ITT	
	Atezo (n = 113)	Chemo (n = 116)	Atezo (n = 312)	Chemo (n = 306)	Atezo (n = 462)	Chemo (n = 461)
Responders, n (%)	26 (23%)	25 (22%)	44 (14%)	45 (15%)	62 (13%)	62 (13%)
95% CI, %	16, 32	15, 30	10, 19	11, 19	11, 17	11, 17
CR, n (%)	8 (7%)	8 (7%)	11 (4%)	13 (4%)	16 (3%)	16 (3%)

- Objective response was similar between arms

Atezo, atezolizumab; Chemo, chemotherapy; CR, complete response.
[a] Confirmed RECIST v1.1 responses were assessed as an exploratory endpoint.

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Confirmed ORR[a]	IC2/3		IC1/2/3		ITT	
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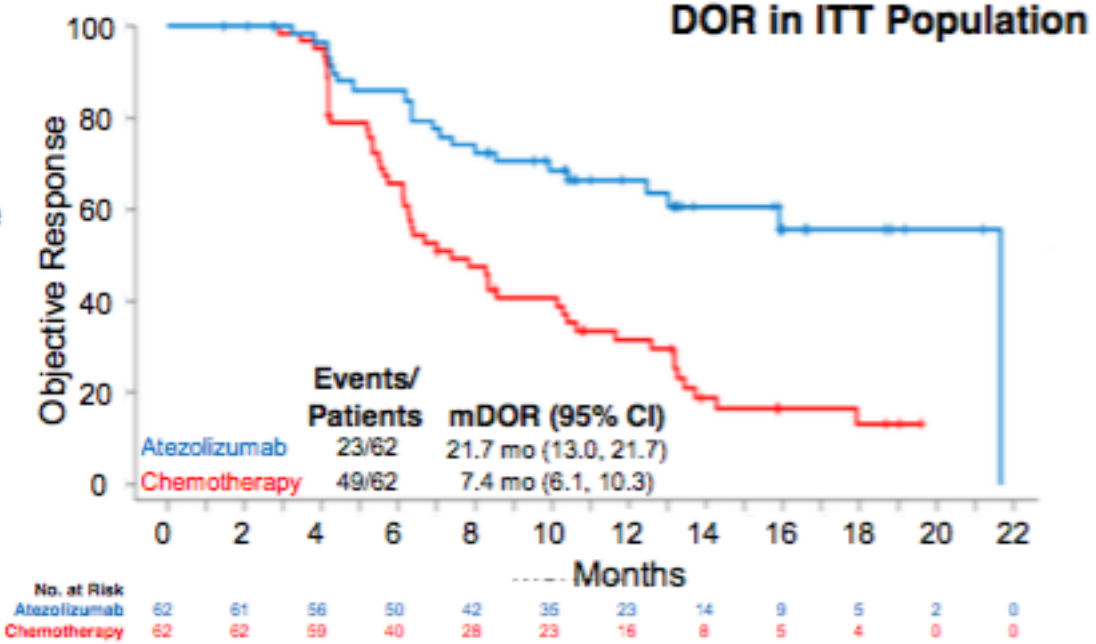
- Objective response was similar between arms
- Responses to atezolizumab were durable regardless of PD-L1 status
  - 63% of patients in the atezolizumab arm and 21% in the chemotherapy arm had ongoing responses at data cutoff

DOR in ITT Population



mDOR, median DOR.
[a] Confirmed RECIST v1.1 responses were assessed as an exploratory endpoint.

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Disease Control

Disease Control	IC2/3		IC1/2/3		ITT	
	Atezo (n = 113)	Chemo (n = 116)	Atezo (n = 312)	Chemo (n = 306)	Atezo (n = 462)	Chemo (n = 461)
DCR, %	34%	33%	26%	28%	24%	28%
95% CI, %	25, 43	24, 42	21, 31	23, 34	20, 28	24, 32

- Disease control was also observed across arms
  - DCR is defined by patients with confirmed CR/PR or SD ≥ 24 weeks per RECIST v1.1

DCR, disease control rate.

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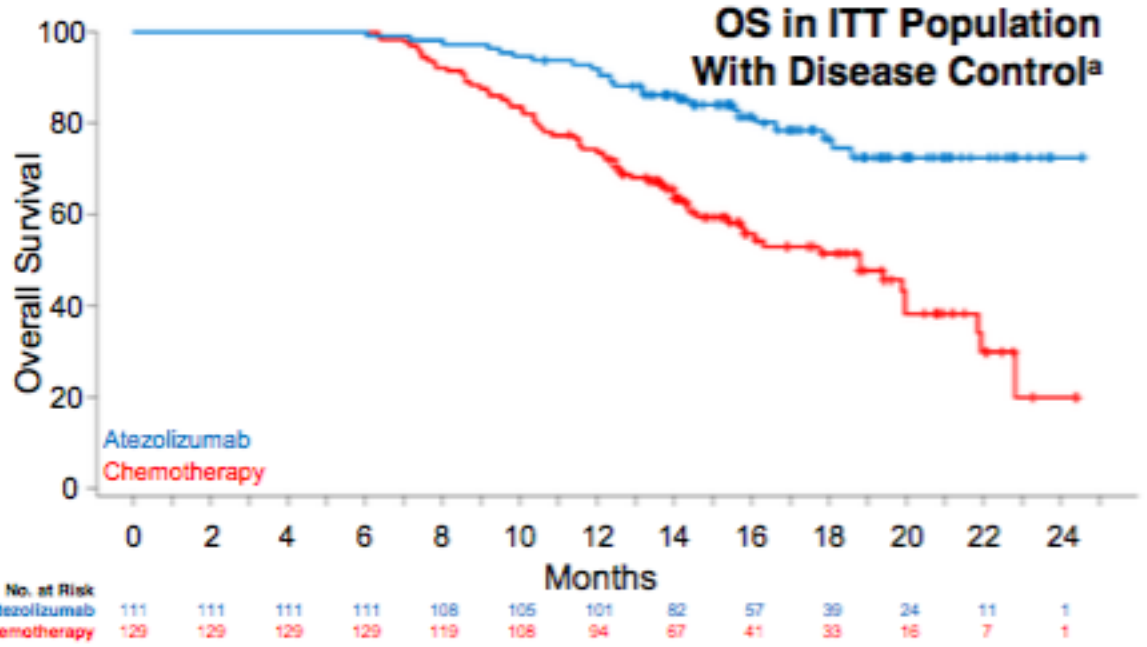
Disease Control

Disease Control	IC2/3		IC1/2/3		ITT	
	Atezo (n = 113)	Chemo (n = 116)	Atezo (n = 312)	Chemo (n = 306)	Atezo (n = 462)	Chemo (n = 461)
DCR, %	34%	33%	26%	28%	24%	28%
95% CI, %	25, 43	24, 42	21, 31	23, 34	20, 28	24, 32

- Disease control was also observed across arms
  - DCR is defined by patients with confirmed CR/PR or SD ≥ 24 weeks per RECIST v1.1
- OS analysis suggests improved survival in patients with disease control in the atezolizumab arm



DCR, disease control rate; PD, progressive disease; SD, stable disease.
[a] Note: Analysis includes patients who survived long enough to be evaluated for disease control.

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Summary

- The primary endpoint of OS was not met in the IC2/3 population (n = 234)
- Due to delayed separation of the Kaplan-Meier curves, the differences in mOS and HR do not fully reflect the clinical activity achieved with atezolizumab
- More patients in the atezolizumab arm were alive and still receiving treatment compared with those in the the chemotherapy arm
- Numerical improvements in OS and median DOR with atezolizumab vs. chemotherapy were observed in ITT patients, with a subset of all patients treated with atezolizumab experiencing long-term remissions
- Improved OS was observed with atezolizumab compared with taxanes
- The safety data showed no new safety signals and demonstrated a more favorable safety profile for atezolizumab than for chemotherapy

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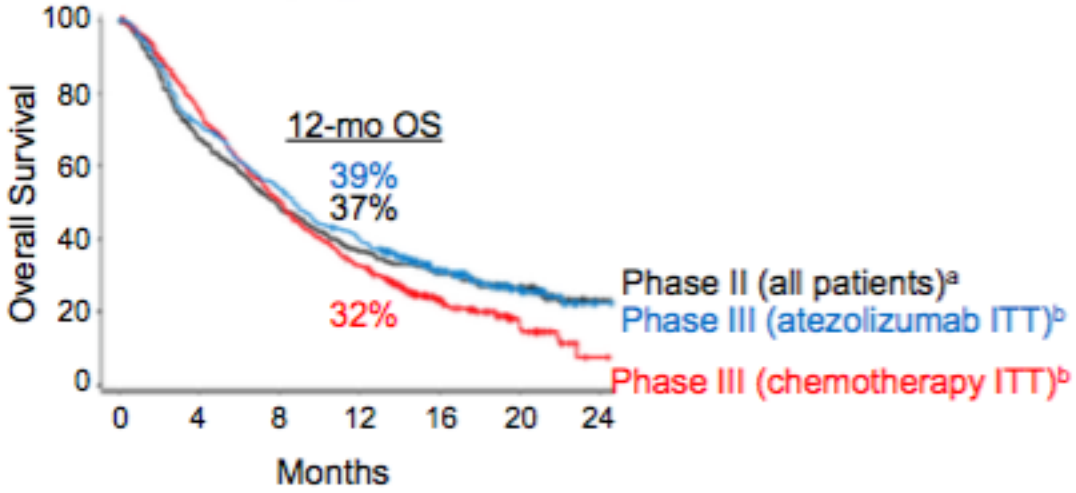
Conclusions

- Atezolizumab OS, ORR and DOR were consistent with the results from IMvigor210 (cohort 2; platinum-treated), confirming the durability of benefit from atezolizumab
  - Atezolizumab 12-mo OS data from IMvigor211 were consistent with Phase I and II data[1,2]



- The positive prognostic (and not predictive) nature of high PD-L1 expression on IC impacted statistical outcomes
- Atezolizumab remains an important treatment option for patients with platinum-treated mUC

1. Petrylak ASCO-GU 2017. 2. Loriot ESMO 2016.
Based on median follow-up of [a] 21.0 mo in reference 2 and [b]17.3 mo in IMvigor211.

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