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INSTITUTO ONCOCLÍNICAS

# DESTAQUES ASCO TUMORES UROLÓGICOS

# Apresentação

A Sociedade Americana de Oncologia Clínica (ASCO) foi fundada em 1964 e, desde então, tornou-se a principal organização voltada para profissionais que lidam diariamente com o câncer em todo o mundo.

Sua missão é promover o combate à doença, habilitando seus membros a oferecer o que existe de melhor em termos de tratamento para o seus pacientes. Para isso, investe maciçamente em pesquisa e é reconhecida por promover educação continuada de alto nível.

Todos os anos, a ASCO organiza seu Congresso, reunindo os mais renomados profissionais do mundo em todas as áreas da Oncologia. O contato direto com profissionais de destaque, o intenso compartilhamento de informações, assim como a troca de experiências cotidianas criam  um ambiente favorável para o aprendizado.

O Grupo Oncoclínicas não poderia deixar de estar presente nesse evento, trazendo para seus pacientes e parceiros todas as novidades apresentadas. Em linha com nosso objetivo de nos transformar no melhor grupo de Oncologia do país, estivemos presentes com mais de 80 Oncologistas em Chicago, coletando os principais e mais atualizados dados científicos.

E por meio do Instituto Oncoclínicas conseguimos compilar as informações mais relevantes, transformando-as em um *slide kit*  didático, versátil e inovador. É com prazer que disponibilizamos a vocês, nossos parceiros, o “Melhor da ASCO 2017”.

Instituto Oncoclínicas

# CONFLITOS DE INTERESSE

Esses slides estão isentos de conflitos de interesses e possuem finalidade essencialmente educacional.

# ROTEIRO

1. **CÂNCER DE PROSTATA**

Primeira linha tumores alto risco: LATITUDE E STAMPEDE

Tempo de Hormoniterapia: 18 x 36 meses

2. **CÂNCER RENAL**

Tratamento adjuvante: PROTECT

3. **CÂNCER DE BEXIGA**

Imunoterapia: KEYNOTE-045

# DESTAQUES ASCO 2017

## *CÂNCER DE PRÓSTATA*

PÓS 2017 ASCO ANNUAL MEETING

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# LATITUDE: A phase 3, double-blind, randomized trial of androgen deprivation therapy with abiraterone acetate plus prednisone or placebos in newly diagnosed high-risk metastatic hormone-naïve prostate cancer patients

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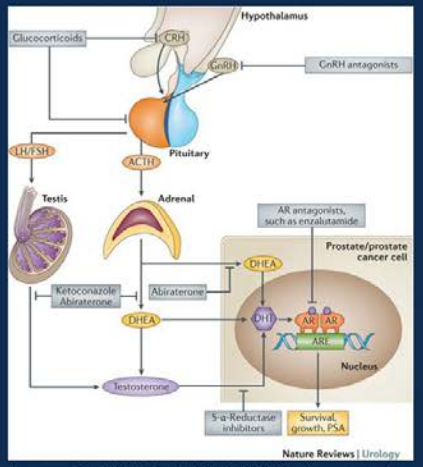
## De novo metastatic prostate cancer

- Metastatic castration-naïve prostate cancer (mCNPC) incidence is[1-5]:
  - ~3% in US and rising;
  - ~6% across Europe
  - ~4-10% in Latin America
  - ~60% in Asia-Pacific
- Historically, androgen deprivation therapy (ADT) has been the standard of care[6]
- Most men with metastases progress to mCRPC largely driven by reactivation of AR signaling[6]




Narayanan S, et al. *Nat Rev Urol*. 2016;13:47-60, with permission from Nature Publishing Group.




1. Weiner AB, et al. *Prostate Cancer Prostatic Dis*. 2016;19:395-397. 2. Buzzoni C, et al. *Eur Urol*. 2015;68:885-890. 3. Chen R, et al. *Asian J Urol*. 2014;1:15-29. 4. Ito K. *Nat Rev Urol*. 2014;11:15-29. 5. Nardi AC. *Int Braz J Urol*. 2012;38:155-166. 6. Yamaoka M, et al. *Clin Cancer Res*. 2010;16:4319-4324.



- Pacientes com câncer de próstata metástatico ao diagnóstico são pacientes não tão comuns, mas com prognóstico mais reservado.

## ADT + docetaxel: a new standard of care for men with mCNPC and high metastatic burden (2015)

| Overall Survival | ADT + DOC | ADT | | |
|---|---|---|---|---|
| | Median (mos) | Median (mos) | HR (95% CI) | *P* Value |
| GETUG-15[1] | 62.1 | 48.6 | 0.88 (0.68-1.14) | 0.3 |
| CHAARTED[2] | 57.6 | 47.2 | 0.73 (0.59-0.89) | 0.0018 |
| STAMPEDE[3] | 60 | 45 | 0.76 (0.62-0.92) | 0.005 |

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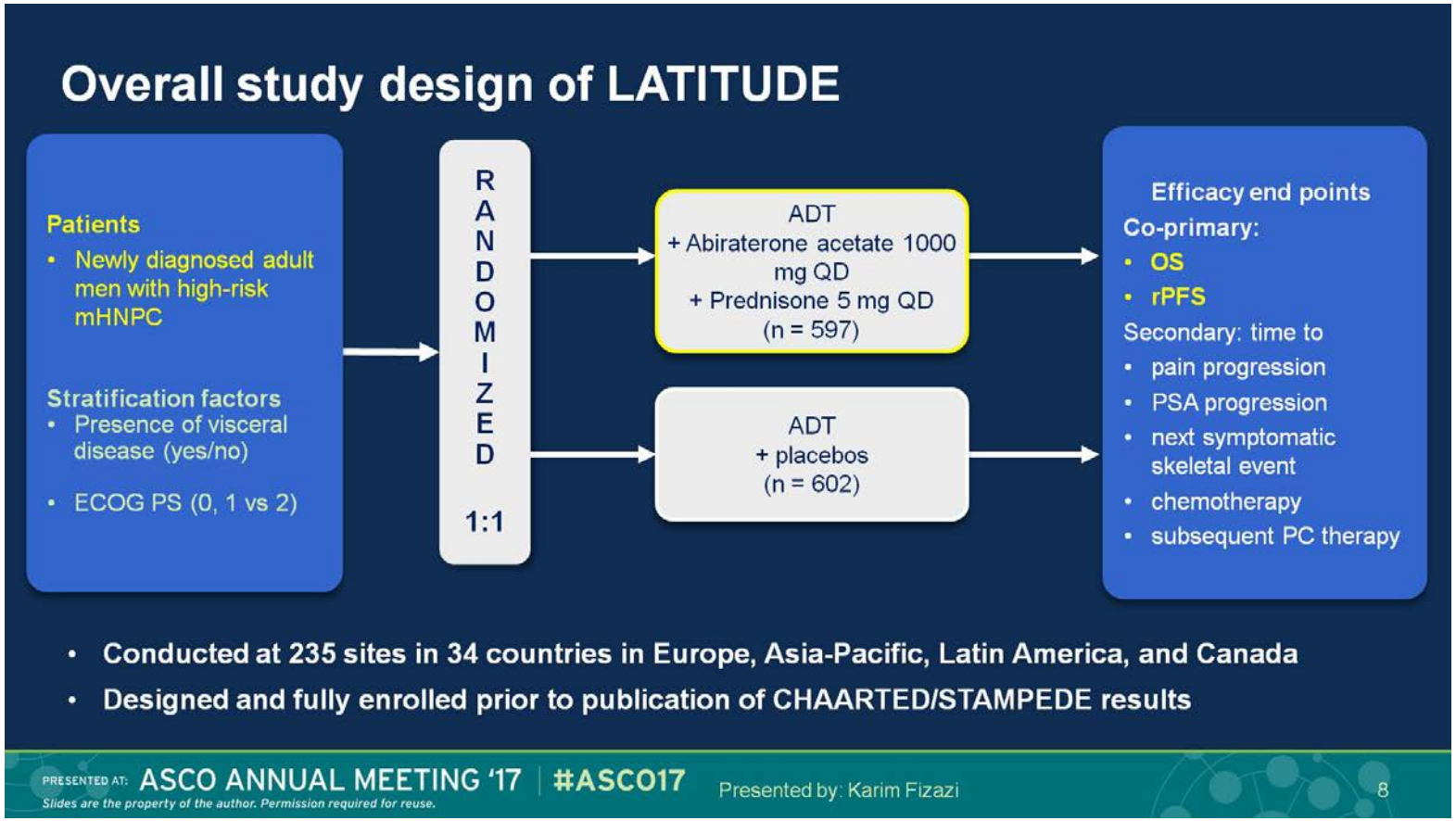
1. Gravis G, et al. *Eur Urol*. 2016;70:256-262. 2. Sweeney C, et al. *N Engl J Med*. 2015;373:737-746; Sweeney C, et al. *Ann Oncol*. 2016;27(Suppl 6):243-265. 3. James N, et al. *Lancet*. 2016;387:1163-1177. and Vale C, et al. *Lancet Oncol* 2016;17:243-256.



- Há 2 anos já é estabelecido que a quimioterapia com docetaxel associada a terapia de deprivação hormonal é o tratamento padrão para este perfil de pacientes



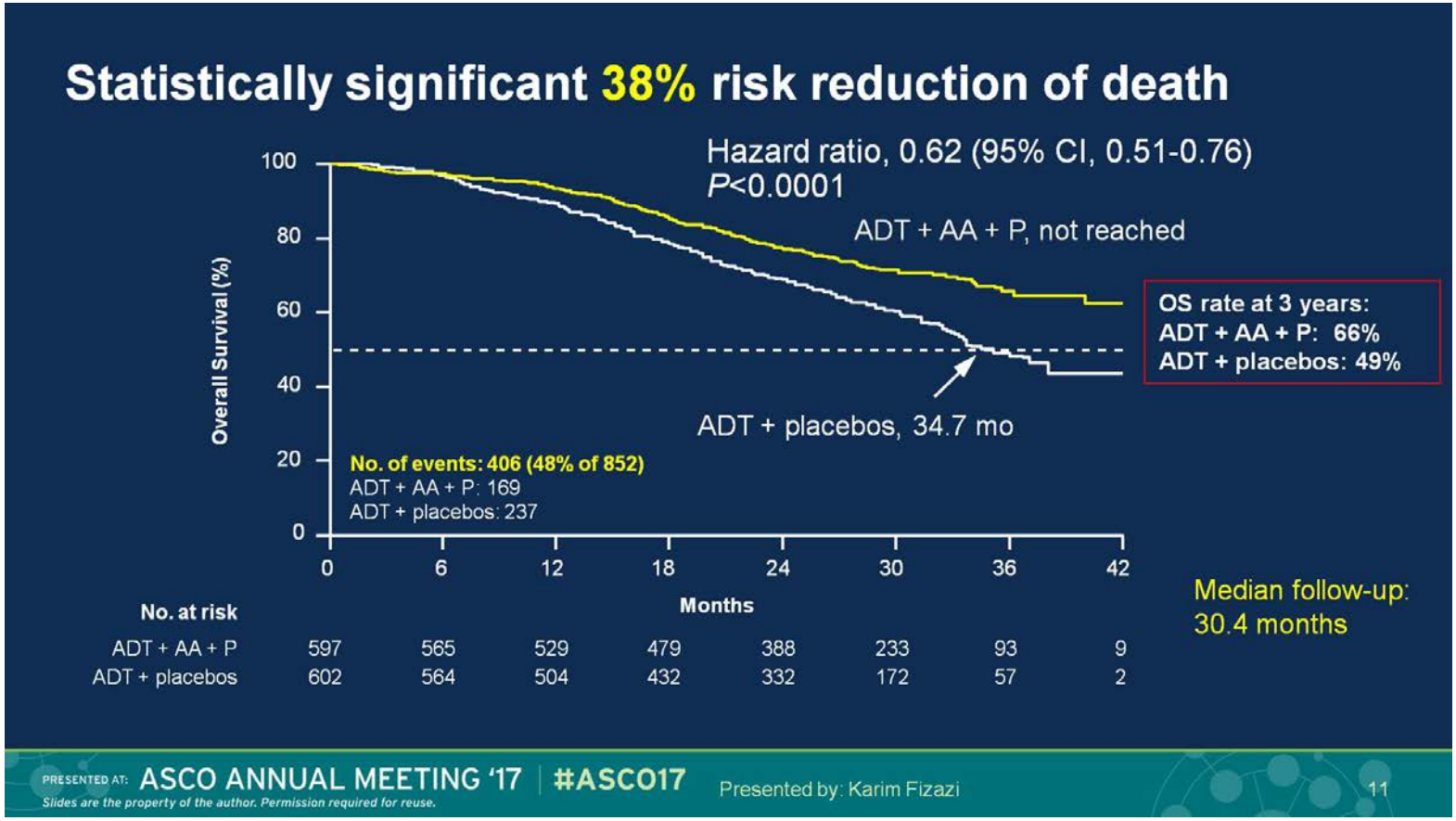

- LATITUDE buscou a abordagem destes pacientes de alto risco, usando a abiraterona ao invés de docetaxel.

## Treatment arms were well balanced

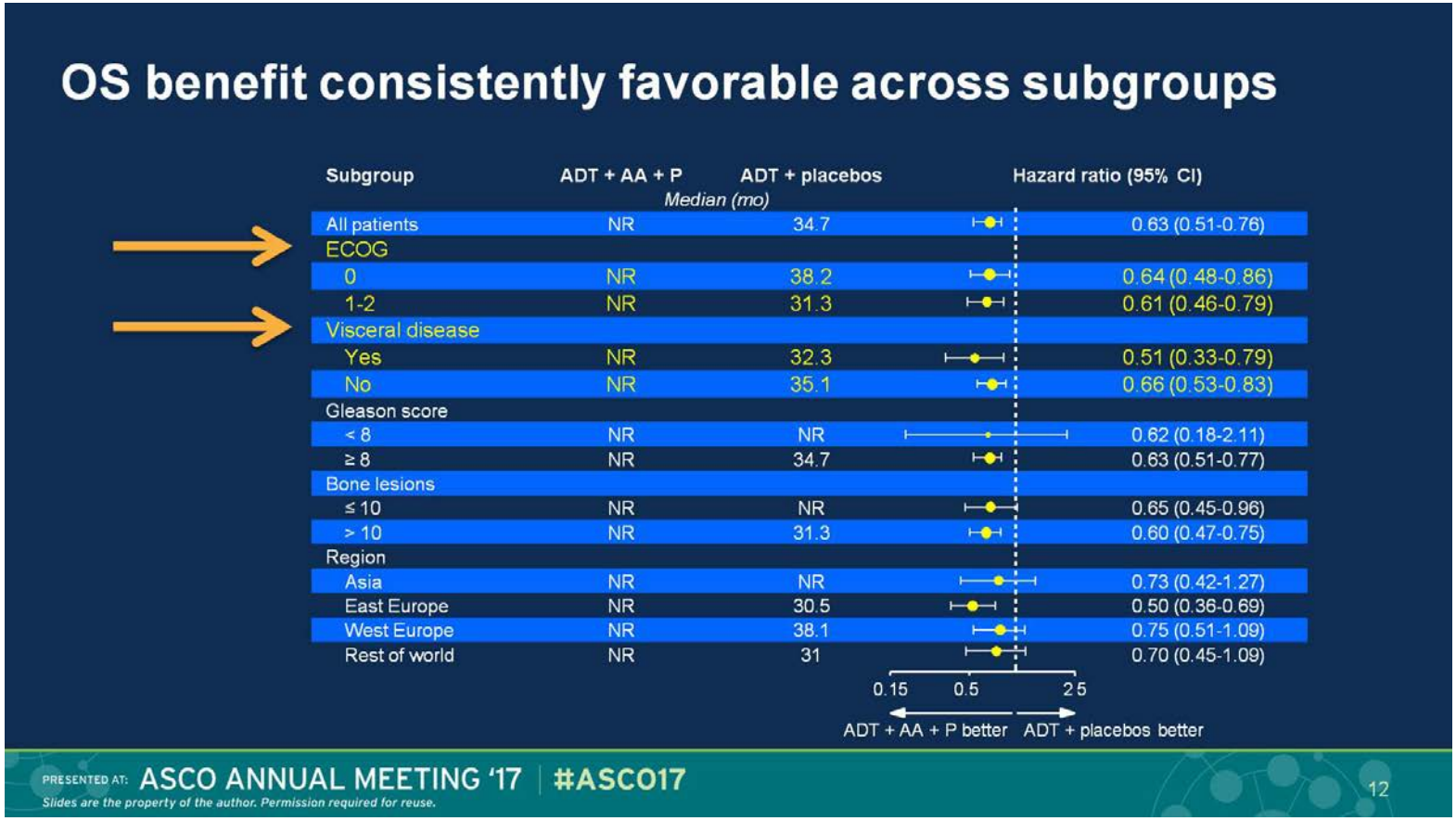
| | ADT + AA + P (n = 597) | ADT + Placebos (n = 602) |
|---|---|---|
| Median age, years (range) | 68.0 (38-89) | 67.0 (33-92) |
| Gleason score ≥ 8 at initial diagnosis | 98% | 97% |
| Patients with ≥ 3 bone metastases at screening | 98% | 97% |
| Extent of disease<br>Bone<br>Liver<br>Lungs<br>Node | 97%<br>5%<br>12%<br>47% | 98%<br>5%<br>12%<br>48% |
| Baseline pain score (BPI-SF Item 3)<br>0-1<br>2-3<br>≥ 4 | 50%<br>22%<br>29% | 50%<br>24%<br>27% |



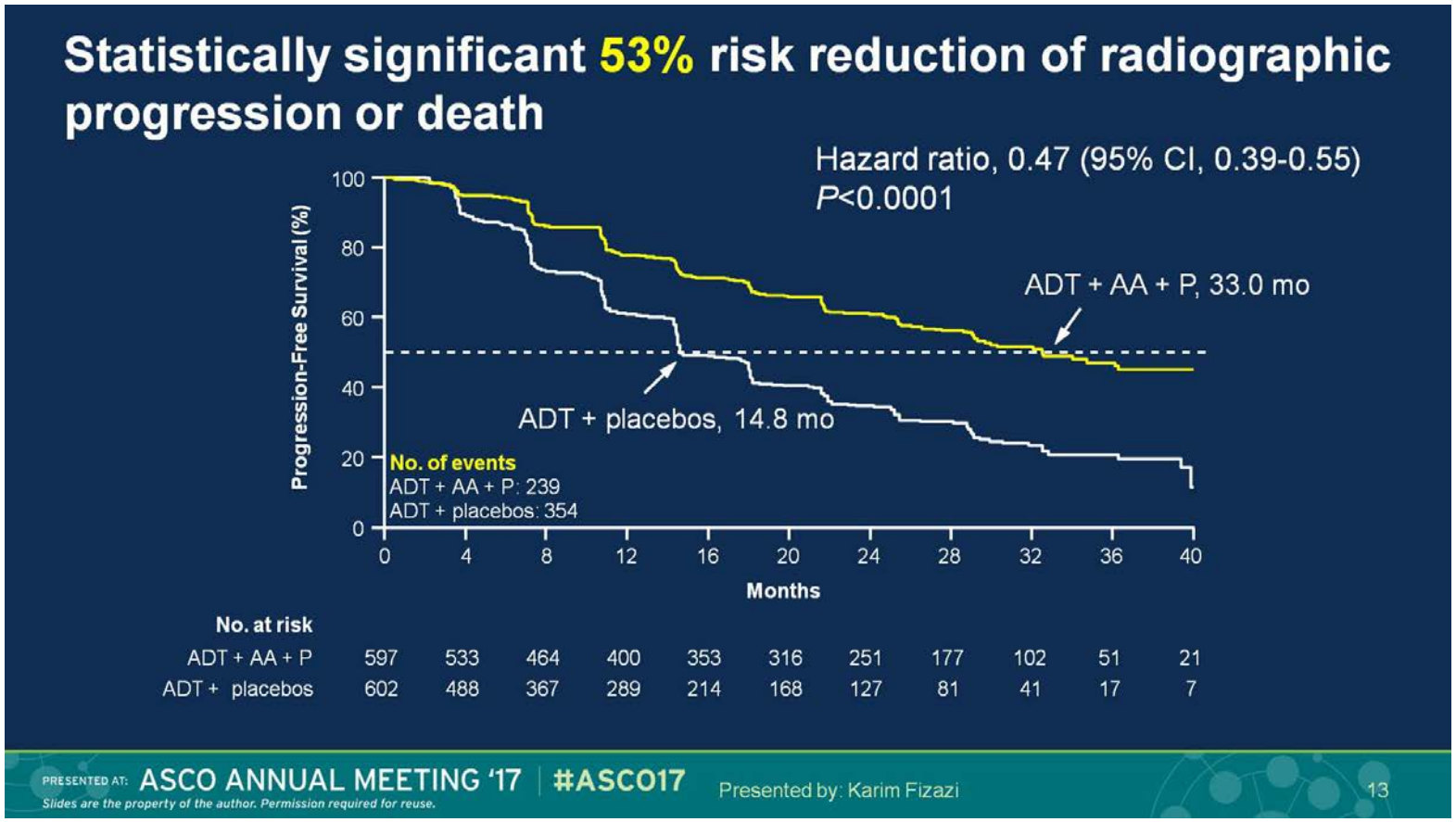

- Pacientes de alto risco, e diferentemente do CHAARTED praticamente todos os pacientes eram gleason 8 ou mais.




- Estudo francamente positivo para sobrevida global!




- Estudo positivo em todos os subgrupos, inclusive nos pacientes com doença visceral.

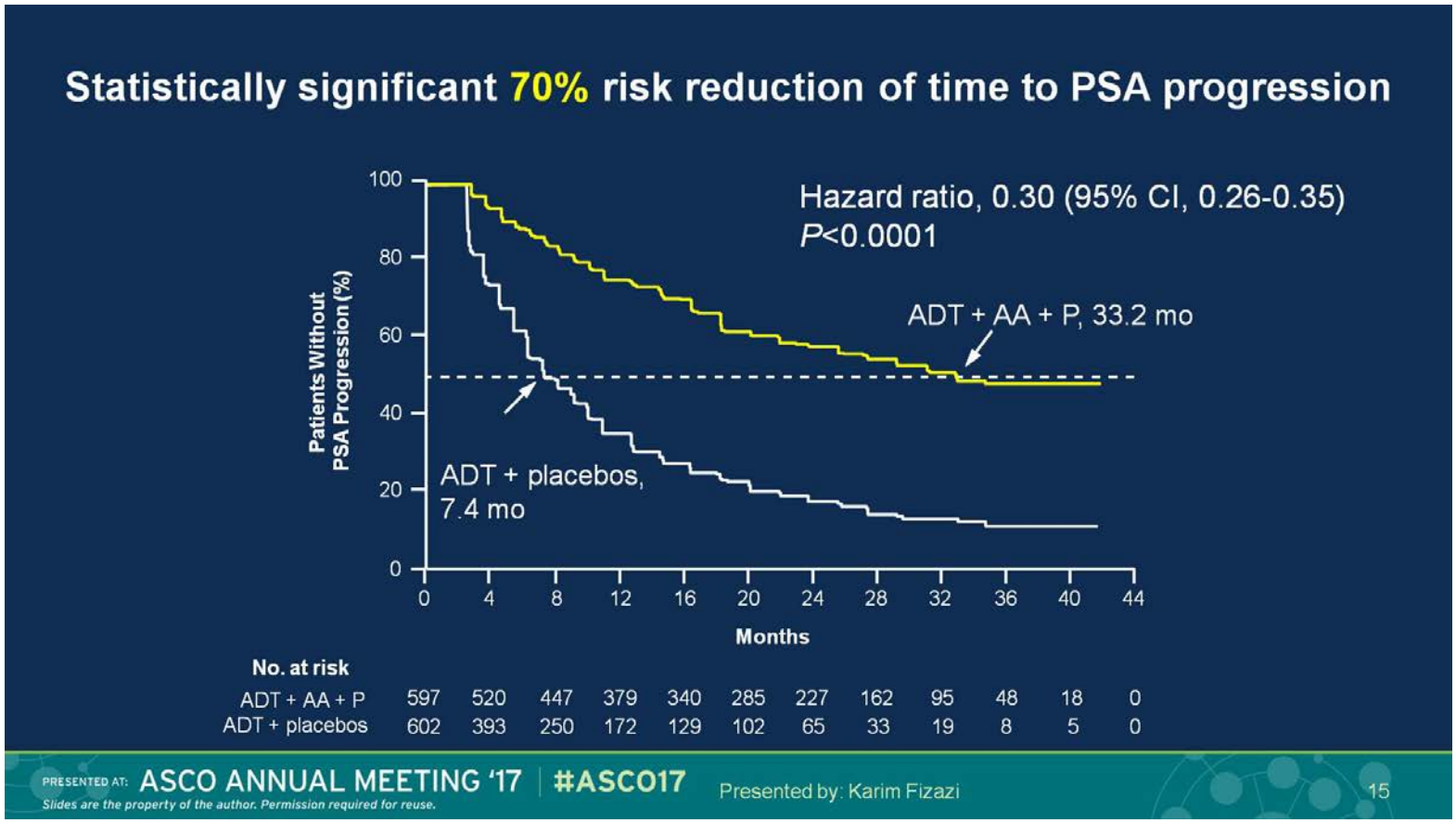



- Estudo positivo em todos os desfechos, primários e secundários.

## Statistically significant improvement in all secondary end points

| Secondary End Points | ADT + AA + P (n = 597) Median (months) | ADT + placebos (n = 602) Median (months) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Time to PSA progression | 33.2 | 7.4 | 0.30 (0.26-0.35) | <0.0001 |
| Time to pain progression | NR | 16.6 | 0.70 (0.58-0.83) | <0.0001 |
| Time to next symptomatic skeletal event | NR | NR | 0.70 (0.54-0.92) | 0.0086 |
| Time to chemotherapy | NR | 38.9 | 0.44 (0.35-0.56) | <0.0001 |
| Time to subsequent prostate cancer therapy | NR | 21.6 | 0.42 (0.35-0.50) | <0.0001 |

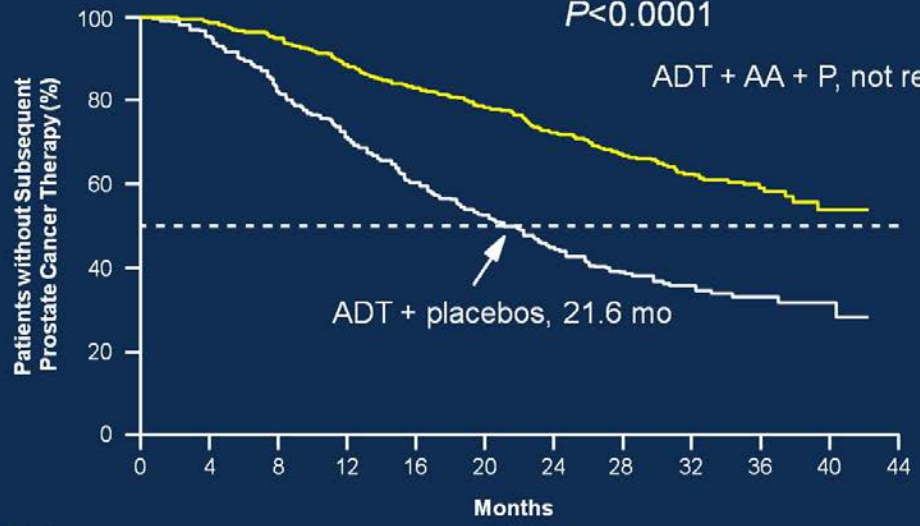
NR = not reached.




- Melhor controle do PSA.

## Statistically significant 58% risk reduction of time to subsequent PC therapy

Hazard ratio, 0.42 (95% CI, 0.35-0.50)
*P*<0.0001




| No. at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ADT + AA + P | 597 | 569 | 531 | 483 | 442 | 399 | 327 | 236 | 141 | 72 | 25 | 0 |
| ADT + placebos | 602 | 558 | 452 | 379 | 299 | 239 | 180 | 116 | 67 | 27 | 10 | 0 |

## Subsequent life-prolonging therapy for prostate cancer

| | ADT + AA + P (n = 597) | ADT + placebos (n = 602) |
|---|---|---|
| | n (%) | n (%) |
| Patients eligible* | n = 314 (53%) | n = 469 (78%) |
| Patients who received life-prolonging therapy | 125 (40) | 246 (52) |
| Docetaxel | 106 (34) | 187 (40) |
| Enzalutamide | 30 (10) | 76 (16) |
| AA-P | 10 (3) | 53 (11) |
| Cabazitaxel | 11 (4) | 30 (6) |
| Radium-223 | 11 (4) | 27 (6) |

*Patients who discontinued treatment and were eligible for subsequent therapy.



- Como terapia subsequente, poucos pacientes no grupo do placebo receberam abiraterona.
- Se o rupo placebo tivesse recebido abiraterona na progressão do PSA desfecho teria sido tão positivo?

## Adverse events of special interest

| Adverse Events | ADT + AA + P (n = 597) | | ADT + placebos (n = 602) | |
|---|---|---|---|---|
| | Grade 3 | Grade 4 | Grade 3 | Grade 4 |
| | % | | % | |
| Hypertension | 20 | 0 | 10 | 0.2 |
| Hypokalemia | 10 | 0.8 | 1 | 0.2 |
| ALT increased | 5 | 0.3 | 1 | 0 |
| AST increased | 4 | 0.2 | 1 | 0 |
| Hyperglycemia | 4 | 0.2 | 3 | 0 |
| Bone pain | 3 | 0 | 3 | 0 |
| Cardiac disorder | 3 | 0.8 | 1 | 0 |
| Anemia | 2 | 0.5 | 4 | 0.2 |
| Back pain | 2 | 0 | 3 | 0 |
| Fatigue | 2 | 0 | 2 | 0 |
| Spinal cord compression | 2 | 0 | 1 | 0.5 |




- Aumento da incidência de efeitos colaterais, especialmente hepáticos e cardiovasculares

## Safety

- Hypertension
  - Only rarely required treatment discontinuation
- Hypokalemia
  - Only 2 patients discontinued treatment due to hypokalemia
  - No hypokalemia-related deaths
- Cardiovascular events
  - 2 patients in each group died of cerebrovascular events;
  - 10 (ADT + AA + P) versus 6 (ADT + placebos) died of cardiac disorders

## Conclusions

- In the phase 3 LATITUDE, addition of AA + P to ADT led to:
  - Significantly improved OS with a 38% reduction in the risk of death
  - Significantly prolonged rPFS (53% reduction) and all secondary end points
- The overall safety profile of ADT + AA + P was consistent with prior studies in patients with mCRPC




- Um novo "standart of care" para este perfil de pacientes.

## Conclusions

- These findings indicate that the addition of AA + P to ADT can potentially be considered a new standard of care for patients with high-risk, newly diagnosed mCNPC

MRC Clinical Trials Unit

Smarter studies
Global impact
Better health

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CANCER RESEARCH UK

UCL

# Adding abiraterone for men with high-risk prostate cancer starting long-term androgen deprivation therapy: Survival results from STAMPEDE

**Nicholas James**
University of Birmingham and Queen Elizabeth Hospital Birmingham
***on behalf of***

Johann De Bono, Melissa R Spears, Noel W Clarke, Malcolm D Mason, David P Dearnaley, Alastair WS Ritchie, J Martin Russell, Clare Gilson, Rob Jones, Silke Gillessen, David Matheson, San Aung, Alison Birtle, Simon Chowdhury, Joanna Gale, Zafar Malik, Joe O'Sullivan, Anjali Zarkar, Mahesh KB Parmar, Matthew R Sydes and the STAMPEDE Investigators

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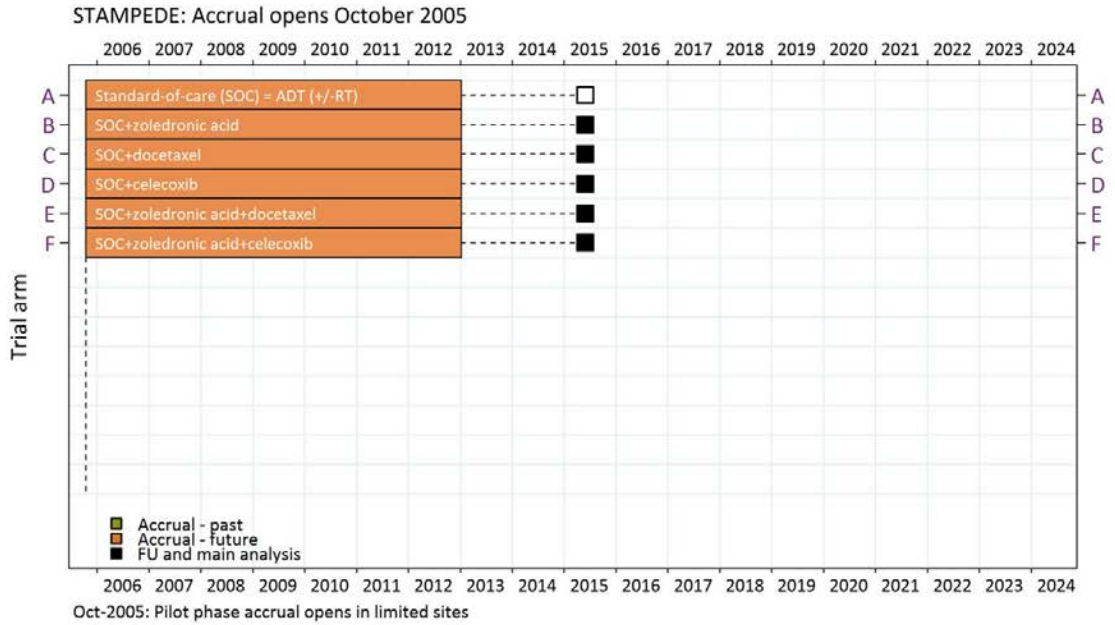
# Setting and hypothesis

- Setting
  - Hormone therapy the mainstay of treatment since 1940s
  - Addition of radiotherapy to N0M0 disease improves outcomes
  - Docetaxel became part of standard of care 2014-5
    - Recruitment to the abiraterone comparison completed prior to this
- Hypothesis
  - Early use of therapies may give a larger absolute benefit in overall survival

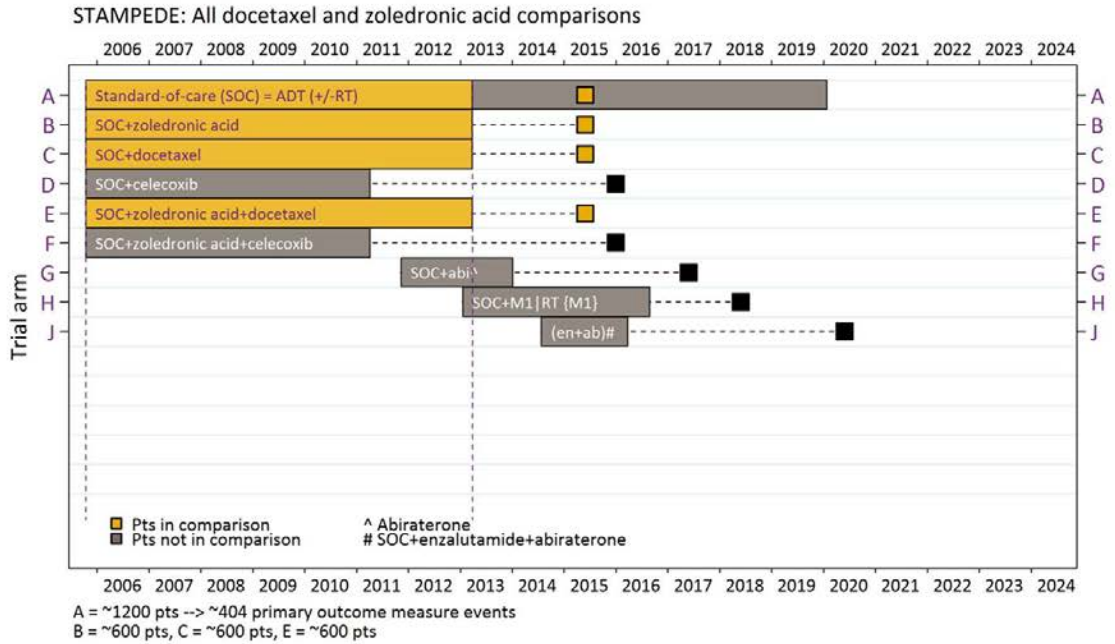
- Um estudo que procurou analisar várias alternativas de tratamento na abordagem dos pacientes de alto risco.

# Trial activity: original research arms



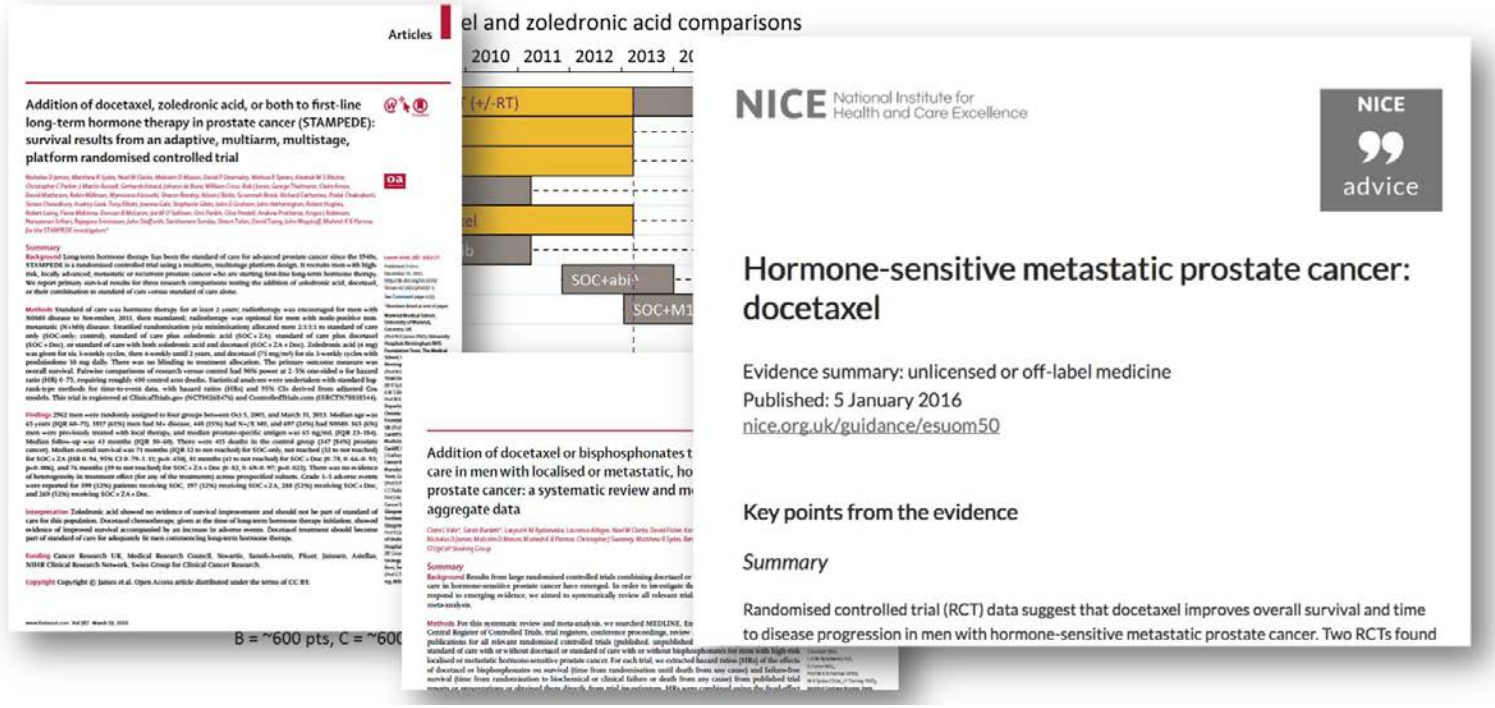

- Pacientes foram inicialmente randomizados para 6 braços diferentes

# Docetaxel & ZA comparisons: patients




- Braços com antiinflamatórios foram descontinuados e posteriormente foram acresecentados o braço com a abiraterona e a combinação abi+enza

# Docetaxel & ZA comparisons: patients




- O braço com a quimioterapia como tratamento inicial associado a deprevação androgência já tinha sido publicado corroborando os dados do estudo CHAARTED

# Inclusion criteria

**Newly-diagnosed**

Any of:

- Metastatic
- Node-Positive
- ≥2 of: Stage T3/4
  PSA≥40ng/ml
  Gleason 8-10

**Relapsing after previous RP or RT with ≥1 of:**

- PSA ≥4ng/ml and rising with doubling time <6m
- PSA ≥20ng/ml
- Node-positive
- Metastatic

**All patients**

- Fit for all protocol treatment
- Fit for follow-up
- WHO performance status 0-2
- Written informed consent

**Full criteria**

www.stampedetrial.org

- População de alto risco, submetida ou não a tratamento definitivo com radio ou cirurgia.

# Outcome measures

**Primary outcome measure**

- Overall survival

**Secondary outcome measures**

- Failure-free survival (FFS)
- Toxicity
- Quality of life
- Skeletal-related events
- Cost effectiveness

**FFS definition**

First of:

- PSA failure
- Local failure
- Lymph node failure
- Distant metastases
- Prostate cancer death

**PSA failure definition**

PSA fall >= 50%

→ 24wk nadir + 50% **and**

→ >4ng/ml

PSA fall of <50%

→ failure at t=0

- População de “menor risco” do que o LATITUDE, com os mesmos desfechos

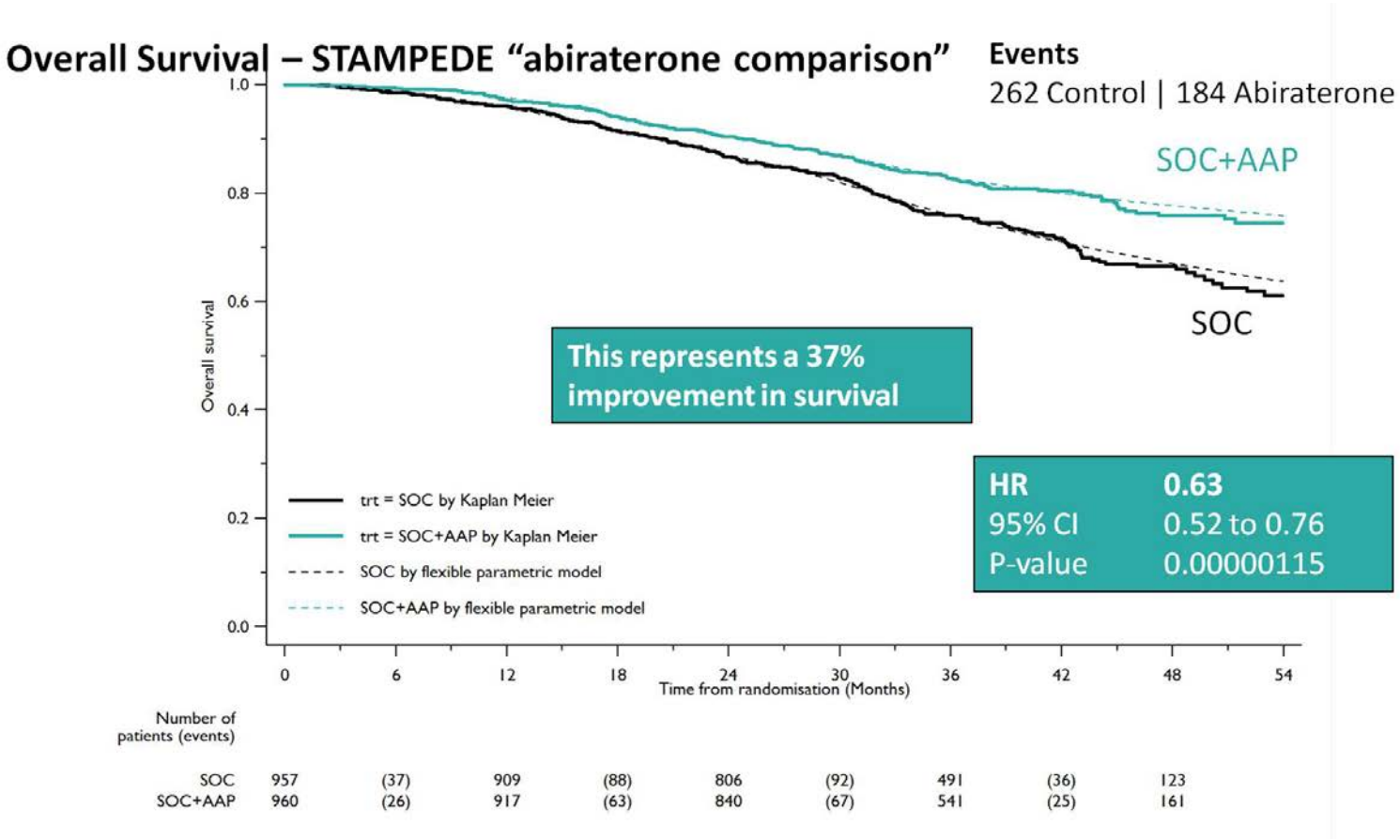
# Patient characteristics

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

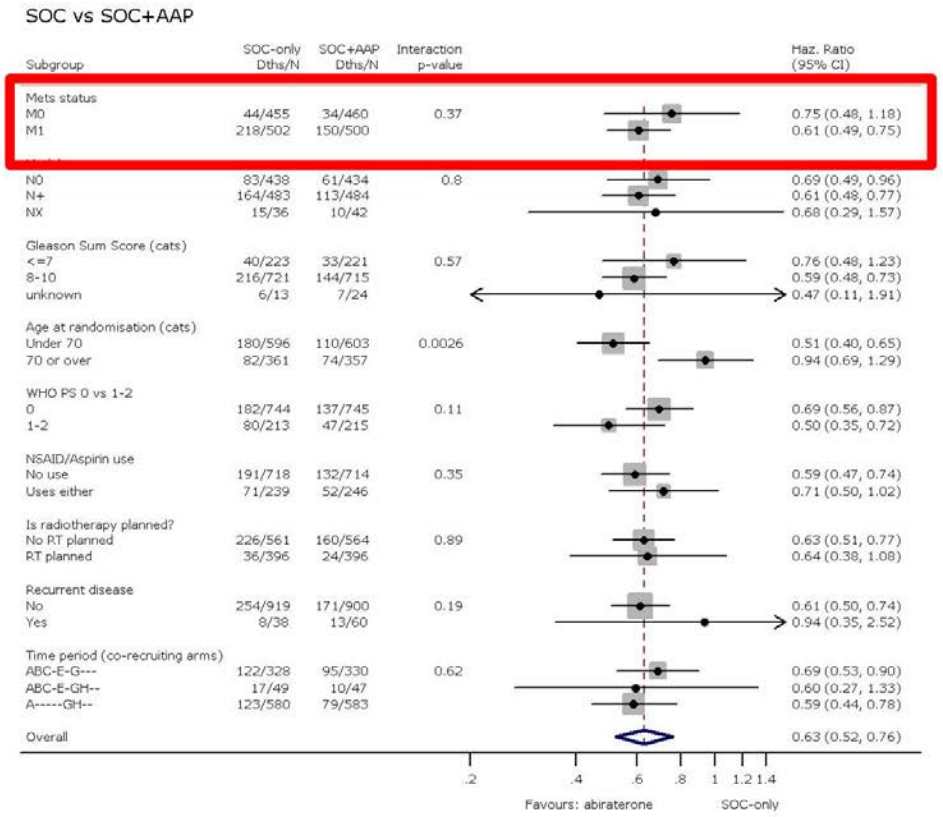
Balanced by arm

[s] = Stratification factors

Also stratified on
:: hospital
:: NSAID/aspirin




- A análise mostra benefício semelhante ao estudo LATITUDE

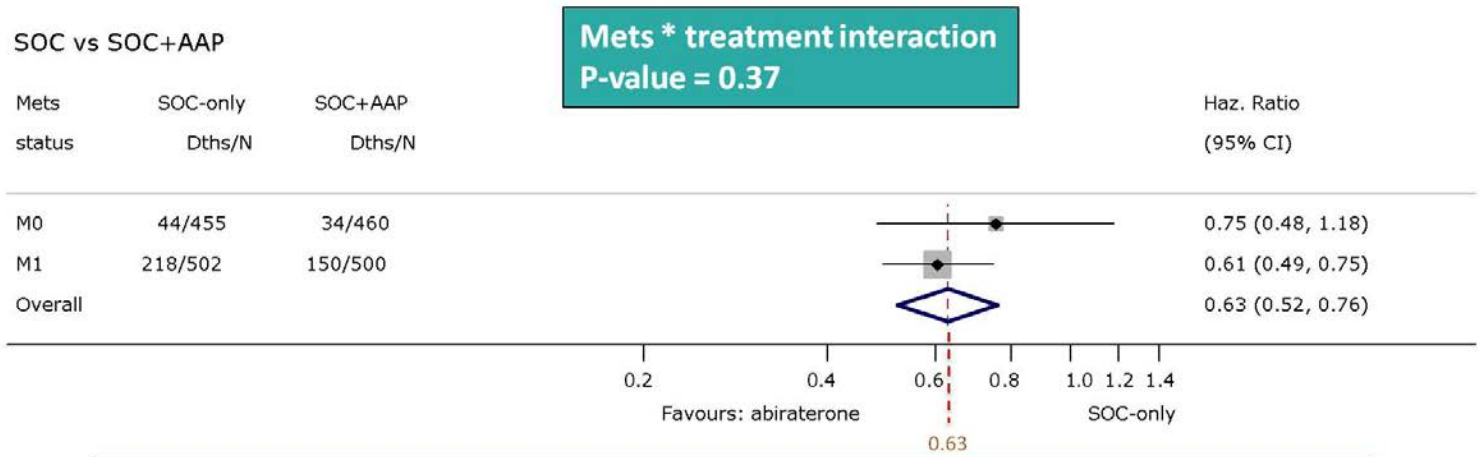



## Overall Survival – STAMPEDE "abiraterone comparison"

**No good evidence of heterogeneity by stratification factors**

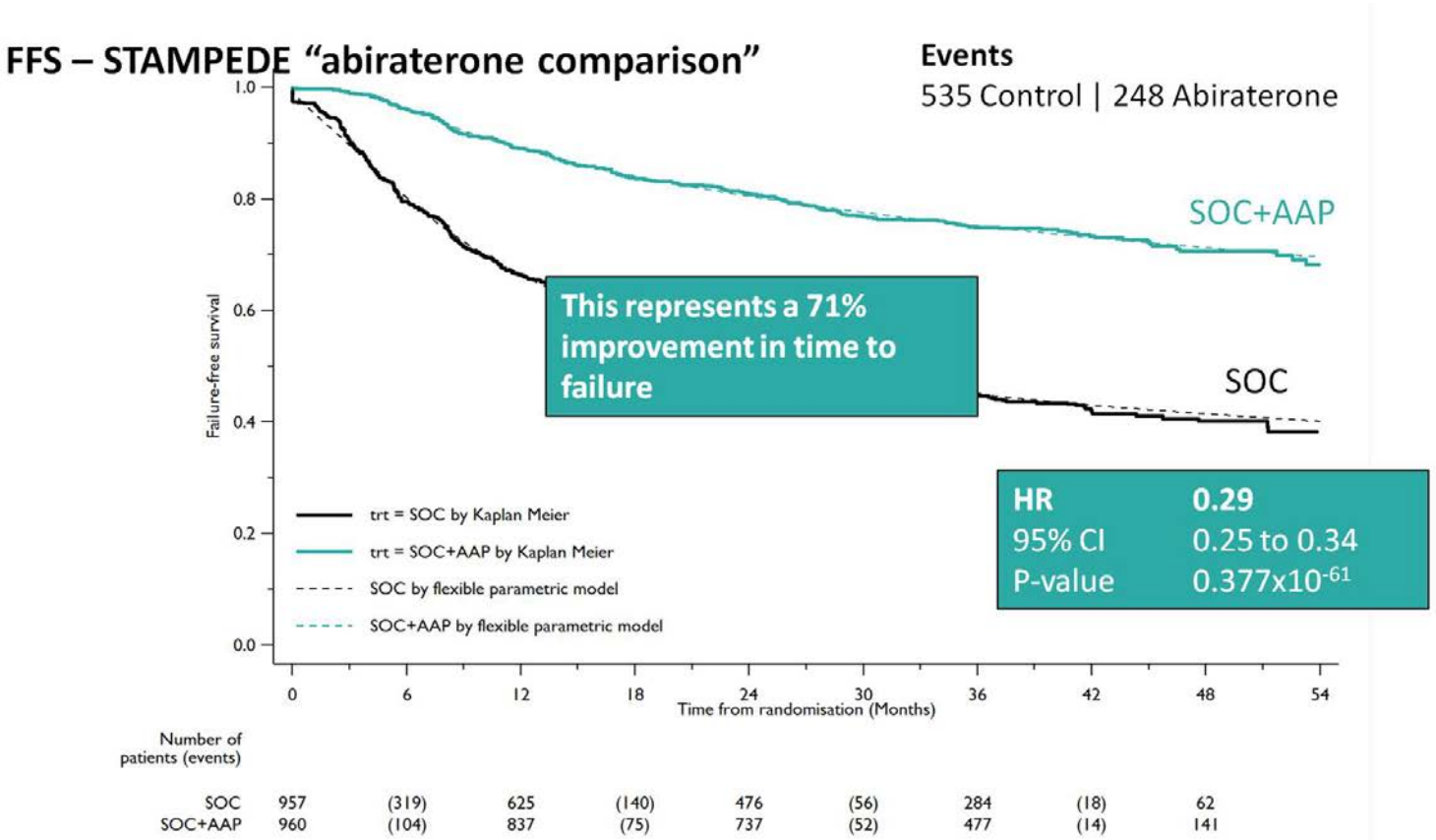
- Benefício parece se estender aos pacientes que são M0.

## STAMPEDE "abiraterone comparison"
## Overall Survival by metastatic status – pre-planned analysis



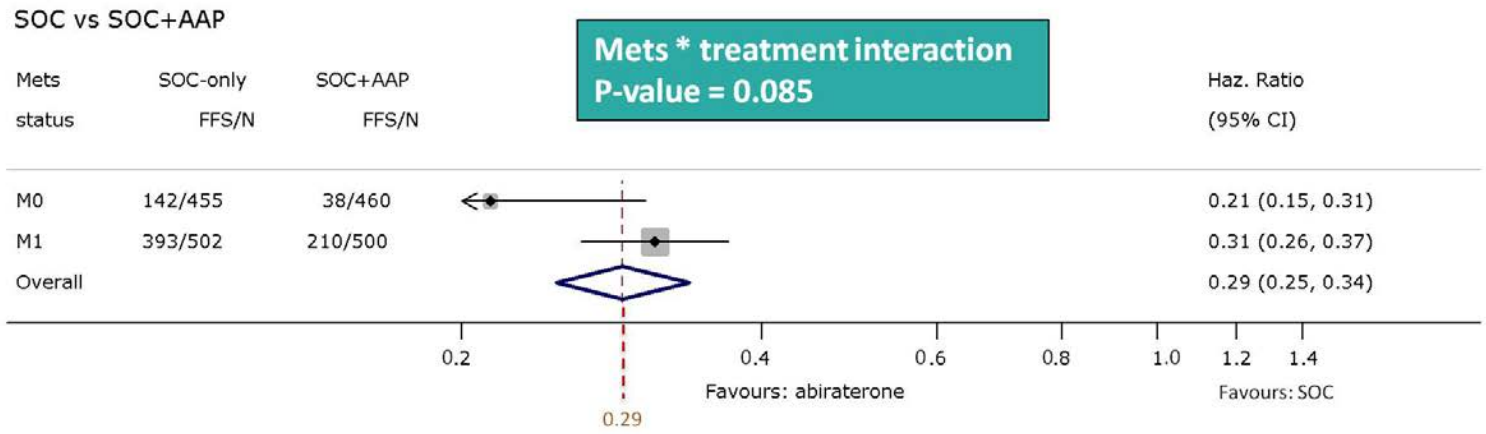

**No good evidence of heterogeneity by metastatic status**

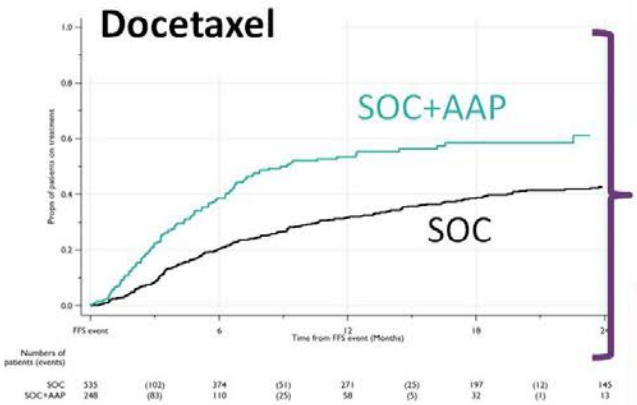
- Mas este benefício é menos evidente

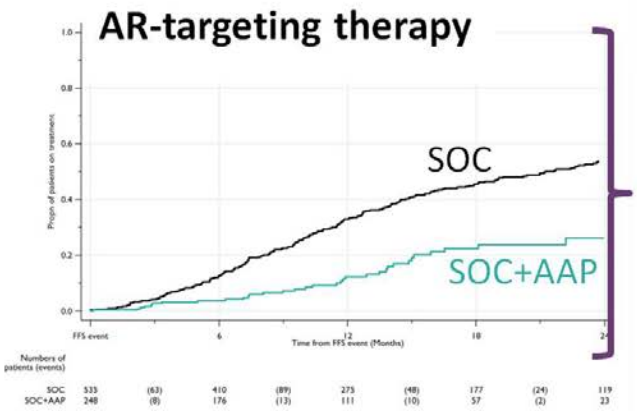



- Desfechos secundários também positivos.

# STAMPEDE "abiraterone comparison"
# FFS by metastatic status – pre-planned analysis






| Treatment started since first progression | A *SOC* | G *SOC+abi* |
|---|---|---|
| Patients randomised | 957 | 960 |
| Patients with progression | 535 (56%) | 248 (26%) |
| Reported new treatment | 477 (89%) | 196 (79%) |
| Reported "life-prolonging" treatment | 310 (58%) | 131 (53%) |
| *Docetaxel* | 200 (37%) | 115 (46%) |
| *Enzalutamide* | 138 (26%) | 25 (10%) |
| *Abiraterone* | 120 (22%) | 8 (3%) |
| *Radium-223* | 24 (5%) | 19 (8%) |
| *Cabazitaxel* | 28 (5%) | 15 (6%) |

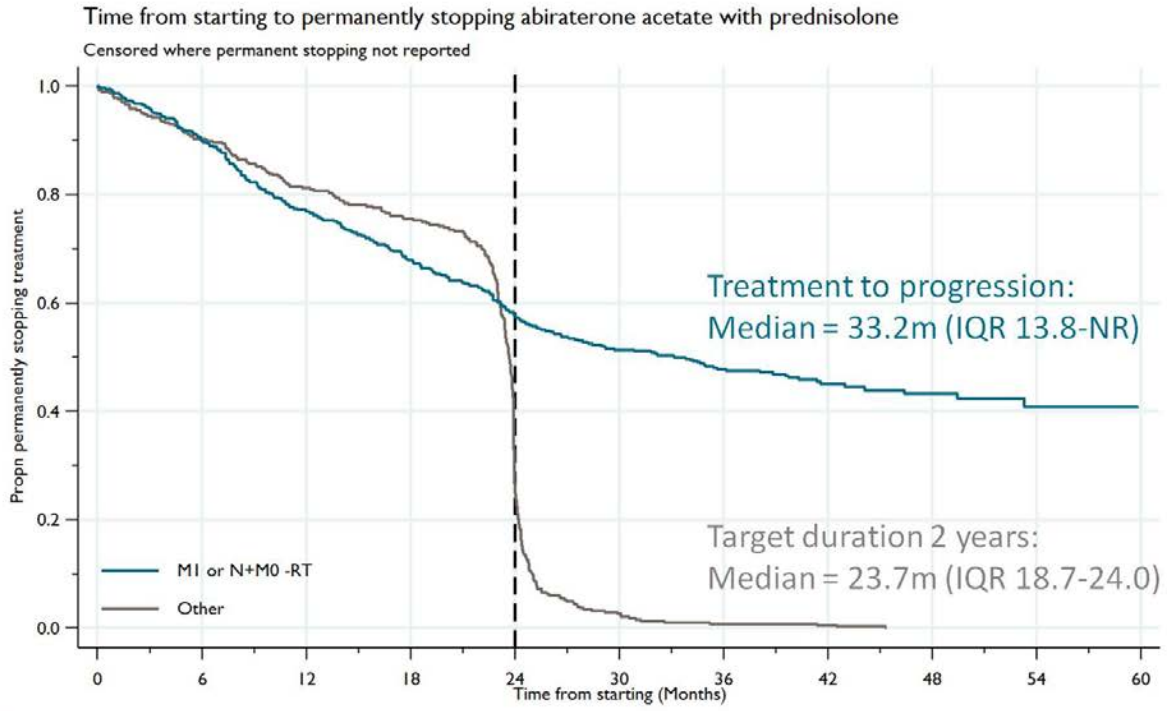
Graph timed from first FFS event

- Também no estudo STAMPEDE os pacientes do grupo controle foram poucos expostos ao uso da abiraterona

| | SOC-only | SOC+AAP |
|---|---|---|
| **Safety population** | | |
| Patients included in adverse event analysis | 960 | 948 |
| Grade 1-5 AE | 950 (99%) | 943 (99%) |
| Grade 3-5 AE | 315 (33%) | 443 (47%) |
| Grade 5 AE | 3 | 9 |
| **Grade 3-5 AEs by category (*incl. expected AEs*)** | | |
| Endocrine disorder (*incl. hot flashes, impotence*) | 133 (14%) | 129 (14%) |
| Cardiovascular disorder (*incl. hypertension, MI, cardiac dysrhythmia*): | 41 (4%) | 92 (10%) |
| Musculoskeletal disorder: | 46 (5%) | 68 (7%) |
| Gastrointestinal disorder: | 40 (4%) | 49 (5%) |
| Hepatic disorder (*incl. increased AST, increased ALT*): | 12 (1%) | 70 (7%) |
| General disorder (*incl. fatigue, oedema*): | 29 (3%) | 45 (5%) |
| Respiratory disorder (*incl. breathlessness*): | 23 (2%) | 44 (5%) |
| Lab abnormalities (*incl. hypokalaemia*): | 21 (2%) | 34 (4%) |

- Perfil de toxicidade conhecido, com alterações hepáticas e cardiovasculares

Abiraterone duration by planned use

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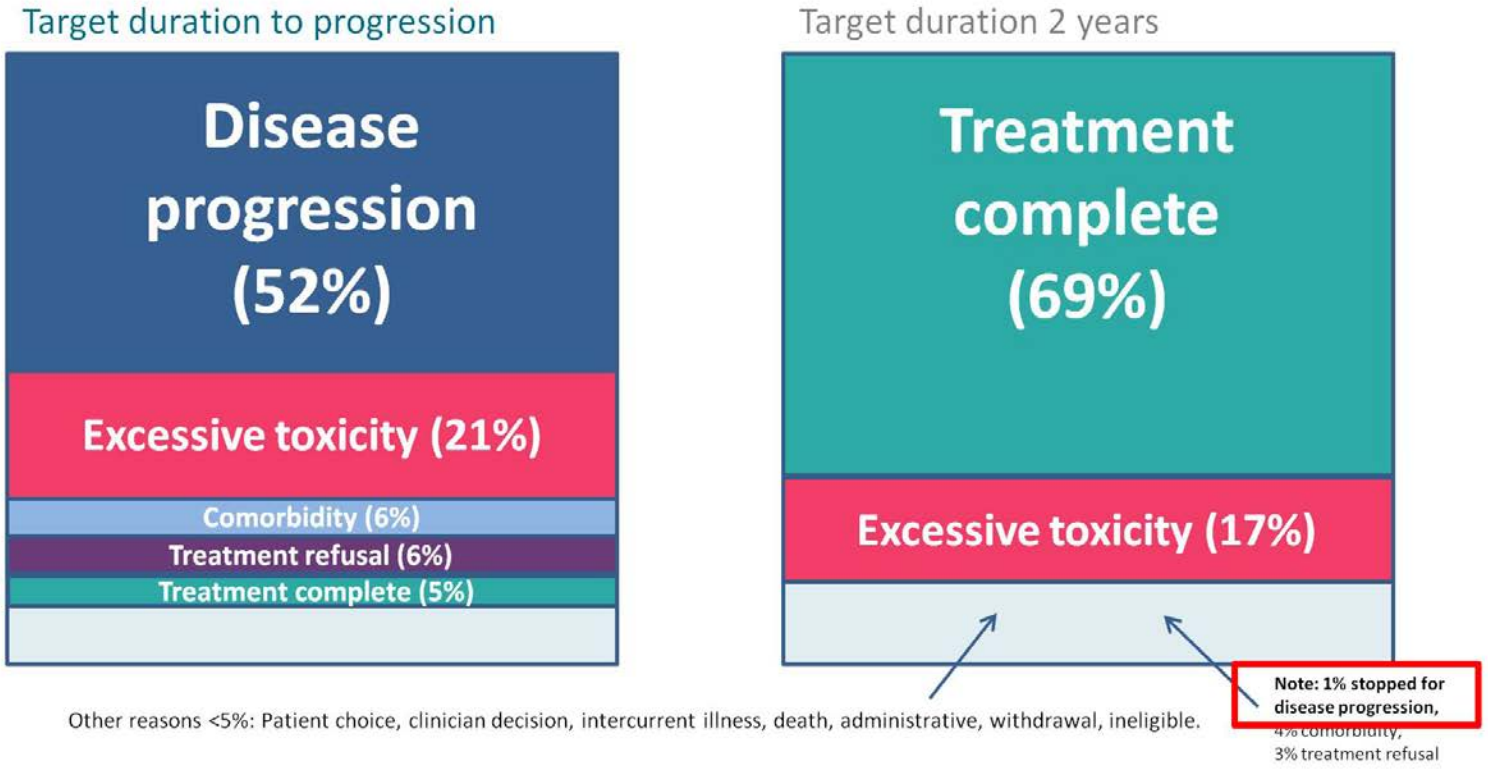
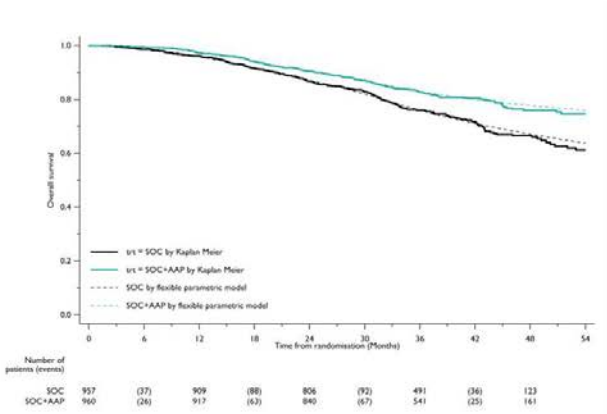
## Reasons for permanently stopping research abiraterone acetate + prednisolone



# Conclusions

- In hormone naïve prostate cancer abiraterone acetate + prednisolone improves
  - **Overall survival by 37%**
  - Failure free survival by 71%
  - Symptomatic skeletal events by 55%
- Treatment was well tolerated
- Abiraterone acetate + prednisolone should be part of the standard of care for men starting long term androgen deprivation therapy

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# DISCUSSÃO

## Qual o melhor desenho para este tipo de estudo?

Este não é um estudo de uma droga nova, mas sim, de um posicionamento de droga. O braço placebo deveria ter sido mais exposto a abiraterona...

## CHAARTED ou LATITUDE?

Duas possibilidade de abordagem para este paciente de alto risco. Não há escolha melhor, mas é certo que este perfil de pacientes deve ser inicialmente tratado de foram mais agressiva, seja com abi ou quimioterapia...

## Toxicidade financeira?

6 ciclos de docetaxel será realmente bem mais barato do que 3 anos de abiraterona...

## Seleção de pacientes

Faremos o tratamento apenas pacientes de muito alto risco?

## Doença M0

# 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*

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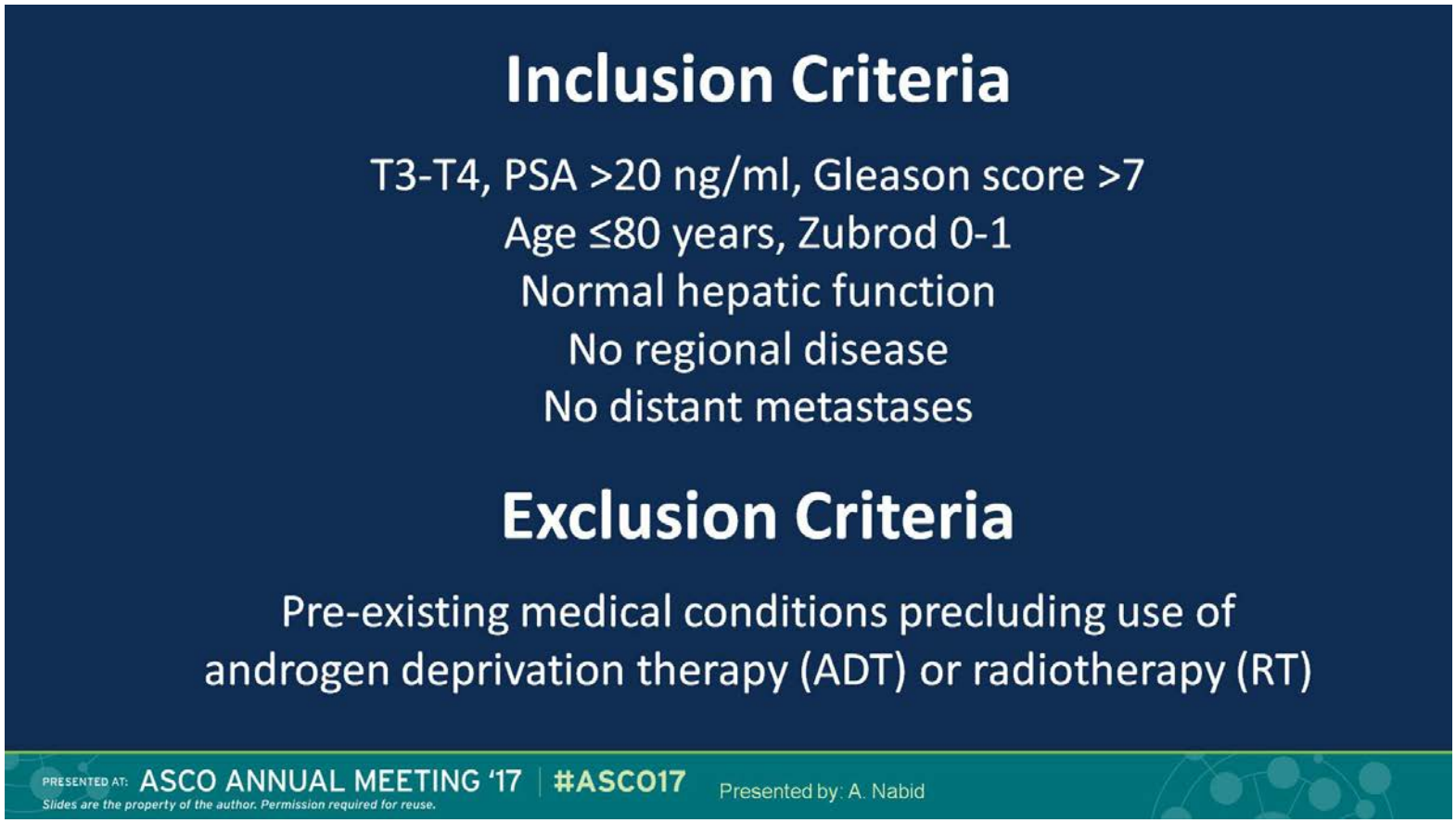
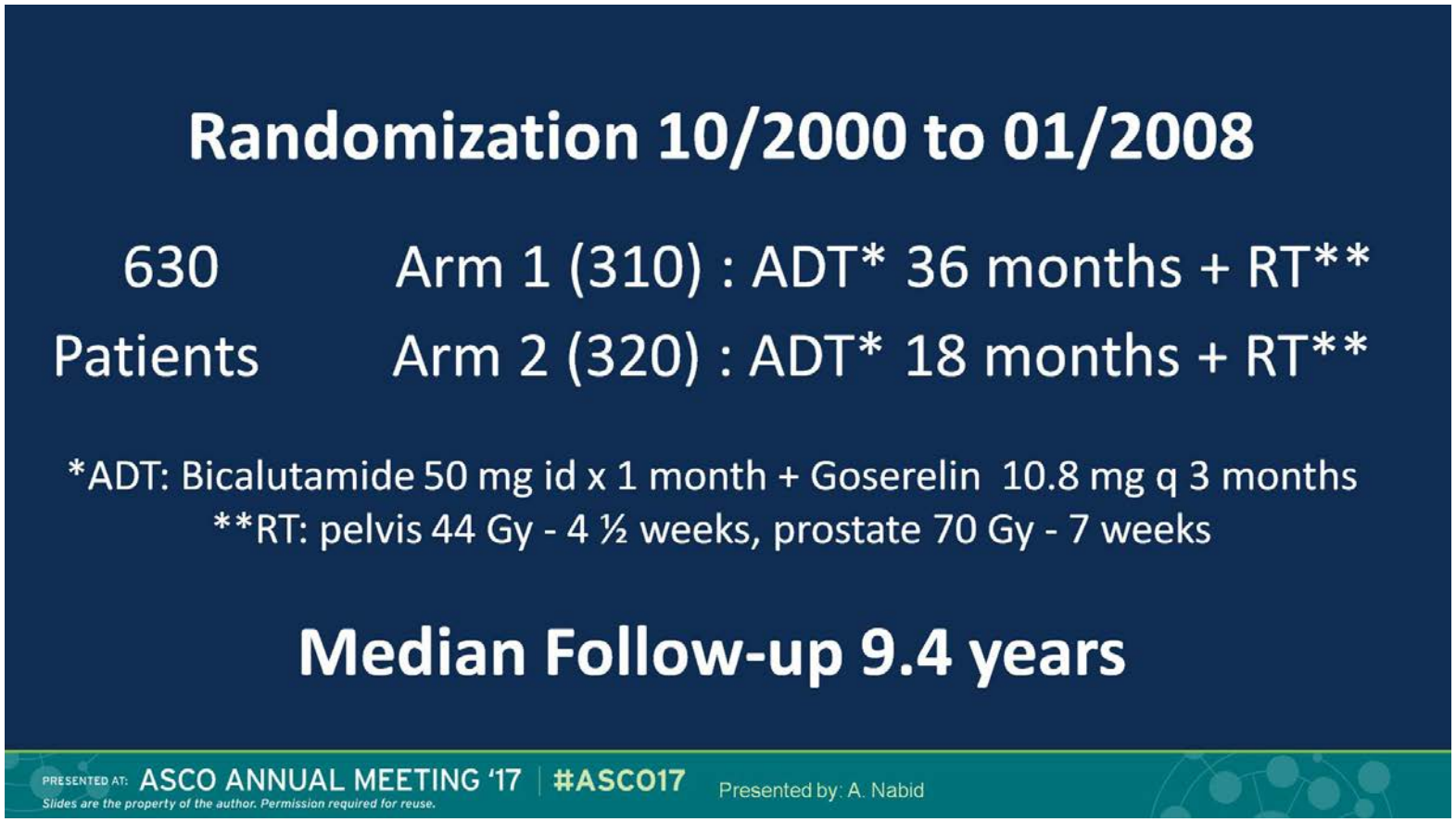



- Qual o melhor tempo de hormonioterapia concomitante a radio?



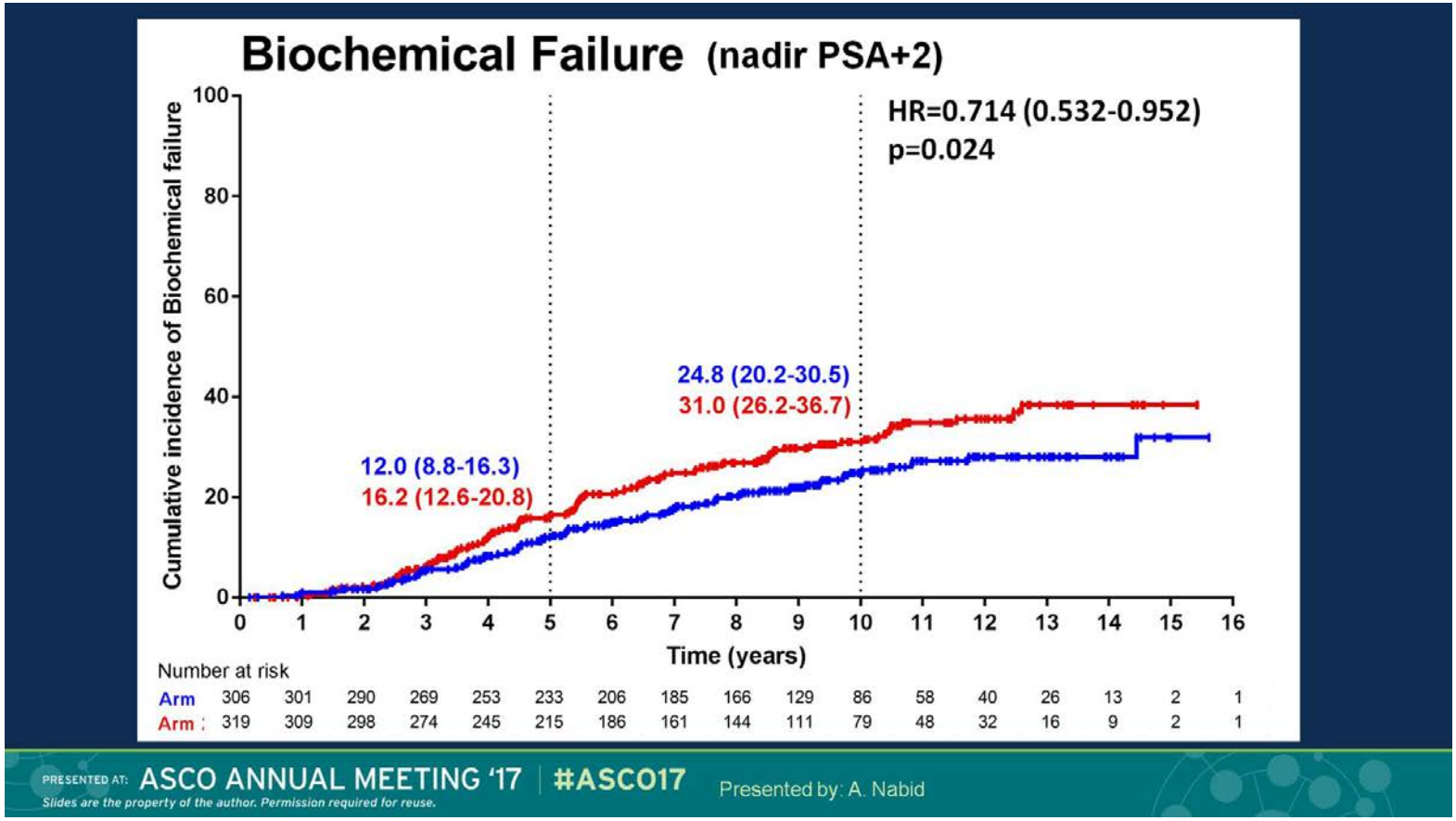

- Estudo com follow-up adequado para câncer de próstata!

# Risk Factors

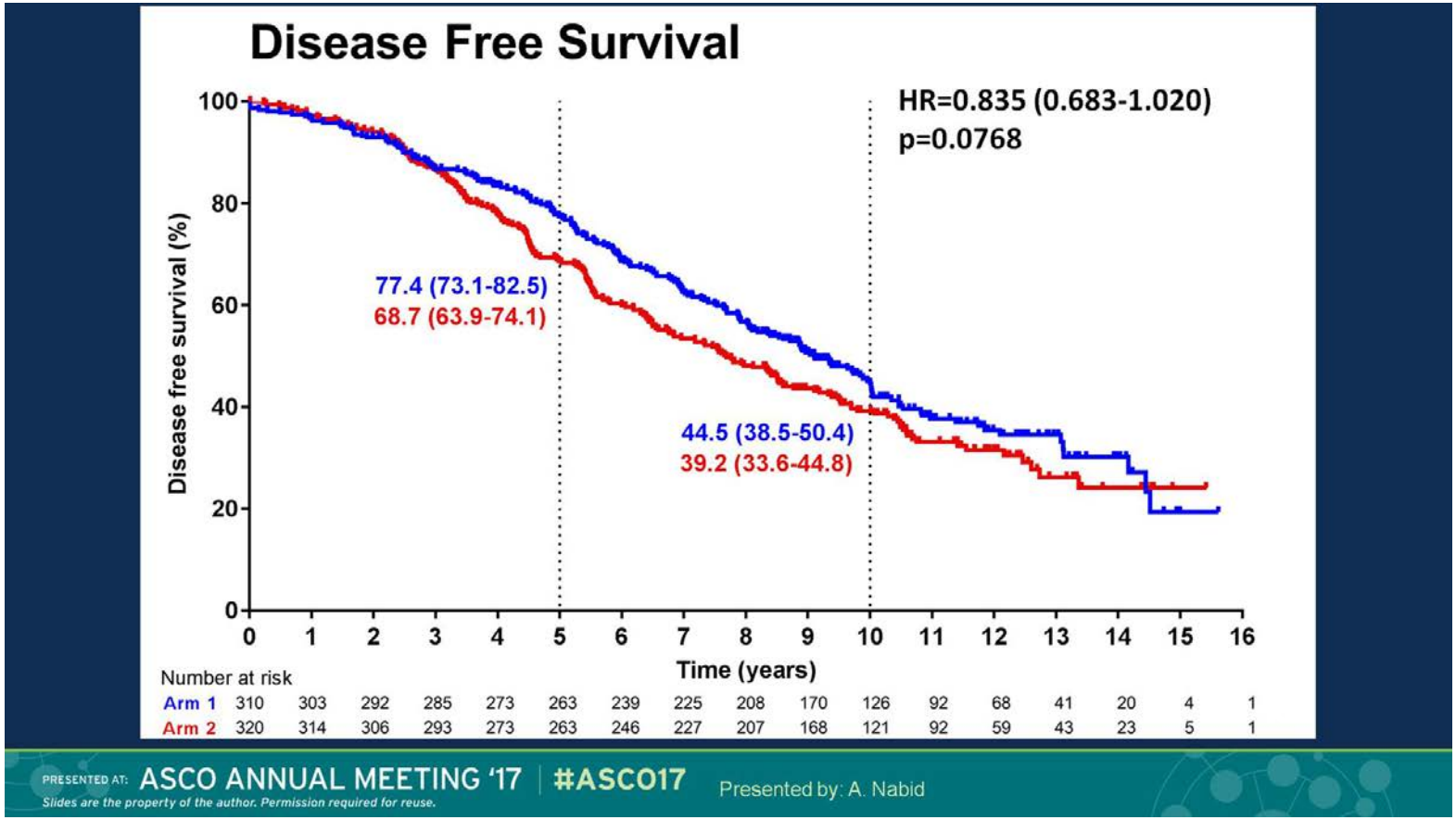
| | 36 months n=310 | 18 months n=320 | Total n=630 |
|---|---|---|---|
| T3 – T4 | 80 (25.8) | 72 (22.5) | 152 (24.1) |
| PSA >20 | 142 (45.8) | 137 (42.8) | 279 (44.3) |
| Gleason score >7 | 183 (59.0) | 193 (60.3) | 376 (59.7) |

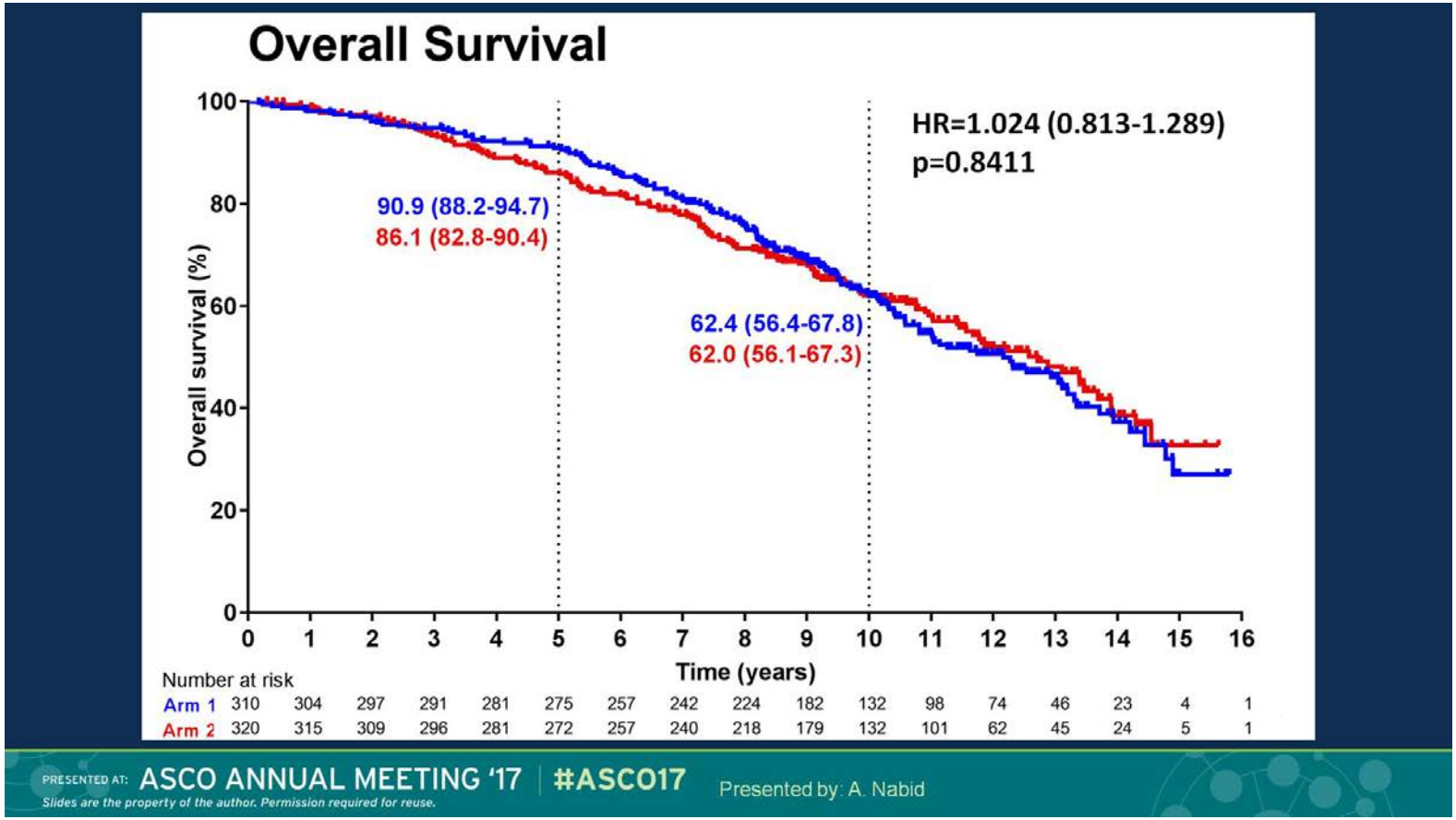


- População com critérios de alto risco de D'Amico comparáveis entre os dois grupos




- Como esperado melhor desfecho sobre a recidiva do PSA para o maior tempo de hormonioterapia






Sem diferença de sobrevida global

## 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%) |

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- Inclusive, sem diferença de sobrevida CÂNCER ESPECÍFICA

# Quality of Life

In favor of 18 months of ADT:

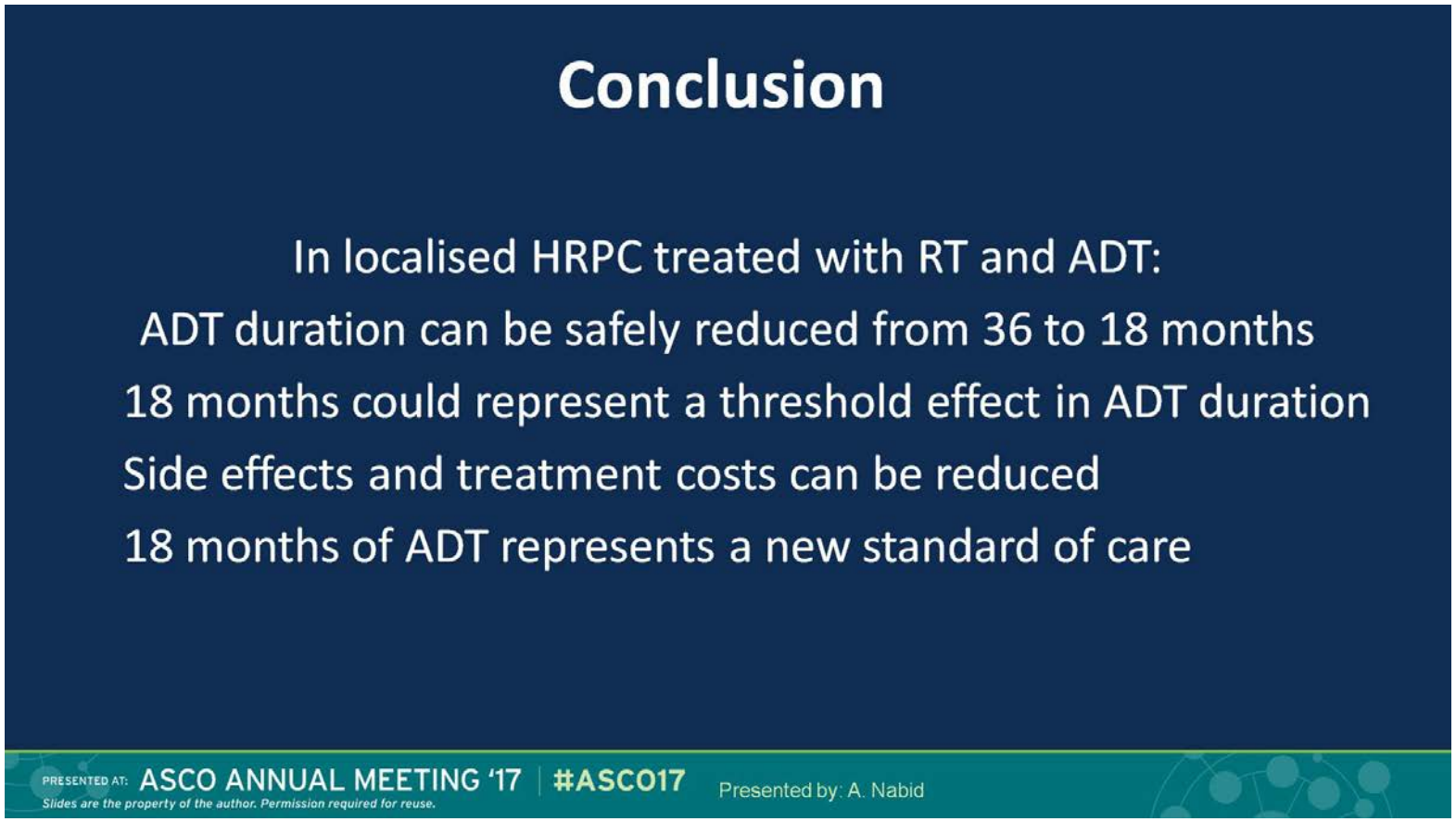
- 13/55 items, 6/21 scales

Clinically significant: p<0.01

-2 items (Hot flushes, enjoyable sex)

Clinically Relevant:

difference in mean scores ≥10 points




- 18 meses de hormonioterapia é o padrão de tratamento.

# DESTAQUES ASCO 2017

## *CÂNCER DE RIM*

# Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT)

Robert Motzer, Naomi Haas, Frede Donskov, Marine Gross-Goupil, Sergei Varlamov, Evgeny Kopyltsov, Jae-Lyun Lee, Bohuslav Melichar, Brian Rini, Toni Choueiri, Milada Zemanova, Lori Wood, Dirk Fahlenkamp, Martin Reaume, Arnulf Stenzl, Weichao Bao, Paola Aimone, Christian Doehn, Paul Russo, Cora Sternberg for the PROTECT investigators

Abstract 4507

PROTECT, **P**azopanib as adjuvant the**R**apy in l**O**calized/locally advanced RCC af**T**er n**E**phre**C**T**o**my (VEG113387).

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Presented by: Robert Motzer, MD

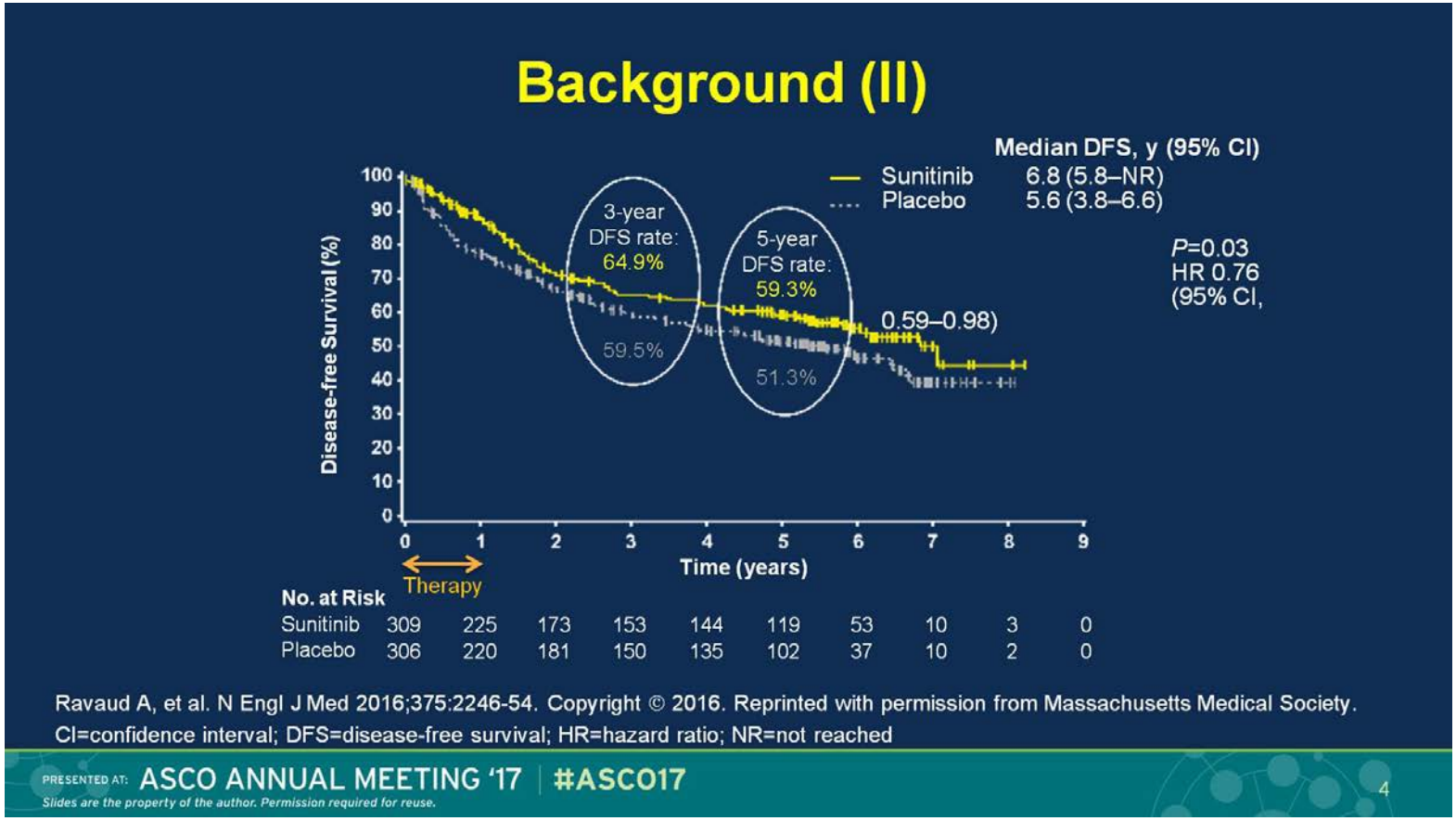
# Introduction

- About 75% of patients with RCC have localized disease and 30% to 40% with high-risk localized RCC relapse following nephrectomy
- Adjuvant VEGFR-TKI therapy is being investigated to improve disease-free survival (DFS)
- ASSURE trial did not meet the primary end point; S-TRAC met the primary end point for sunitinib[1,2]

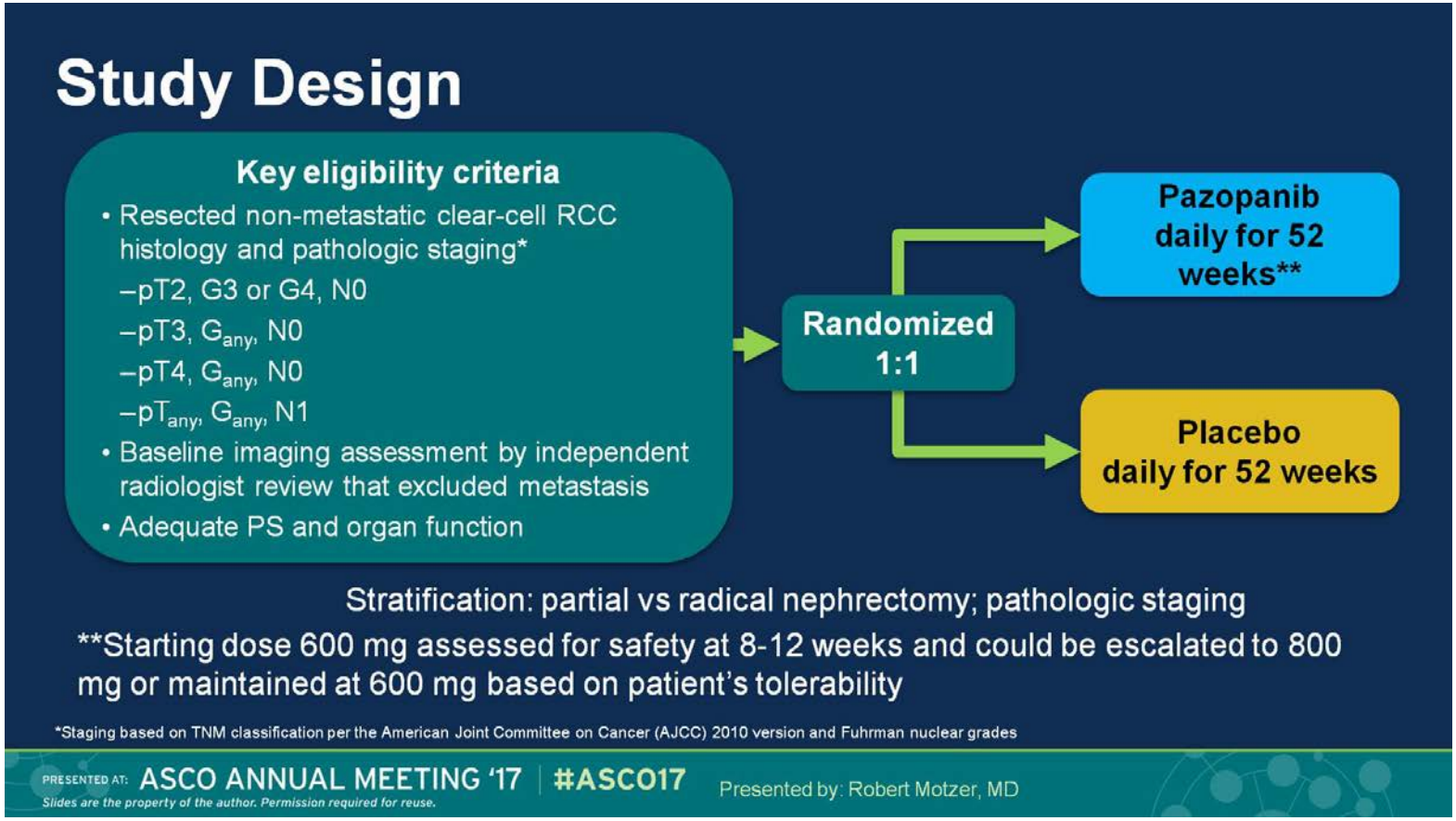
TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor.
1. Haas NB, et al. *Lancet*. 2016;387:2008. 2. Ravaud A, et al. *N Engl J Med*. 2016;375:2246-2254.



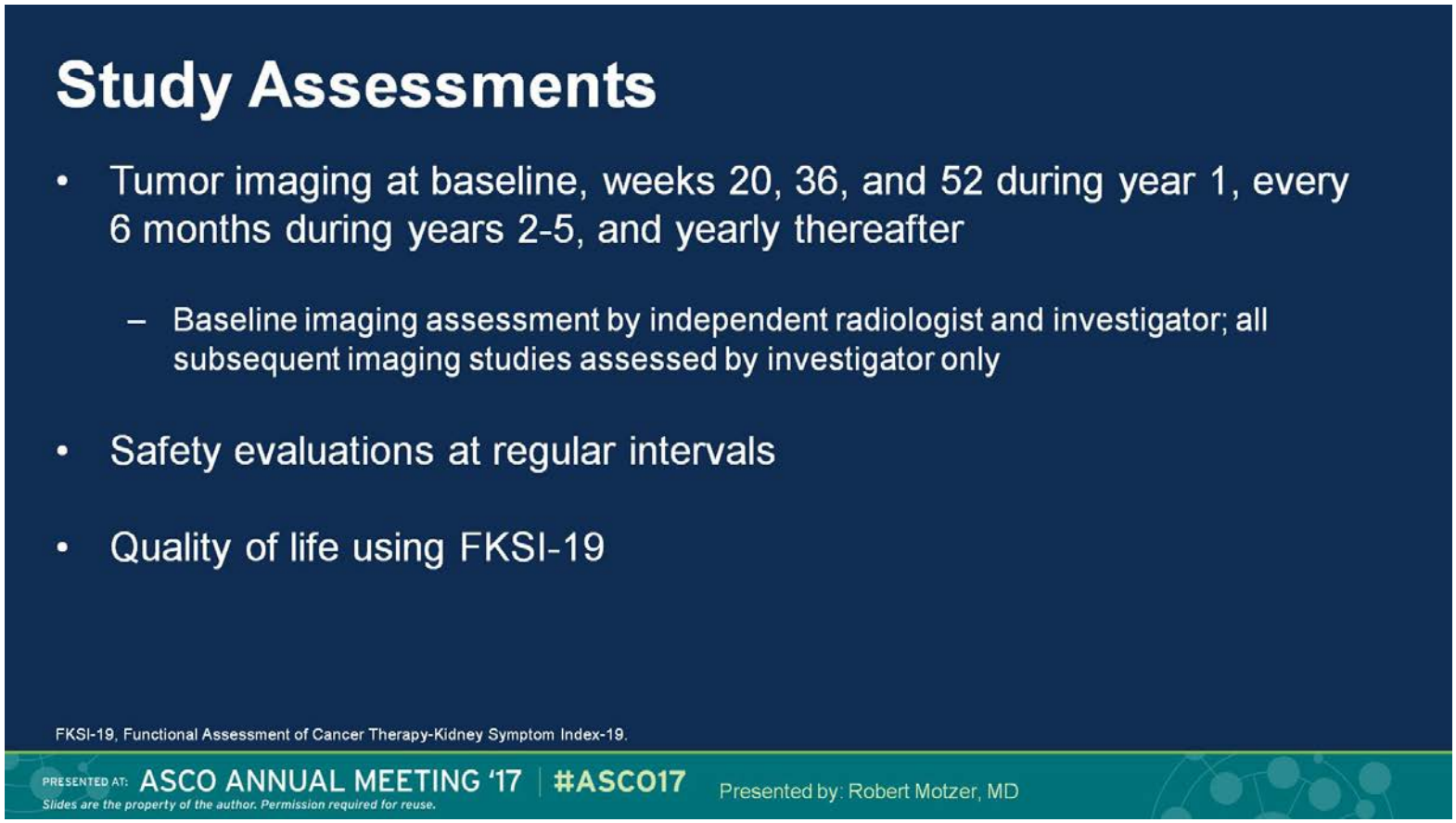
- Será o câncer de rim o único tumor em que um agente anti VEGF tem eficácia no tratamento adjuvante?




- Benefício do STRAC visto mesmo antes do tempo de uso do sunitinibe…




- Pacientes foram inicialmente tratados com 600mg/dia.
- Menor parte da amostra foi levada a dose de 800mg/dia




- Seguimento adequado para detectar recidivas.

# Baseline Characteristics (n=1538)

| | $ITT_{600mg}$ (n=1135) | | $ITT_{800mg}$ (n=403) | |
|---|---|---|---|---|
| | Pazopanib n = 571 | Placebo n = 564 | Pazopanib n = 198 | Placebo n = 205 |
| Age, years, median (range) | 58 (22–83) | 58 (21–82) | 56 (29–80) | 60 (30–79) |
| Gender, % | | | | |
| • Male | 70 | 71 | 70 | 75 |
| • Female | 30 | 29 | 30 | 25 |
| KPS,* % | | | | |
| • 100 | 67 | 69 | 66 | 72 |
| • 80 or 90 | 33 | 31 | 34 | 28 |
| Nephrectomy, % | | | | |
| • Partial | 7 | 7 | 4 | 5 |
| • Radical | 93 | 93 | 96 | 95 |
| Fuhrman grade,** % | | | | |
| • High (Grade 3 or 4) | 69 | 63 | 71 | 63 |
| • Low (Grade 1 or 2) | 31 | 37 | 29 | 37 |

*KPS was unknown for one patient in the $ITT_{600mg}$ placebo group; **Fuhrman grade was missing for two patients in the $ITT_{600mg}$ placebo group.

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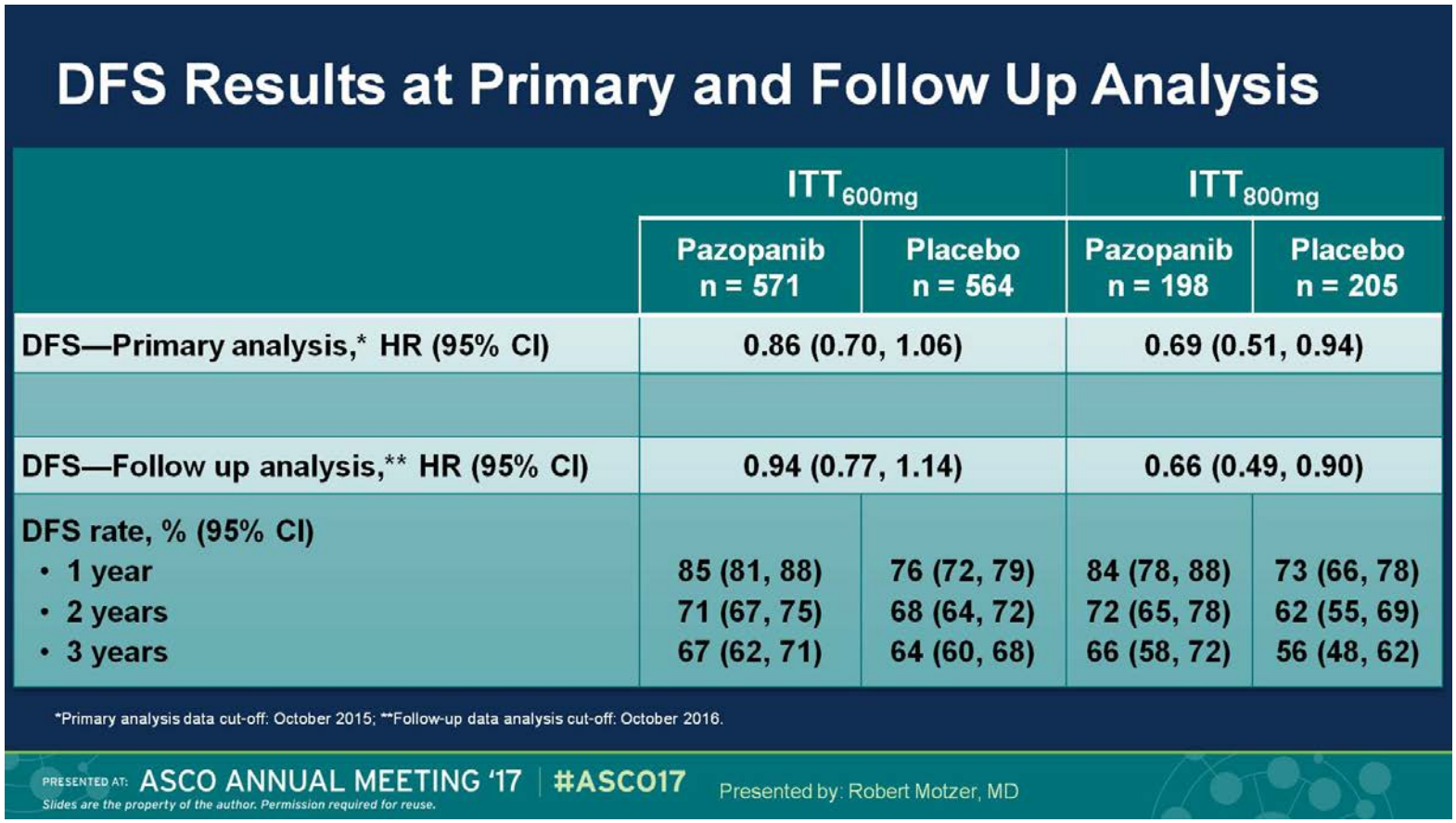
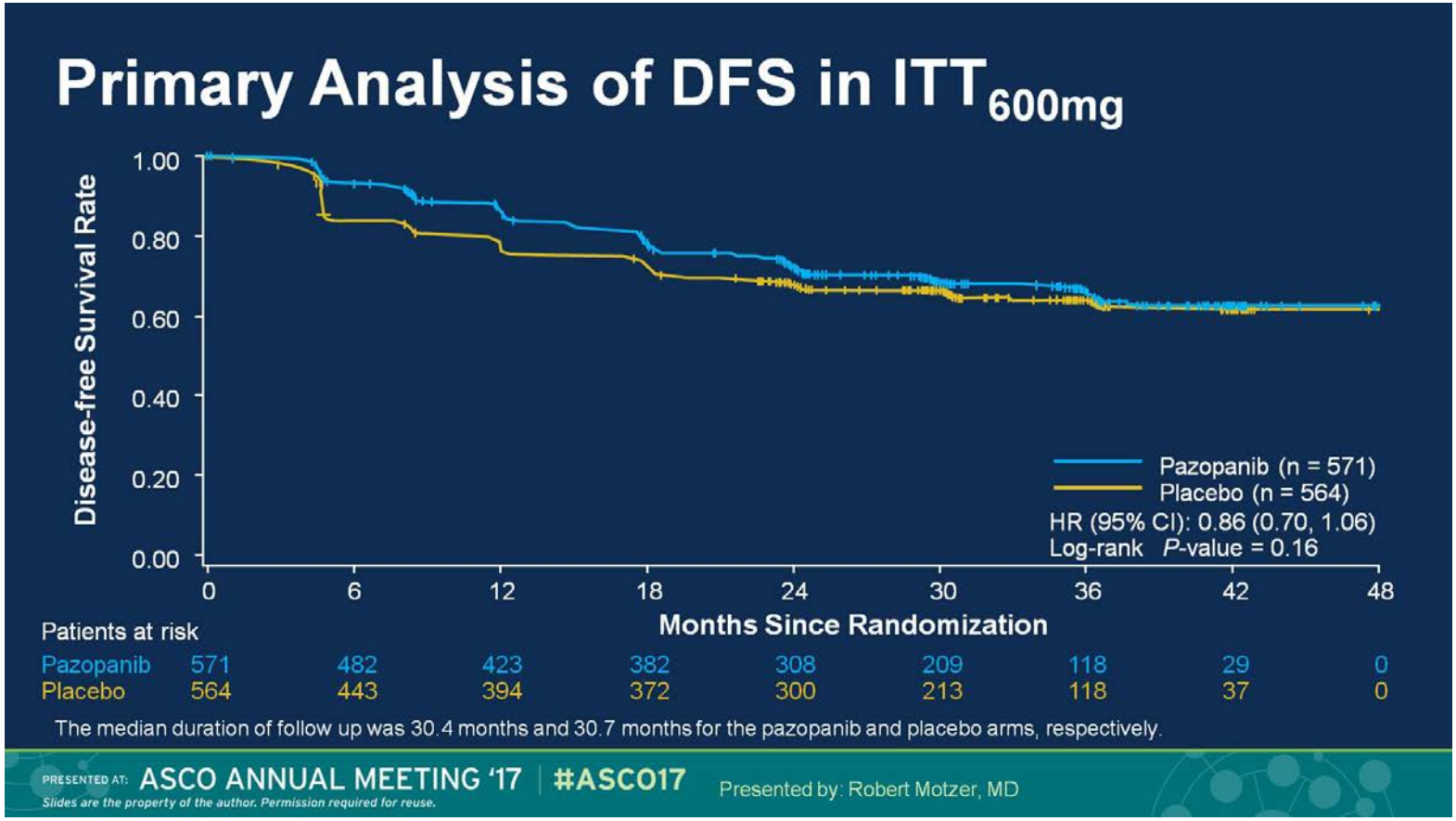
- Sem diferenças significativas dos fatores prognósticos entre os grupos.

# Baseline Characteristics

| | $ITT_{600mg}$ | | $ITT_{800mg}$ | |
|---|---|---|---|---|
| | Pazopanib n = 571 | Placebo n = 564 | Pazopanib n = 198 | Placebo n = 205 |
| **Primary tumor stage, %** | | | | |
| • T1 | <1 | <1 | 1 | <1 |
| • T2 | 15 | 15 | 14 | 15 |
| • T3 | 82 | 82 | 83 | 82 |
| • T4 | 2 | 3 | 3 | 3 |
| **Regional lymph node status, %** | | | | |
| • N0 | 94 | 95 | 93 | 95 |
| • N1 | 6 | 5 | 7 | 5 |
| **Tumor staging and grade, %** | | | | |
| • pT2G3–G4N0 | 14 | 14 | 14 | 14 |
| • $pT3G_{any}N0$ | 78 | 78 | 77 | 79 |
| • $pT4G_{any}N0$ and $pT_{any}G_{any}N1$ | 8 | 8 | 9 | 7 |




- Existiram diferenças de desfecho nos grupos de 600mg/dia e 800mg/dia.
- Mas o grupo de 800mg com número de pacientes insuficiente




- Estudo francamente negativo no corte de pacientes com 600mg

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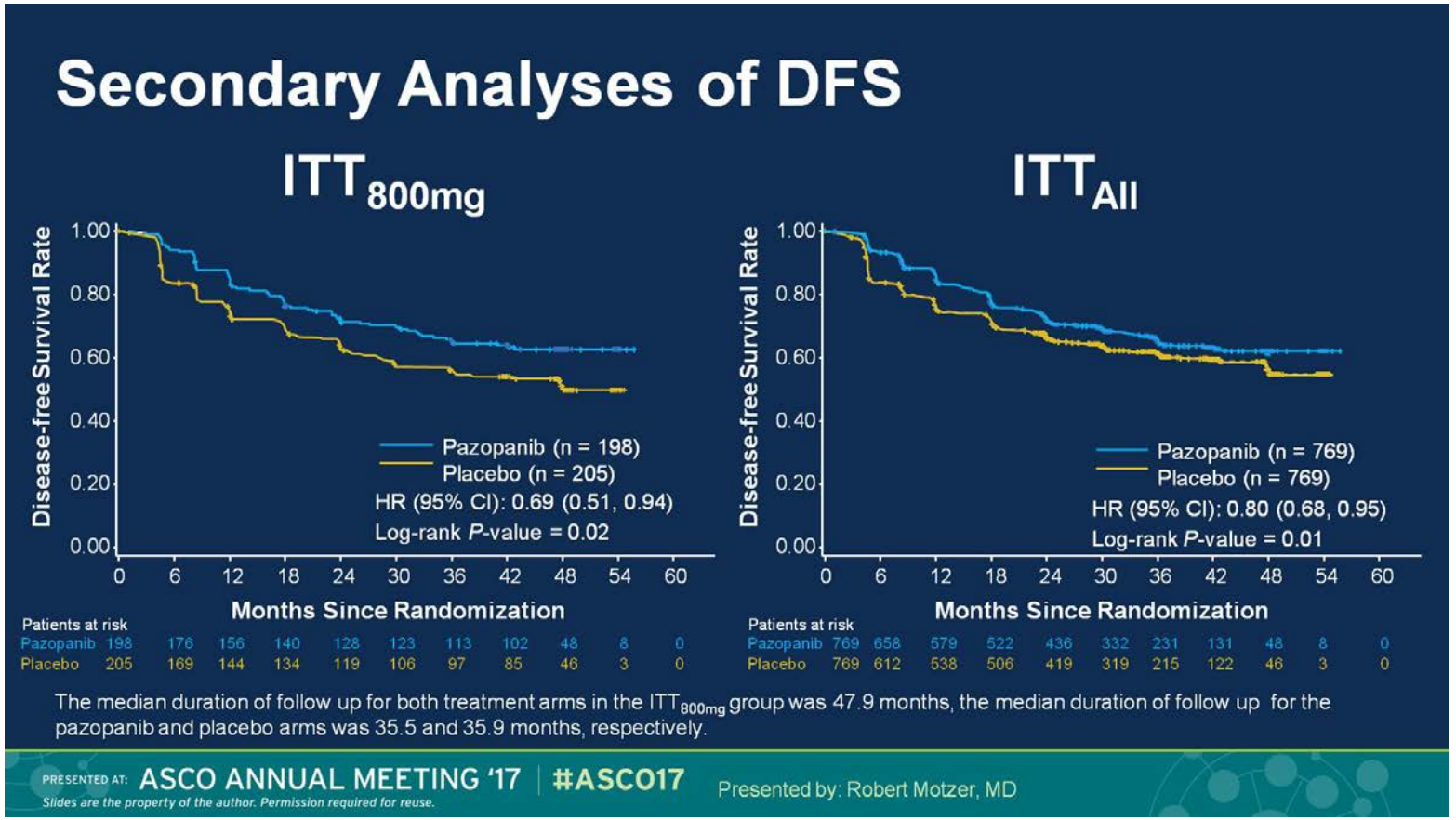
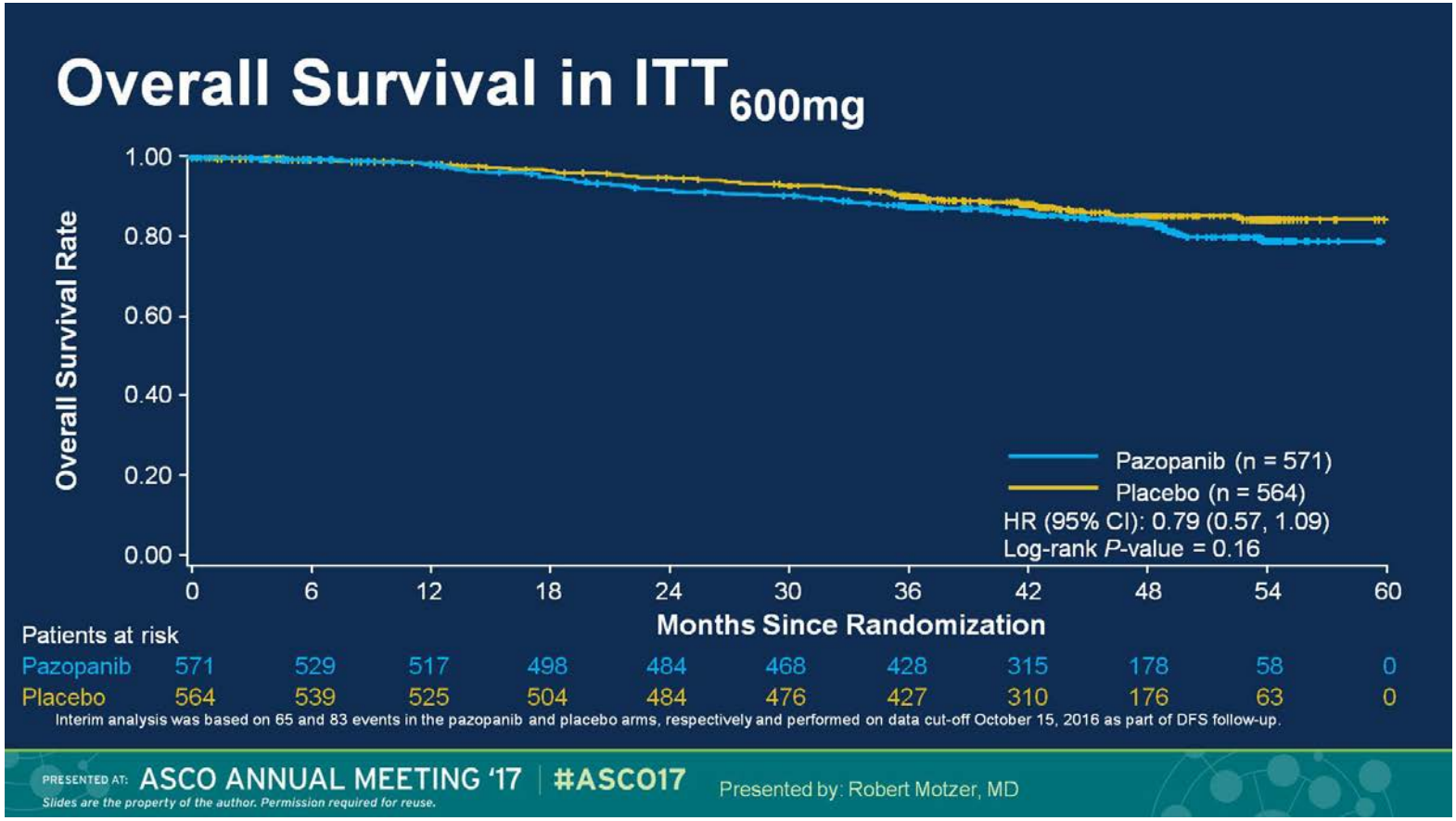



- Dados positivos para a menor população que foi escalada a dose até 800mg/dia N insuficiente para conclusões no estudo.




- Desfecho de sobrevida francamente negativo no corte de 600mg

# Quality-of-Life Assessment by FKSI-19 for $ITT_{600mg}$ vs Placebo


| Evaluable patients (n) | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Pazopanib | 558 | 435 | 485 | 451 | 423 | 364 | 335 | 253 | 161 | 71 |
| Placebo | 547 | 513 | 493 | 432 | 401 | 359 | 340 | 252 | 153 | 74 |

# Conclusions

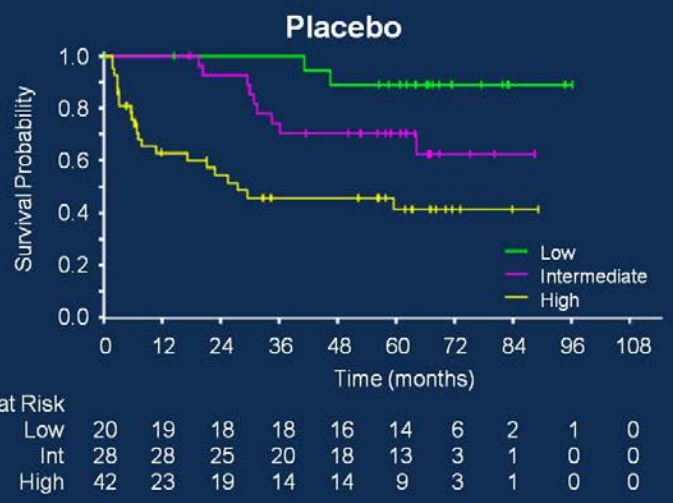
- Pazopanib 600 mg daily dose as adjuvant therapy did not prolong DFS
- Pazopanib 800 mg starting dose resulted in a 31% decrease in the risk of recurrence or death, but this was a secondary objective of the study
- The safety profile was similar between 600 mg and 800 mg dose cohorts, and consistent with prior experience in advanced RCC
- Pazopanib is not recommended for adjuvant therapy following resection of locally advanced RCC

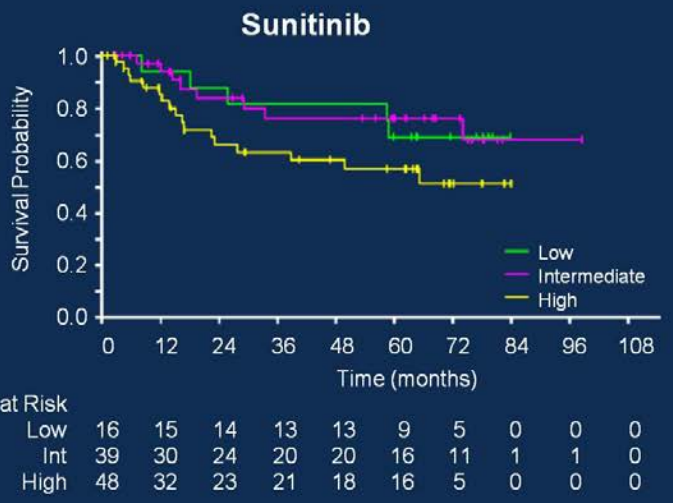



- Há ainda espaço para algum tratamento adjuvante em câncer de rim hoje?
- Em algum perfil específico?


- Este estudo tentou validar um teste biomolecular ("tipo Oncotype") para validar o tratamento adjuvante em câncer renal.

# Secondary objective: Recurrence risk by RS groups




| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Low | 20 | 19 | 18 | 18 | 16 | 14 | 6 | 2 | 1 | 0 |
| Int | 28 | 28 | 25 | 20 | 18 | 13 | 3 | 1 | 0 | 0 |
| High | 42 | 23 | 19 | 14 | 14 | 9 | 3 | 1 | 0 | 0 |

| No. at Risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Low | 16 | 15 | 14 | 13 | 13 | 9 | 5 | 0 | 0 | 0 |
| Int | 39 | 30 | 24 | 20 | 20 | 16 | 11 | 1 | 1 | 0 |
| High | 48 | 32 | 23 | 21 | 18 | 16 | 5 | 0 | 0 | 0 |

| | Placebo (n=90) | Sunitinib (n=103) |
|---|---|---|
| High vs Low RS group, HR (95% CI) | 9.18 (2.15–39.24) *P*<0.001 | 1.86 (0.68–5.06) *P*=0.20 |

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- Teste conseguiu ser prognóstico...
- MAS NÃO PREDITIVO!

# Conclusions

- RS was associated with TTR, DFS, and RCSS in both arms, with the strongest associations observed in the placebo arm, thus confirming the overall prognostic value of the 16-gene assay
- The predictive value of RS to select patients for adjuvant sunitinib therapy has not been demonstrated, but would warrant further investigation in adequately powered and prospectively designed adjuvant trials
- RS results may help identify patients with clear-cell, stage III high-risk RCC who could derive higher absolute benefit from adjuvant therapy

# DISCUSSÃO

## Qual a diferença entre o PROTECT e o STRAC?

Estudos são bem parecidos com populações parecidas.

Protect fez um escalonamento de dose não realizado no STRAC.

## Há papel para adjuvância com TKI? Em quais pacientes?

O tratamento adjuvante em câncer de rim ainda pede por uma novidade mais eficaz.

Tratamento hoje deve ser individualizado e amplamente discutido com o paciente

## Trials em andamento

A maior esperança ainda continua sendo a imunoterapia...

# DESTAQUES ASCO 2017

## *CÂNCER DE BEXIGA*

# Updated Survival Analysis From KEYNOTE-045: Phase 3, Open-Label Study of Pembrolizumab Versus Paclitaxel, Docetaxel, or Vinflunine in Recurrent, Advanced Urothelial Cancer

Dean F. Bajorin,[1] Ronald de Wit,[2] David J. Vaughn,[3] Yves Fradet,[4] Jae Lyun Lee,[5] Lawrence Fong,[6] Nicholas J. Vogelzang,[7] Miguel A. Climent,[8] Daniel P. Petrylak,[9] Toni K. Choueiri,[10] Andrea Necchi,[11] Winald Gerritsen,[12] Howard Gurney,[13] David I. Quinn,[14] Stéphane Culine,[15] Cora N. Sternberg,[16] Yabing Mai,[17] Markus Puhlmann,[17] Rodolfo F. Perini,[17] Joaquim Bellmunt[10]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [3]Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA, USA; [4]CHU de Québec-Université Laval, Québec City, QC, Canada; [5]Asan Medical Center and University of Ulsan College of Medicine, Seoul, Republic of Korea; [6]University of California, San Francisco, San Francisco, CA, USA; [7]Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; [8]Fundación Instituto Valenciano de Oncología, Valencia, Spain; [9]Smilow Cancer Hospital at Yale University, New Haven, CT, USA; [10]Dana-Farber Cancer Institute, Boston, MA, USA; [11]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [12]Radboud University Medical Center, Nijmegen, Netherlands; [13]Westmead Hospital and Macquarie University, Sydney, NSW, Australia; [14]University of Southern California Norris Comprehensive Cancer Center and Hospital, Los Angeles, CA, USA; [15]Hôpital Saint-Louis, Paris, France; [16]San Camillo Forlanini Hospital, Rome, Italy; [17]Merck & Co., Inc., Kenilworth, NJ, USA

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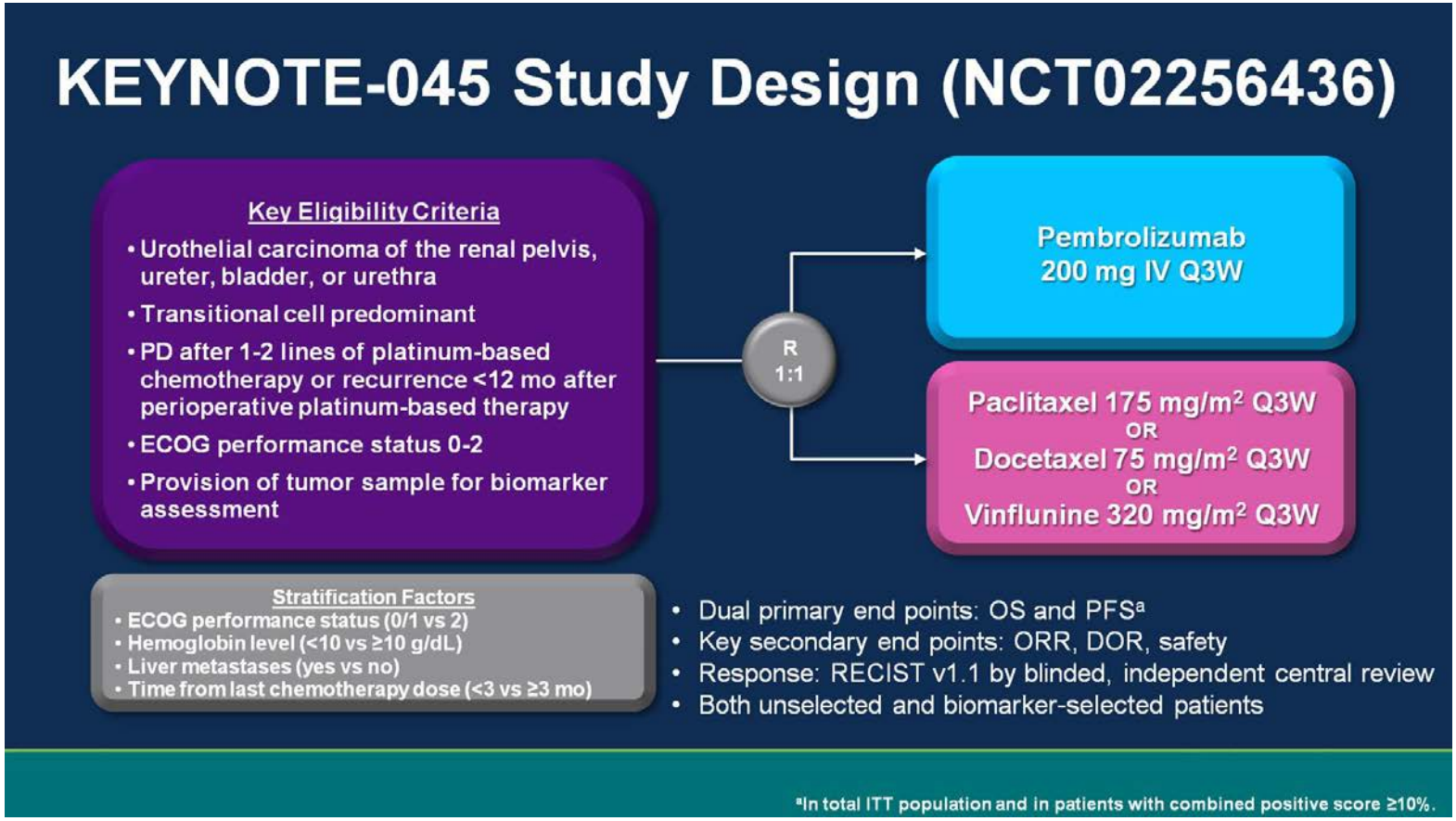
# Challenges of Treating Recurrent Urothelial Carcinoma After Platinum Therapy

- Currently no universally accepted second-line therapy
  - Vinflunine: approved, commonly used in European Union[1]
  - Taxanes: supported by consensus guidelines[2]
  - Checkpoint inhibitors (atezolizumab, nivolumab, durvalumab, avelumab) received accelerated approvals in United States based on response rates
- Level 1 evidence for enhanced survival and safety over chemotherapy is of critical importance in advancing the treatment of urothelial cancer

1. Houede N et al. *BMC Cancer.* 2016;16:752.
2. NCCN Guidelines. Bladder cancer. 2017:version 1.2017.

- Este estudo evidenciou os dados de sobrevida de pembrolizumabe em câncer de bexiga de segunda linha.




- Podemos observar que a segunda linha padrão em vários locais pode ser tanto um taxane com a vinflunina...

# Baseline Characteristics

| n (%) | Pembro (n = 270) | Chemo (n = 272) |
|---|---|---|
| Age, median (range), y | 67 (29-88) | 65 (26-84) |
| Men | 200 (74.1) | 202 (74.3) |
| Upper tract disease | 38 (14.1) | 37 (13.6) |
| Lower tract disease | 232 (85.9) | 235 (86.4) |
| ECOG PS[a] | | |
| 0 | 120 (44.4) | 106 (39.0) |
| 1 | 143 (53.0) | 158 (58.1) |
| 2 | 2 (0.7) | 4 (1.5) |
| Visceral disease | 241 (89.3) | 234 (86.0) |
| Disease in lymph node only | 28 (10.4) | 38 (14.0) |

| n (%) | Pembro (n = 270) | Chemo (n = 272) |
|---|---|---|
| Liver metastases | 91 (33.7) | 95 (34.9) |
| Hemoglobin <10 g/dL[b] | 43 (15.9) | 44 (16.2) |
| Time since completion of most recent prior therapy | | |
| ≥3 months | 167 (61.9) | 168 (61.8) |
| <3 months | 103 (38.1) | 104 (38.2) |
| Setting of most recent prior therapy[c] | | |
| Neoadjuvant | 19 (7.0) | 22 (8.1) |
| Adjuvant | 12 (4.4) | 31 (11.4) |
| First line | 184 (68.1) | 158 (58.1) |
| Second line | 55 (20.4) | 59 (21.7) |
| Third line | 0 | 2 (0.7) |

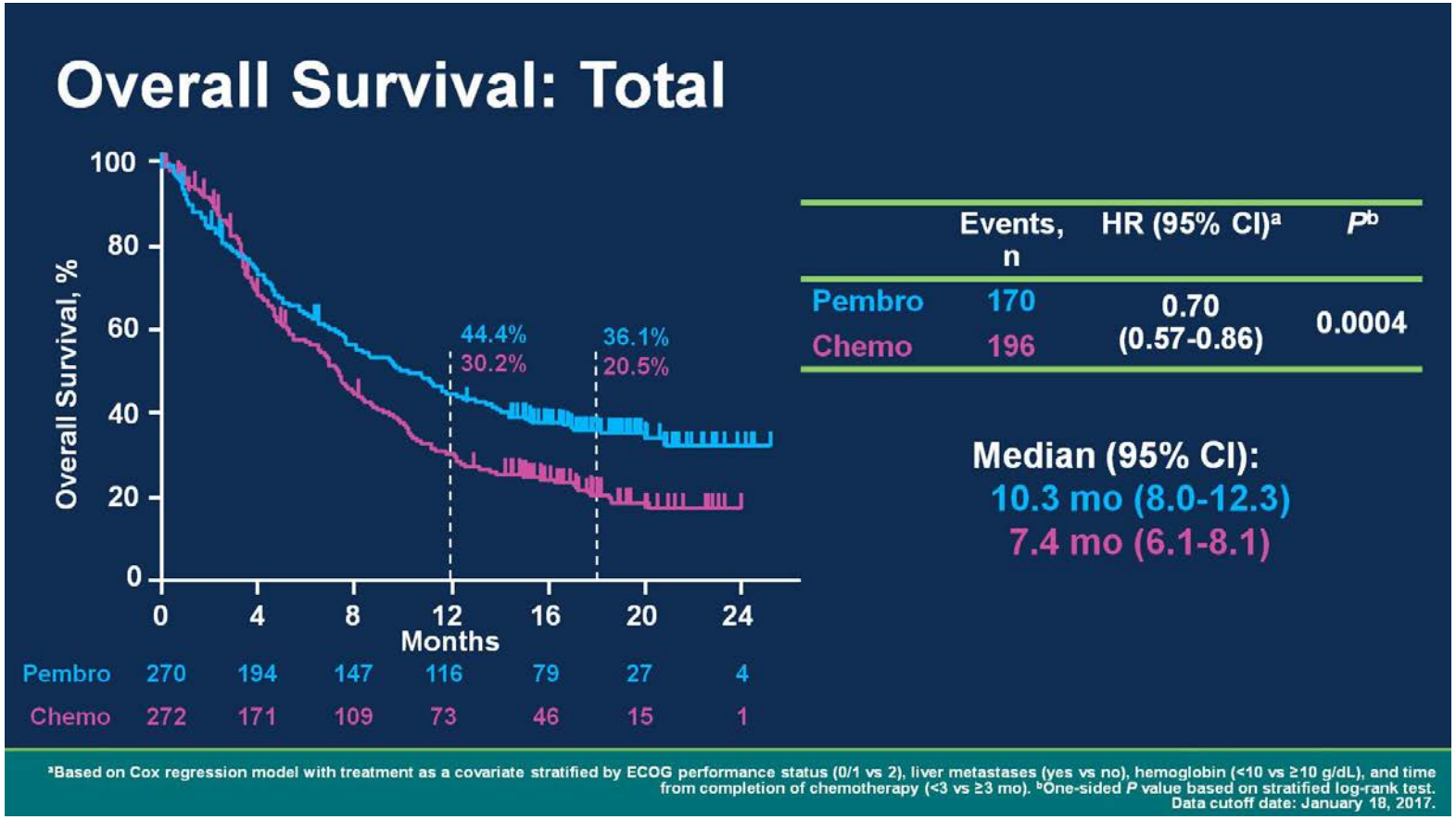
[a]Missing for 5 patients in the pembro arm and 4 patients in the chemo arm. [b]Missing for 8 patients in the pembro arm and 4 patients in the chemo arm.
[c]Setting and time from completion were missing for 1 patient in each arm.
Data cutoff date: January 18, 2017.

# Baseline Characteristics

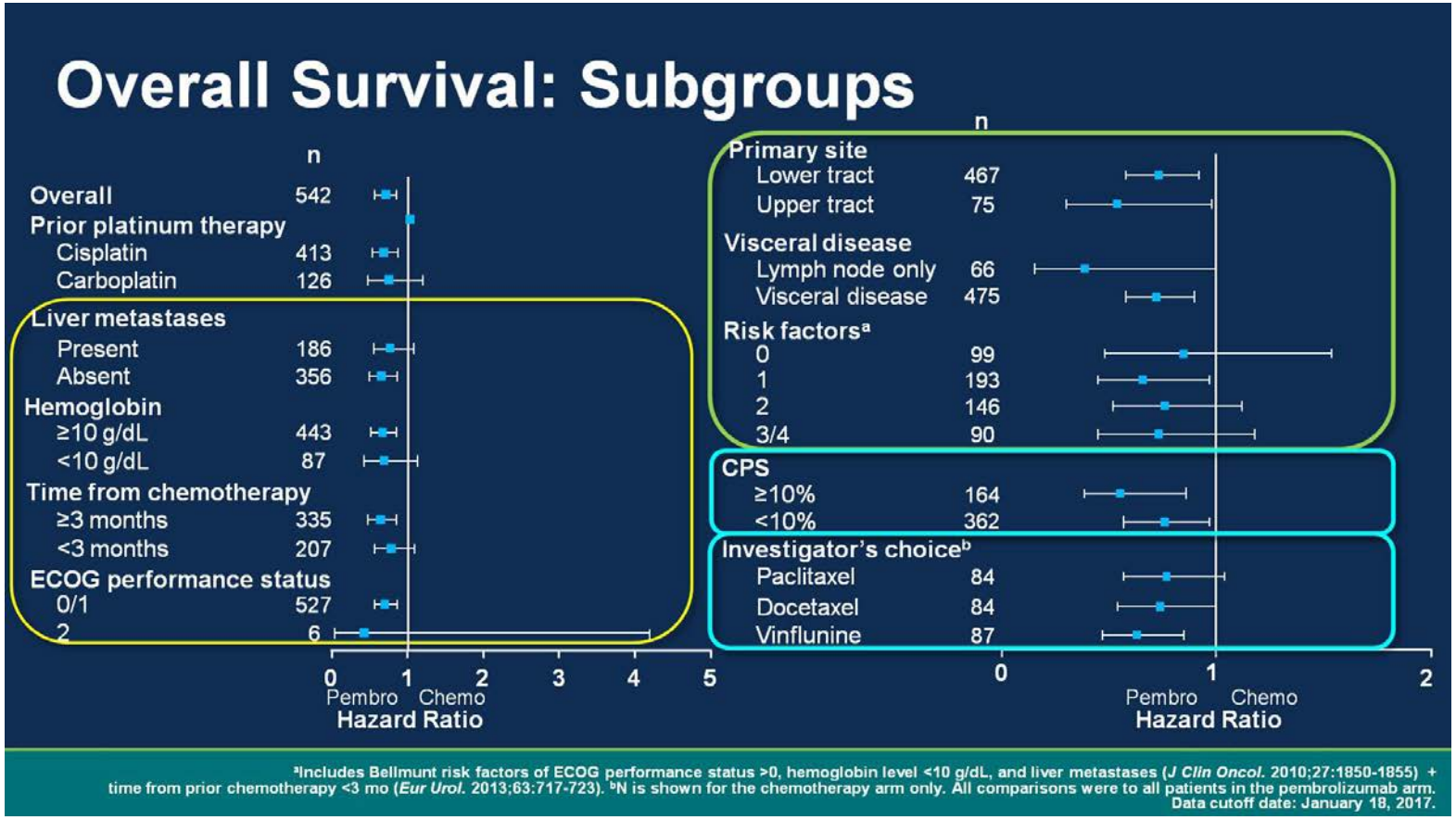
| n (%) | Pembro (n = 270) | Chemo (n = 272) |
|---|---|---|
| Prior platinum therapy | | |
| Cisplatin | 199 (73.7) | 214 (78.7) |
| Carboplatin | 70 (25.9) | 56 (20.6) |
| Other[a] | 1 (0.4) | 2 (0.7) |
| Smoking status[b] | | |
| Never | 104 (38.5) | 83 (30.5) |
| Former | 136 (50.4) | 148 (54.4) |
| Current | 29 (10.7) | 38 (14.0) |
| PD-L1 CPS ≥10% | 74 (27.4) | 90 (33.1) |

| n (%) | Pembro (n = 270) | Chemo (n = 272) |
|---|---|---|
| Risk Factors[c] | | |
| 0 | 54 (20.0) | 45 (16.5) |
| 1 | 96 (35.6) | 97 (35.7) |
| 2 | 66 (24.4) | 80 (29.4) |
| 3-4 | 45 (16.7) | 45 (16.5) |

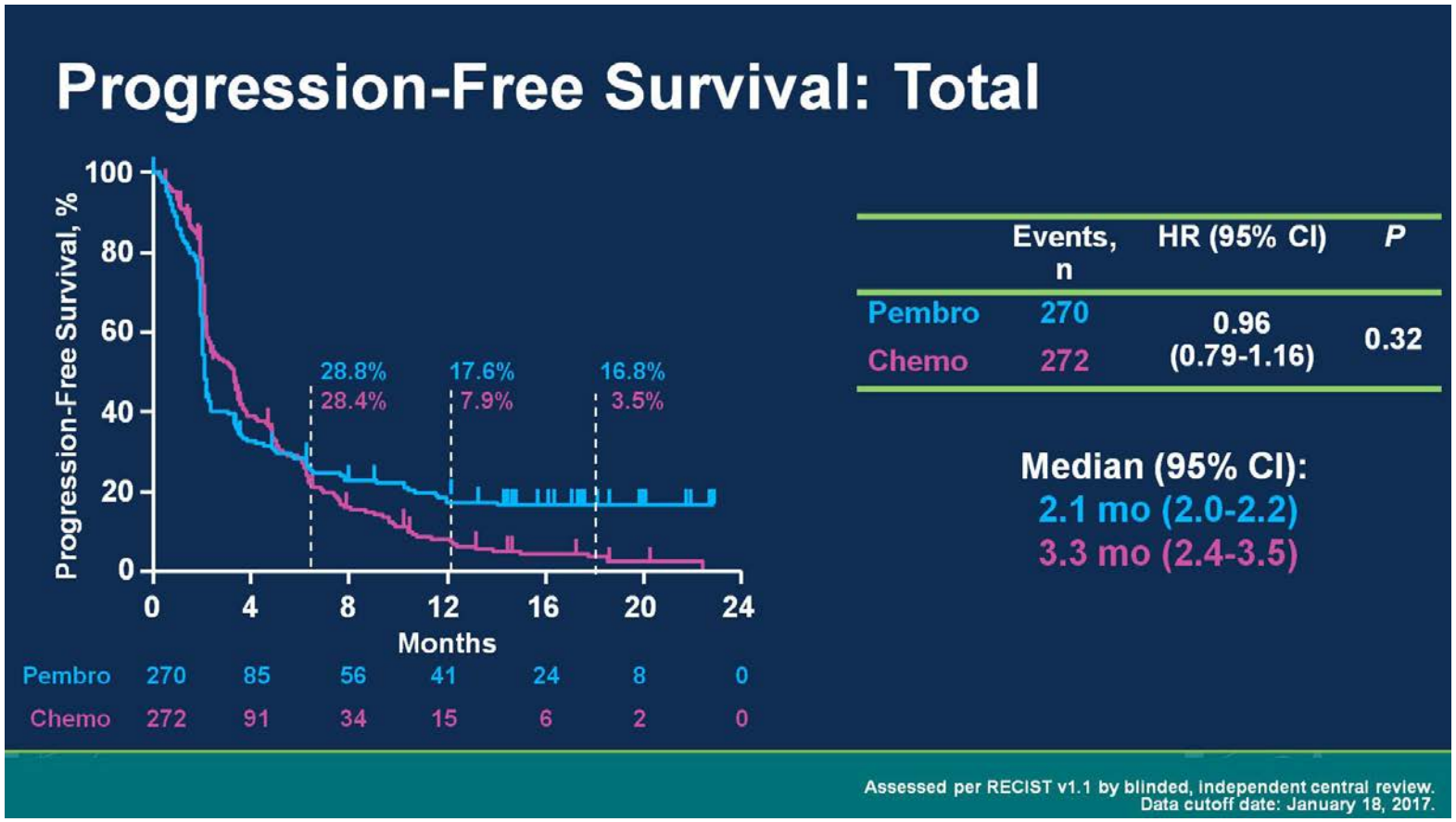
[a]Oxaliplatin, nedaplatin. [b]Missing for 1 patient in the pembro arm and 3 patients in the chemo arm. [c]Includes Bellmunt risk factors of ECOG performance status >0, hemoglobin level <10 g/dL, and liver metastases (*J Clin Oncol* 2010;27:1850-1855) + time from prior chemotherapy <3 mo (*Eur Urol* 2013;63:717-723). Missing for 9 patients in the pembro arm and 5 patients in the chemo arm.
Data cutoff date: January 18, 2017.



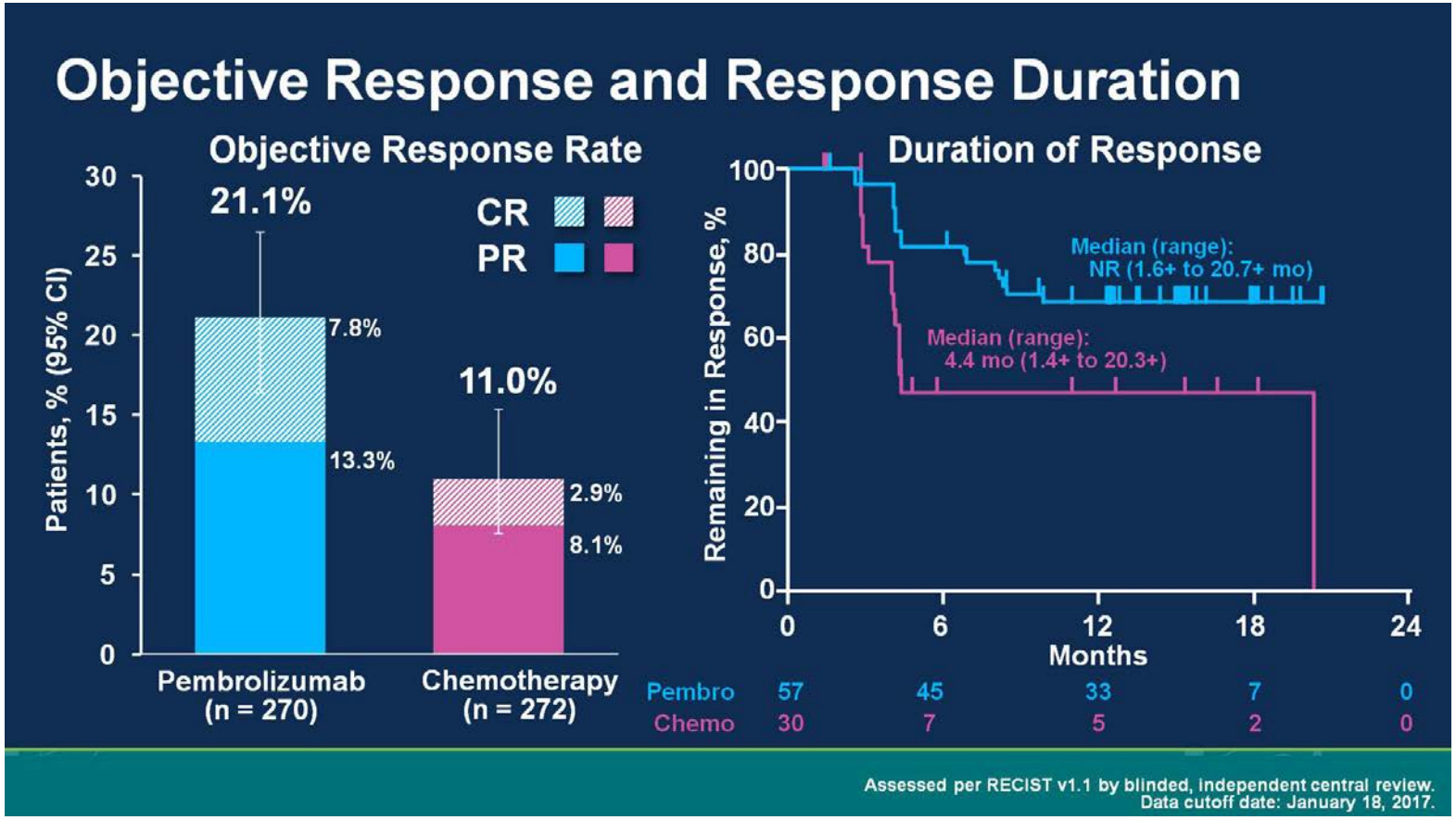

- Ganho inequívoco de sobrevida global em favor da imunoterapia




- Ganho mais acentuado no subgrupo com expressão do PDL1 acima de 10%

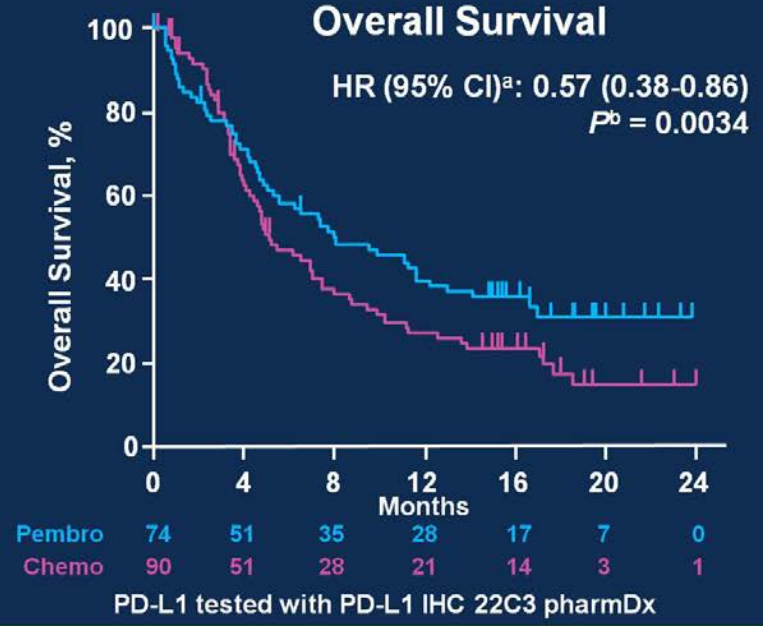


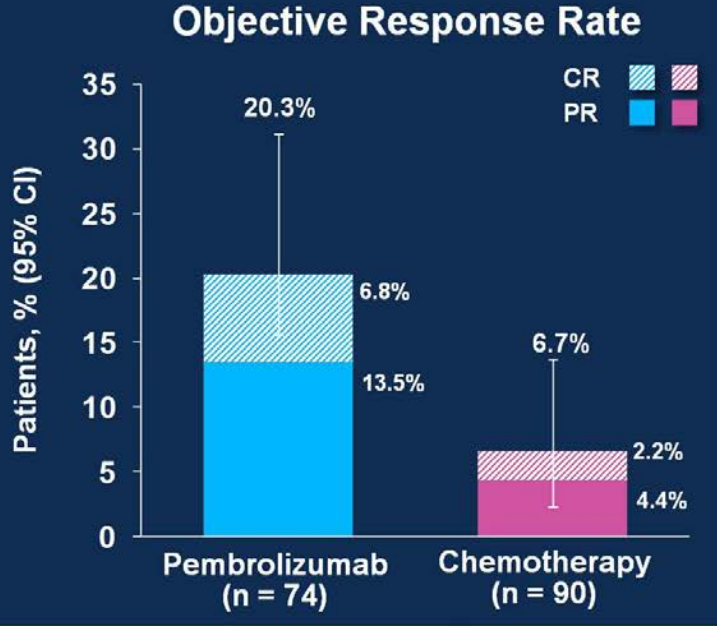

- Devido as dificuldades de se avaliar resposta pelo RECIST, o SLP pode ser inferior no braço da imunoterapia mesmo com ganho de sobrevida global…



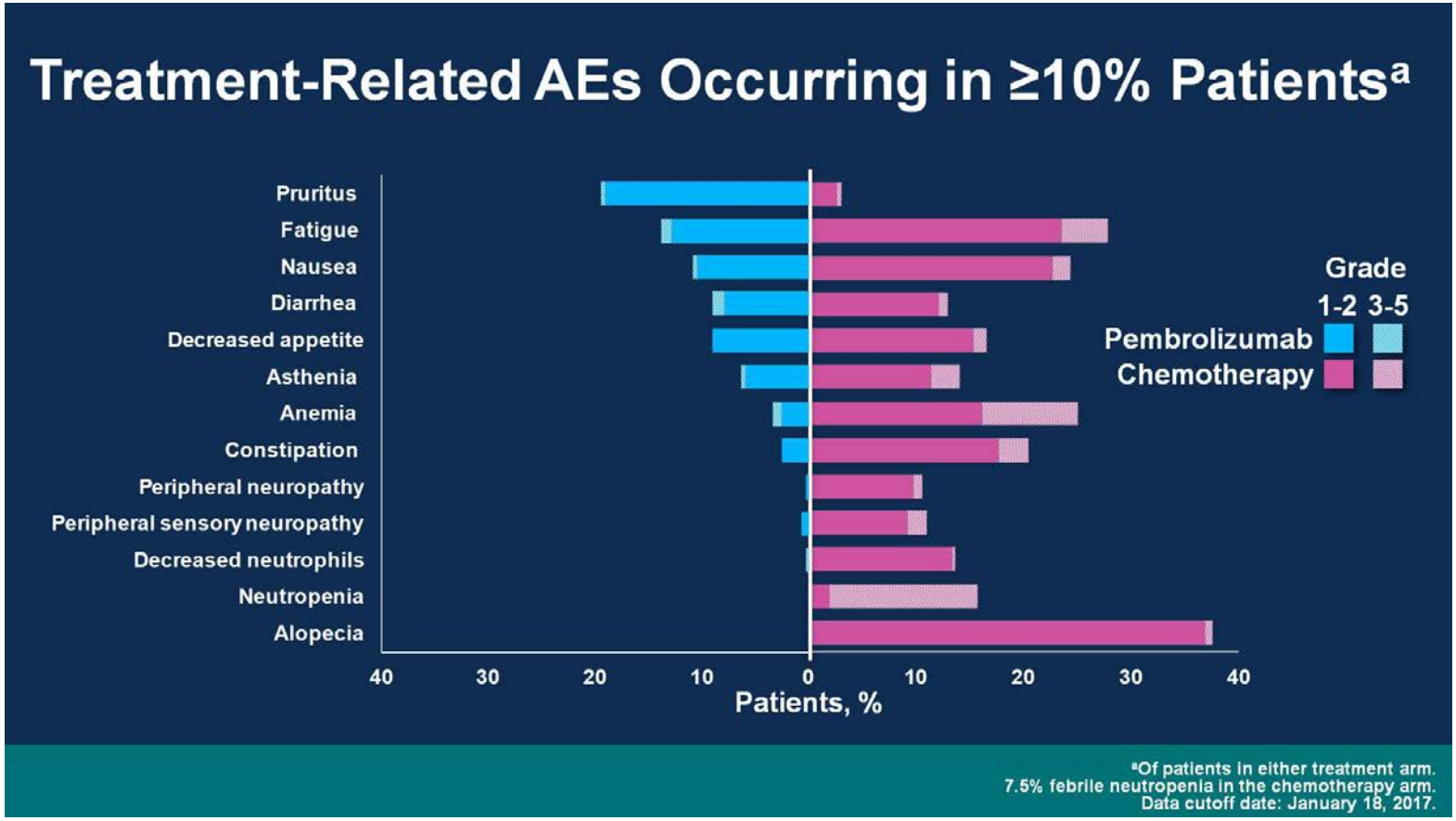

- Melhor resposta objetiva para a imunoterapia…
- Boa parte do benefício da QT é doença estável…

# Efficacy: PD-L1 CPS ≥10%




[a]Based on Cox regression model with treatment as a covariate stratified by ECOG performance status (0/1 vs 2), liver metastases (yes vs no), hemoglobin (<10 vs ≥10 g/dL), and time from completion of chemotherapy (<3 vs ≥3 mo). [b]One-sided *P* value based on stratified log-rank test.
Data cutoff date: January 18, 2017.




- Efeitos colaterais esperados para a imunoterapia…

# Summary

- Pembrolizumab survival benefit maintained with longer follow-up
  - Median OS, 10.3 versus 7.4 mo; HR, 0.70; *P* = 0.0004; median follow-up, 18.5 mo
  - OS at 12 months (44.4% vs 30.2%) and 18 months (36.1% vs 20.5%)
- Continued higher ORR with pembrolizumab versus chemotherapy
- Responses more durable with pembrolizumab versus chemotherapy
  - Median duration of response: Not reached versus 4.4 mo
  - Responses lasting ≥12 months: 69% versus 36%
- Better safety profile with pembrolizumab versus chemotherapy
  - Treatment-related AEs: 61.3% versus 90.2%
  - Grade ≥3 treatment-related AEs: 16.5% versus 49.8%

# Conclusions

- Pembrolizumab is the first immunotherapy to demonstrate superior survival over chemotherapy in patients with advanced urothelial carcinoma after failure of platinum-based therapy
- Pembrolizumab should be considered a standard of care for these patients, supported by level 1 evidence
- Based on these data, the FDA provided full approval of pembrolizumab for the treatment of advanced urothelial carcinoma after failure of platinum-based therapy without the need for PD-L1 staining

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- Pembrolizumabe é o novo padrão para segunda linha de tratamento para tumores uroteliais avançados

# DISCUSSÃO

Só a imunoterapia vale?

Hoje a imunoterapia é o tratamento padrão para tumores uroteliais em segunda linha e para tumores não elegíveis a tratamento com platina na primeira linha.

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