

Phase II study of tasquinimod in chemotherapy naïve patients with metastatic castrate-resistant prostate cancer (CRPC) - safety and efficacy analysis including subgroups

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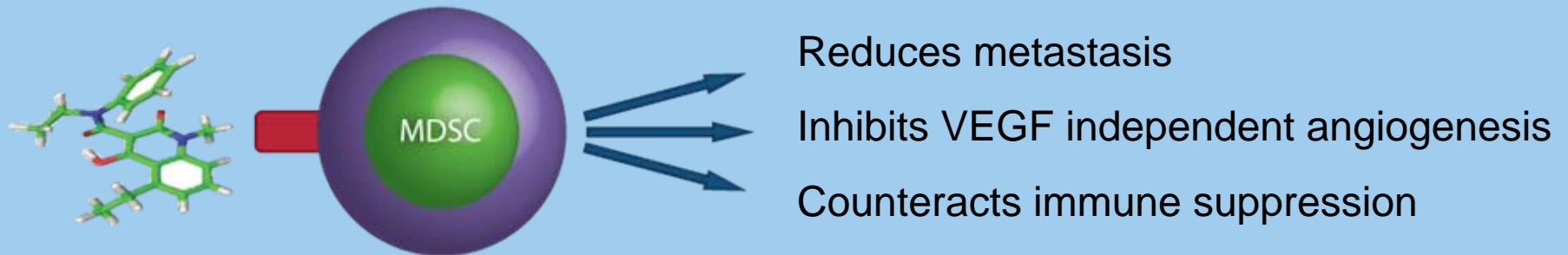
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Background

Tasquinimod (TASQ) is an oral quinoline-3-carboxamide derivative that binds to S100A9 and displays anti-angiogenic properties and anti-tumor activity in prostate cancer (PC) models. S100A9 has a role in cancer through myeloid derived suppressor cells (MDSC).

TASQ:

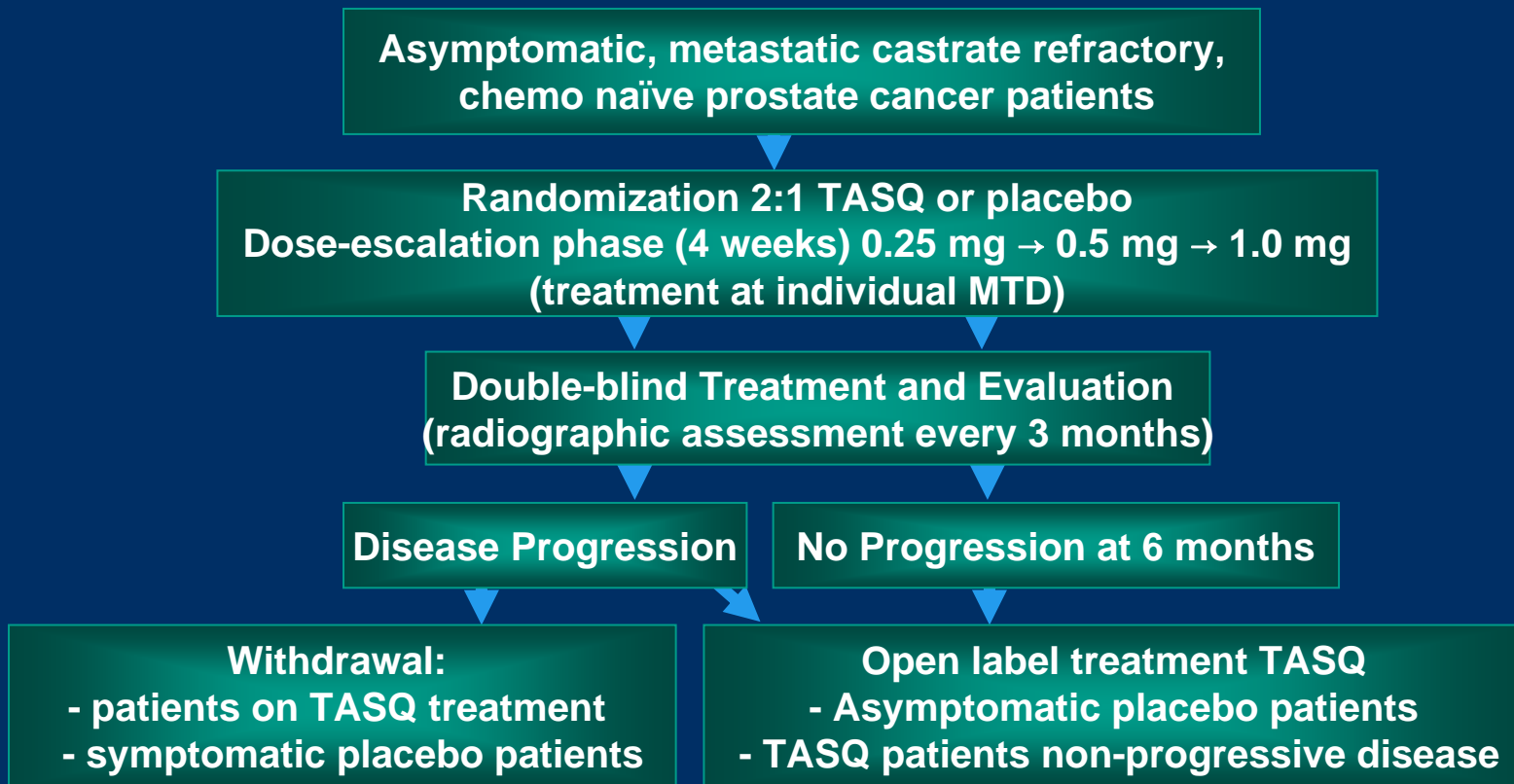
- Inhibits tumor growth in several prostate cancer models
- Binds to S100A9 (MRP14) on myeloid derived suppressor cells (MDSC) (3)
- Inhibits the “angiogenic switch” by up-regulation of Thrombospondin-1



Background, continued

In a randomized blinded phase II study, 206 (136 TASQ, 70 Placebo) men with metastatic castrate resistant (CRPC) were assigned to TASQ/P once-daily at an initial dose level of 0.25 mg/day escalating to 1.0 mg/day over 4 weeks. The primary endpoint to demonstrate an improvement in PCWG2 criteria-defined progression at 6 months was met and presented at ASCO 2010. This poster provides an update on safety and efficacy including CRPC subgroups and laboratory findings.

Schema



Eligibility Criteria

- **Main Inclusion Criteria**

Asymptomatic metastatic CRPC (VAS pain score ≤ 3)

Evidence of metastatic disease from CT or Bone scan

Evidence of progressive disease after castration levels of testosterone

- *Increased serum prostate-specific antigen (PSA) levels*

- *Progression of soft tissue or bone disease*

Karnofsky score 70-100

- **Main Exclusion Criteria**

Prior chemotherapy within 3 years

Anticancer therapy (biologics or vaccines) last 6 months (bevacizumab not allowed)

Concurrent use of other anti-cancer agents or treatments (stable doses of LHRH agonists, bicalutamide (e.g. Casodex) or other antiandrogens allowed).

Update for ASCO GU 2011

Update on Progression Free Survival (PFS) data

201 (134 TASQ, 67 Placebo) patients with a median age of 72.6 years received treatment and were evaluable. The updated analysis based on 5 additional PFS events confirmed an improved PFS of **7.6 vs. 3.3** months for pts on TASQ vs. Placebo. Most progression events in both arms were radiographic, but more pts progressed on bone scan in the placebo group. Radiographic PFS was 8.8 vs 4.4 months. Significant PFS improvements were observed in the PCWG2 risk groups with bone metastatic and visceral disease. The primary endpoint was reached – 69 vs 34 % of patients were progression free at 6 months.

PFS Kaplan Meier Curves

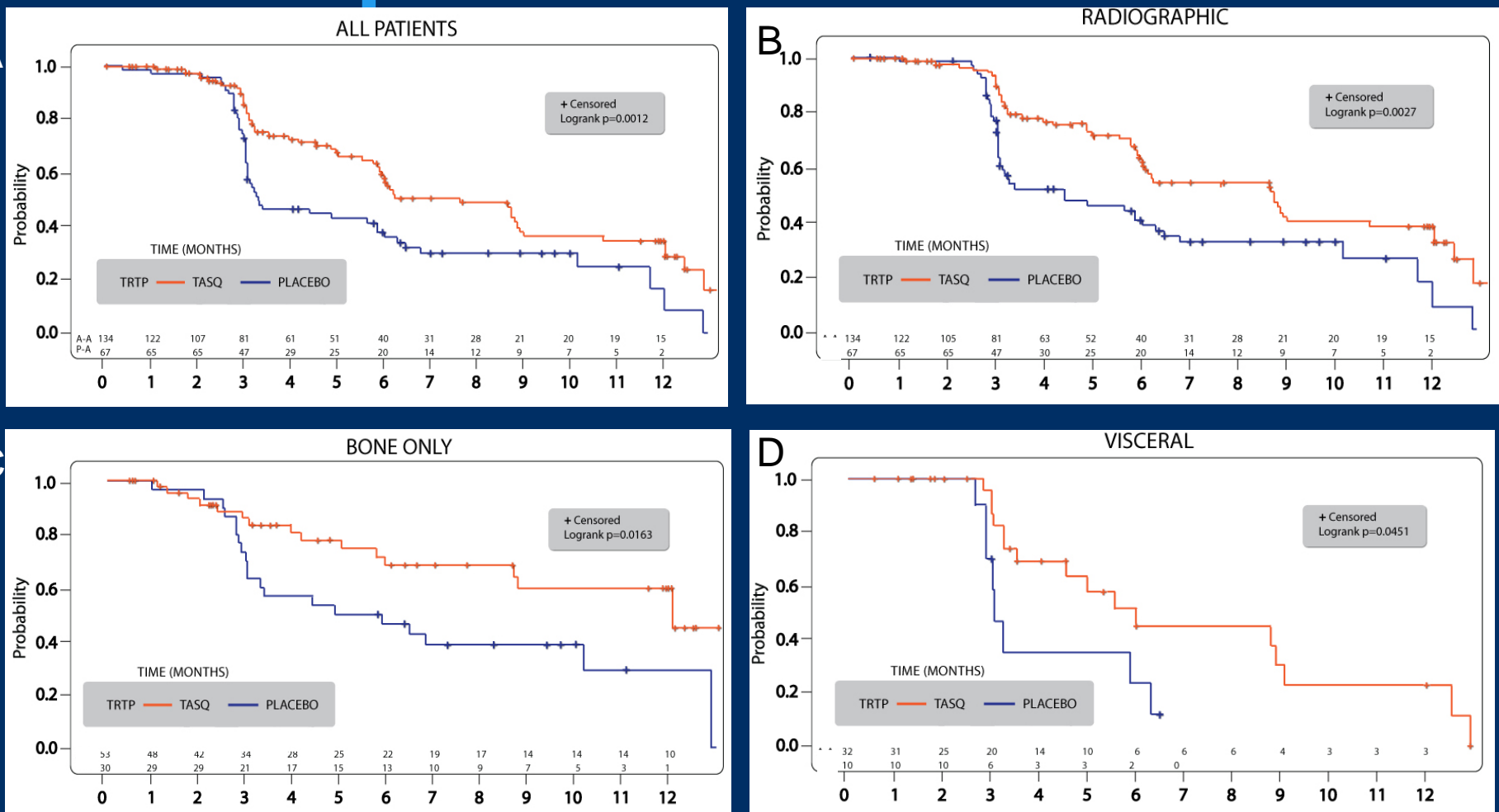


Fig 2. Progression Free Survival (PFS) analysis. A. PFS for all patients $N=201$, $n=134/67$ Median PFS= 7.6/ 3.3 months. B. Radiographic PFS $N=201$, $n=134/67$ Median PFS= 8.8/ 4.4 months. C. PFS for patients with Bone metastases only at baseline $N=83$, $n=53/30$ Median PFS=12.1/ 5.4 months. D. PFS for patients with Visceral metastasis at baseline $N=42$, A-A/P-A $n=32/10$ Median PFS= 6.0/ 3.0 months. Notably, placebo patients were allowed to cross over to active treatment after 6 months.

Safety and Toxicities

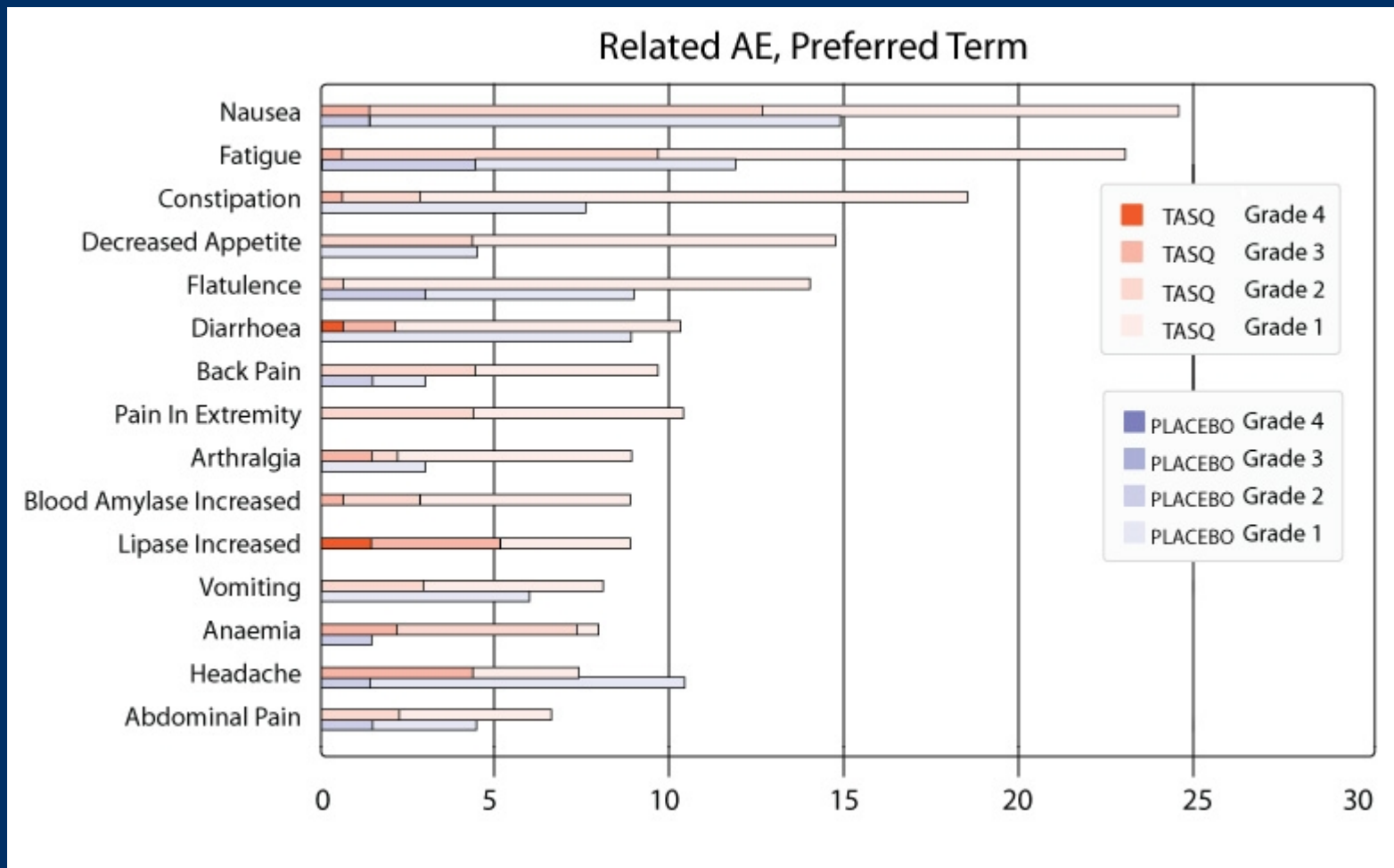


Fig 3. Most common AE-s and percent of patients with grade 1, 2, 3-5 in Doubleblind phase. Total number of related AE-s; TASQ 537, placebo 136. As illustrated to the right, the majority of AE-s were of grade 1 or 2.

Subgroup Analyses

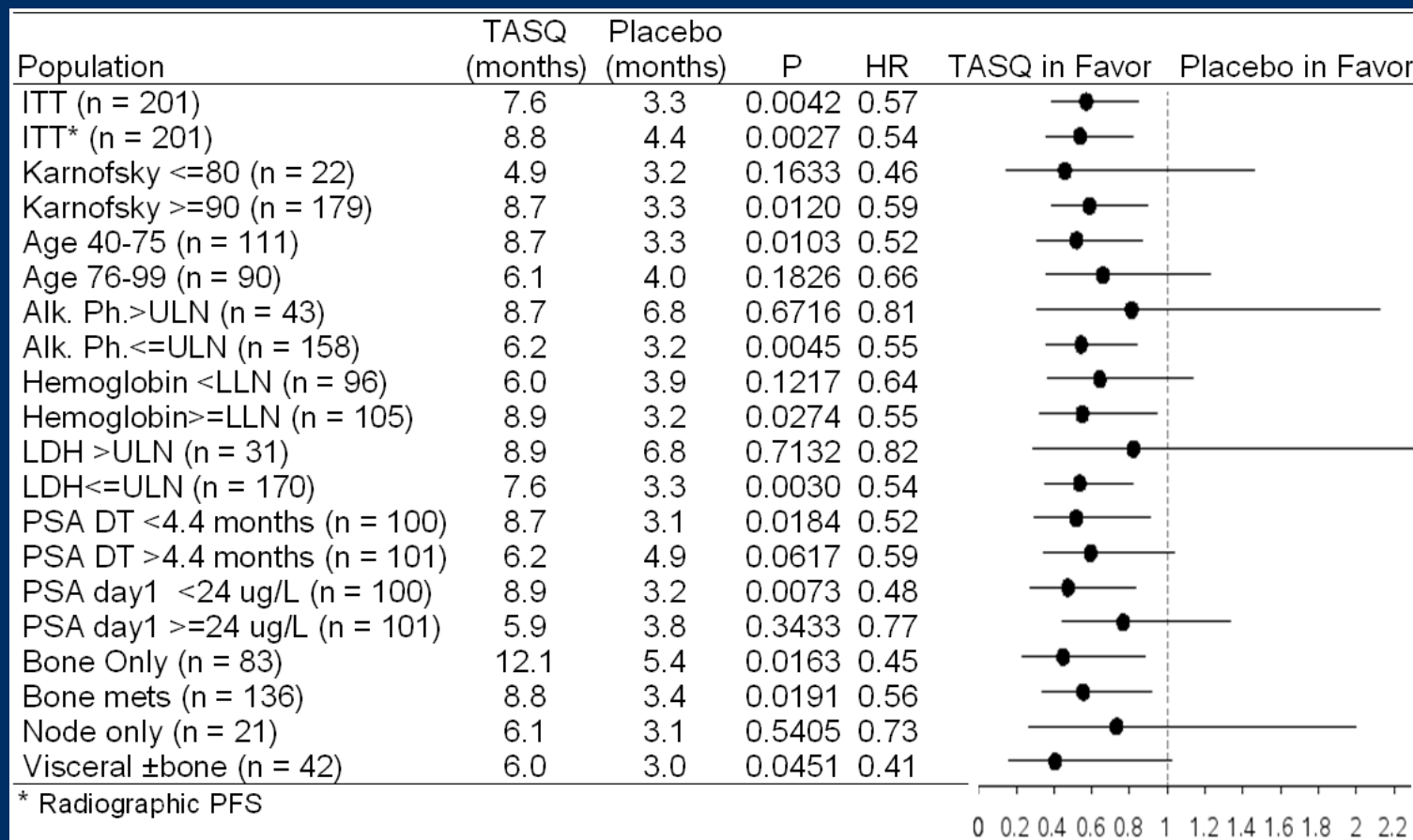
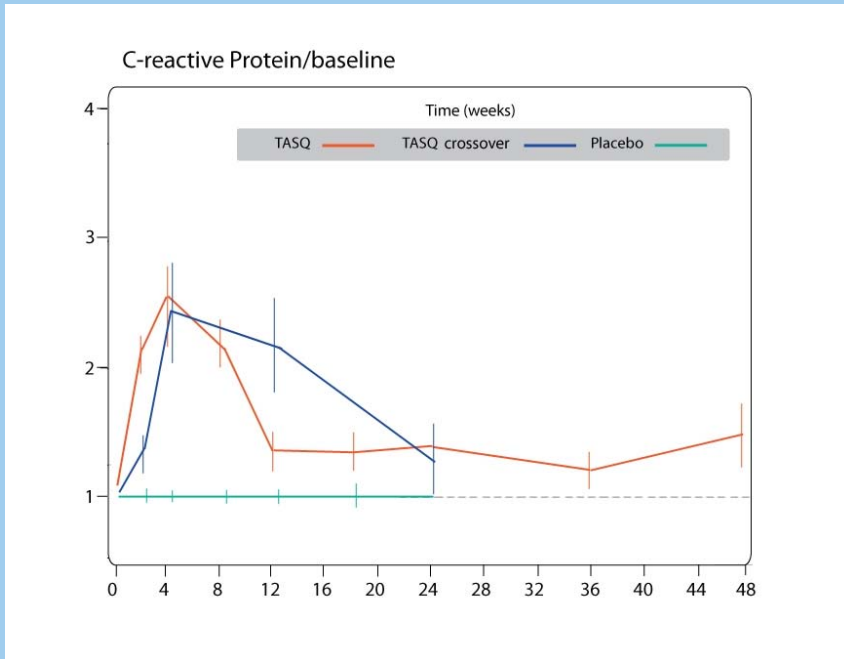


Fig 4. Table with Forest plot showing median PFS and Hazard Ratio (HR) with 95% CI for all patients and subgroups.

Biomarker Analyses

A



B

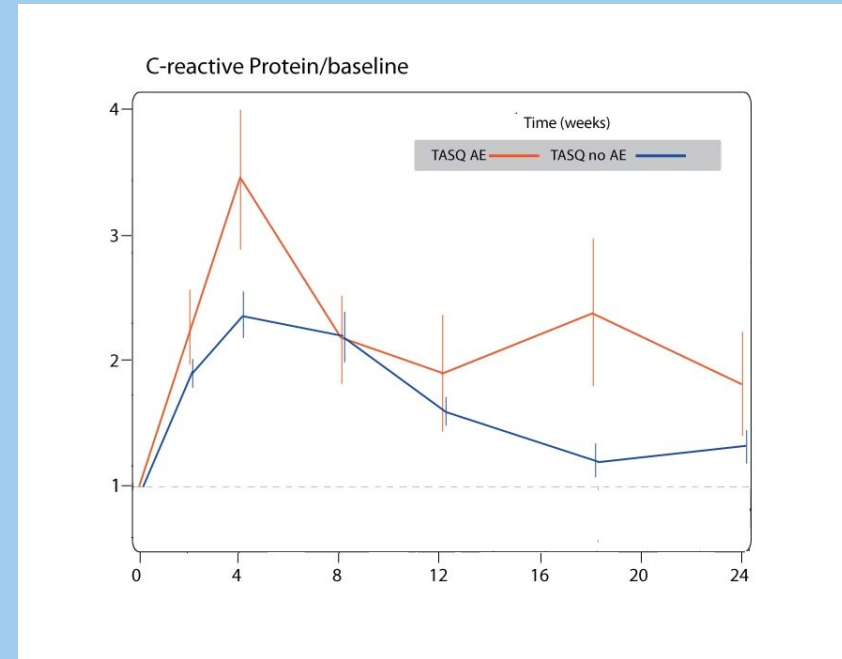


Fig. 5.

A. Changes in CRP levels over time in the various treatment groups.

B. CRP levels in TASQ treated men with (red) or without (blue) pain in extremity grade 1-4 (Median \pm SE).

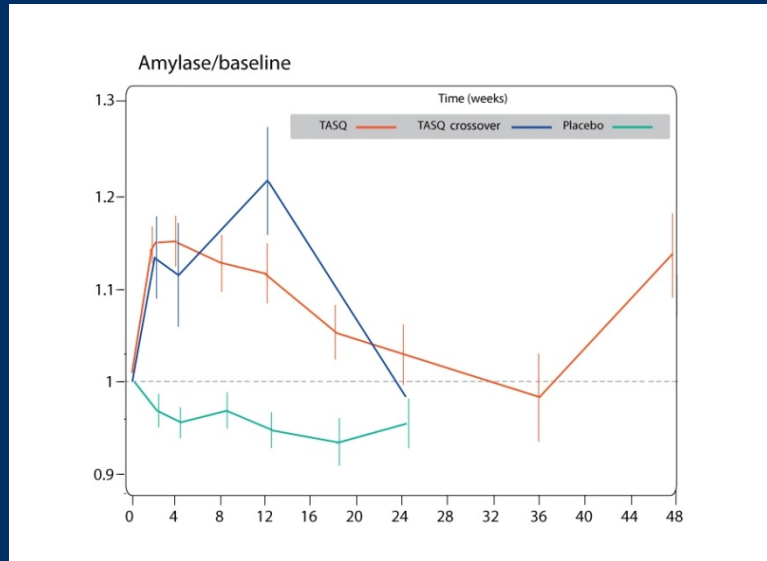
Analysis of lab parameters and impact on adverse events

TASQ treatment led to a transient increase in lab markers e.g. CRP, fibrinogen, and amylase/lipase.

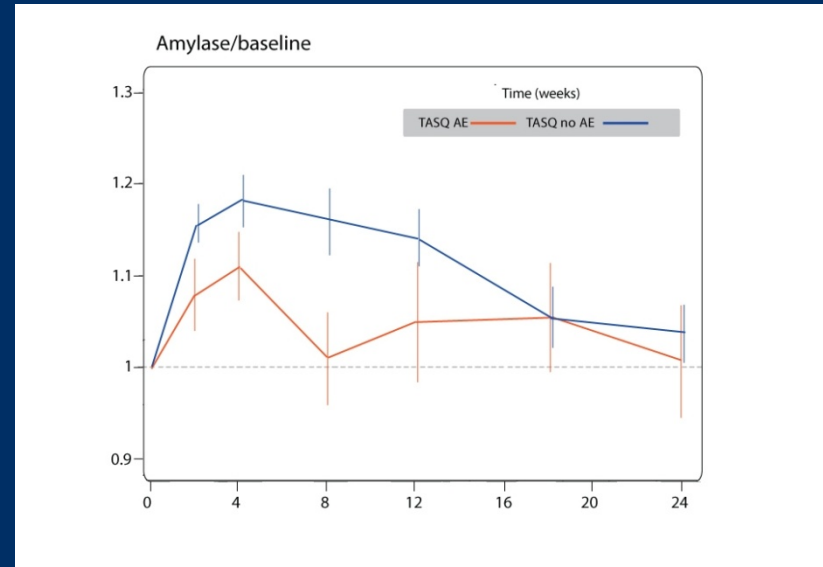
CRP increase was associated with AE-s such as muscle and joint pain, while increased amylase was associated with a lower risk for gastrointestinal (GI) AE-s.

Biomarker Analyses (cont)

C



D



C. Changes in amylase levels over time in the various treatment groups (median \pm SE).

D. Amylase levels in patients with (red) or without (blue) GI AE grade 2-4.

Cardiac Safety

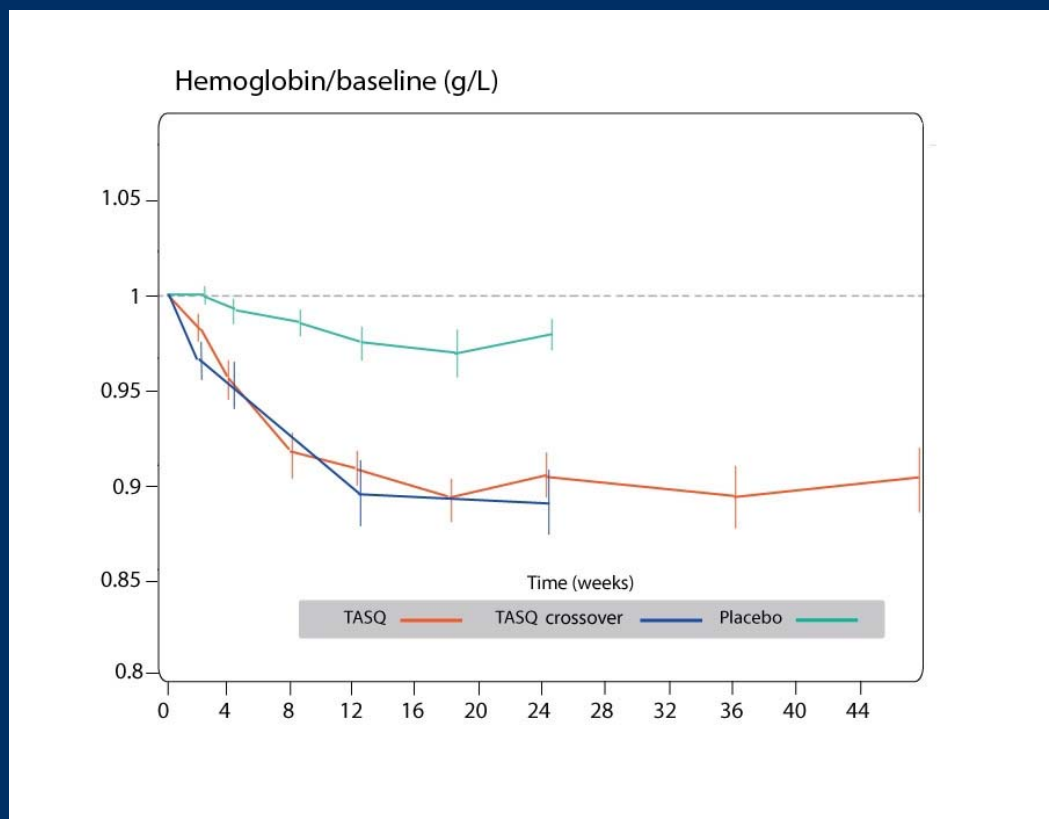


Fig 6. Hemoglobin levels over time in various treatment groups.

Effect on cardiac risk factors

TASQ treatment was associated with anaemia, but did not affect CV risk factors such as hypertension or QTc prolongation, and the rate of composite cardiac events was acceptably low.

Cardiac Safety

AE Group	TASQ (N=134)	Placebo (N=67)	Open label (N=76)
Arterial thrombotic	4 (3%)	2 (3%)	5 (7%)
<i>Myocardial infarction</i>	1 (1%)	0 (0%)	1 (1%)
<i>Cardio-respiratory arrest</i>	0 (0%)	1 (1%)	0 (0%)
Atrial arrhythmias	8 (6%)	2 (3%)	3 (4%)
<i>Atrial fibrillation</i>	5 (4%)	2 (3%)	2 (3%)
<i>Cardiac failure</i>	2 (1%)	0 (0%)	0 (0%)
Venous thrombotic	5 (4%)	0 (0%)	1 (1%)
<i>Deep vein thrombosis</i>	5 (4%)	0 (0%)	1 (1%)
Other	0 (0%)	1 (1%)	2 (3%)
<i>Cardiac tamponade</i>	0 (0%)	1 (1%)	0(0%)

Table 1. Most common cardiovascular events (all grades).

Thromboembolic Events Were Uncommon

- Patients experiencing DVT had relatively high baseline PSA (median 70 vs 26 ng/mL), higher mass of soft tissue lesions (median 120 vs 38 mm) and more rapidly increasing Alkaline Phosphatase (median at week 4 +48% vs +6%).
- Notably, patients on TASQ treatment had more advanced disease (median PSA 29 vs 19 ng/ml and higher incidence of visceral metastases) (4).

Age and Tolerability

- TASQ generally well tolerated but several patients terminated early due to grade 2 or 3 AE-s. Mean age of patients terminating due to AE was 74.9 years; higher than the total population (median 72.6 years).
- Patients with higher age have lower clearance - an increase in age with one year lowered the typical CL/F value with ~1.4 %.

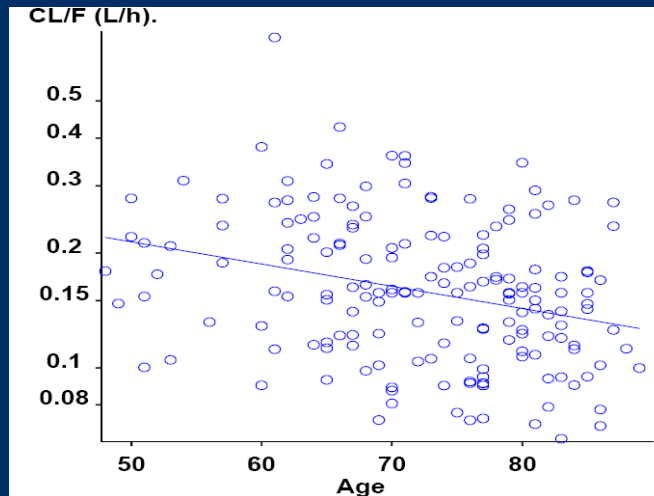


Fig 7. PK analysis showing the relationship between age and clearance indicating a lowered clearance of TASQ and higher exposure with age.

Age and Pharmacokinetics

- Patients above 80 years old much more likely to have AE-s within the first 2 months of therapy as compared to younger patients. Patients between 75 and 80 have an intermediate risk as compared to older and younger patients.
- The majority of AE-s were observed during the first two months (the dose escalation phase), especially in the older population.

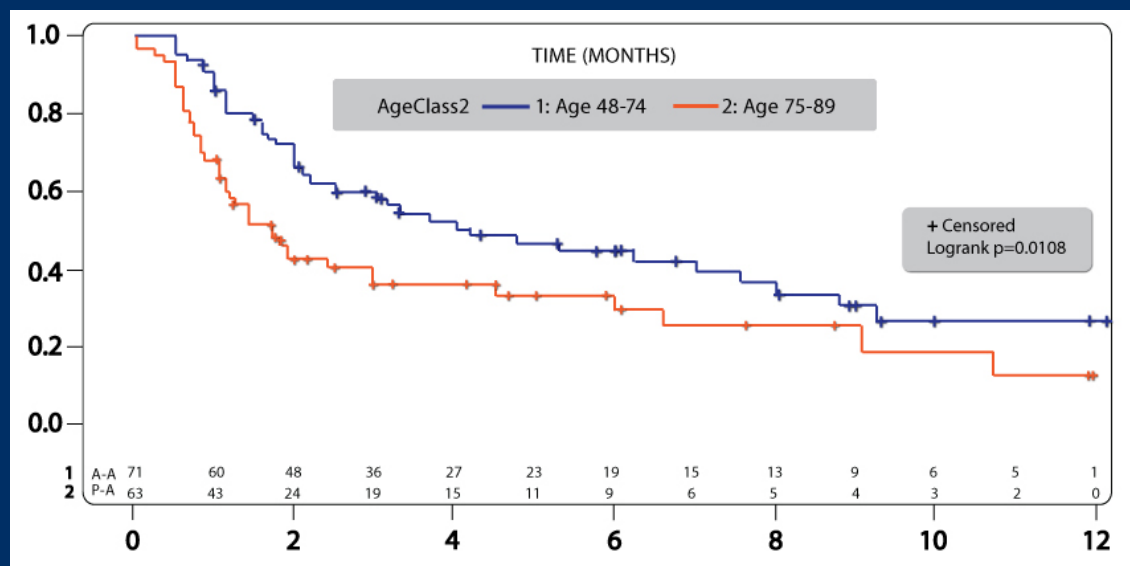


Fig 8. Time to withdrawal due to AE or AE grade 2 by Age Class for patients treated with TASQ.

Conclusions

- **TASQ improved PFS in men with asymptomatic to minimally symptomatic metastatic CRPC.**
- **Side effects are manageable and specific AE-s can be correlated with laboratory markers. Age is a risk factor for early TASQ toxicity, perhaps due to lower systemic clearance. Individualized dosing based on tolerability is recommended and may improve long term tolerability in men over 75 years of age.**
- **A Phase III trial investigating TASQ in the pre-chemotherapy (docetaxel) setting in men with CRPC will be initiated during first quarter 2011 to further confirm the overall clinical benefit in this population.**

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References

References

1. *Bratt et al, Br J of Cancer 2009 (1-8)*
2. *Olsson et al, Mol Cancer 9:107, 2010*
3. *Björk et al PLoS Biology, April 2009 7:4, p. 800-812*
4. *Pili et al J of Clin Oncology, 2010 ASCO Annual Meeting Proceedings, Vol 28, 2010: 4510*
5. *Murdoch et al, Nature Reviews Cancer (2008), 8,618-631.*
6. *Gabrilovich and Nagaraj, Nature Reviews Immunology, (2009), 9, 162-174.*
7. *Dalrymple et al, the Prostate, May 2007, p. 790–797.*
8. *Cheng et al, J. Exp. Med. Vol. 205 No. 10 2235-2249.*

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