CD68+ Tumor-Associated Myeloid Cells as the Target of Adenosine-Induced Gene Products and Predictor of Response to Adenosine Blockade with Ciforadenant (Cifo) in Renal Cell Cancer (RCC)

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ADENOSINE INHIBITS ANTI-TUMOR IMMUNITY BY RECRUITMENT OF MYELOID CELLS

- Adenosine in the tumor microenvironment induces expression of gene products derived from myeloid cells which correlate with unfavorable prognosis in RCC
- Fong et al.¹ showed tumors with an adenosine-induced gene signature are responsive to A2A receptor blockade with ciforadenant
- McDermott et al.² showed that an identical myeloid signature was associated with poor prognosis and poor response to anti-PD-L1
- Hakimi et al.³ (abstract# 5082 at ASCO) demonstrated shorter disease-free survival in myeloid/Adenosine Signature (AdenoSig) positive patients
- AdenoSig genes include chemokines that signal through CCR2 and CXCR2 to recruit myeloid and granulocytic cells (e.g. immunosuppressive tumor associated-M2 macrophages), thought to mediate resistance to anti-PD-(L)1
- Ciforadenant is currently under investigation for safety and anti-tumor activity
- We now describe a refinement of the AdenoSig based on adenosine-induced tumor infiltrating CD68+ myeloid cells which further enriches for patients likely to respond to ciforadenant +/- atezolizumab

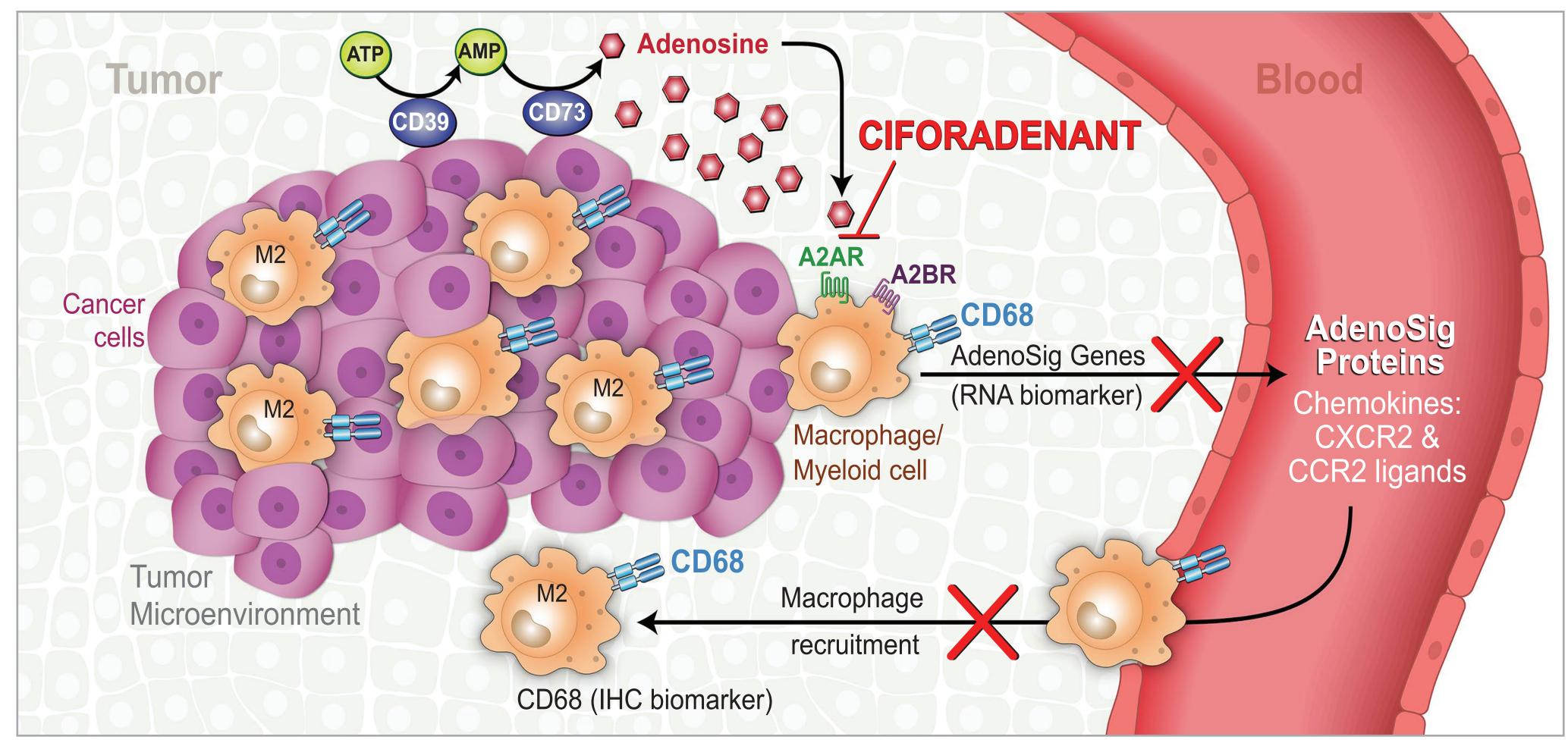


Figure 1. AdenoSig recruits CD68+ macrophages.

A2AR=adenosine-2A receptor; A2BR=adenosine-2B receptor; AMP=adenosine monophosphate; ATP=adenosine triphosphate

1. Fong et al. Cancer Discov. 2020; 2. McDermott et al. Nature Medicine. 2018; 3. Hakimi et al. ASCO 2020, abstract 5082

PROTOCOL DESIGN SUMMARY

Ciforadenant Monotherapy
(n=22)
100 mg BID 28 days/cycle

Renal Cell Cancer
(n=51)

Ciforadenant + Atezolizumab
(n=29)
100-200 mg BID 28 days/cycle + 840 mg, Q2W

Tumor Biomarker
Assessment

AdenoSig (RNA expression
using NanoString or RNASeq

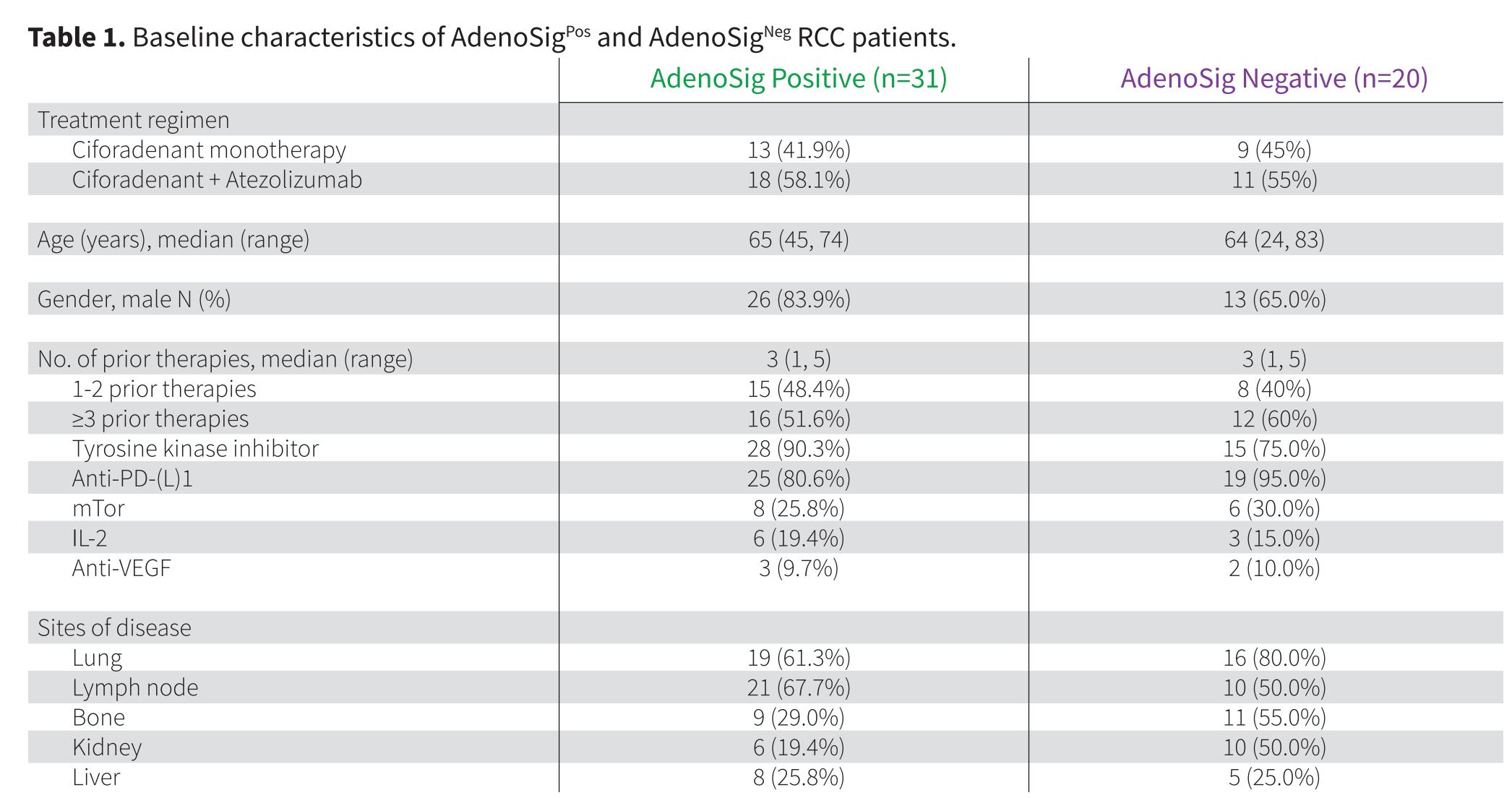
CD68+ Infiltration (IHC)

Eligibility

 Measurable disease
 Failed up to 5 prior therapies (depending on cohort)
 Progressive disease on prior therapy
 Treatment

 Measurable disease
 Prior anti-PD-(L)1 allowed (mandatory depending on cohort)
 No selection for PD-L1 expression
 Treated until disease progression or toxicity

PATIENT CHARACTERISTICS



TREATMENT EMERGENT ADVERSE EVENTS

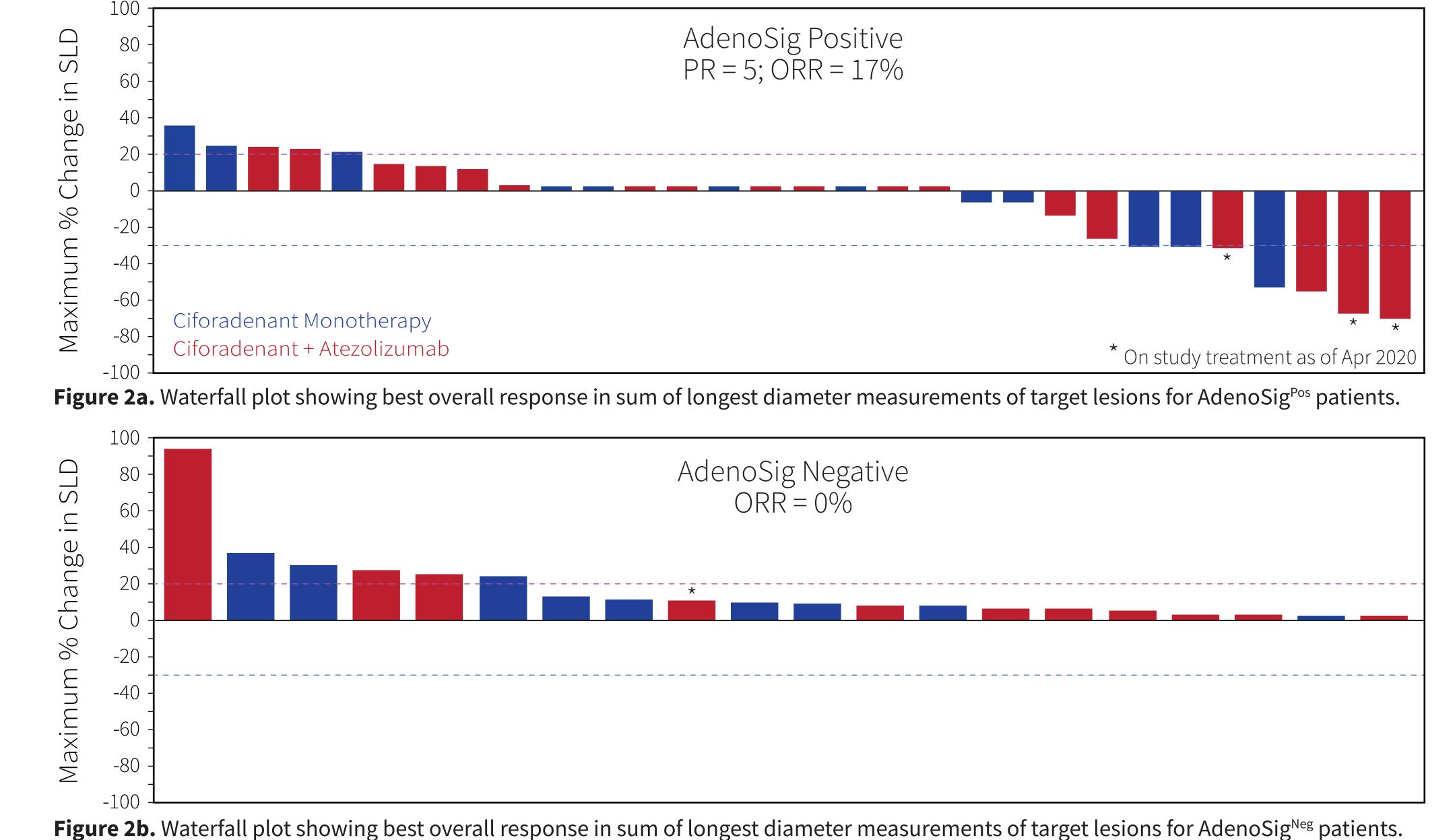
Table 2. Treatment emergent adverse events with an incidence of ≥10% of any grade in any treatment category

Ciforadenant (n=22)

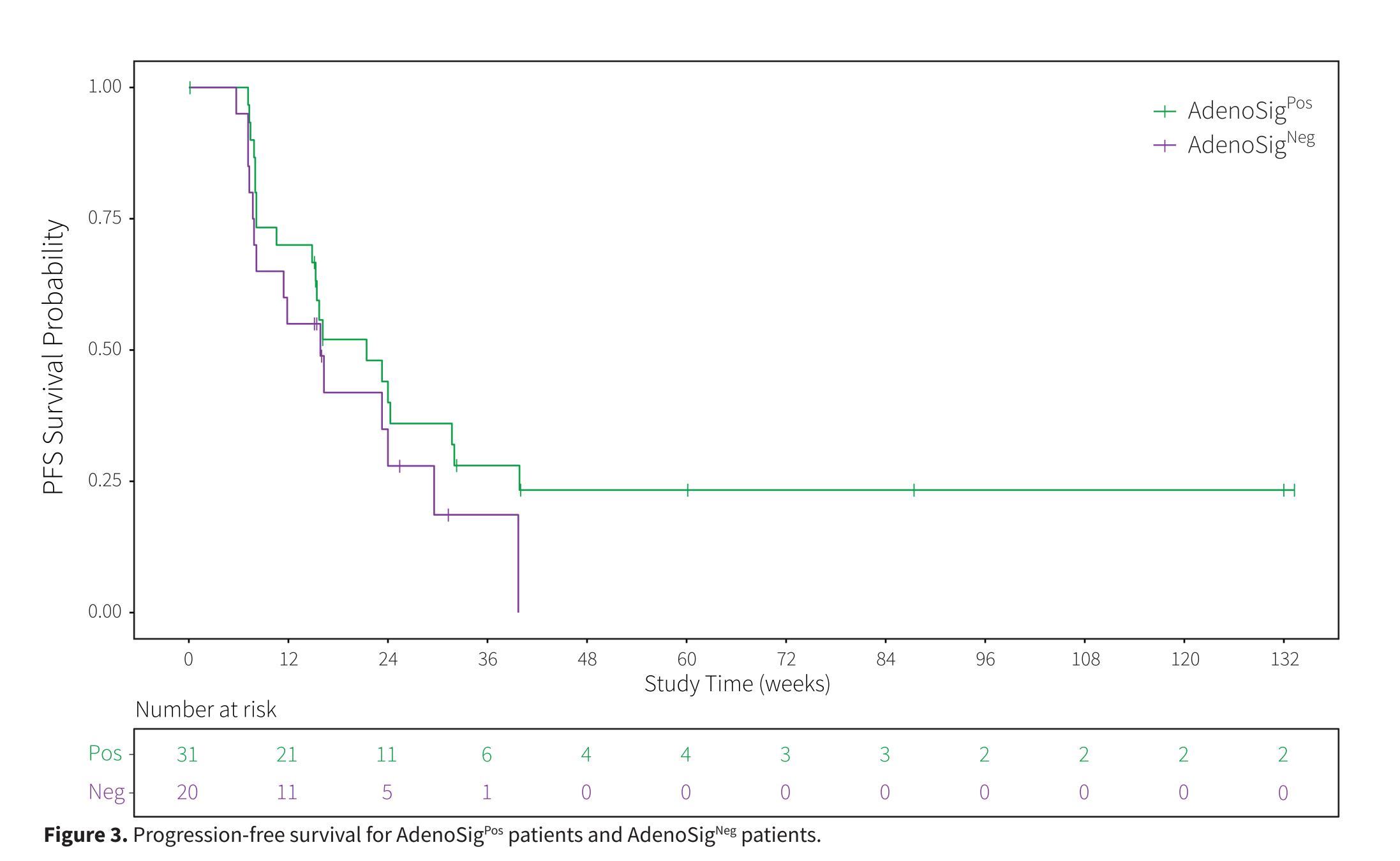
Ciforadenant + Atezolizumab (n=29)

Event, number of patients, (%)				
	Any Grade	Grade 3+	Any Grade	Grade 3+
Anaemia	4 (18.2)	1 (4.5)	5 (17.2)	3 (10.3)
Nausea	6 (27.3)	0	13 (44.8)	1 (3.4)
Constipation	3 (13.6)	0	10 (34.5)	0
Diarrhoea	3 (13.6)	0	7 (24.1)	0
Vomiting	4 (18.2)	0	3 (10.3)	0
Abdominal pain upper	1 (4.5)	0	4 (13.8)	0
Gastrooesophageal reflux disease	3 (13.6)	0	2 (6.9)	0
Abdominal pain	1 (4.5)	0	3 (10.3)	1 (3.4)
Dry mouth	0	0	3 (10.3)	0
Fatigue	7 (31.8)	0	14 (48.3)	0
Pyrexia	2 (9.1)	0	5 (17.2)	0
Non-cardiac chest pain	2 (9.1)	0	3 (10.3)	0
Oedema peripheral	2 (9.1)	1 (4.5)	3 (10.3)	0
Upper respiratory tract infection	3 (13.6)	0	3 (10.3)	0
Blood creatinine increased	2 (9.1)	0	3 (10.3)	0
Blood alkaline phosphatase increased	3 (13.6)	0	0	0
Decreased appetite	6 (27.3)	2 (9.1)	4 (13.8)	0
Arthralgia	3 (13.6)	1 (4.5)	8 (27.6)	1 (3.4)
Back pain	3 (13.6)	0	7 (24.1)	0
Musculoskeletal pain	2 (9.1)	0	6 (20.7)	0
Myalgia	2 (9.1)	0	4 (13.8)	0
Musculoskeletal chest pain	2 (9.1)	0	3 (10.3)	0
Neck pain	2 (9.1)	0	3 (10.3)	0
Bone pain	1 (4.5)	1 (4.5)	3 (10.3)	0
Pain in extremity	1 (4.5)	0	3 (10.3)	0
Dizziness	6 (27.3)	0	2 (6.9)	0
Headache	3 (13.6)	0	5 (17.2)	0
Neuropathy peripheral	0	0	3 (10.3)	0
Insomnia	4 (18.2)	0	2 (6.9)	0
Acute kidney injury	3 (13.6)	2 (9.1)	0	0
Cough	6 (27.3)	0	7 (24.1)	0
Dyspnoea	2 (9.1)	0	5 (17.2)	0
Dyspnoea exertional	4 (18.2)	0	3 (10.3)	0
Nasal congestion	2 (9.1)	0	5 (17.2)	0
Wheezing	1 (4.5)	0	4 (13.8)	0
Productive cough	1 (4.5)	0	3 (10.3)	0
Pruritus	6 (27.3)	0	5 (17.2)	0
Rash	2 (9.1)	0	5 (17.2)	0

ANTI-TUMOR ACTIVITY WITH CIFO ± ATEZOLIZUMAB



PROGRESSION-FREE SURVIVAL



INFILTRATING CD68+ CELLS FURTHER ENRICHES FOR RESPONDERS

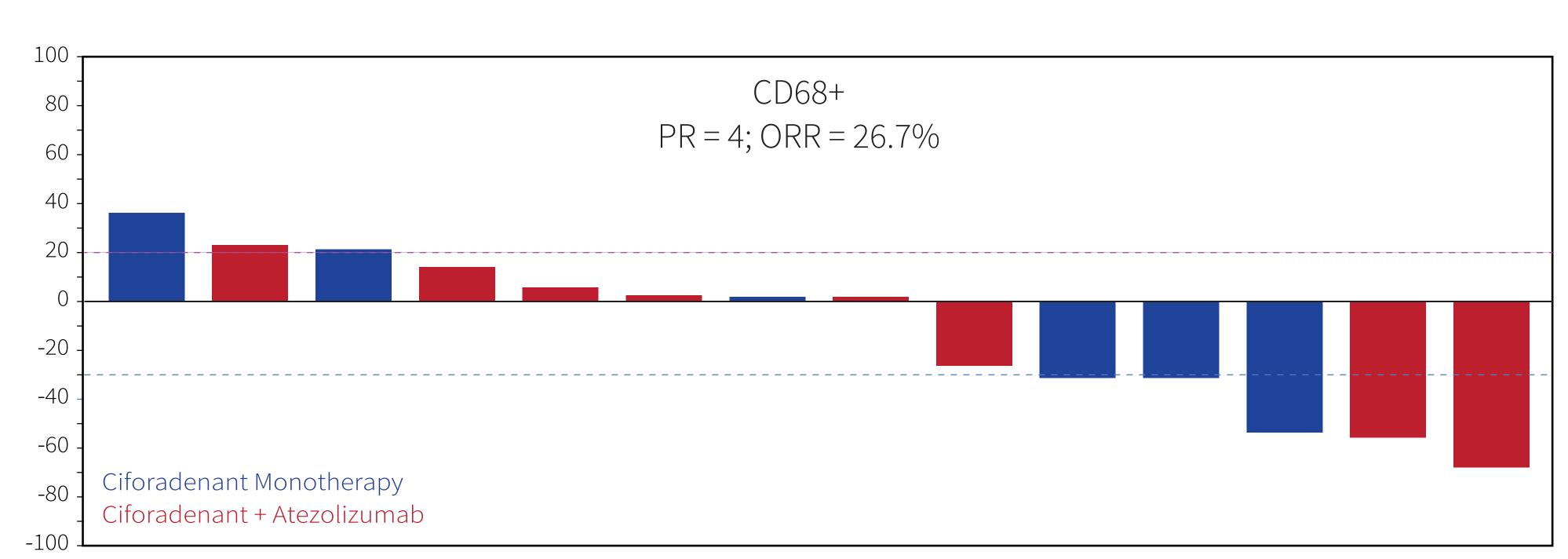


Figure 4a. Waterfall plot showing best overall response in sum of longest diameter measurements of target lesions for CD68+ patients. Waterfall plot for CD68– patients is not provided. ORR for CD68– patients is 2.6%.

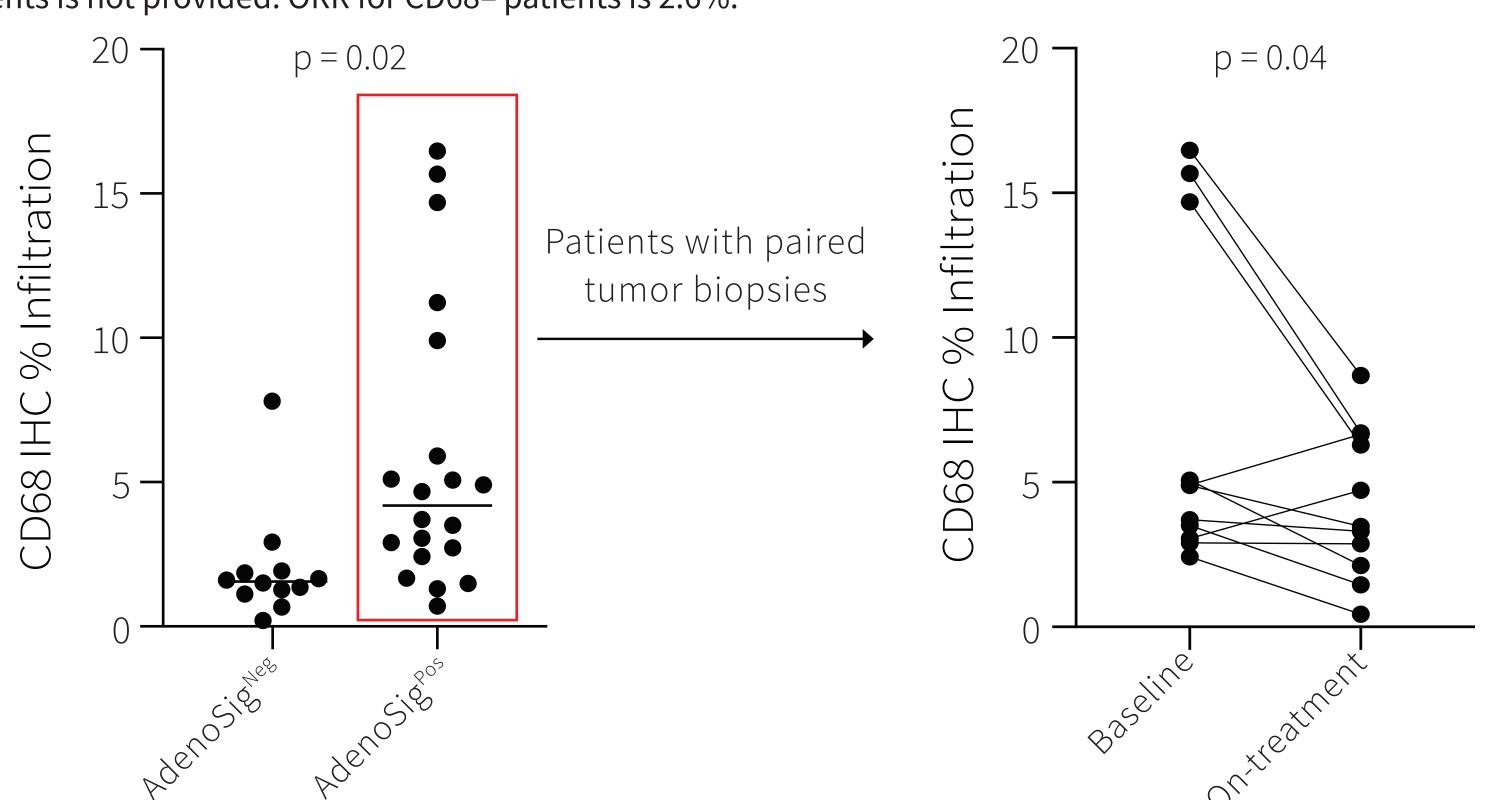


Figure 4b. AdenoSig^{Pos} RCC patients have higher levels of CD68+ tumor-associated macrophages (TAM); TAMs are reduced with ciforadenant +/-atezolizumab treatment in these patients. CD68+ cells measured using immunohistochemistry (IHC) and a cut-off of 4% positivity in the tumor area. CD68+ cells are statistically significantly more frequently detected in AdenoSig^{Pos} tumor biopsies. Treatment is associated with a reduction of CD68+ cells infiltrating the tumor.

CONCLUSIONS

- In these heavily pretreated patients with metastatic RCC, >50% of which had received 3 or more prior lines, including >80% prior anti-PD(L)1, ciforadenant +/- atezolizumab is well tolerated and shows efficacy
- AdenoSig identifies a subset of RCC patients with an unfavorable prognosis, but are more responsive to treatment with ciforadenant +/- atezolizumab
- ORR (RECIST v1.1) = 17% in AdenoSig^{Pos} plus 2 additional patients with tumor regression vs 0% in AdenoSig^{Neg}
- A plateau on the PFS curve (Fig 3) suggests that some patients (approx. 25%) may experience prolonged remission
- CD68+ cell infiltration as a single biomarker in the tumor further enriches for responding patients
- CD68+ myeloid cells are downstream targets of adenosine and are immunosuppressive in tumors
- CD68+ myeloid cells may be enumerated by standard immunohistochemical techniques
- ORR (RECIST v1.1) is 27% in CD68+ tumors
- 4 PRs plus 2 other tumor responders out of 15 patients; 1 responder (AdenoSig^{Pos}) out of 38 patients in CD68– - Treatment is associated with a reduction in infiltrating CD68+ cells
- The relationship between CD68 and the AdenoSig supports the role of CD68+ M2 macrophages in adenosine-mediated immunosuppression
- This study confirms the role of the AdenoSig biomarker in RCC and further refines the biomarker to a more simple and practical IHC test based on CD68+ cells

For questions or comments, email ContactCP@corvuspharma.com