Incidence and Management of Proteinuria in the IMbrave150 Clinical Trial

This article responds to your request for information on Tecentriq® (atezolizumab) in combination with Avastin® (bevacizumab) and the incidence and management of proteinuria in the IMbrave150 clinical trial.

In brief

- Proteinuria is a common adverse event associated with Avastin.
- At trial enrolment, patients were tested for pre-existing proteinuria.
- Avastin management guidance was provided in the study protocol.
- The incidence of all grade proteinuria during the study was 30%.
- Patients could still continue single-agent therapy with Tecentriq if they discontinued Avastin due to proteinuria.

IMbrave 150 Study design

IMbrave150 was a Phase III, open-label, randomised study of Tecentriq in combination with Avastin compared with sorafenib, in patients with unresectable or advanced hepatocellular carcinoma (HCC) who had not received prior systemic therapy.[1]

Inclusion criteria related to proteinuria

Within 7 days prior to IMbrave150 trial initiation, patients underwent dipstick urinalysis for proteinuria. Table 1 shows the recruitment criteria.[2]

Table 1: Proteinuria analysis at IMbrave150 initiation

If dipstick urinalysis was...	Then...
1	patients could be enrolled
≥2	patients underwent a 24-hour urine collection and had to demonstrate <1 g of protein in 24 hours before they could be enroled

Incidence of proteinuria in IMbrave150

Table 2 shows the incidence of proteinuria in the IMbrave150 trial. In clinical trials investigating Tecentriq in combination with different therapies in different indications, all grade proteinuria arose at an of incidence of 8.2%.[3] In clinical trials studying Avastin in different indications, proteinuria arose within a range of 0.7% to 54.7% of patients receiving Avastin.[4] In these trials proteinuria ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome.[3,4]

Table 2. Incidence of all-cause proteinuria during IMbrave150 in safety-evaluable population[5]

Proteinuria grade	Tecentriq IV 1200 mg Q3W + Avastin IV 15 mg/kg Q3W (n=329)	Sorafenib oral 400 mg bid continuously (n=156)
Any grade (%)	30%	8%
Grade 1-2 (%)	26%	8%
Grade 3-4 (%)	4%	<1%
Grade 5 (%)	0%	0%
Abbreviations: IV=intravenous; Q3W=every 3 weeks; bid=twice a day; Data Cutoff: Aug 31st 2020		

Management of proteinuria in IMbrave150

Proteinuria was managed in the IMbrave150 trial as per Table 3.

Table 3. Management guidelines for proteinuria associated with Avastin[5]

If proteinuria is...	Then...
Grade 1 (1+ proteinuria; urinary protein <1.0 g/24 hour)	administer Avastin.
Grade 2 (2+ proteinuria; urinary protein 1.0 to 3.4 g/24 hour)	• may administer Avastin and collect 24-hour urine prior to subsequent Avastin administration if 2+ dipstick • obtain 24-hour urine prior to administering Avastin if 3+ dipstick • withhold Avastin if urinary protein ≥2 g/24 hour or • resume Avastin if proteinuria is <2 g/24 hour.
Grade 3 (urinary protein ≥3.5 g/24 hour)	withhold Avastin then resume Avastin when proteinuria is <2 g/24 hour.
Grade 4 or with diagnosis of nephrotic syndrome	permanently discontinue Avastin.

Avastin discontinuation as a result of proteinuria

The protocol of the IMbrave150 study allowed patients who discontinued either Tecentriq or Avastin due to adverse event to continue on single-agent therapy, until loss of clinical benefit or unacceptable toxicity associated with the single agent.[5] Table 4 shows the incidence of Avastin treatment interruptions and withdrawals due to proteinuria.

Table 4: Avastin treatment interruptions/dose modifications and withdrawals due to proteinuria[6]

Proteinuria events	Tecentriq IV 1200 mg Q3W + Avastin IV 15 mg/kg Q3W (n=329)	Sorafenib oral 400 mg bid continuously (n=156)
Lead to study treatment interruption (%)	13.7 %	1.3 %
Lead to withdrawal of Avastin (%)	3.3 %	0 %
Abbreviations: IV=intravenous; Q3W=every 3 weeks; bid=twice a day, Data Cutoff: Feb 2023		

Additional information

For further information related to Avastin-related proteinuria, please refer to the article "Monitoring and Management of Avastin-Associated Proteinuria".

References

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3. Roche Internal Regulatory Document, accessed on 03-Jul-2023.

4. Roche Internal Regulatory Document, accessed on 03-Jul-2023.

5. Cheng A, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: Atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. See supplementary data " Multimedia component 4" for protocol and safety data. J Hepatol 2022;76:862-873. https://www.ncbi.nlm.nih.gov/pubmed/34902530

6. Roche Clinical Study Report, accessed on 14-Sept-2023.