Dose Modification Schedule & Management of adverse reactions to Vemurafenib

Dose modification schedule for adverse reactions based on grade.

Grade	Recommended dose modification
Grade 1 or Grade 2 (tolerable)	Maintain dose of 960 mg twice daily.
1st occurrence of any Grade 2 (intolerable) or Grade 3	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of any grade 2 or 3 AE or persistence after treatment interruption	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of any grade 2 or 3 AE or persistence after 2nd dose reduction	Discontinue permanently.
1st occurrence of any grade 4 AE	Discontinue permanently or interrupt vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
2nd occurrence of any grade 4 AE or persistence of any grade 4 AE after 1st dose reduction	Discontinue permanently.

Dose modification schedule based on prolongation of QT interval

QT c value	Recommended dose modification
QTc > 500ms at baseline	Treatment not recommended
QTc increase meets values of both > 500 ms and >60 ms change from pre-treatment values.	Discontinue permanently.
1st occurrence of QTc>500ms during treatment and change from pre-treatment value remains <60 ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Resume dosing at 720 mg twice daily (or 480 mg twice daily if the dose has already been lowered).
2nd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Temporarily interrupt treatment until QTc decreases below 500 ms. Electrolyte abnormalities (including magnesium) should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Resume dosing at 480 mg twice daily (or discontinue permanently if the dose has already been lowered to 480 mg twice daily).
3rd occurrence of QTc>500 ms during treatment and change from pre-treatment value remains <60ms	Discontinue permanently.

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N.B. Version numbers re-started from 1 when adverse reaction information separated from proforma