

AstraZeneca	AZD9150
Mechanism of Action	Signal transducer and activator of transcription 3 (STAT3) antisense http://www.ncbi.nlm.nih.gov/gene/6774
Overview	AZD9150 is a 16 oligonucleotide antisense molecule (ASO) targeting the 3' untranslated part of STAT3, thereby preventing the production of the protein. AZD9150 knocks down mRNA and protein in multiple tumor cell screens and demonstrated a good correlation between mRNA knockdown and protein knockdown <i>in vitro</i> . Control ASOs did not impact STAT3 mRNA or protein levels at any dose. STAT3 inhibition leads to apoptosis in lymphoma cells. <i>In vivo</i> , a dose-dependent and time-dependant knockdown of STAT3 mRNA and protein were shown in multiple xenografts and explants. <i>In vivo</i> tumor growth inhibition (TGI) has been shown in xenografts and explants, with TGI shown predominately in explants.
Safety/Tolerability	AZD9150 has been administered i.v. to patients with diffuse large B-cell lymphoma (DLBCL) and hepatocellular carcinoma (HCC) in multiple doses up to 3 mg/kg. AZD9150 is given as three-hour i.v. infusions on the initial cycle (Cycle 0) Days 1, 3 and 5, and weekly three-hour i.v. infusions in subsequent (Cycles 1 and beyond) on Days 1, 8, and 15 of each cycle. The most frequent and dose-limiting adverse effect is thrombocytopenia.
Additional Information	Responses have been seen in the DLBCL study and enrollment continues. Escalation continues in the HCC study and knockdown of STAT3 in peripheral blood mononuclear cells (PBMCs) has been shown.
Suitable for and Exclusions	Suitable for clinical studies that investigate the mode of action of AZD9150, e.g., tumor STAT3 knockdown and/or immunomodulatory effects. See http://www.clinicaltrials.gov/ct2/show/NCT01839604 for a list of exclusions in the ongoing trial. These are likely to apply to a proposal study as well. Suitable for study in indications, sub-populations and/or endpoints that are manifestly distinct from those previously studied for this compound or mechanism of action.
Clinical Trials	http://www.clinicaltrials.gov/ct2/results?term=ISIS-STAT3Rx&Search=Search
Additional Characteristics: CNS Penetration/Pediatric Diseases	AZD9150 has low CNS penetration and, thus, is probably not suitable for a CNS indication. Pediatric disease projects cannot be supported at this time.
Publications	http://meetinglibrary.asco.org/content/112636-132 ; http://conference.ncri.org.uk/abstracts/2013/abstracts/B56.htm ; http://cancerres.aacrjournals.org/cgi/content/meeting_abstract/73/8_MeetingAbstracts/LB-317