**Halichondrin Analog**

**Halichondrin B (NSC 609395)**

**Background**

Halichondrin B isolated from the marine sponge *Halichondria okadai* (New Zealand) in 1985.

- Highly potent cytotoxic agent.
- A synthetic macrocyclic ketone derivative of the marine natural product Halichondrin B.
- Produced by chemical synthesis by the Eisai Corporation of America.
- Harvard licensed Dr. Y. Kishi's synthetic method to Eisai. Eisai developed and produced Halichondrin B or Taxol® against NCI-H522 and MDA-MB-435 under conditions of the assay.

**Eisai 7389 (NSC 707389)**

**Background**

- A synthetic analog of Halichondrin B with similar tubulin binding than the parent Halichondrin.
- Produced by chemical synthesis by Dr. E. Hamel.
- Halichondrin B accepted into DN in March of 1982 based on in vitro and in vivo data.
- Difficulty in obtaining additional material from the natural sponge stimulated research.
- Formulation of 5% ethanol in water for injection developed for i.v. administration.
- E7389 approved for clinical trials in April 2002.

**Studies**

- **Toxicology Studies**
- In Vitro
  - **IC 90 (nM)**
    - Human: 21.7
    - Dog: 19.8
  - Drug-related body weight loss (ketoconazole, amoxicillin, and a drug combination of both) mainly in female rats, which indicates that E7389 is a substrate for p-glycoprotein.
- E7389 clearly showed better activity than that produced by the natural product, Halichondrin B.

- **PK/TK Studies**
- Single Dose PK in Rats (1.5 mg/kg given i.v.)
  - TDI: 0.13 mg/kg/dose.
  - Toxicology Studies: dose-related increases in AST.
  - Drug-related body weight loss (ketoconazole, amoxicillin, and a drug combination of both) mainly in female rats, which indicates that E7389 is a substrate for p-glycoprotein.

**Clinical Formulation**

- **Clinical Formulation**
- E7389, a highly complex, synthetic analog of Halichondrin B prepared at Eisai Research Institute, is a synthetic partner of more than 60 steps.
- E7389 approved for clinical trials in April 2002.

**Rapid Tissue Distribution.**

- Halichondrin B was a more effective inhibitor of tubulin binding than the parent halichondrin.

**In Vivo Studies**

- **Intertumoral treatment regimen (transcutaneous dose of 2.25–3.8 mg/kg) with chromatic probe: 1994 A172 glioma tumor regimen in mice.**
- NSC-609395 (E7389) at 10 mg/kg was given i.v. for 14 days to five mice bearing the NCI-H522 human lung metastatic cell line.
- **Mean Graphs**

**High Volumes Levels**

- Halichondrin B was a more effective inhibitor of tubulin binding than the parent halichondrin.

**Bone Marrow Assay**

- **Mean Graphs**

**Drug-Related Body Weight Loss**

- Drug-related body weight loss (ketoconazole, amoxicillin, and a drug combination of both) mainly in female rats, which indicates that E7389 is a substrate for p-glycoprotein.

**Toxicity**

- E7389 clearly showed better activity than that produced by the natural product, Halichondrin B.

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