One Year Experience with the New Pharmaceutical Legislation

Conditional Marketing Authorisation

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Type of Approvals

- Conditional approval (“early access” mechanism)
  - Comprehensive (clinical) data not available to be provided after approval
  - Must fulfil scope (orphan drugs, emergency threats, serious and life-threatening diseases) and requirements
  - Approval valid for 1 year, renewable
- Normal
  - Comprehensive data
- Exceptional circumstances
  - Comprehensive data not available and cannot be provided
  - Must meet criteria (rarity, medical ethics, state of scientific knowledge)

Conditional Marketing Authorization (CMA)

Requirements (Art. 4)

A conditional approval may be granted where although comprehensive clinical data have not been supplied, all of the requirements (a)-(d) are met

- (a) The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive
- (b) It is likely that comprehensive data can be provided
- (c) Unmet medical needs will be fulfilled (no satisfactory methods or major therapeutic advantage)
- (d) Benefits of immediate availability outweigh risks due to additional data to be provided

In case of emergency situations only, also non-clinical or pharmaceutical data may be missing

What Specific Obligations for CMA?

- Pharmacovigilance data
- Other required data important for understanding of benefit-risk, e.g.:
  - Confirm final clinical outcome for likely surrogate endpoints
  - Confirm long-term effects
  - Study effect in subgroups (“selective approval”*)
  - Confirm results of interim analysis

*Roberts and Chabner, *N Engl J Med* 2004; **351**(5):501-5

Example: sunitinib (Sutent)

http://www.emea.europa.eu/humandocs/Humans/EPAR/sutent/sutent.htm

Renal Cell Cancer (RCC)

- Diagnosis
  - Clinical symptoms are infrequent; 25%-40% incidentally discovered
  - Substantial proportion of patients have advanced disease at diagnosis
- Worldwide: 102,000 deaths per year (2000 estimate)
- 5-year survival 0%-13% for advanced or metastatic disease

Sunitinib 2nd-Line Therapy of RCC

	Reference	*N*	*ORR(%)*
Sunitinib second-line therapy			
Trial 1	Motzer et al[1]	63	37%
Trial 2	Motzer et al[2]	10	36%
		6	
Conventional second-line therapy			
Cytokines	Escudier et al[3]	113	3%
Various (historical data)	Motzer et al[4]	251	4%
Conventional first-line therapy			
Interferon-alfa	Motzer et al[5]	463	11%
High-dose Interleukin-2	Fyfe et al[6]	255	14%

[1]JCO 2006;24:16-24; [2]ASCO 2005; Abs 4508; [3]JCO 1999;17:2039-2043; [4]JCO 2004;22:454-463; [5]JCO 2002;20:289-296; [6]JCO 1995;13:688-696

Conditional MA Sutent

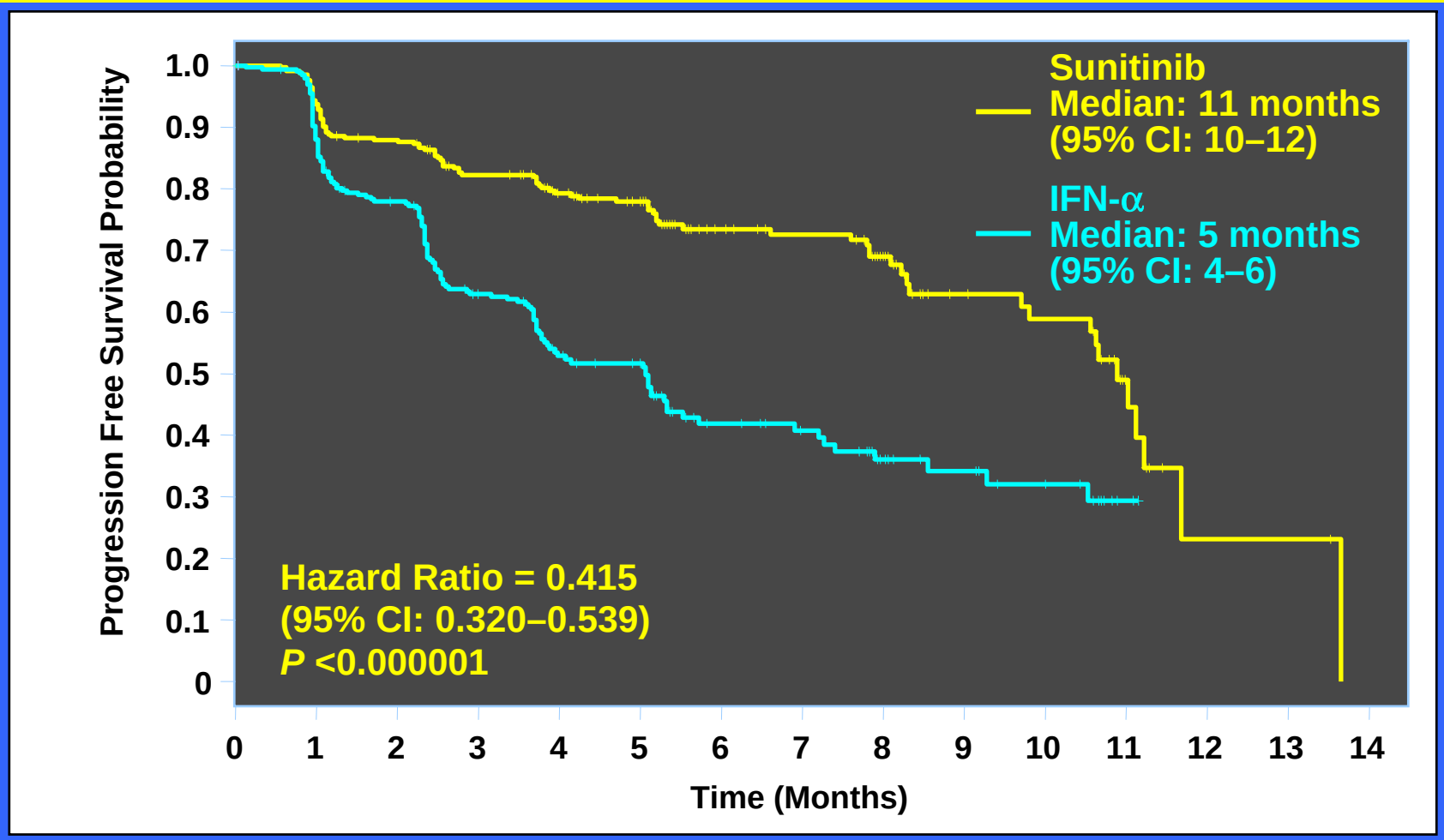
a) Risk-Benefit in refractory patients
   - Reassuring safety profile
   - Dramatic effect, historical comparison possible
     - Reasonably likely surrogate, effect on symptoms and survival judged as very likely
     - Effect on time-related endpoints to be extrapolated from study in first-line indication ⇒ Specific obligation

b) Likely that applicant will provide comprehensive clinical data
   - Recruitment completed, awaiting analysis

c) Unmet medical needs will be fulfilled
   - Activity non-overlapping with other agents (sorafenib)

d) Benefit to public health of immediate availability outweighs risks

First-line therapy in RCC
Progression-Free Survival



Motzer et al. ASCO 2006

Example: stiripentol (Diacomit)

Adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy

http://www.emea.eu.int/humandocs/PDFs/EPAR/diacomit/H-664-en6.pdf

Conditional MA Diacomit

(a) Positive benefit-risk
- Significant improvement in controlling the seizure frequencies *v.* placebo
- Need data on clinical efficacy with maximally safe doses of the co-medication
- The safety profile was considered acceptable

(b) Likely that applicant will provide comprehensive clinical data
- Need protocol assistance (feasibility?)
- Results by 2009 (based on synopsis)

(c) Unmet medical needs will be fulfilled
- Major therapeutic advantage?

(d) Benefit to public health of immediate availability outweighs risks

FAQ on Conditional MA

- Conditional MA applies to the whole of the MA (*v.* part of indication, variation)
- Normal $\not\Rightarrow$ Conditional
- Conditional $\not\Leftrightarrow$ Exceptional Circumstances
- Failure to fulfil obligations does not mean automatic suspension/revocation of conditional MA
- Guideline in public consultation

Summary and Conclusions

- All approvals require positive benefit-risk
- Conditional MA is a new EU provision for early access to new drugs
- Must strike right balance between early approval for patients in desperate needs and preventing harmful drugs from the market

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