Regulatory Agencies' Perspective on "Progression-Free Survival" (PFS)

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Background:

This work is part of a larger piece of work comparing how **regulatory bodies**, **HTA agencies**, and **medical associations** worldwide value the endpoint "progression-free survival" (PFS) in the assessment of drugs for the treatment of solid tumours.

The aim of the work presented in this poster was to systematically review how **FDA** (USA), **EMA** (Europe) and **PMDA** (Japan) evaluate PFS and its importance compared to overall survival (OS).

Methods:

- FDA's, EMA's and PMDA's websites were systematically searched to identify formal and methodological standards & individual drug assessments (see Table 1 & References).
- Only methodological standards affecting cancer drugs and specifically relating to endpoints were considered.
- The searches were conducted on 21/04/2015 (FDA / EMA), 21-22/03/2016 (PDMA).

Tab. 1: Systematic Identification of Relevant Information

Criterion	Description
Search plattform / interface	Websites of regulators publicly available on the Internet
Data sources/ databases	• U.S. Food and Drug Administration (FDA) • European Medicines Agency (EMA) • Japan (PDMA)
Study type	1) Publicly-available methods and recommendations that make statements about endpoints in the medical benefit assessment of drugs. 2) Assessments of drugs for the treatment of solid tumours as made by regulators.
Time period	1) Methods / recommendations from regulators, as on 01 Jan. 2000 or earlier. 2) Assessments completed for oncological products since 01 Jan. 2011.
Language	Publications in German, English, Italian, French or Japanese.

Tab. 2: General Hierarchy of Endpoints in Solid Tumors

EMA (Europe)	FDA (USA)	PMDA (Japan)
Favourable effects on survival are considered the most persuasive outcome.	In regular approval of cancer drugs all parameters besides OS and PROs are considered surrogates.	Overall survival is the gold standard in clinical studies.

Tab. 3: Disease Specifics on NSCLC (none identified for PMDA)

EMA (Europe)	FDA (USA)
• OS should be chosen as primary endpoint for confirmatory trials. • PFS might enable a proper benefit – risk assessment, if experimental regimen is likely to be well tolerated and supported by data on HRQoL/PRO. • OS is recommended for maintenance trials vs. placebo / best supportive care	• OS is considered the standard clinical benefit endpoint to establish efficacy in locally advanced or mNSCLC. • PFS may be appropriate as primary endpoint for approval if the trial is designed to demonstrate a large magnitude for the treatment effect and an acceptable risk-benefit profile is demonstrated. • For NSCLC …to consider PFS as the basis for accelerated approval, the treatment differences had to be substantial (e.g., 3 months or more).

Tab. 2: PFS Importance Relative to Overall Survival (OS)

EMA (Europe)	FDA (USA)	PMDA (Japan)
• For confirmatory trials, prolonged PFS / DFS are considered to be of benefit to the patient. However, favourable effects on survival are most persuasive. • When there is a large effect on PFS, or a long expected survival after progression, and / or a clearly favourable safety profile, precise estimates of OS may not be needed for approval. • Choice of endpoints linked to treatment setting as well as to expected toxicity. E. g. in long-term treatment and expected toxicity of new therapy is comparable or lessened, PFS is considered appropriate.	• Consideration of improvement in PFS as a direct clinical benefit or a surrogate depends on the magnitude of the effect and the risk-benefit compared to available therapies. • Precise definition of tumour progression is important. • For serious / life-threatening illnesses, accelerated approval is possible on the basis of surrogates when an association with the endpoint has been sufficiently validated, specific to the indication. However, even then PFS is still considered a surrogate parameter.	• PMDA requires OS to be used as an endpoint for clinical studies. Surrogate endpoints may be used in phase 1, phase 2 and phase 2.5 studies. • A potential factor of approval based on PFS may be orphan drug status or an accelerated approval by the FDA.

Results:

The perspective of the regulatory bodies analyzed can be summarized by a few common denominators:

- OS and PROs the outcomes of choice in the evaluation of cancer drugs.
- defined situations where surrogate parameters might be sufficient for approval.
- • …accept of PFS as a relevant outcome (for regulatory purposes, which may interfere with requirements of HTA-agencies!) under specific circumstances.
- • … require an association of PFS with another endpoint
- Specific results for PDMA are consistent which what is outlined by EMA and FDA. PMDA requires OS to be used as an endpoint for clinical studies. However, surrogate endpoints may be used in phase 1, phase 2 and phase 2.5 studies3. Studies with PFS as an endpoint may deliver important basic data for confirmatory studies. So in some cases PFS is accepted as a surrogate endpoint. Another important fact to be considered is the relationship between surrogate endpoints and true clinical endpoints.

References: Included methods papers

FDA:

- Guidance for Industry: Cancer Drug and Biological Products — Clinical Data in Marketing Applications. October 2001 (Section: Clinical Medical).
- Guidance for Industry: Clinical Trail Endpoints for the Approval of Cancer Drugs and Biologics. May 2007 (Section: Clinical Medical).
- Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics. April 2015 (Section: Clinical Medical).

EMA:

- Guideline on the evaluation of anticancer medicinal products in man. 13 December 2012; EMA/CHMP/205/95/Rev.4
- Appendix 1 to the Guideline on the evaluation of anticancer medicinal products in man. 13 December 2012; EMA/CHMP/27994/2008/Rev.1
- Appendix 4 to the Guideline on the evaluation of anticancer medicinal products in man. Condition Specific Guidance 13 December 2012; EMA/CHMP/703715/2012

PDMA:

- Guidance on Cancer Immunotherapy Development - Early-Phase Clinical Studies – For Development of Safe and Effective Immunotherapy - 2015
- Basic principles on Global Clinical Trials – 2007
- Publication Acceptance of surrogate endpoints in clinical trials supporting approval of drugs for cancer treatment by the Japanese regulatory agency - 2015

Conclusion :

- In general, EMA, FDA & PDMA value OS as the primary choice of outcome and consider PFS as a surrogate (FDA, PDMA) or complementary (EMA) outcome in the approval procedure.
- FDA and EMA are quite restrictive in defining the requirements for considering an improvement in PFS as direct benefit to patients.
- EMA offers a very nuanced matrix of criteria for the selection of outcome parameters.

Related Podium presentation:

HTA Agencies' Perspective on progression-free survival (PFS), Breakouts – Session VI, P10: HTA & Value Assessment Studies, Tuesday, 1 Nov. 2016 (13.45h)