# Acceptance of Progression-Free Survival 2 (PFS2) by EU5 and Canadian Health Authorities for Cancer Drug Reimbursement

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## INTRODUCTION

Approval of oncology drugs have typically been based on overall survival (OS) or progression-free survival (PFS) data, a commonly used surrogate endpoint for OS [1,2]. However, PFS lacks a common definition, that may be subject to bias and has seldom been validated as a surrogate for OS. Furthermore, OS is confounded by subsequent lines of therapy, and the post-progression period is treated as a 'black box'. Cancer treatment is typified by successive rounds of treatment following disease progression, and there is growing interest in evaluating follow-up and treatment post-progression. PFS2, time from randomization to second disease progression or death, is recommended by the EMA as a surrogate for OS, and to assess effect of maintenance therapy or the impact of treatment on the efficacy of a subsequent line of therapy [3]. The acceptance of PFS2 by other regulators and by reimbursement agencies is not well established.

## OBJECTIVE & METHODOLOGY

To evaluate the acceptance of PFS2 by national reimbursement or HTA agencies in EU4 (Germany, Italy, France, Spain), UK and Canada.

A *clinicaltrials.gov* database search identified cancer drug trials evaluating PFS2 as an endpoint. The EMA SmPC for each drug was reviewed for inclusion of PFS2 data. For those drugs, the Canadian Drug Monograph was reviewed for inclusion of PFS2. The EU4, UK and Canadian reimbursement agencies' assessment reports were reviewed for consideration/inclusion and acceptance of PFS2 data for reimbursement.

**Clinical Trials [4]**
Phase II/III intervention trials including Progression free survival 2, PFS2, PFS-2, or second progression.
Total Hits = 7,905 (as of 31-Sept-2021)
Confirmed = 206

**Regulatory [5,6]**
EMA Approved drugs = 66
EMA SmPC containing PFS2 data = 7
Canadian Drug Monograph containing PFS2 = 7

**National Reimbursement or HTA reports [7,8,9,10,11,12]**
G-BA, AIFA, HAS, AEMPS, NICE, CADTH

## RESULTS

**PFS2 data were included in the EMA SmPC for seven drugs across 13 indications for the treatment of solid tumors and hematological cancer**

**NICE** have accepted PFS2 in the final appraisal determination. PFS2, as an exploratory or a secondary endpoint, was considered in-scope to support the clinical assessment, cost-effectiveness analysis and End-of-Life criteria assessment. PFS2 data were considered to support OS surrogacy and confirm the lack of a negative effect on subsequent treatment lines. Acceptance of PFS2 depended on data maturity, a clear relationship between PFS2 and OS, and relevance to NHS clinical practice.

**AIFA** have accepted PFS2, as a secondary endpoint, to support the *Innovative Status* of osimertinib (Tagrisso). Acceptance in other assessments is unknown due to a lack of publicly available reports.

**HAS** have accepted PFS2 in the TC clinical assessment. PFS2, as an exploratory or a secondary endpoint, was considered. Acceptance of PFS2 depended on data maturity and statistical significance (multiplicity-adjusted).

**AEMPS** acceptance of PFS2 in the final decision is unclear. PFS2, as an exploratory or a secondary endpoint, was considered in scope of the IPT to support a lack of effect on subsequent treatment. While data immaturity was discussed, PFS2 was not included in the conclusion of any IPT.

**G-BA** have not accepted PFS2 as a patient-relevant endpoint, despite being considered in the G-BA assessment as a secondary endpoint.

**CADTH** have not accepted PFS2. PFS2, as a secondary endpoint, has been submitted and considered in the CADTH guidance documents. PFS2 data (as a surrogate for OS data) was not accepted in the clinical or economic guidance due to data immaturity.

| | | | | SmPC | Monograph | National HTA or Reimbursement Assessment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Drug | Cancer | Subclassification (Trial) | PFS2 | | | | | | | | |
| Lenalidomide (*Revlimid*) | MM | 1L; post-ASCT (CALGB 100104/IFM 2005-02) | | ✓ | ✓ | ✗ | N/A | ✓ | ✓ | ✗ | ✗ |
| | | 1L; SCT ineligible (MM-020 / MM-015) | | ✓ | ✓ | ✗ | N/A | ✗ | ✓ | ✓ | ✗ |
| Osimertinib (*Tagrisso*) | NSCLC | 1L; EGFRm, adv./meta (FLAURA) | | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✗ |
| Niraparib (*Zejula*) | Ovarian | Maint. PS, adv. (PRIMA) | | ✓ | ✓ | ✓ | N/A | ✓ | N/A | ✓ | ✓ |
| | | Maint. PSR, rec. (NOVA) | | ✓ | ✓ | ✓ | N/A | ✓ | ✓ | ✓ | ✓ |
| Olaparib (*Lynparza*) | Ovarian | 1L; maint. gBRCAm adv. (SOLO 1) | | ✓ | ✓ | ✓ | N/A | ✓ | ✓ | ✓ | ✓ |
| | | Maint. PSR gBRCAm (SOLO 2) | | ✓ | ✓ | ✓ | N/A | ✗ | ✓ | ✓ | ✓ |
| | | Maint. adv PSR (PAOLA-1) | | ✓ | ✓ | ✓ | N/A | ✓ | N/A | ✓ | ✗ |
| | Breast | gBRCAm, HER2–, meta. (OlympiAD) | | ✓ | ✓ | ✓ | N/A | ✓ | N/A | ✗ | ✗ |
| | Pancreas AC | Maint. gBRCAm meta. (POLO) | | ✓ | ✓ | ✗ | N/A | ✓ | N/A | ✗ | ✗ |
| Ibrutinib (*Imbruvica*) | CLL | 2L; +/- rituximab (PCYC-1112-CA) | | ✓ | ✓ | ✓ | N/A | ✗ | ✗ | ✗ | ✗ |
| Durvalumab (*Imfinzi*) | NSCLC | 2L; PD-L1≥1%, PS (PACIFIC) | | ✓ | ✓ | ✗ | N/A | ✓ | ✓ | ✓ | ✗ |
| Ribociclib (*kisqali*) | Breast | HR+, HER2– adv./meta. (MONALEESA-7) | | ✓ | ✓ | ✗ | N/A | ✗ | ✗ | ✗ | ✓ |

✓ PFS2 **considered/submitted** in the HTA and **accepted** in decision making
✓ PFS2 **considered/submitted** in the HTA but **not accepted** in decision making
PFS2 **included** in SmPC/Monograph
✓ PFS2 **considered/submitted** but acceptance unknown
✗ PFS2 **not considered/submitted** in the HTA
PFS2 **not included** in SmPC/Monograph
✗ **Not assessed** for reimbursement
N/A Assessment **not publicly available**
**Not indicated**
Secondary endpoint
Exploratory endpoint

**Abbreviations**:1L: first line; 2L: second line; AC: adenocarcinoma; adv.: advanced; AEMPS: Spanish Agency of Medicines and Medical Devices; AIFA: Italian Medicines Agency; ASCT: autologous stem cell transplantation; CADTH: Canadian Agency For Drugs And Technologies In Health; CEA: cost-effectiveness analysis; CLL: chronic lymphocytic leukemia; EU5: France, Germany, Italy, Spain, UK; EGFRm: epidermal growth factor receptor mutation; EMA: European Medicines Agency; G-BA: German Federal Joint Committee; gBRCA: germline BRCA mutation; HAS: French National Authority for Health; HER2–: human epidermal growth factor receptor 2; HR+: hormone receptor-positive; HTA: health technology assessment; IPT: Therapeutic Positioning Report; maint: maintenance; meta: metastatic; MM: multiple myeloma; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NSCLC: non-small cell lung cancer; OS: overall survival; PD-L1: programmed cell death ligand 1; PFS: progression-free survival; PFS2: progression-free survival 2; PS: platinum-sensitive; PSR: platinum-sensitive relapsed; rec: recurrent; SCT: stem cell transplant; SmPC: Summary of Product Characteristic; TC: Transparency Committee

**CONCLUSIONS:** Although examples are limited, PFS2, as either a secondary endpoint or an exploratory endpoint, has been accepted by European and Canadian regulators and has been considered in some reimbursement assessments for solid tumor and hematological oncology drugs. The acceptance of PFS2 data for reimbursement often depends on data maturity, statistical-power, relevance to clinical practice and patients. The validity of PFS2 in drug reimbursement will continue to be established with the availability of mature data from investigation in over 200 Phase II and III clinical trials.

1. Ellis LM, Bernstein DS, Voest EE, et al. American Society of Clinical Oncology perspective: raising the bar for clinical trials by defining clinically meaningful outcomes. J Clin Oncol. 2014;32:1277-1280.
2. US FDA Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Guidance for Industry. https://www.fda.gov/media/71195/download
3. EMA Guideline on the evaluation of anticancer medicinal products in man. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-evaluation-anticancer-medicinal-products-man-revision-5_en.pdf
4. ClinicalTrials.gov. https://clinicaltrials.gov/
5. European Medicines Agency. https://www.ema.europa.eu/en
6. Health Canada. https://www.canada.ca/en/health-canada/
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12. AIFA . https://www.aifa.gov.it/web/guest/home