

The melanoma study of Findeisen et al. (114) concerned early-stage melanoma, which has a relatively good prognosis. Staging of melanoma is according to the criteria set forth by the American Joint Committee on Cancer (AJCC) (115). The Findeisen study consisted of screening of serum proteins with the goal of discovering useful biomarkers. Screening involved the technique of mass spectroscopy, a technique that provided a unique fingerprint of peptides derived from each serum protein, where the fingerprint took the form of a number, that is, the mass/charge (m/z) ratio. This technique is outlined below. The Findeisen study reported the discovery of a protein identified as $m/z = 11.680$. This protein was later identified as *serum amyloid A*. The authors found that stage I melanoma patients expressing high levels of serum amyloid A had worse survival, compared to stage I melanoma patients with high serum amyloid A. Moreover, the authors also found that stage IV melanoma patients with high serum amyloid A had worse survival.

The following introduces CRP into this narrative. In view of the fact that serum amyloid A is an “acute phase protein,” the researchers also sought correlations between other established acute-phase proteins, such as CRP, and survival to melanoma. The Findeisen study discovered that CRP expression was able to distinguish between poor-prognosis stage I melanoma patients and good-prognosis stage I melanoma patients. The authors concluded that the *combination of expression data on serum*

amyloid A and CRP serves as an excellent prognostic biomarker for early-stage melanoma patients. Findeisen et al. (116) were also careful to note that serum lactic dehydrogenase, a traditional biomarker for advanced melanoma, failed to have any prognostic significance for early-stage melanoma. In another study, by Fang et al. (117), it was discovered that elevated CRP is associated with poorer survival to melanoma.

c. FDA’s Decision-Making Process in Evaluating the Study Drug’s Influence on CRP, for a Cancer Clinical Trial

FDA’s *Medical Reviews*, *Pharmacological Reviews*, and *Statistical Reviews*, are published at the time that FDA publishes its *Approval Letter*. These reviews provide an intimate picture of the FDA’s decision-making process.

This concerns a clinical trial on ruxolitinib (Jakafi[®]), for treating myelofibrosis, a type of cancer. The information is from December 2014 of the FDA’s website. The FDA reviewer observed that plasma levels of biomarkers associated with inflammation, such as CRP, *were elevated in myelofibrosis patients*, as compared to healthy persons. The reviewer also observed that *the study drug reduced CRP*, writing that, “[t]he levels of **C-reactive protein showed an 86% decrease** within 4 weeks of treatment with ruxolitinib.” The study drug inhibits the enzyme, Janus kinase (JAK2).

The FDA reviewer described the connection between Janus kinase, a signaling protein

¹¹⁴Findeisen P, Zapatka M, Peccerella T, et al. Serum amyloid A as a prognostic marker in melanoma identified by proteomic profiling. *J. Clin. Oncol.* 2009;27:2199–208.

¹¹⁵Balch CM, Buzaid AC, Soong SJ, et al. Final version of the American Joint Committee on Cancer staging system for cutaneous melanoma. *J. Clin. Oncol.* 2001;19:3635–48.

¹¹⁶Findeisen P, Zapatka M, Peccerella T, et al. Serum amyloid A as a prognostic marker in melanoma identified by proteomic profiling. *J. Clin. Oncol.* 2009;27:2199–208.

¹¹⁷Fang S, Wang Y, Sui D, et al. C-reactive protein as a marker of melanoma progression. *J. Clin. Oncol.* 2015;12:1389–96.