Usefulness of time-dependent Cox model with cause-specific competing risk analyses for assessing prognosis during the course of Waldenström macroglobulinemia (WM) : Onset of progression is a prognostic factor for survival after first treatment initiation and for the risk of related death, but not onset of response.

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In WM, survival prediction, whatever the cause of death, rests on baseline International Prognostic scoring System (IPSSWM). Improvement in outcome is associated with 2 unresolved issues. 1) prognostic assessment during the prolonged course of the disease is a frequent unmet need 2) long-term retrospective analyses highlighted the frequency of death unrelated to WM. Addressing these issues mainly requires an accurate report of events observed during a very long period of time, whatever treatment received. Therefore, we took advantage of the availability of 2 large continuously updated databases with prolonged follow-up for assessing the prognostic role of baseline IPSSWM and events observed during the course of WM (response, progression according to VIth workshop criteria and next treatment initiation) on survival and on the 2 competing risks of death related and unrelated to WM. In 121 WM patients treated between 1993 and 2016 (median age 70, IQR : 61-80, M/F :2.0, high-risk IPSSWM : 42%, chemoimmunotherapy first-line: 33%, distribution of events presented in Figure 1), high-risk IPSSWM was an adverse prognostic factor for survival after first treatment initiation (SAFTI, p=0.001, HR: 2.30). Nevertheless, corresponding Dxy concordance index obtained in multiple landmark analyses decreased from 0.24 to 0.08, during the first 6 years, in accordance with a departure from the proportional hazard (PH) assumption. In time-dependent Cox models, onset of any response level retained no prognostic value. By contrast, onset of progression (OOP) and initiation of second treatment (IST) were significantly associated with SAFTI (HR=2.94, p=0.02 and HR=2.56, p=0.006 respectively). These findings were confirmed in models adjusted for IPSSWM, taking the departure from PH into account. OOP and IST were also significantly

associated with the risk of deaths related to WM (cause-specific HR [CSHR]=3.12, p=0.02 and CSHR=3.94, p=0.0021 respectively) but not with unrelated deaths. Times to OOP after first-line treatment and to IST had no prognostic value for survival after these 2 events. Results on OOP and IST were confirmed in an independent validation series of 119 patients (median age : 71, IQR :65-77 years, M/F=2.4, high-risk IPSSWM : 56%) homogeneously treated with first-line chemoimmunotherapy between 2005 and 2015. Finally, after second-line and third-line treatment, OOP, also had significant prognostic value for the risk of related death only (CSHR=3.07, p=0.02 and CSHR=35.8, p=0.0003 respectively). Thus, taking initial IPSSWM and delayed response to treatment into account, only OOP and IST, and not response, provided additional prognostic information for SAFTI and for the risk of death related to WM. OOP was also a prognostic factor for the risk of death related to WM after 2nd and 3rd line therapy. Our results support the need of further studies for demonstrating that PFS may be a satisfactory surrogate endpoint of survival and cause specific survival after treatment initiation in WM. Similar analyses should be useful with new treatment such as btk inhibitors, when a sufficient number of events will be recorded.

Figure 1 : Cumulative incidences after first-line treatment. 1A : Response levels ; 1B: Progression ; 1C: Second treatment initiation and 1D: Related and unrelated death.