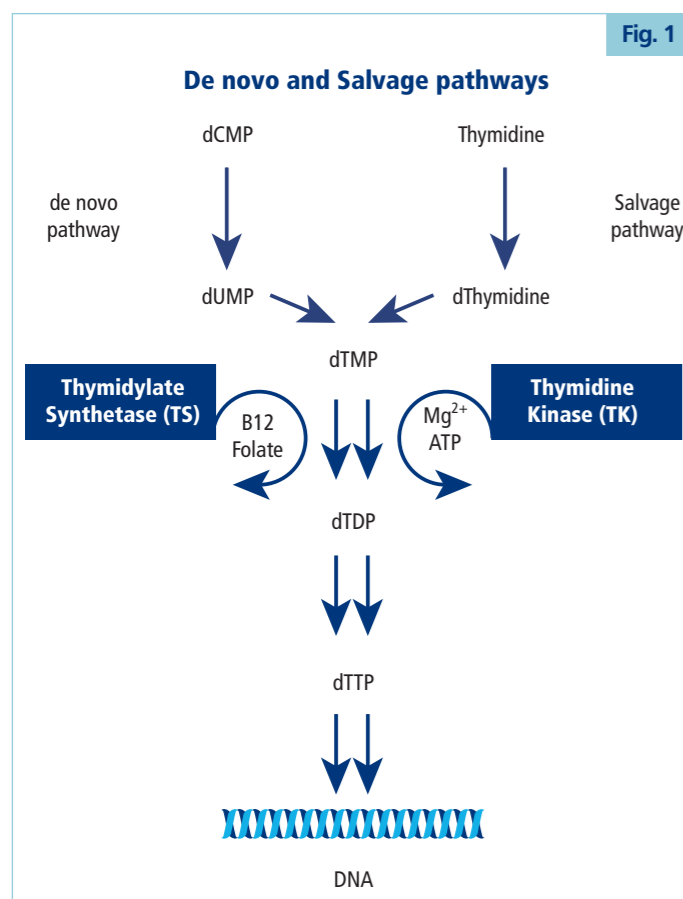


# Thymidine Kinase (TK)

## Thymidine Kinase reflects proliferative activity of the tumour

Thymidine Kinase is a cytosolic enzyme known to be involved in DNA synthesis<sup>(1)</sup>. DNA is synthesized following one of two possible pathways (Fig. 1): the de novo pathway or the Salvage pathway. In the latter thymidine kinase catalyzes conversion of deoxythymidine to deoxythymidine monophosphate. Subsequent steps lead to DNA-synthesis as shown in Figure 1. The pathway catalyzed by TK is called the Salvage pathway since it uses either exogenous or endogenous deoxythymidine.



Mammalian cells contain two different Thymidine Kinase isoenzymes<sup>(2)</sup>, cytosolic Thymidine Kinase 1 (TK1) and mitochondrial Thymidine Kinase 2 (TK2). TK1 is associated with cell proliferation whereas TK2 is needed for mitochondrial DNA synthesis. TK1 activity increases markedly in the G1/S phase of the cell cycle. TK1 has therefore been shown to be a reliable marker of cell proliferation – the only proliferation marker that can be measured in serum (S-TK)<sup>(3)</sup>.

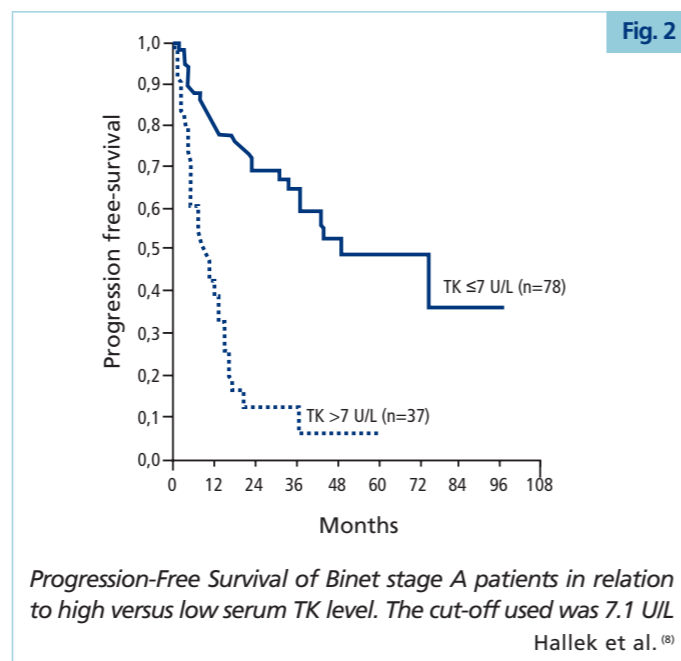
## TK in Haematological Malignancies

### Non-Hodgkin's Lymphoma (NHL)

Several studies have shown the value of S-TK as a prognostic marker<sup>(5)</sup>. Pretreatment levels have been found to be a powerful discriminator of disease stage and to provide prognostic information. S-TK levels are able to predict response to treatment and survival. S-TK values seem also to be higher in high-grade NHL than on low-grade NHL<sup>(6-9)</sup>. Furthermore S-TK levels are useful in predicting the disease course in low-grade NHL. S-TK values are found to return to normal if the treatment is successful. A renewed increase indicates recurrence and/or transformation into a more malignant form of the disease<sup>(10)</sup>.

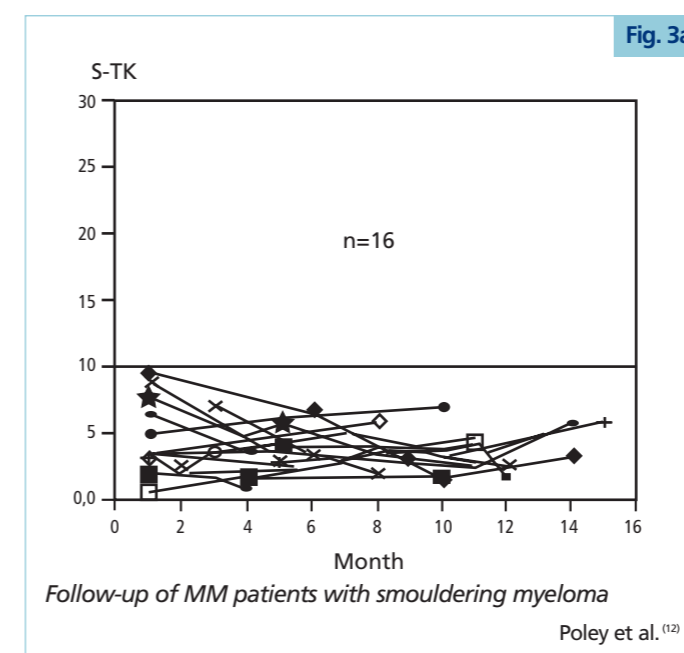
### Chronic Lymphocytic Leukaemia (CLL)

The current staging systems in CLL such as Binet or Rai classification do not accurately predict the individual risk of disease progression. The S-TK levels in patients with CLL have been shown to have a remarkably prognostic capability. Patients with a serum level above 7.1 U/L have an average time of Progression-Free Survival of about 8 months, whereas patients with levels below this concentration have a Progression-Free Survival of almost 49 months, which is similar to that of patients with smouldering CLL (Fig. 2)<sup>(8,11)</sup>.



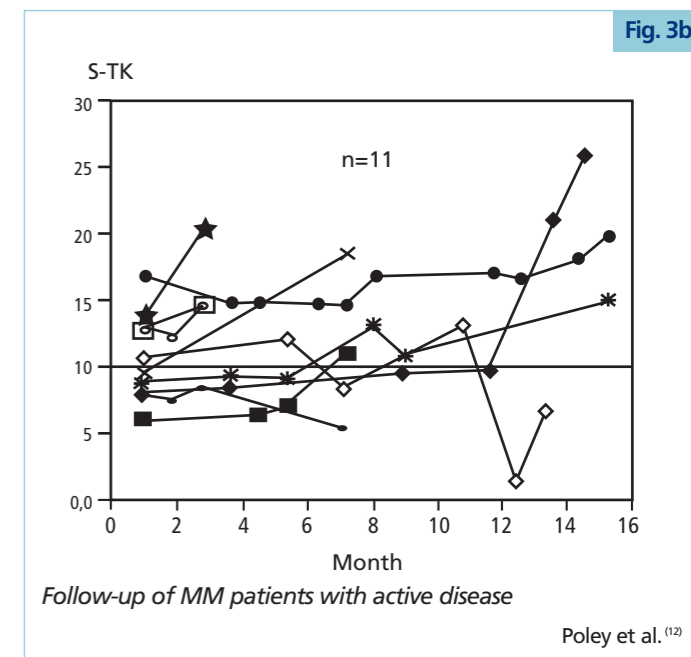
### Multiple Myeloma (MM)

It has been shown that S-TK levels correlate with clinical stage and survival time. Furthermore S-TK levels have been found to be useful in distinguishing between MM and monoclonal gammopathy of undetermined significance (MGUS) (Fig. 3)<sup>(12,13)</sup>.



### Hodgkin's lymphoma

Significant correlations have been found between S-TK levels and the stage of the disease. When the prognostic ability was examined, patients in stages IA and IIA could be divided according to S-TK levels into two different groups in relation to Disease-Free Survival. This finding makes S-TK interesting as an additional tool in clinical evaluation and in the therapeutic decision concerning patients with Hodgkin's disease<sup>(14)</sup>.



### Acute Myeloid Leukaemia (AML) and Acute Lymphocytic Leukaemia (ALL)

S-TK determinations detect recurrent disease at an early stage, before it can be detected microscopically. There is a close correlation between S-TK levels and the count of leukocytes, the percentage of blasts in the blood, the therapeutic response and the length of survival after the initial diagnosis. Therefore S-TK levels indicate the aggressiveness of leukaemic cells and predict the response to the treatment and the length of survival<sup>(15-17)</sup>.

### MyeloDysplastic Syndrome (MDS)

High S-TK in MDS predicts transformation of MDS to Acute Myeloid Leukaemia. Multivariate analysis confirmed the independent prognostic value of S-TK for both overall survival and risk of acute transformation. We conclude that S-TK may be an important prognostic factor in MDS, which is strongly correlated to development of AML.

## Conclusions

- S-TK has proven to be a reliable marker of tumour cell proliferation
- S-TK provides a valuable tool to assess disease activity in untreated haematological malignancies and for monitoring of treatment, remission and smouldering disease
- S-TK predicts clinical relapse months before the onset of clinical symptoms