

# *DUSP22*-rearranged ALK-negative anaplastic large cell lymphoma is a pathogenetically distinct disease but can have variable clinical outcome

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In comparison to ALK-positive anaplastic large cell lymphoma (ALCL), ALK-negative ALCL has been more difficult to define. It was first characterized by morphological similarity to ALK-positive ALCL, including the presence of pathognomonic ‘hallmark cells’, but lacking expression of the ALK protein. Very early reports suggested a similar prognosis to peripheral T-cell lymphoma – not otherwise specified<sup>1</sup> but larger studies indicated that the prognosis, although still unsatisfactory, was better than that of peripheral T-cell lymphoma – not otherwise specified.<sup>2</sup> However, outcomes are notably variable across studies, as described by Hapgood and Savage.<sup>3</sup> This is in part due to clinical risk factors as captured by the International Prognostic Index score.<sup>2,4</sup> Firm recognition of ALK-negative ALCL as a distinct entity came in the World Health Organization’s (WHO) 4<sup>th</sup> edition update following the description of unique molecular features.<sup>5,6</sup>

The identification of two recurrent rearrangements represented key milestones in deciphering ALK-negative ALCL. The first rearrangement involves the *DUSP22-IRF4* locus on 6p25.3 (*DUSP22* rearrangement [*DUSP22-R*]) and the other involves *TP63* on 3p28 (*TP63* rearrangement [*TP63-R*]). The clinical significance of the *DUSP22-R* was first evaluated in a series of 73 patients with ALK-negative ALCL in which 22 cases were found to harbor the rearrangement, representing 30% of all ALK-negative ALCL. The *TP63-R* was identified in six cases (8%) and the remainder were deemed to have ‘triple-negative’ ALK-negative ALCL meaning they lacked any rearrangement and are also referred to as *DUSP22-NR* (non-rearranged)/*TP63-NR*. Cases with a *DUSP22-R* had a 5-year overall survival (OS) of 90%, which was similar to that of a comparison group of cases of ALK-positive ALCL. In contrast, those with a *TP63-R* had a dismal 5-year OS of only 17%. The majority of cases in the series were triple-negative and had an intermediate prognosis

(5-year OS of 42%). Pathological evaluation of *DUSP22-R* tumors revealed sheet-like growth of classic hallmark cells, fewer pleomorphic cells and, as assessed by immunohistochemistry (IHC), reduced expression of epithelial membrane antigen (EMA) and cytotoxic markers (TIA1, granzyme B, perforin) (Table 2). Subsequent studies of these cases described characteristic ‘doughnut’ cells,<sup>7</sup> and a molecular profile characterized by overexpression of immunogenic cancer testis antigen (CTA) genes, a signature of marked DNA hypomethylation and diminished expression of STAT3 and programmed death ligand (PDL), with consequential lack of pSTAT3 and PDL as determined by IHC.<sup>8</sup> Exome sequencing identified a recurrent mutation in *MSC<sup>E116K</sup>* in almost all cases.<sup>9</sup>

Two subsequent small series of four and five patients each with *DUSP22-R* ALK-negative ALCL also demonstrated a favorable prognosis<sup>10,11</sup> (Table 1). In contrast, in our BC Cancer study of 12 cases, a less favorable prognosis was observed with a 5-year progression-free survival (PFS) and OS of only 40%.<sup>12</sup> A range of clinical courses were noted including one patient with central nervous system relapse and another patient managed palliatively had a relapsing/remitting disease course over 4 years, which was reminiscent of cutaneous ALCL. In contrast, IHC features were as expected: EMA-negative, infrequent expression of cytotoxic markers and all cases were pSTAT3- and PDL1-negative (Table 2).

In this issue of *Haematologica*, two studies have further evaluated the pathological characteristics and prognostic significance of *DUSP22-R* ALK-negative ALCL.<sup>13,14</sup> The study by Sibon and colleagues represents the largest series to date of 47 cases of *DUSP22-R* ALK-negative ALCL derived from the TENOMIC database, a translational lymphoma research consortium of the LYSA group. In total, 47/104 (45%) cases harbored a *DUSP22-R* which is a significantly higher proportion than in other studies, and

**Table 1.** Summary of studies to date evaluating the prognosis in *DUSP22*-rearranged ALK-negative anaplastic large cell lymphoma.

Feature	First author (Study location/group)					
	Parilla-Castellar (Mayo) <sup>6</sup>	Pedersen (Denmark) <sup>10</sup>	Hapgood (BC Cancer) <sup>12</sup>	Onaindia (Spain) <sup>11</sup>	Sibon (LYSA) <sup>13</sup>	Qiu (MDACC) <sup>14</sup>
<i>DUSP22</i> -R cases, N	22	5	12	4	47	22
<i>DUSP22</i> -R among ALK-negative cases, %	30	19	19	18	45	28
Age in years, median	53.5	49	61.5	57.5	60	52
Range	36-76	35-85	50-86	39-71	40-86	33-79
Stage 3 or 4, %	85	80	75	100	64	71
Missing data, %	68			25	2	37
PS $\geq 2$ , %	nr	0	25	40	30	nr
Missing data, %		50				
IPI $\geq 3$ , %	42	40	42	0	48	33
Missing data, %	36			50	2	32
Extranodal sites, %						
Bone	nr	nr	33	nr	32	nr
Bone marrow	nr	nr	17	25	13	6
Skin	28 <sup>a</sup>	60	25	25	15	nr
Liver	nr	nr	8	nr	19	nr
CNS relapse %	nr	nr	8	nr	nr	nr
Treatment, %						
CHOP(like)	90	100	92	50 <sup>b</sup>	94 <sup>c</sup>	90
Consolidative auto-SCT	5	50 <sup>d</sup>	8	0	19	27
Missing treatment data	36			25		
5-year PFS, %	nr	nr	40	nr	57	40 <sup>d</sup>
5-year OS, %	90	80	40	100	65	40

<sup>a</sup>Reported as skin involvement during disease course. <sup>b</sup>Remaining patient received radiotherapy alone. <sup>c</sup>Includes CHOP (N=22); CHOEP (N=11); Ro-CHOP (N=1); CH(E)P-BV (N=3); mini-CHOP (N=5); ACVBP (N=2). <sup>d</sup>5-year point estimate not reported in the paper but estimated from its Figure 6B. *DUSP22*-R: *DUSP22*-rearranged; nr: not reported; PS: Performance Status; IPI: International Prognostic Index; CNS: central nervous system; CHOP: cyclophosphamide, doxorubicin, vincristine; prednisone; auto-SCT: autologous stem cell transplantation; PFS: progression-free survival; OS: overall survival.

the authors acknowledge a selection bias as cases are submitted to the LYSA TENOMIC database with an aim of compiling those of clinical interest.<sup>13</sup> In the subset enrolled on clinical trials, estimates are more in keeping with other studies (23-35%). Regardless, this is an extensively curated database with detailed clinical information which has been lacking in most prior studies (Table 1). Frequent bone involvement was observed, which was also found in the BC Cancer series. Pathologically, cases had the expected morphology and immunophenotype (Table 2) although, curiously, 27% of cases expressed at least one cytotoxic marker ('cytotoxic profile'), which appears to be higher incidence than in other reports although most other studies only reported on individual marker frequency (Table 2). With a median follow-up of 5 years, the PFS was superior in *DUSP22*-R cases than in non-rearranged cases (5-year PFS: 48% vs. 25%, respectively;  $P=0.025$ ); however, the point estimates are far lower than in the original series, and what would be expected for ALK-positive ALCL. Furthermore, OS was not statistically different (5-year OS: 58% vs. 44%,

respectively;  $P=0.20$ ). Confining the analysis to the 39 *DUSP22*-R cases treated with curative intent, anthracycline chemotherapy (all but 3 cases), and confirmed to have *TP63*-NR status, demonstrated a more favorable PFS (5-year PFS: 57% vs. 26%, respectively;  $P=0.001$ ) but not OS (5-year OS: 65% vs. 41%, respectively;  $P=0.07$ ) although it must be acknowledged that there was limited power to detect a smaller difference. This larger dataset enabled exploration of factors associated with survival. Those cases with a poor performance status (PS) ( $\geq 2$ ) and elevated  $\beta_2$ -microglobulin had an inferior PFS and OS. Cytotoxic marker expression was also associated with an inferior PFS and the individual factors of granzyme B or perforin expression, but not TIA1, were associated with inferior PFS and OS. However, only PS and *DUSP22*-NR status were included in the final model because of missing information, and both were associated with PFS, but only PS was also associated with OS. Using these two factors, *DUSP22*-R patients with a poor PS, a group representing 29% of all cases (11/38, with one patient not included due to missing PS), had a 5-year PFS and OS of only 27% and

**Table 2.** Immunophenotypic features of *DUSP22* ALK-negative anaplastic large cell lymphoma cases across studies.

Immunohistochemical Feature	First author (study location/group)					
	Parilla-Castellar (Mayo) <sup>6</sup>	Pedersen (Denmark) <sup>10</sup>	Hapgood (BC Cancer) <sup>12</sup>	Onaindia (Spain) <sup>11</sup>	Sibon (LYSA) <sup>13</sup>	Qiu (MDACC) <sup>14</sup>
<i>DUSP22</i> -R, N	22	5	12	4	47	22
CD2 <sup>+</sup> , % (N/N)	83 (15/18)*	nr	83 (10/12)*	nr	87 (33/38)*	77 (13/17)
CD3 <sup>+</sup> , % (N/N)	81 (17/21)*	nr	83 (10/12)*	100 (4/4)	62 (29/47)*	76 (16/21)
CD5 <sup>+</sup> , % (N/N)	12 (2/17) <sup>#</sup>	nr	nr	nr	43 (19/44)	35 (14/19)
CD4 <sup>+</sup> , % (N/N)	53 (9/17) <sup>#</sup>	nr	nr	nr	72 (34/47)	74 (14/19)
CD8 <sup>+</sup> , % (N/N)	12 (2/17) <sup>#</sup>	nr	nr	nr	11 (6/44)	28 (5/18)*
TIA1 <sup>+</sup> , % (N/N)	10 (2/21)*	nr	8 (1/12)*	0 (4/4)	13 (5/38)*	30 (3/10)
Granzyme B <sup>+</sup> , % (N/N)	5 (1/21)*	nr	0 (0/12)*	0 (4/4)	11 (5/44)*	0 (0/12)*
Perforin <sup>+</sup> , % (N/N)	0 (0/10) <sup>#</sup>	nr	8 (1/12)*	0 (4/4)	12 (4/33)*	25 (1/4)
Positive for any cytotoxic marker, % (N/N)	nr	nr	8 (1/12)*	0 (4/4)	27 (8/30)*	nr
EMA <sup>+</sup> , % (N/N)	0 (0/20)*	nr	0 (0/12)*	nr	13 (5/38)*	18 (2/11)*
pSTAT3 <sup>+</sup> , % (N/N)	nr	nr	0 (0/12)*	0 (3/3)	10 (2/20)*	2* <sup>^</sup>
PD-L1 <sup>+</sup> , % (N/N)	nr	nr	0 (0/12)*	nr	nr	3* <sup>^</sup>

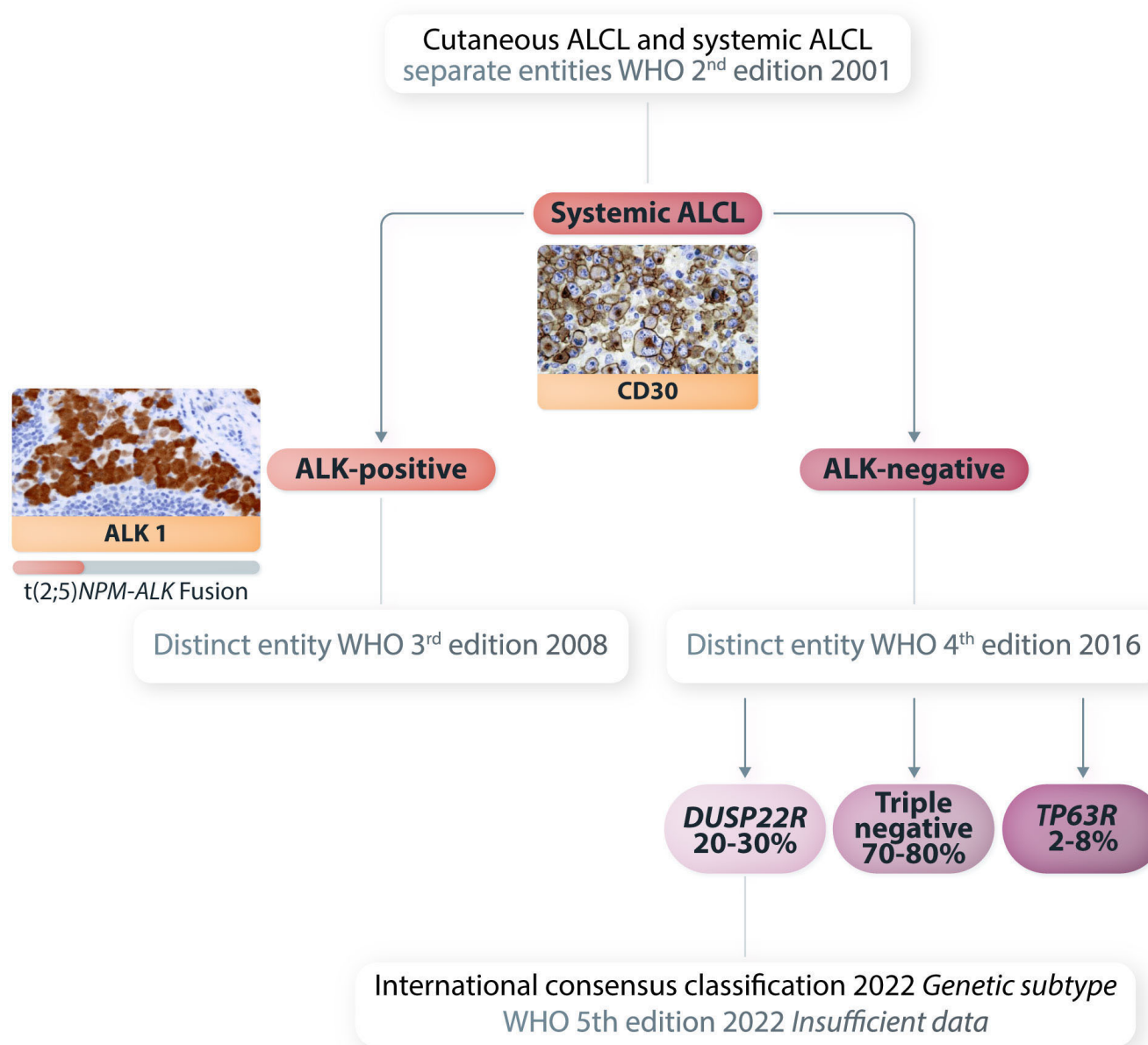
*DUSP22*-R: *DUSP22*-rearranged; nr: not reported; TIA-1: T-cell intracellular antigen; EMA: epithelial membrane antigen; PD-L1: programmed death ligand 1. \* $P < 0.05$  vs. *DUSP22*-not rearranged. <sup>#</sup>Not compared. <sup>^</sup>Reported as % mean of lymphoma cells (2% of lymphoma cells in *DUSP22*-R cases are pSTAT3-positive vs. 36% in non-rearranged cases; 3% of lymphoma cells in *DUSP22*-R cases are PDL1-positive vs. 26% in non-rearranged cases).

29%, respectively, which was indistinguishable from the survival outcomes of triple-negative cases (see Figure 6E, F in the accompanying article).<sup>13</sup>

In the second paper, Qiu and colleagues from the MD Anderson Cancer Center evaluated 22 cases of *DUSP22*-R ALK-negative ALCL, representing 28% of all ALK-negative ALCL cases with pathological features, also consistent with previous reports (Table 2).<sup>14</sup> Treatment information was available for 16 patients with *DUSP22*-R, 13 of whom received anthracycline-based chemotherapy; follow-up information was available for 18 patients and nine (50%) had died. With a median follow-up of 19 months, the projected 5-year OS was only 40%, which was similar to that of *DUSP22*-NR cases ( $P=0.275$ ) and inferior to that of ALK-positive ALCL cases (5-year OS 82%;  $P=0.005$ ). Similarly, 5-year PFS was only 40% ( $P=0.275$  vs. *TP63*-NR). The treatment landscape of ALCL has changed over the last decade with the approval of brentuximab vedotin (BV) for the treatment of relapsed/refractory ALCL<sup>15</sup> and more recently, approval of CHP (cyclophosphamide, doxorubicin, prednisone)-BV for newly diagnosed systemic ALCL based on superior PFS and OS over CHOP (cyclophosphamide, doxorubicin, vincristine; prednisone), as shown in the ECHELON-2 study in CD30<sup>+</sup> peripheral T-cell lymphomas.<sup>16</sup> In the LYSA study, survival was notably poor from first relapse/progression, regardless of *DUSP22*-R status, suggesting that any prognostic relevance may diminish in this high-risk setting (4-year OS 21% [*DUSP22*-R] vs. 34% [triple-negative];  $P=0.62$ ) (Figure 5A in the accompanying

article).<sup>13</sup> The use of BV in relapsed/refractory ALCL improved outcomes across genetic subgroups but similarly, no outcome difference was noted (Figure 5E, F in the accompanying article).<sup>13</sup> Of note, the prognostic impact of *DUSP22*-R in patients with treatment-naïve ALK-negative ALCL who were treated with CHP-BV remains unknown. Collectively, unique morphological, immunophenotypic and molecular features support the designation of *DUSP22*-R ALK-negative ALCL as a distinct entity as proposed by the International Consensus Classification<sup>17</sup> although the WHO 5<sup>th</sup> edition update (WHO-HAEM5) applied only a provisional designation due to uncertainty around prognosis<sup>18</sup> (Figure 1). In contrast, cases with a *TP63*-R are important to recognize given the poor prognosis, but further genetic studies are still required to fully characterize them. Furthermore, although these rearrangements are usually mutually exclusive, rare 'double-hit' cases have been reported.<sup>19</sup> Considering all studies to date, the prognosis of *DUSP22*-R ALK-negative ALCL is more variable than that of the typically favorable ALK-positive ALCL, but even that entity can have a poor outcome.<sup>2</sup> The LYSA study highlights that clinical information, such as PS, must also be taken into consideration when making management decisions. Of note, as a composite risk score, the International Prognostic Index did not reach statistical significance and, with limited numbers, it was not specifically applied to *DUSP22*-R cases to judge its utility. There may also still be unknown pathobiological and





**Figure 1. Current classification of systemic anaplastic large cell lymphoma.** The most common t(2;5) (ALK-NPM) is shown. Rare variant rearrangements involving the ALK gene on 2p23 and different partner genes on other chromosomes can occur in 15-25% of cases of ALK-positive anaplastic large cell lymphoma. ALCL: anaplastic large cell lymphoma; WHO: World Health Organization; ALK: anaplastic lymphoma kinase.

genetic factors contributing to outcome in *DUSP22*-R ALK-negative ALCL. Cases are typically negative for cytotoxic markers but rare cases may be positive, and previous studies have shown an association with inferior outcomes across ALK-negative ALCL.<sup>6</sup> *DUSP22*-R in ALCL was originally shown to occur as a result of a balanced translocation involving the *DUSP22* phosphatase gene on 6p25.3 and the *FRA7H* fragile site on 7q32.3, resulting in downregulation of the *DUSP22* gene.<sup>20</sup> Subsequent studies assessing *DUSP22*-R in ALCL have used break-apart fluorescence *in situ* hybridization and the translocation partner has not been determined. Could alternate translocation partners occur in *DUSP22R* ALCL and might these account for the more aggressive clinical behavior seen in some cases? Further investigations are required to

extend our understanding of the underlying molecular mechanisms that result in these phenotypic and behavioral differences.

**Disclosures**

*KJS has received honoraria from and acted as a consultant for BMS, Merck, Seagen, Kyowa, Novartis, Janssen and Abbvie; has participated in a steering committee for Beigene; and has sat on a Data and Safety Monitoring Committee for Regeneron. GWS has received honoraria from and acted as a consultant for Seattle Genetics.*

**Contributions**

*KJS and GWS wrote and approved the manuscript.*

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