XL
TP53/17cen
Deletion Probe

Order No.:
D-5103-100-OG

Clinical Performance

Clinical performance means the ability of a device to yield results that are correlated with a particular clinical condition or a physiological or pathological process or state in accordance with the target population and intended use. FISH probes generally are used in symptomatic individuals and are not to be used to screen asymptomatic individuals. Genetic aberrations detected by FISH diagnostics are usually rare and therefore large-scale cohort testing is difficult. Data gained from routine diagnostic testing accumulated over time allows performance assessment in such cases.

The test population for this product consists of patients with confirmed or suspected multiple myeloma (MM). MM is a mature cell disease of the lymphatic system in more than 90% of cases, which means that the clonal plasma cells usually do not show any proliferation activity (Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF): Diagnostik, Therapie und Nach-sorge für Patienten mit monoklonaler Gammopathie unklarer Signifikanz (MGUS) oder Multiplem Myelom, Langversion 1.0, 2022, AWMF-Registernummer: 018/035OL, https://www.leitlinienprogramm-onkologie.de/leitlinien/multiples-myelom/)). Therefore, classical chromosome banding analysis is normally not performed in routine diagnostics and cannot be used as a reference technology to confirm FISH data.

For this reason, the evaluation of this probe follows the Prevalence Comparison approach. The prevalence of positive rearrangements detected by the product in the test population in selected reference laboratories is compared with the prevalence of the corresponding rearrangement in the test population reported in scientific literature. An overlap of the CI 0.95 determined from the validation data with the confidence level interval across all evaluated publications/studies demonstrate conformance of the prevalence data determined with the product with prevalence data from published literature.

Specimens examined were CD138$^+$ cells.

| Rearrangement	Total No. of Cases	Prevalence	CI 0.95
Deletions of the *TP53* gene region at 17p13	659	8.50 %	6.48 %-10.89 %

The prevalence determined from routine data is 8.50 %, the confidence interval is 6.48 %-10.89 % at a confidence level of 0.95.

Prevalence of positive rearrangements in the test population reported in peer-reviewed scientific literature.

Publication #	Test Population	Sample Size	Positive	Prev. Literature	CI 0.95
1	MM	532	58	10.90 %	8.38 %-13.86 %
2	MM	260	22	8.46 %	5.38 %-12.53 %
3	MM	251	15	5.98 %	3.38 %-9.67 %
4	MM	1765	145	8.22 %	6.98 %-9.60 %
5	MM	408	22	5.39 %	3.41 %-8.05 %
6	MM	350	37	10.57 %	7.55 %-14.28 %
7	MM	2642	359	13.59 %	12.30 %-14.95 %
8	MM	333	22	6.61 %	4.19 %-9.83 %
Cross-publication CI 0.95 Literature #1-8					3.38 %-14.95 %

1. Avet-Loiseau et al (2007) Blood 109:3489-3495
2. Gutierrez et al (2007) Leukemia 21:143-150
3. Bacher et al (2010) Cancer Genet Cytogenet 203:169-175
4. Ross et al (2010) Haematologica 95:1221-1225
5. Avet-Loiseau et al (2012) J Clin Oncol 30:1949-1952
6. Neben at al (2012) Blood 119:940-948
7. Avet-Loiseau et al (2013) Leukemia 27:711-717
8. An et al (2015) Clin Cancer Res 21:2148-2156

The prevalence reported in published literature ranges from 5.39 % to 13.59 %, the cross-publication confidence interval is 3.38 % to 14.95 % at a confidence level of 0.95.
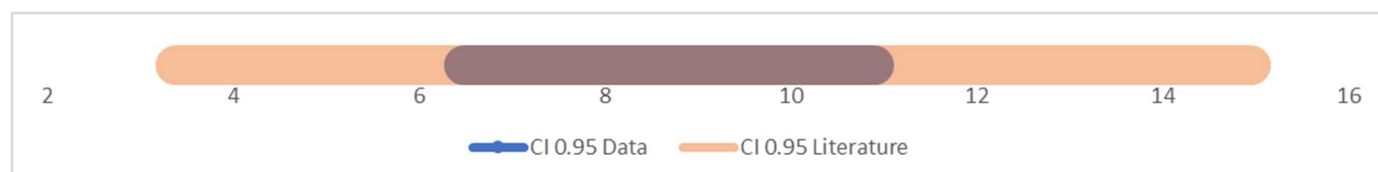
The results demonstrate that the prevalence determined with XL TP53/17cen are compliant with the prevalence of the aberration as expected from published literature, which reinforces confidence in the clinical performance of the product.

Analytical Performance

Analytical performance means the ability of a device to correctly detect or measure a particular analyte. Relevant analytical performance parameters related to FISH probes are analytical specificity, analytical sensitivity, reproducibility, and cut-off.

Analytical specificity is calculated as the percentage of correct targets detected on metaphases out of the total number of targets detected. Lymphocytes of 5 different chromosomally characterized males with no indication of the genetic aberration of interest were included in the analysis. Calculated analytical specificity is 100 % after 20 evaluated metaphases from 5 different chromosomally characterized males. The acceptance criterion for analytical specificity is ≥98 %.

Analytical sensitivity is calculated as the percentage of interphase nuclei that have the expected normal signal pattern out of the total number of interphase nuclei analyzed. The signal patterns of 400 nuclei of 10 karyotypically normal individuals each were analyzed. The degree of deviation from the mean is represented by the relative standard deviation (% RSD). The acceptance criterion for analytical sensitivity is ≥95 %.

Pattern	Sensitivity	% RSD
2G 2O (normal)	97.5 %	0.7 %

Reproducibility is the degree of agreement between the results of analytical sensitivity studies conducted under different conditions (day, lot and sample). For each condition, three analyses with 100 nuclei each were performed. Reproducibility is given as the degree of deviation from the mean by the relative standard deviation (% RSD). The acceptance criterion for reproducibility is a relative standard deviation ≤5 %.

Conditions	Reproducibility (% RSD)
Day-to-Day (same lot and same individual at three days)	1.0 %
Lot-to-Lot (same individual and day with three lots)	1.6 %
Sample-to-Sample (same lot and day with three individuals)	0.6 %

The cut-off for a qualitative test is the threshold above which the result is reported as positive and below which the result is reported negative. The cut-off value was calculated based on probe hybridizations on interphase nuclei of 10 karyotypically normal individuals. Cut-off values are based on 400 scored nuclei each.

Pattern	Cut-off
2G 1O	4.8 %

The cut-off value is informative and depends on several laboratory-related parameters. Therefore, for diagnostic use, cut-off values have to be determined individually by each laboratory.

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