In Germany, a comparative effectiveness assessment in the form of an early benefit assessment (EBA) is mandatory for new medicines.1,2 The G-BA (Federal Joint Committee) is charged with evaluating a medicine’s additional benefit.1,2 Besides the extent of additional benefit versus an appropriate comparator, the quality of the evidence base, i.e. the evidence level, is evaluated in the EBA.2,3

Pre-defined treatment switching, also called ‘cross-over’, is often seen in oncology clinical trials. Cross-over is usually implemented for ethical reasons, i.e. to ensure access to a beneficial treatment for all patients,4,5 but may confound data analysis, especially intention-to-treat (ITT)-analysis, by improving efficacy in the control arms.5,6

OBJECTIVES

Accounting for the ethical demand and the methodological issues, we investigated the impact of cross-over in clinical trials of oncology medicines evaluated by the EMA as well as by the G-BA in the German EBA process. Specifically, we determined whether the G-BA reflected the circumstances under which cross-over was implemented in its decision and if drugs with a cross-over were disadvantaged in their benefit assessment with regards to the evidence level.

METHODS

Oncology medicines (excluding orphan drugs due to their automatically granted additional benefit) with EBAs finalised before 1 January 2015 were evaluated. Trials considered in the G-BA decisions were regarded as relevant for the analyses. Source documents included manufacturer’s dossiers, G-BA decisions, European Public Assessment Reports and original trial publications. Presence of cross-over, analysis of clinical data (availability of, and evidence of significant differences in data on OS; data availability before cross-over for drugs with cross-over studies), EMA requests for additional data (i.e. conditional approval or post-authorisation measures [PAMs]), benefit ratings and evidence levels assigned by the G-BA were analysed.

RESULTS

Cross-over was frequently used in oncology trials. For 11 of the 21 evaluated EBAs (52%), at least one trial assessed by the G-BA included cross-over (Figure 1). Significant differences in survival data between treatment groups were presented in 6 of the 11 trials (55%) with and in 6 of the 10 trials (60%) without cross-over. For all medicines with cross-over, significance was demonstrated prior to cross-over (Table 1).

The EMA most frequently required additional data if cross-over was performed, particularly if no survival data were available before cross-over (Table 1). Medicines with cross-over received better additional benefit ratings than those without (73% vs 40%). The granted evidence levels showed an opposite trend (52% vs 75%). None of the medicines received an evidence level of proof (Table 1 and Figure 2).

CONCLUSIONS

• Oncology medicines with cross-over trials received better additional benefit ratings than those without. Evidence levels were worse, although cross-over was ethically justified (i.e. implemented following demonstration of significant survival differences), indicating that the G-BA considers evidence standards to be only partially fulfilled in these cases.

• Highly efficacious drugs with ethically mandated cross-over are therefore disadvantaged with regard to the achievable evidence level.

• The requirements for an evidence level of proof should be reconsidered. Medicines with a demonstration of superior efficacy in OS and cross-over recommended by a Data and Safety Monitoring Board (DSMB) deserve an evidence level of proof, irrelevant of the number of studies available for the assessment.

• In addition, the analysis of the hazard ratio for OS prior to cross-over should be acknowledged as final and meaningful data.

Table 1: (Co-)primary endpoints, data availability, EMA requests for OS data, G-BA benefit ratings and G-BA evidence levels

<table>
<thead>
<tr>
<th>Medicine</th>
<th>(Co-)primary endpoint</th>
<th>OS data*</th>
<th>EMA requests for OS data</th>
<th>G-BA benefit rating†</th>
<th>G-BA evidence level‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abiraterone acetate (2nd indication)</td>
<td>OS and PFS</td>
<td>s.¹</td>
<td>no</td>
<td>considerable</td>
<td>indication</td>
</tr>
<tr>
<td>Afatinib</td>
<td>PFS</td>
<td>n.s.</td>
<td>no</td>
<td>considerable</td>
<td>indication</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>PFS</td>
<td>n.s.</td>
<td>no</td>
<td>considerable</td>
<td>indication</td>
</tr>
<tr>
<td>Dabrafenib</td>
<td>PFS</td>
<td>n.s.</td>
<td>no</td>
<td>no</td>
<td>not significant</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>OS</td>
<td>s.¹</td>
<td>no</td>
<td>considerable</td>
<td>indication</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>OS</td>
<td>s.¹</td>
<td>no</td>
<td>minor</td>
<td>hint</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>Proportion of subjects achieving ≥35% reduction in spleen volume</td>
<td>n.s.</td>
<td>PAM related to OS</td>
<td>considerable</td>
<td>indication</td>
</tr>
<tr>
<td>Trastuzumab emtansine</td>
<td>OS and PFS</td>
<td>s.¹</td>
<td>PAM related to OS</td>
<td>considerable</td>
<td>indication</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>PFS</td>
<td>n.s.</td>
<td>conditional approval</td>
<td>PAM related to OS</td>
<td>minor</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>OS and PFS</td>
<td>s.¹</td>
<td>PAM related to OS</td>
<td>considerable</td>
<td>indication</td>
</tr>
</tbody>
</table>

** Oncology drugs granted no additional benefit were excluded from the evaluation of evidence level (1 EBA in the group with and 2 EBAs in the group without cross-over).

** Number of EBAs with the best G-BA ratings in the granted set (i.e. overall considerable additional benefit and evidence level of indication) were used to compare products with and without cross-over.

REFERENCES

2. Roche Pharma AG, Grenzach-Wyhlen, Germany; 2 Medical School of Hanover, Hanover, Germany; 3 Bayer Vital GmbH, Leverkusen, Germany; 4 Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

3. Roche Pharma AG, Grenzach-Wyhlen, Germany

4. Medical School of Hanover, Hanover, Germany

5. Bayer Vital GmbH, Leverkusen, Germany

6. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

7. Roche Pharma AG, Grenzach-Wyhlen, Germany

8. Medical School of Hanover, Hanover, Germany


10. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

11. Roche Pharma AG, Grenzach-Wyhlen, Germany

12. Medical School of Hanover, Hanover, Germany

13. Bayer Vital GmbH, Leverkusen, Germany

14. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

15. Roche Pharma AG, Grenzach-Wyhlen, Germany

16. Medical School of Hanover, Hanover, Germany

17. Bayer Vital GmbH, Leverkusen, Germany

18. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

19. Roche Pharma AG, Grenzach-Wyhlen, Germany

20. Medical School of Hanover, Hanover, Germany


22. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

23. Roche Pharma AG, Grenzach-Wyhlen, Germany

24. Medical School of Hanover, Hanover, Germany

25. Bayer Vital GmbH, Leverkusen, Germany

26. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

27. Roche Pharma AG, Grenzach-Wyhlen, Germany

28. Medical School of Hanover, Hanover, Germany

29. Bayer Vital GmbH, Leverkusen, Germany

30. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

31. Roche Pharma AG, Grenzach-Wyhlen, Germany

32. Medical School of Hanover, Hanover, Germany

33. Bayer Vital GmbH, Leverkusen, Germany

34. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

35. Roche Pharma AG, Grenzach-Wyhlen, Germany

36. Medical School of Hanover, Hanover, Germany

37. Bayer Vital GmbH, Leverkusen, Germany

38. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

39. Roche Pharma AG, Grenzach-Wyhlen, Germany

40. Medical School of Hanover, Hanover, Germany

41. Bayer Vital GmbH, Leverkusen, Germany

42. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

43. Roche Pharma AG, Grenzach-Wyhlen, Germany

44. Medical School of Hanover, Hanover, Germany

45. Bayer Vital GmbH, Leverkusen, Germany

46. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

47. Roche Pharma AG, Grenzach-Wyhlen, Germany

48. Medical School of Hanover, Hanover, Germany

49. Bayer Vital GmbH, Leverkusen, Germany

50. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

51. Roche Pharma AG, Grenzach-Wyhlen, Germany

52. Medical School of Hanover, Hanover, Germany

53. Bayer Vital GmbH, Leverkusen, Germany

54. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

55. Roche Pharma AG, Grenzach-Wyhlen, Germany

56. Medical School of Hanover, Hanover, Germany

57. Bayer Vital GmbH, Leverkusen, Germany

58. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

59. Roche Pharma AG, Grenzach-Wyhlen, Germany

60. Medical School of Hanover, Hanover, Germany

61. Bayer Vital GmbH, Leverkusen, Germany

62. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

63. Roche Pharma AG, Grenzach-Wyhlen, Germany

64. Medical School of Hanover, Hanover, Germany

65. Bayer Vital GmbH, Leverkusen, Germany

66. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

67. Roche Pharma AG, Grenzach-Wyhlen, Germany

68. Medical School of Hanover, Hanover, Germany

69. Bayer Vital GmbH, Leverkusen, Germany

70. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

71. Roche Pharma AG, Grenzach-Wyhlen, Germany

72. Medical School of Hanover, Hanover, Germany

73. Bayer Vital GmbH, Leverkusen, Germany

74. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

75. Roche Pharma AG, Grenzach-Wyhlen, Germany

76. Medical School of Hanover, Hanover, Germany

77. Bayer Vital GmbH, Leverkusen, Germany

78. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

79. Roche Pharma AG, Grenzach-Wyhlen, Germany

80. Medical School of Hanover, Hanover, Germany

81. Bayer Vital GmbH, Leverkusen, Germany

82. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

83. Roche Pharma AG, Grenzach-Wyhlen, Germany

84. Medical School of Hanover, Hanover, Germany

85. Bayer Vital GmbH, Leverkusen, Germany

86. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany

87. Roche Pharma AG, Grenzach-Wyhlen, Germany

88. Medical School of Hanover, Hanover, Germany

89. Bayer Vital GmbH, Leverkusen, Germany

90. Department of Public Health, Heinrich Heine University, Düsseldorf, Germany