Biomarker testing in non-small cell lung cancer in routine care: analysis of the first 3,717 patients in the German prospective, observational, nation-wide CRISP Registry (AIO-TRK-0315) – Griesinger et al.

Supplementary Material

Figure S1. Participating sites
Actively recruiting sites in Germany at data cut (June 30, 2019).

Table S1. Overall testing rate

	Non-Squamous (n = 2,921)	Squamous (n = 796)
Biomarker tested [a]	**2,692 (92.2%)**	**563 (70.7%)**
EGFR	2,119 (72.5%)	205 (25.8%)
ROS1	1,930 (66.1%)	164 (20.6%)
ALK	2,176 (74.5%)	193 (24.2%)
BRAF	1,547 (53.0%)	145 (18.2%)
PD-L1	1,934 (66.2%)	476 (59.8%)
RET	786 (26.9%)	36 (4.5%)
C-MET	1,034 (35.4%)	109 (13.7%)
KRAS	1,311 (44.9%)	123 (15.5%)
TP53	806 (27.6%)	82 (10.3%)
HER2	443 (15.2%)	35 (4.4%)
Other [b]	1,202 (41.2%)	205 (25.8%)
Missing [c]	81 (2.8%)	27 (3.4%)

Data are number (%), unless indicated otherwise.
[a] Number of patients, for whom data on testing of specific biomarkers is documented; multiple answers possible.
[b] Biomarkers not explicitly collected, but documented as free text
[c] Patients with documented biomarker testing at inclusion, but no documentation on the biomarker

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Table S2. Combination of testing methods – non-squamous NSCLC

Testing method, n (%)	NGS (n=1,131)	Other seq. (n=1,005)	IHC (n=2,000)	FISH (n=979)	Unknown (n=283)	Any (n=2,692)
NGS	x	144 (14.3%)	947 (47.3%)	482 (49.2%)	42 (14.8%)	1,131 (42.0%)
Other seq.	144 (12.7%)	x	683 (34.2%)	440 (44.9%)	25 (8.8%)	1,005 (37.3%)
IHC	947 (83.7%)	683 (68.0%)	x	746 (76.2%)	93 (32.9%)	2,000 (74.3%)
FISH	482 (42.6%)	440 (43.8%)	746 (37.3%)	x	45 (15.9%)	979 (36.4%)
Unknown	42 (3.7%)	25 (2.5%)	93 (4.7%)	45 (4.6%)	x	283 (10.5%)
Any	1,131 (100%)	1,005 (100%)	2,000 (100%)	979 (100%)	283 (100%)	x

Multiple answers possible. Percentages refer to the number of patients tested with the test method specified in the table header. **Abbreviations:** FISH, fluorescence *in-situ* hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; seq.; sequencing.

Table S3. Combination of testing methods – squamous NSCLC

Testing method, n (%)	NGS (n=115)	Other seq. (n=92)	IHC (n=464)	FISH (n=80)	Unknown (n=51)	Any (n=563)
NGS	x	4 (4.3%)	91 (19.6%)	31 (38.8%)	5 (9.8%)	115 (20.4%)
Other seq.	4 (3.5%)	x	63 (13.6%)	29 (36.3%)	2 (3.9%)	92 (16.3%)
IHC	91 (79.1%)	63 (68.5%)	x	60 (75.0%)	10 (19.6%)	464 (82.4%)
FISH	31 (27.0%)	29 (31.5%)	60 (12.9%)	x	7 (13.7%)	80 (14.2%)
Unknown	5 (4.3%)	2 (2.2%)	10 (2.2%)	7 (8.8%)	x	51 (9.1%)
Any	115 (100%)	92 (100%)	464 (100%)	80 (100%)	51 (100%)	x

Multiple answers possible. Percentages refer to the number of patients tested with the test method specified in the table header. **Abbreviations:** FISH, fluorescence *in-situ* hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; seq.; sequencing.

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Table S4. Combination of alterations in patients with non-squamous NSCLC

Alteration, n (%)	EGFR (n=320)	ROS1 (n=59)	PD-L1 (n=1,160)	ALK (n=118)	RET (n=16)	BRAF (n=65)	C-MET (n=96)	KRAS (n=504)	TP53 (n=411)	HER2 (n=17)
EGFR	x	12 (20.3%)	115 (9.9%)	13 (11.0%)	4 (25.0%)	7 (10.8%)	8 (8.3%)	16 (3.2%)	62 (15.1%)	1 (5.9%)
ROS1	12 (3.8%)	x	33 (2.8%)	11 (9.3%)	1 (6.3%)	5 (7.7%)	2 (2.1%)	9 (1.8%)	8 (1.9%)	-
PD-L1	115 (35.9%)	33 (55.9%)	x	49 (41.5%)	7 (43.8%)	40 (61.5%)	61 (63.5%)	260 (51.6%)	227 (55.2%)	9 (52.9%)
ALK	13 (4.1%)	11 (18.6%)	49 (4.2%)	x	2 (12.5%)	5 (7.7%)	3 (3.1%)	14 (2.8%)	18 (4.4%)	1 (5.9%)
RET	4 (1.3%)	1 (1.7%)	7 (0.6%)	2 (1.7%)	x	2 (3.1%)	2 (2.1%)	7 (1.4%)	7 (1.7%)	1 (5.9%)
BRAF	7 (2.2%)	5 (8.5%)	40 (3.4%)	5 (4.2%)	2 (12.5%)	x	6 (6.3%)	13 (2.6%)	24 (5.8%)	1 (5.9%)
C-MET	8 (2.5%)	2 (3.4%)	61 (5.3%)	3 (2.5%)	2 (12.5%)	6 (9.2%)	x	34 (6.7%)	42 (10.2%)	-
KRAS	16 (5.0%)	9 (15.3%)	260 (22.4%)	14 (11.9%)	7 (43.8%)	13 (20.0%)	34 (35.4%)	x	143 (34.8%)	1 (5.9%)
TP53	62 (19.4%)	8 (13.6%)	227 (19.6%)	18 (15.3%)	7 (43.8%)	24 (36.9%)	42 (43.8%)	143 (28.4%)	x	4 (23.5%)
HER2	1 (0.3%)	-	9 (0.8%)	1 (0.8%)	1 (6.3%)	1 (1.5%)	-	1 (0.2%)	4 (1.0%)	x

Multiple answers possible. Percentages refer to the number of patients tested for the molecular alteration (irrespective of druggability) specified in the table header. Alteration is used interchangeably and can refer to a mutation, alteration or overexpression, depending on the biomarker tested.

Table S5. Combination of alterations in patients with squamous NSCLC

Alteration, n (%)	EGFR (n=9)	ROS1 (n=2)	PD-L1 (n=289)	ALK (n=1)	RET (n=1)	BRAF (n=2)	C-MET (n=12)	KRAS (n=7)	TP53 (n=56)	HER2 (n=1)
EGFR	x	--	5 (1.7%)	-	-	-	-	-	-	-
ROS1	-	x	2 (0.7%)	-	-	-	-	1 (14.3%)	-	-
PD-L1	5 (55.6%)	2 (100%)	x	1 (100%)	-	2 (100%)	8 (66.7%)	7 (100%)	25 (44.6%)	1 (100%)
ALK	-	-	1 (0.3%)	x	-	-	1 (8.3%)	-	1 (1.8%)	-
RET	-	-	-	-	x	-	-	-	1 (1.8%)	-
BRAF	-	-	2 (0.7%)	-	-	x	-	-	1 (1.8%)	-
C-MET	-	-	8 (2.8%)	1 (100%)	-	-	x	-	7 (12.5%)	-
KRAS	-	1 (50.0%)	7 (2.4%)	-	-	-	-	x	1 (1.8%)	-
TP53	-	-	25 (8.7%)	1 (100%)	1 (100%)	1 (50.0%)	7 (58.3%)	1 (14.3%)	x	-
HER2	-	-	1 (0.3%)	-	-	-	-	-	-	x

Multiple answers possible. Percentages refer to the number of patients tested for the molecular alteration (irrespective of druggability) specified in the table header. Alteration is used interchangeably and can refer to a mutation, alteration or overexpression, depending on the biomarker tested.

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Table S6. Testing results by detection method – non-squamous NSCLC

	2016	2017	2018	2019	Total
Patients (N)	**N=403**	**N=817**	**N=1253**	**N=448**	**N=2921**
EGFR detected n (%) [a]	60 (14.9%)	78 (9.5%)	137 (10.9%)	45 (10.0%)	320 (11.0%)
NGS n (%) [b]	31 (7.7%)	39 (4.8%)	82 (6.5%)	31 (6.9%)	183 (6.3%)
Other sequencing n (%) [b]	36 (8.9%)	32 (3.9%)	49 (3.9%)	12 (2.7%)	129 (4.4%)
Unknown method n (%) [b]	4 (1.0%)	11 (1.3%)	8 (0.6%)	2 (0.4%)	25 (0.9%)
ROS1 detected n (%) [a]	6 (1.5%)	16 (2.0%)	27 (2.2%)	10 (2.2%)	59 (2.0%)
NGS n (%) [b]	2 (0.5%)	2 (0.2%)	5 (0.4%)	3 (0.7%)	12 (0.4%)
Other sequencing n (%) [b]	1 (0.2%)	-	1 (0.1%)	-	2 (0.1%)
IHC n (%) [b]	3 (0.7%)	12 (1.5%)	14 (1.1%)	4 (0.9%)	33 (1.1%)
FISH (%) [b]	-	1 (0.1%)	7 (0.6%)	3 (0.7%)	11 (0.4%)
Unknown method n (%) [b]	-	2 (0.2%)	-	-	2 (0.1%)
PD-L1 detected n (%) [a]	53 (13.2%)	301 (36.8%)	598 (47.7%)	208 (46.4%)	1160 (39.7%)
IHC n (%) [b]	51 (12.7%)	288 (35.3%)	563 (44.9%)	198 (44.2%)	1100 (37.7%)
Unknown method n (%) [b]	2 (0.5%)	14 (1.7%)	39 (3.1%)	12 (2.7%)	67 (2.3%)
ALK detected n (%) [a]	25 (6.2%)	25 (3.1%)	52 (4.2%)	16 (3.6%)	118 (4.0%)
NGS n (%) [b]	6 (1.5%)	8 (1.0%)	14 (1.1%)	7 (1.6%)	35 (1.2%)
Other sequencing n (%) [b]	6 (1.5%)	2 (0.2%)	4 (0.3%)	1 (0.2%)	13 (0.4%)
IHC n (%) [b]	11 (2.7%)	12 (1.5%)	22 (1.8%)	4 (0.9%)	49 (1.7%)
FISH (%) [b]	8 (2.0%)	7 (0.9%)	20 (1.6%)	6 (1.3%)	41 (1.4%)
Unknown method n (%) [b]	3 (0.7%)	1 (0.1%)	3 (0.2%)	-	7 (0.2%)
BRAF detected n (%) [a]	8 (2.0%)	25 (3.1%)	26 (2.1%)	6 (1.3%)	65 (2.2%)
NGS n (%) [b]	6 (1.5%)	17 (2.1%)	20 (1.6%)	6 (1.3%)	49 (1.7%)
Other sequencing n (%) [b]	2 (0.5%)	7 (0.9%)	2 (0.2%)	-	11 (0.4%)
Unknown method n (%) [b]	-	4 (0.5%)	4 (0.3%)	-	8 (0.3%)

[a] Patients for whom an alteration was detected (with any method) for this biomarker.
[b] Patients for whom an alteration was detected (with this method) for this biomarker. Multiple answers possible.
Percentages refer to the number of patients in the respective subgroup (N). „*EGFR* detected" includes all patients with a documented test result (mutation) for *EGFR* with NGS, other sequencing or unknown test method, irrespective of documentation of further details

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Table S7. Testing results by detection method – squamous NSCLC

	2016	2017	2018	2019	Total
Patients (N)	**N=103**	**N=230**	**N=308**	**N=155**	**N=796**
EGFR detected n (%) [a]	-	2 (0.9%)	6 (1.9%)	1 (0.6%)	9 (1.1%)
NGS n (%) [b]	-	-	2 (0.6%)	1 (0.6%)	3 (0.4%)
Other sequencing n (%) [b]	-	2 (0.9%)	2 (0.6%)	-	4 (0.5%)
Unknown method n (%) [b]	-	-	2 (0.6%)	-	2 (0.3%)
ROS1 detected n (%) [a]	-	2 (0.9%)	-	-	2 (0.3%)
IHC n (%) [b]	-	2 (0.9%)	-	-	2 (0.3%)
PD-L1 detected n (%) [a]	11 (10.7%)	65 (28.3%)	137 (44.5%)	76 (49.0%)	289 (36.3%)
IHC n (%) [b]	11 (10.7%)	62 (27.0%)	131 (42.5%)	72 (46.5%)	276 (34.7%)
Unknown method n (%) [b]	-	3 (1.3%)	6 (1.9%)	4 (2.6%)	13 (1.6%)
ALK detected n (%) [a]	1 (1.0%)	-	-	-	1 (0.1%)
NGS n (%) [b]	1 (1.0%)	-	-	-	1 (0.1%)
BRAF detected n (%) [a]	-	-	2 (0.6%)	-	2 (0.3%)
NGS n (%) [b]	-	-	2 (0.6%)	-	2 (0.3%)

[a] Patients for whom an alteration was detected (with any method) for this biomarker.
[b] Patients for whom an alteration was detected (with this method) for this biomarker. Multiple answers possible. Percentages refer to the number of patients in the respective subgroup (N). „*EGFR* detected" includes all patients with a documented test result (mutation) for *EGFR* with NGS, other sequencing or unknown test method, irrespective of documentation of further details

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Table S8. Patient and tumor characteristics for survival curves

Characteristic at start of first-line treatment	Druggable *EGFR* alteration (n=169)	Druggable *ALK* alteration (n=61)	Non-squamous No test/alter.* TPS ≥50% (n=238)	Non-squamous No test/alter.* 1%≤ TPS <50% (n=265)	Non-squamous No test/alter.* TPS <1%/unkn. (n=1.003)	Squamous No test/alter.* TPS ≥50% (n=55)	Squamous No test/alter.* 1%≤ TPS <50% (n=76)	Squamous No test/alter.* TPS <1%/unkn. (n=355)
Age, yrs, median (25-75% quartile)	69.0 (61.0-76.0)	64.0 (55.0-70.0)	66.0 (58.0-73.0)	65.0 (59.0-72.0)	66.0 (60.0-73.0)	72.0 (65.0-77.0)	68.5 (63.5-77.0)	68.0 (62.0-75.0)
Histology								
Non-squamous NSCLC	165 (97.6%)	61 (100%)	238 (100%)	265 (100%)	1.003 (100%)	-	-	-
Squamous NSCLC	4 (2.4%)	-	-	-	-	55 (100%)	76 (100%)	355 (100%)
Sex								
Female	110 (65.1%)	30 (49.2%)	99 (41.6%)	108 (40.8%)	375 (37.4%)	20 (36.4%)	19 (25.0%)	96 (27.0%)
Male	59 (34.9%)	31 (50.8%)	139 (58.4%)	157 (59.2%)	628 (62.6%)	35 (63.6%)	57 (75.0%)	259 (73.0%)
Patients with any comorbidity [a]	138 (81.7%)	46 (75.4%)	207 (87.0%)	218 (82.3%)	827 (82.5%)	53 (96.4%)	72 (94.7%)	318 (89.6%)
Comorbidities acc. to the CCI [a,b]								
CCI =0 [b]	100 (59.2%)	37 (60.7%)	137 (57.6%)	154 (58.1%)	587 (58.5%)	16 (29.1%)	30 (39.5%)	160 (45.1%)
CCI ≥1 [b]	69 (40.8%)	24 (39.3%)	101 (42.4%)	111 (41.9%)	416 (41.5%)	39 (70.9%)	46 (60.5%)	195 (54.9%)
Other comorbidities [c]	128 (75.7%)	40 (65.6%)	185 (77.7%)	196 (74.0%)	725 (72.3%)	48 (87.3%)	66 (86.8%)	281 (79.2%)
Diabetes [d]	17 (10.1%)	8 (13.1%)	35 (14.7%)	28 (10.6%)	134 (13.4%)	7 (12.7%)	10 (13.2%)	72 (20.3%)
Arterial hypertension	87 (51.5%)	23 (37.7%)	97 (40.8%)	112 (42.3%)	426 (42.5%)	31 (56.4%)	32 (42.1%)	164 (46.2%)
Vasosclerosis	11 (6.5%)	6 (9.8%)	42 (17.6%)	37 (14.0%)	147 (14.7%)	12 (21.8%)	16 (21.1%)	58 (16.3%)
Performance Status								
ECOG 0	60 (35.5%)	22 (36.1%)	76 (31.9%)	64 (24.2%)	294 (29.3%)	12 (21.8%)	15 (19.7%)	79 (22.3%)
ECOG 1	70 (41.4%)	26 (42.6%)	98 (41.2%)	129 (48.7%)	460 (45.9%)	31 (56.4%)	40 (52.6%)	188 (53.0%)
ECOG ≥2	20 (11.8%)	8 (13.1%)	32 (13.4%)	37 (14.0%)	109 (10.9%)	5 (9.1%)	13 (17.1%)	48 (13.5%)
Unknown	19 (11.2%)	5 (8.2%)	31 (13.0%)	34 (12.8%)	139 (13.9%)	7 (12.7%)	8 (10.5%)	39 (11.0%)
Missing	-	-	1 (0.4%)	1 (0.4%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.3%)

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Smoking status [a]								
Current smoker	15 (8.9%)	14 (23.0%)	70 (29.4%)	83 (31.3%)	303 (30.2%)	12 (21.8%)	27 (35.5%)	113 (31.8%)
Former smoker	76 (44.9%)	29 (47.5%)	137 (57.6%)	156 (58.9%)	489 (48.7)	40 (72.7%)	57.9%)	172 (48.4%)
Never smoker	60 (35.5%)	14 (23.0%)	20 (8.4%)	14 (5.3%)	96 (9.6%)	2 (3.6%)	2 (2.6%)	19 (5.4%)
Unknown	18 (10.7%)	4 (6.6%)	11 (4.6%)	12 (4.5%)	115 (11.5%)	1 (1.8%)	3 (3.9%)	51 (14.4%)
Metastasis [a]								
Yes	161 (95.3%)	55 (90.2%)	213 (89.5%)	237 (89.4%)	890 (88.7%)	47 (85.5%)	59 (77.6%)	272 (76.6%)
No	6 (3.6%)	5 (8.2%)	19 (8.0%)	15 (5.7%)	68 (6.8%)	6 (10.9%)	9 (11.8%)	55 (15.5%)
Not derivable (MX or missing)	2 (1.2%)	1 (1.6%)	6 (2.5%)	13 (4.9%)	45 (4.5%)	2 (3.6%)	8 (10.5%)	28 (7.9%)
Selected metastatic sites [a, c]								
Adrenal Gland	15 (8.9%)	6 (9.8%)	55 (23.1%)	55 (20.8%)	167 (16.7%)	5 (9.1%)	9 (11.8%)	41 (11.5%)
Bones	76 (45.0%)	17 (27.9%)	50 (21.0%)	87 (32.8%)	272 (27.1%)	19 (34.5%)	15 (19.7%)	55 (15.5%)
Brain	44 (26.0%)	19 (31.1%)	61 (25.6%)	66 (24.9%)	245 (24.4%)	6 (10.9%)	6 (7.9%)	37 (10.4%)
Liver	33 (19.5%)	12 (19.7%)	27 (11.3%)	42 (15.8%)	131 (13.1%)	16 (29.1%)	9 (11.8%)	48 (13.5%)
Lung (contralateral)	34 (20.1%)	18 (29.5%)	53 (22.3%)	55 (20.8%)	210 (20.9%)	14 (25.5%)	21 (27.6%)	70 (19.7%)

All patients recruited up to and including June 30, 2018 were included into this outcome analysis. Data are presented as n (%), unless indicated otherwise. * Patients who were not tested, or for whom no druggable alteration (in *EGFR*, *ROS1*, *ALK*, or *BRAF*) could be detected. **Abbreviations:** acc., according; alter., alteration; CCI, Charlson Comorbidity Index; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation; unkn., unknown; w/o, without; yrs., years.

[a] for all patients with values for this variable
[b] Charlson Comorbidity Index (CCI) according to Quan [12]
[c] multiple answers possible
[d] without end organ damage