Online data supplement

Manuscript Title: Risk Assessment in Pulmonary Arterial Hypertension and Chronic Thromboembolic Pulmonary Hypertension

Authors: Marc Humbert, Harrison W. Farber, Hossein-Ardeschir Ghofrani, Raymond L. Benza, Dennis Busse, Christian Meier, and Marius M. Hoeper

PATENT-1 and -2

PATENT-1 was a 12-week, double-blind, randomized Phase III study that enrolled 443 patients with pulmonary arterial hypertension (PAH). Patients were randomly assigned (4:2:1) to riociguat individually dose adjusted according to tolerability up to 2.5 mg three times daily (tid), placebo, or riociguat 1.5 mg tid (exploratory dose). The primary endpoint was change from baseline to Week 12 in 6-minute walking distance (6MWD). After completing PATENT-1, eligible patients were invited to participate in an open-label extension study, PATENT-2. All patients in PATENT-2 received riociguat individually adjusted up to 2.5 mg tid in an 8-week blinded phase (the former riociguat 2.5 mg–maximum arm underwent sham titration), followed by an open-label study phase that will continue until all patients transition to the commercially available drug.

CHEST-1 and -2

CHEST-1 was a 16-week, double-blind, randomized Phase III study that enrolled 261 patients with chronic thromboembolic pulmonary hypertension (CTEPH). Patients were excluded if they had received an endothelin-receptor antagonist, prostacyclin analog, phosphodiesterase type 5 inhibitor, or nitric oxide donor within the 3 months before study entry. Patients were randomly assigned (2:1) to riociguat, individually adjusted according to tolerability up to 2.5 mg tid, or placebo. The primary endpoint was change from baseline to Week 16 in 6MWD. After completing CHEST-1, eligible patients were invited to participate in an open-label extension study, CHEST-2. All patients in CHEST-2 received riociguat individually adjusted up to 2.5 mg tid in an 8-week blinded phase (the former riociguat arm underwent sham titration), followed by an open-label study phase that that will continue until all patients transition to the commercially available drug.

Cox Proportional Hazards Analyses

Cox proportional hazards analyses were undertaken in patients who were receiving riociguat (2.5 mg tid-maximum) in PATENT-1/CHEST-1, and went on to participate in PATENT-2/CHEST-2.

The Cox proportional hazards analyses performed assessed the change in risk of death or clinical worsening in patients achieving ≥1 low-risk criteria, compared with those achieving none (according to the French registry methods), and the number of patients achieving a low-risk stratum, compared with those achieving an intermediate-risk stratum (according to the Swedish/COMPERA method). Due to no or few events in some risk groups/strata, hazards ratios could not be calculated in some cases.

Analyses were based on observed cases without imputation.

Table E1. Estimated survival rates over 3 years based on risk stratification at PATENT-1 follow-up

Number of low-risk criteria/risk stratum achieved according to abbreviated ESC/ERS risk stratification methods	Estimated survival rate (95% CI)		
	1 year	2 years	3 years
French invasive method			
0 criteria	91.7 (53.9–98.8)	91.7 (53.9–98.8)	91.7 (53.9–98.8)
1 criterion	92.8 (79.3–97.6)	90.2 (76.0–96.2)	87.6 (72.6–94.6)
2 criteria	100.0	93.4 (83.5–97.5)	85.0 (73.1–91.9)
3 criteria	100.0	93.8 (84.2–97.6)	91.9 (81.6–96.6)
4 criteria	97.0 (80.4–99.6)	93.8 (77.5–98.4)	90.6 (73.6–96.9)
French non-invasive method			
0 criteria	95.9 (84.7–99.0)	86.7 (72.6–93.8)	76.6 (60.7–86.8)
1 criterion	96.8 (87.8–99.2)	93.4 (83.4–97.5)	88.0 (76.4–94.1)
2 criteria	100.0	93.4 (83.4–97.5)	91.5 (80.8–96.4)
3 criteria	97.7 (84.9–99.7)	97.7 (84.9–99.7)	95.2 (82.2–98.8)
Swedish/COMPERA method			
Intermediate-risk	96.4 (90.6–98.6)	90.3 (82.8–94.7)	84.0 (75.1–89.9)
Low-risk	99.1 (93.6–99.9)	95.2 (88.8–98.0)	92.0 (84.6–95.9)

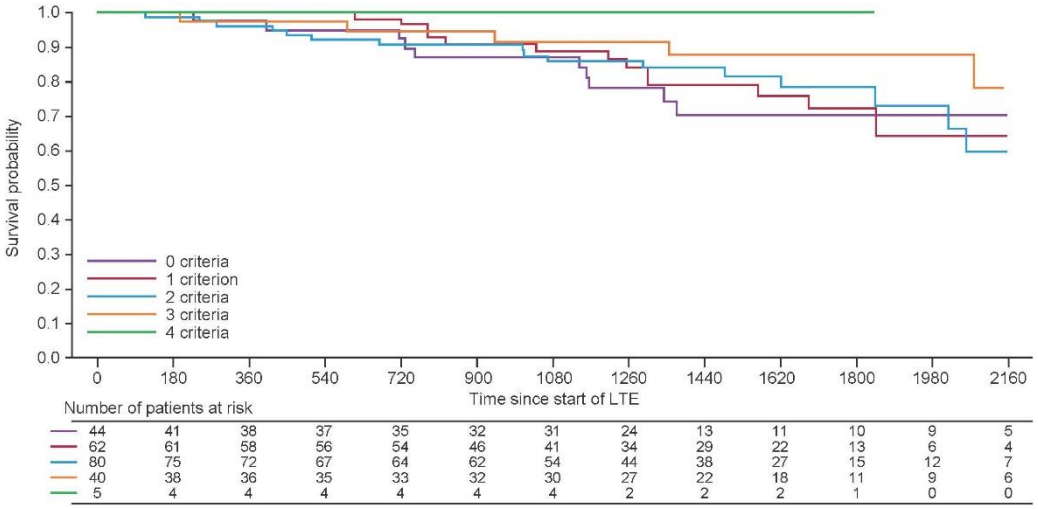
Definitions of abbreviations: CI, confidence interval; ERS, European Respiratory Society; ESC, European Society of Cardiology

Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

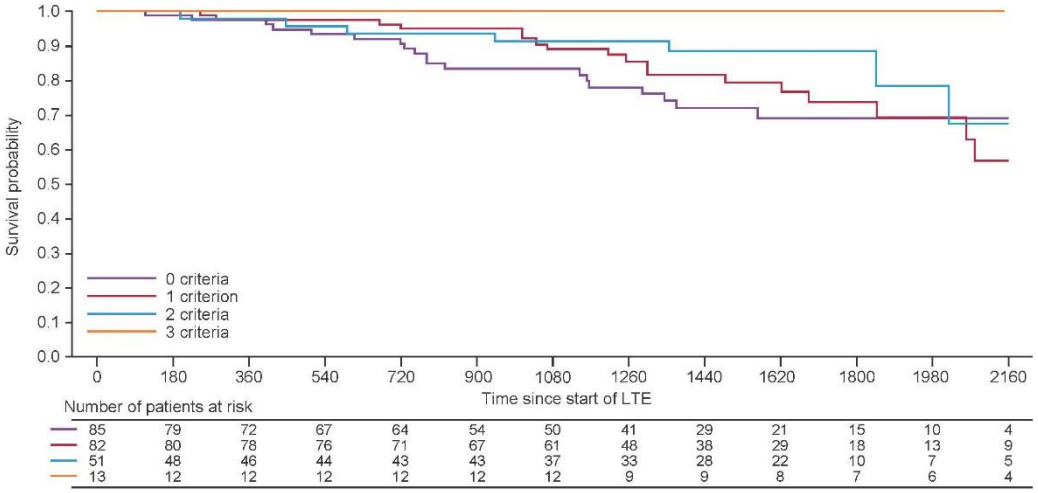
French registry invasive method: Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m^2; ***French registry non-invasive method***: Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, *N*T-proBNP <300 pg/mL; ***Swedish/COMPERA method*** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO_2) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

Figure E1. Kaplan–Meier curves for survival in patients based on risk stratification at PATENT-1 baseline: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.

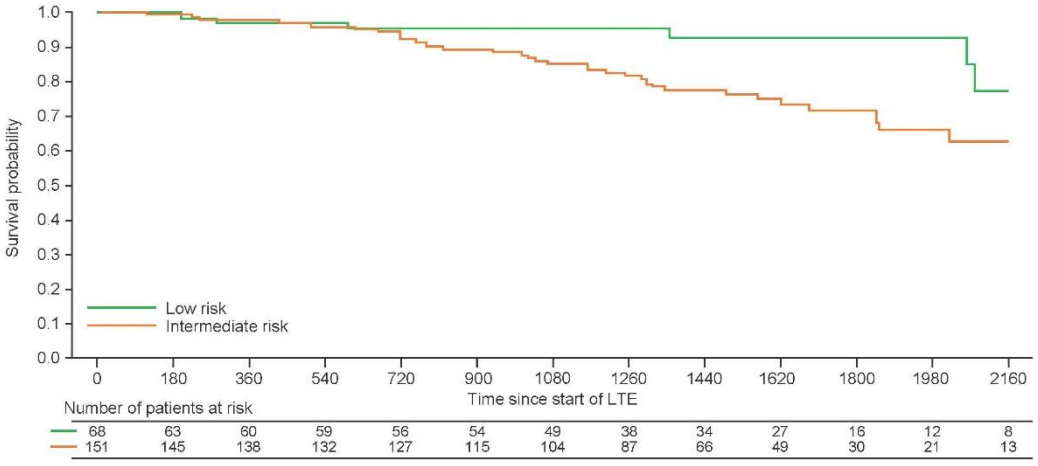
a)


Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 criteria
1 criterion
2 criteria
3 criteria
4 criteria
0 180 360 540 720 900 1080 1260 1440 1620 1800 1980 2160
Time since start of LTE
Number of patients at risk
44 41 38 37 35 32 31 24 13 11 10 9 5
62 61 58 56 54 46 41 34 29 22 13 6 4
80 75 72 67 64 62 54 44 38 27 15 12 7
40 38 36 35 33 32 30 27 22 18 11 9 6
5 4 4 4 4 4 4 2 2 2 1 0 0

b)


Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0 criteria
1 criterion
2 criteria
3 criteria
0 180 360 540 720 900 1080 1260 1440 1620 1800 1980 2160
Time since start of LTE
Number of patients at risk
85 79 72 67 64 54 50 41 29 21 15 10 4
82 80 78 76 71 67 61 48 38 29 18 13 9
51 48 46 44 43 43 37 33 28 22 10 7 5
13 12 12 12 12 12 12 9 9 8 7 6 4

c)


Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Low risk
Intermediate risk
0 180 360 540 720 900 1080 1260 1440 1620 1800 1980 2160
Time since start of LTE
Number of patients at risk
68 63 60 59 56 54 49 38 34 27 16 12 8
151 145 138 132 127 115 104 87 66 49 30 21 13

Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

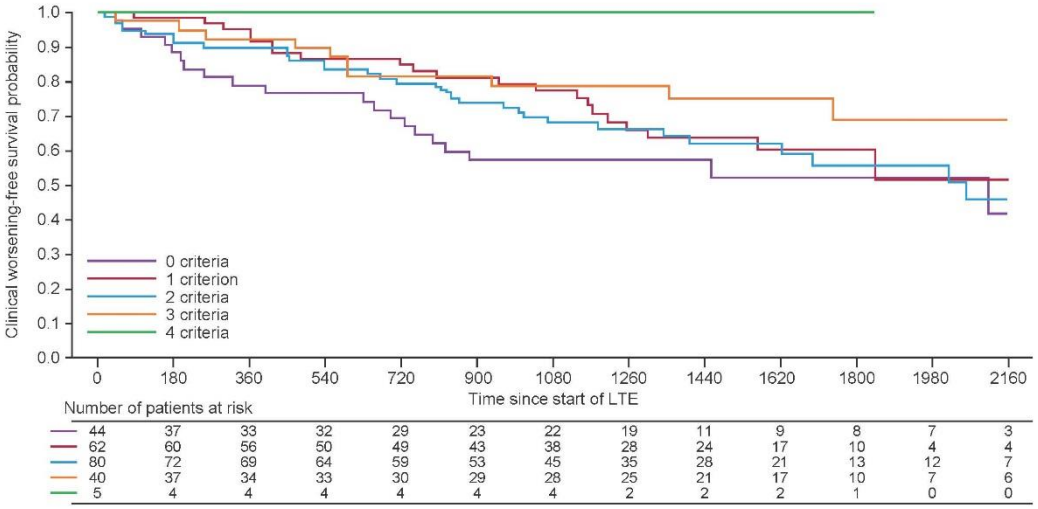
Only 12 patients were in the Swedish/COMPERA high-risk group at PATENT-1 baseline (most of whom died during PATENT-2 follow-up) and are therefore not included in the analysis for this method.

French registry invasive method: Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m^2; ***French registry non-invasive method***: Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, *N*T-proBNP <300 pg/mL; ***Swedish/COMPERA method*** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO_2) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

Log-rank test: invasive *P* = 0.4276, non-invasive *P* = 0.0283, Swedish/COMPERA *P* = 0.0355.

Figure E2. Kaplan–Meier curves for clinical worsening-free survival in patients based on risk stratification at PATENT-1 baseline: a) French registry invasive method; b) French registry non-invasive method; and c) Swedish/COMPERA method.

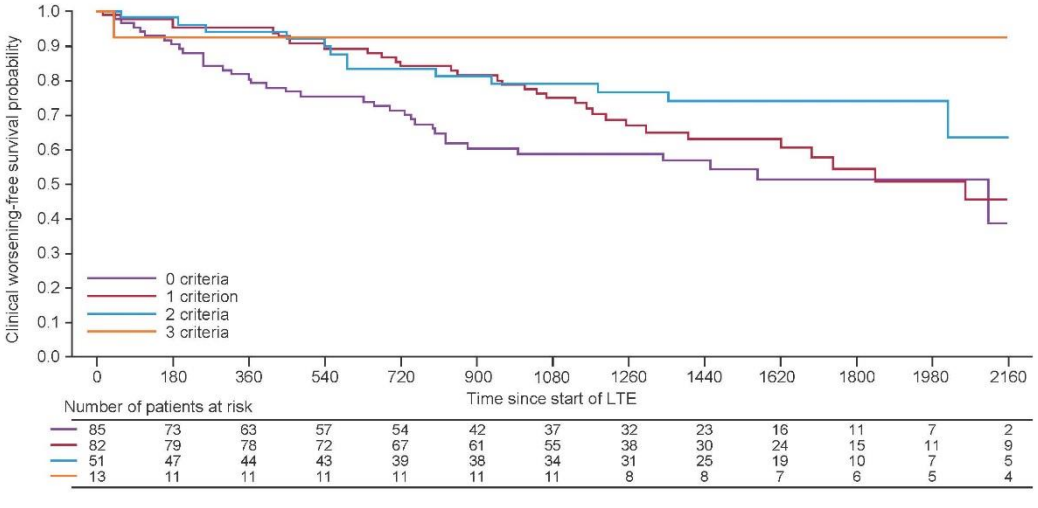
a)



Number of patients at risk

44	37	33	32	29	23	22	19	11	9	8	7	3
62	60	56	50	49	43	38	28	24	17	10	4	4
80	72	69	64	59	53	45	35	28	21	13	12	7
40	37	34	33	30	29	28	25	21	17	10	7	6
5	4	4	4	4	4	4	2	2	2	1	0	0

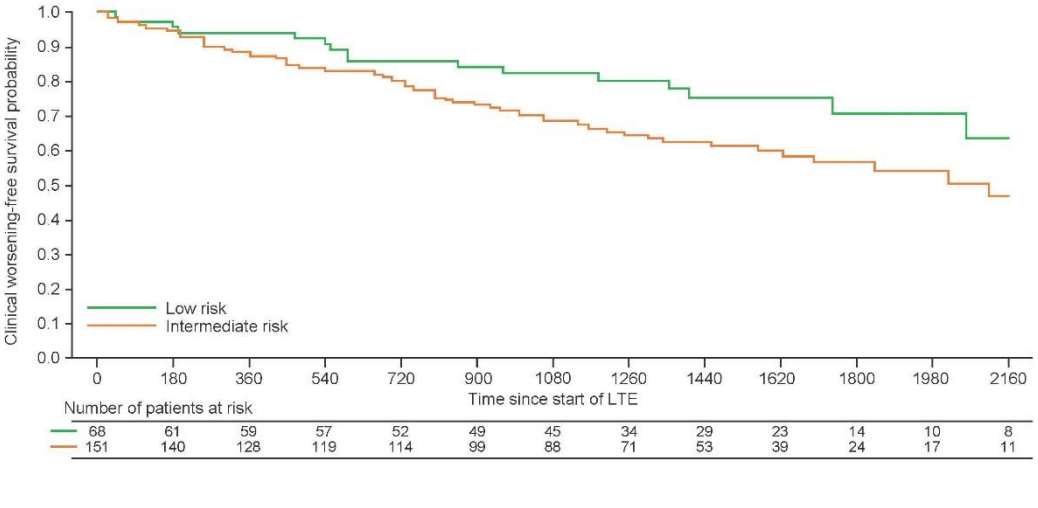
b)



Number of patients at risk

85	73	63	57	54	42	37	32	23	16	11	7	2
82	79	78	72	67	61	55	38	30	24	15	11	9
51	47	44	43	39	38	34	31	25	19	10	7	5
13	11	11	11	11	11	11	8	8	7	6	5	4

c)



Number of patients at risk

68	61	59	57	52	49	45	34	29	23	14	10	8
151	140	128	119	114	99	88	71	53	39	24	17	11

Only patients receiving riociguat 2.5 mg tid–maximum in PATENT-1 who participated in PATENT-2 were considered in this analysis.

Data were based on observed cases with no imputation.

Day 0 = start of extension study.

Only 12 patients were in the Swedish/COMPERA high-risk group at PATENT-1 baseline (most of whom died during PATENT-2 follow-up) and are therefore not included in the analysis for this method.

French registry invasive method: Number of low-risk criteria fulfilled: 6MWD >440 m, WHO FC I/II, right atrial pressure <8 mmHg, cardiac index ≥ 2.5 L/min/m^2; ***French registry non-invasive method***: Number of low-risk criteria fulfilled: 6WMD >440 m, WHO FC I/II, *N*T-proBNP <300 pg/mL; ***Swedish/COMPERA method*** mean of grades (1–3: low, intermediate, high) of 6 available criteria (6MWD, WHO FC, NT-proBNP, RAP, cardiac index and SvO_2) as defined in the European Society of Cardiology/European Respiratory Society 2015 treatment guidelines, rounded to the nearest integer.

Log-rank test: Invasive *P* = 0.0602, non-invasive *P* = 0.0036, Swedish/COMPERA *P* = 0.0236.