Adjuvância em pacientes com tumores luminais

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Presidente Sociedade Brasileira de Mastologia – Regional PR

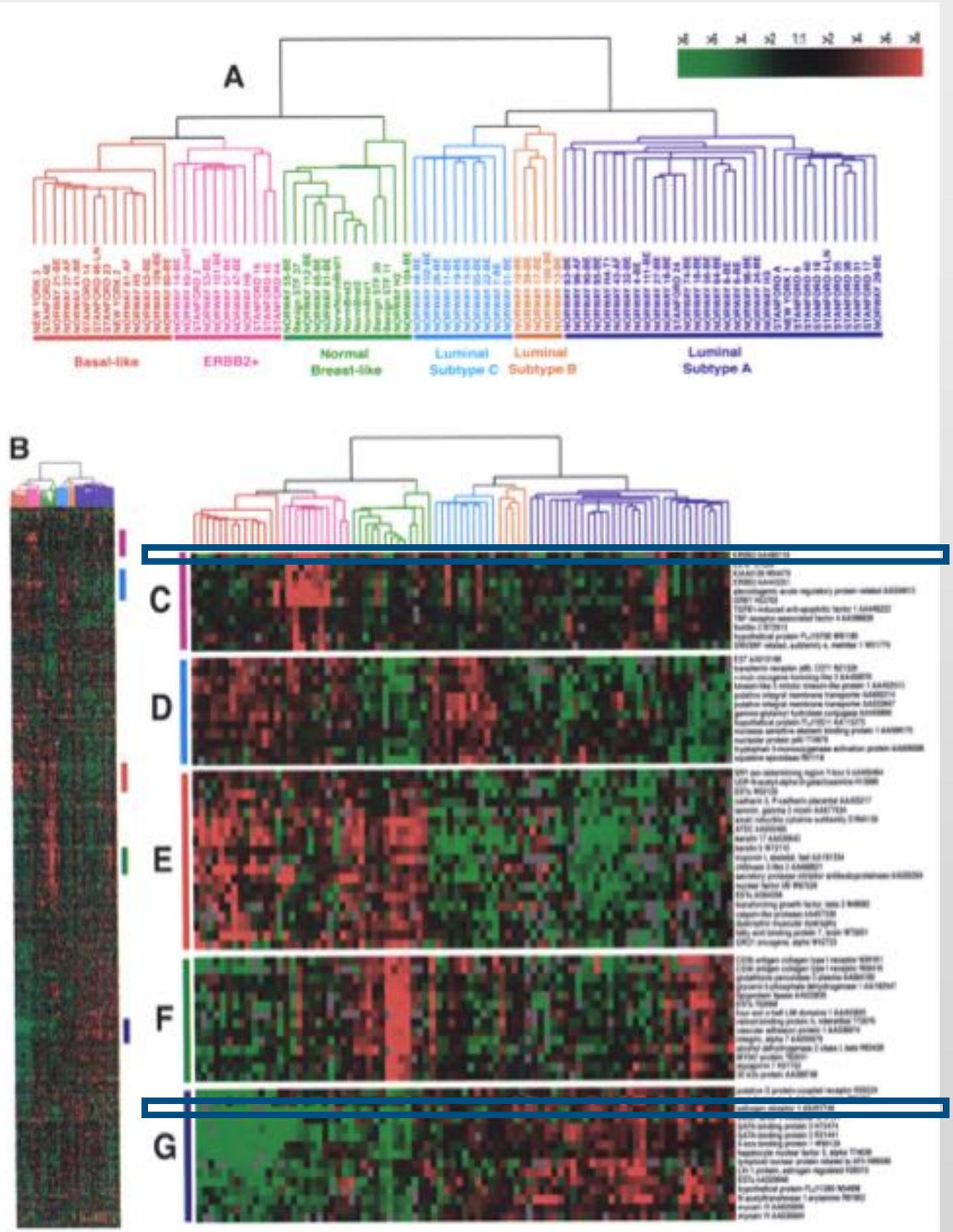
Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications

Therese Sørlie[a,b,c], Charles M. Perou[a,d], Robert Tibshirani[e], Turid Aas[f], Stephanie Geisler[g], Hilde Johnsen[b], Michael B. Eisen[h], Matt van de Rijn[i], Stefanie S. Jeffrey[i], Thor Thorsen[k], Hanne Quist[l], John C. Matese[c], Patrick O. Brown[m], David Botstein[c], Per Eystein Lønning[g], and Anne-Lise Børresen-Dale[b,n]

Subtipos com expressão genica LUMINAL

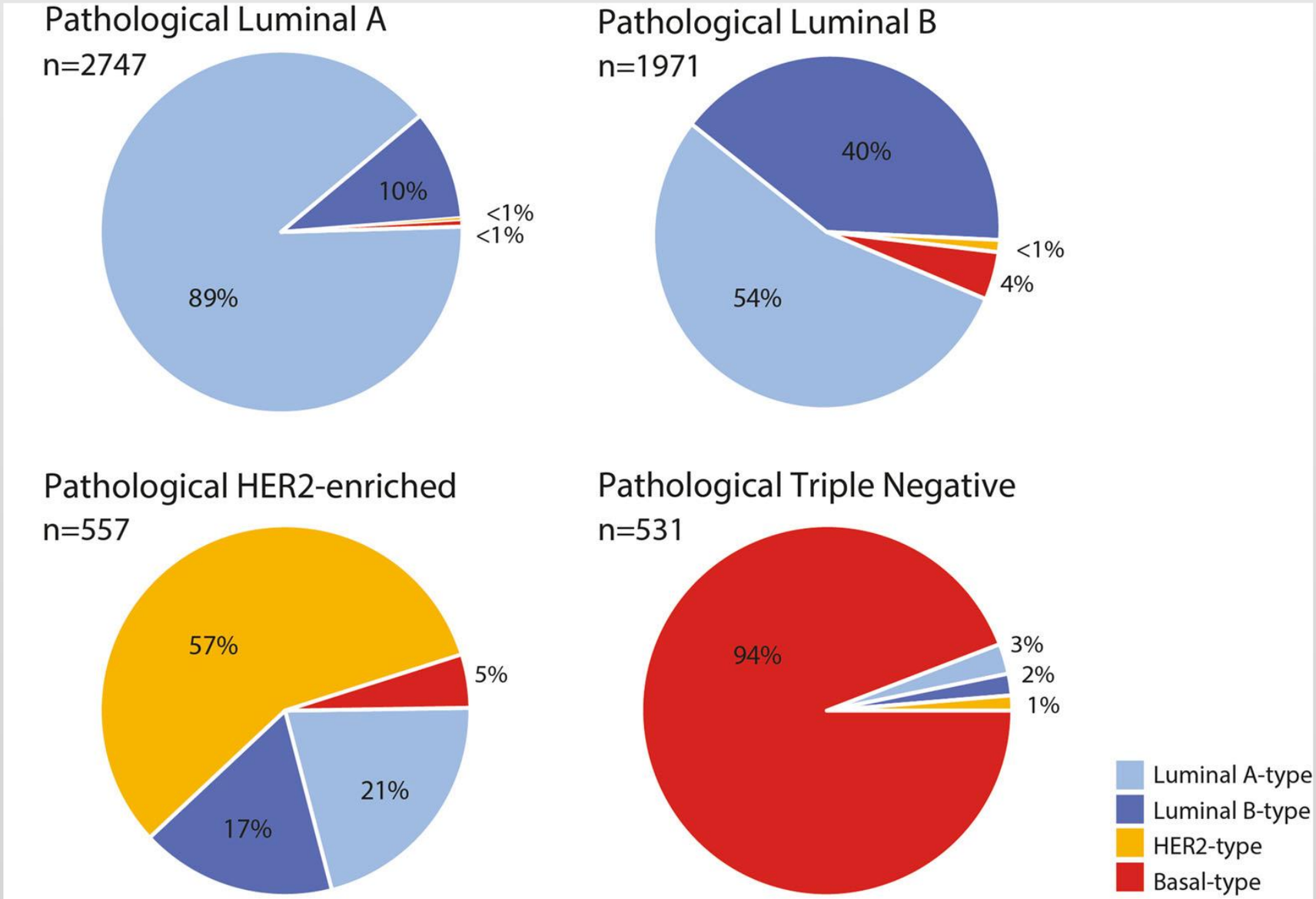
Alta expressão de RE

60%



Immunohistochemical versus molecular (BluePrint and MammaPrint) subtyping of breast carcinoma. Outcome results from the EORTC 10041/BIG 3-04 MINDACT trial

G. Viale[1] · F. A. de Snoo[2] · L. Slaets[3] · J. Bogaerts[3] · L. van 't Veer[4] · E. J. Rutgers[5] · M. J. Piccart-Gebhart[6] · L. Stork-Sloots[2] · A. Glas[2] · L. Russo[1] · P. Dell'Orto[1] · K. Tryfonidis[3] · S. Litière[3] · F. Cardoso[7] · for the MINDACT investigators



Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials

*Early Breast Cancer Trialists' Collaborative Group (EBCTCG)**

RR 0,64 e 0,85

Estimativa clínica para indicar benefício de QT
Biomarcadores de quimiossensibilidade: ER + / HER2 -

1 - Expressão do Receptor de Estrogênio

Pós menopausa ER+ / N+
DFS 0,81 - 13y —> Níveis baixos ou intermediários de RE

Similar em ER intermediário e PR baixo

Is adjuvant chemotherapy of benefit for postmenopausal women who receive endocrine treatment for highly endocrine-responsive, node-positive breast cancer? International Breast Cancer Study Group Trials VII and 12–93

Olivia Pagani · Shari Gelber · Edda Simoncini · Monica Castiglione-Gertsch · Karen N. Price · Richard D. Gelber · Stig B. Holmberg · Diana Crivellari · John Collins · Jurij Lindtner · Beat Thürlimann · Martin F. Fey · Elizabeth Murray · John F. Forbes · Alan S. Coates · Aron Goldhirsch · for the International Breast Cancer Study Group

Predicting response to systemic treatments: Learning from the past to plan for the future

Meredith M. Regan*, Richard D. Gelber

IBCSG Statistical Center, Department of Biostatistics and Computational Biology, Dana-Farber Cancer Institute, 44 Binney St., Boston, MA 02115, USA

2 - Grau tumoral histológico

Biomarcador Prognóstico
Grau 2 (intermediário): Gray zone

Indice de expressão gênica - GGI (genes relacionados a expressão)
Alto e baixo grau: Correlaciona com Oncotype e Luminal A e B

Gene Expression Profiling in Breast Cancer: Understanding the Molecular Basis of Histologic Grade To Improve Prognosis

Christos Sotiriou, Pratyaksha Wirapati, Sherene Loi, Adrian Harris, Steve Fox, Johanna Smeds, Hans Nordgren, Pierre Farmer, Viviane Praz, Benjamin Haibe-Kains, Christine Desmedt, Denis Larsimont, Fatima Cardoso, Hans Peterse, Dimitry Nuyten, Marc Buyse, Marc J. Van de Vijver, Jonas Bergh, Martine Piccart, Mauro Delorenzi

3 - Índices de proliferação celular

Ki67 - Porcentagem de proliferação celular em um tumor

Diferenciação entre Luminal A e B
Pior prognóstico porém sem benefício da QT
Alto Ki demonstrou benefício de taxanos nos ER +

Predictive Value of Tumor Ki-67 Expression in Two Randomized Trials of Adjuvant Chemoendocrine Therapy for Node-Negative Breast Cancer

Giuseppe Viale, Meredith M. Regan, Mauro G. Mastropasqua, Fausto Maffini, Eugenio Maiorano, Marco Colleoni, Karen N. Price, Rastko Golouh, Tiziana Perin, R. W. Brown, Anikó Kovács, Komala Pillay, Christian Öhlschlegel, Barry A. Gusterson, Monica Castiglione-Gertsch, Richard D. Gelber, Aron Goldhirsch, Alan S. Coates

Ki67 Expression and Docetaxel Efficacy in Patients With Estrogen Receptor–Positive Breast Cancer

Frédérique Penault-Llorca, Fabrice André, Christine Sagan, Magali Lacroix-Triki, Yves Denoux, Veronique Verriele, Jocelyne Jacquemier, Marie Christine Baranzelli, Frederic Bibeau, Martine Antoine, Nicole Lagarde, Anne-Laure Martin, Bernard Asselain, and Henri Roché

4 - Assinaturas Prognósticas Multigênicas

TAILORx

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

J.A. Sparano, R.J. Gray, D.F. Makower, K.I. Pritchard, K.S. Albain, D.F. Hayes, C.E. Geyer, Jr., E.C. Dees, E.A. Perez, J.A. Olson, J.A. Zujewski, T. Lively, S.S. Badve, T.J. Saphner, L.I. Wagner, T.J. Whelan, M.J. Ellis, S. Paik, W.C. Wood, P. Ravdin, M.M. Keane, H.L. Gomez Moreno, P.S. Reddy, T.F. Goggins, I.A. Mayer, A.M. Brufsky, D.L. Toppmeyer, V.G. Kaklamani, J.N. Atkins, J.L. Berenberg, and G.W. Sledge

MINDACT

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*

Prospective Validation of a 21-Gene Expression Assay in Breast Cancer

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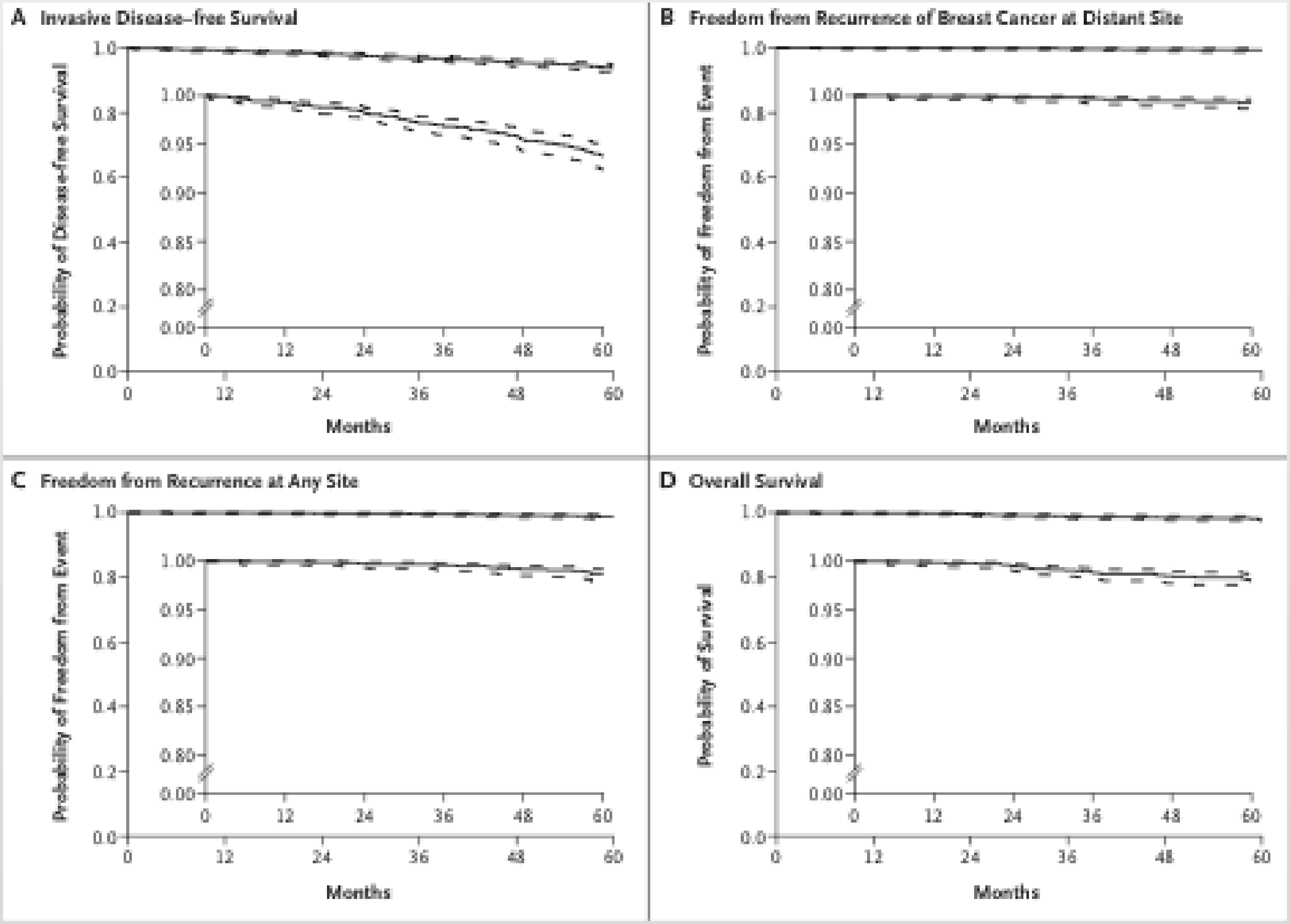
Oncotype DX

T: 1,1 cm - 5 cm, RE+, N -
T: 0,6cm - 1 cm (GH 2 ou 3), RE +, N - **Prospectivo**
RS < 10 **Somente HT**
70 meses



Sobrevida livre doença invasiva: 93,8%
Recorrência a distância: 99,3%
Recorrência a distância ou loco-regional: 98,7%
OS: 98%

5 anos

70-Gene Signature as an Aid to Treatment Decisions in Early-Stage Breast Cancer

F. Cardoso, L.J. van't Veer, J. Bogaerts, L. Slaets, G. Viale, S. Delaloge, J.-Y. Pierga, E. Brain, S. Causeret, M. DeLorenzi, A.M. Glas, V. Golfinopoulos, T. Goulioti, S. Knox, E. Matos, B. Meulemans, P.A. Neijenhuis, U. Nitz, R. Passalacqua, P. Ravdin, I.T. Rubio, M. Saghatchian, T.J. Smilde, C. Sotiriou, L. Stork, C. Straehle, G. Thomas, A.M. Thompson, J.M. van der Hoeven, P. Vuylsteke, R. Bernards, K. Tryfonidis, E. Rutgers, and M. Piccart, for the MINDACT Investigators*

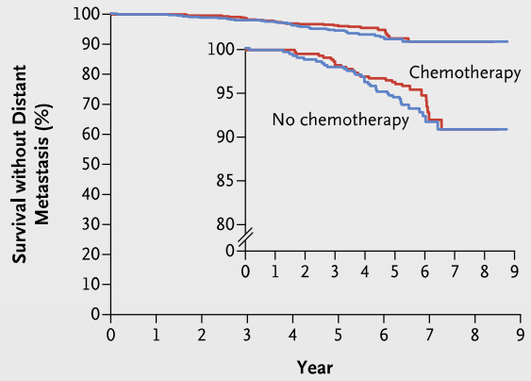
Mammaprint

Ca mama inicial com alto risco clínico (AdjuvantOnline)
Baixo risco genômico (Mammaprint)

Probabilidade de sobrevida específica para câncer em 10 anos
88% RH +
92% RH -
4% —> Benefício da HT

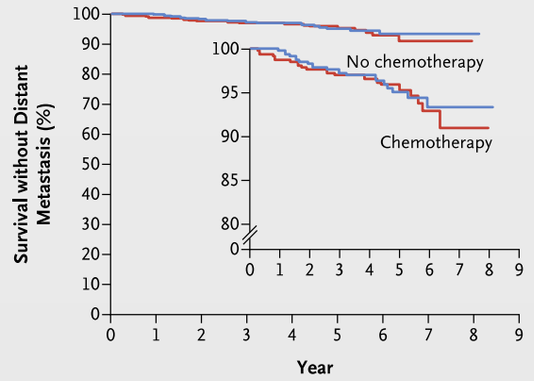
QT x NÃO QT

A High Clinical Risk, Low Genomic Risk



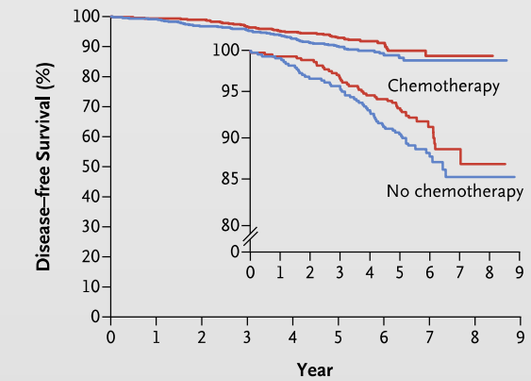
No. at risk									
Chemotherapy	749	714	698	677	611	346	145	41	3
No chemotherapy	748	727	708	696	655	424	160	41	4

B Low Clinical Risk, High Genomic Risk



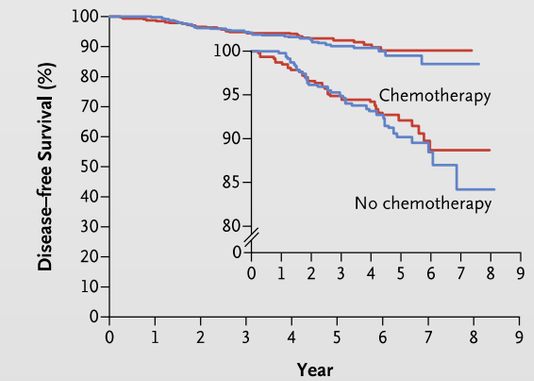
No. at risk									
Chemotherapy	344	321	316	306	281	179	81	22	0
No chemotherapy	346	336	327	319	291	178	82	24	3

C High Clinical Risk, Low Genomic Risk



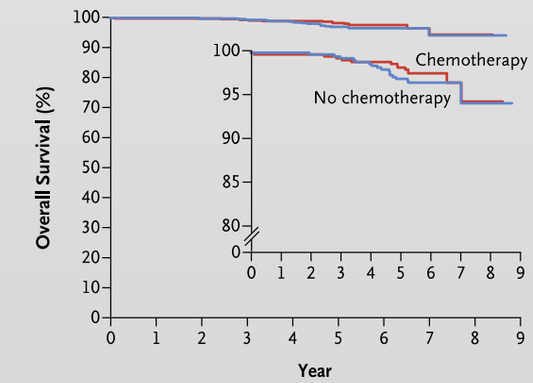
No. at risk									
Chemotherapy	749	712	694	666	597	336	142	41	3
No chemotherapy	748	722	695	681	633	405	152	38	4

D Low Clinical Risk, High Genomic Risk



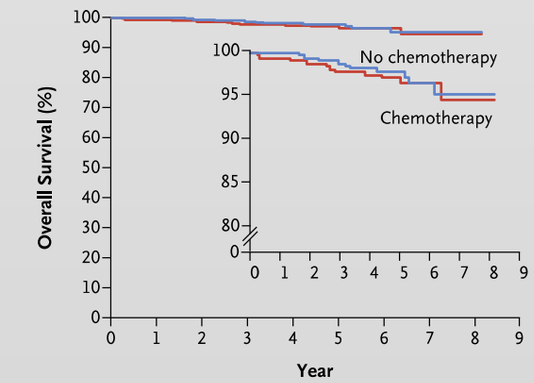
No. at risk									
Chemotherapy	344	321	313	300	274	172	75	20	0
No chemotherapy	346	336	320	311	278	167	73	23	3

E High Clinical Risk, Low Genomic Risk



No. at risk									
Chemotherapy	749	719	702	687	625	363	154	44	4
No chemotherapy	748	733	719	713	676	439	168	43	4

F Low Clinical Risk, High Genomic Risk



No. at risk									
Chemotherapy	344	325	320	311	286	182	81	22	2
No chemotherapy	346	339	332	324	296	184	88	24	3

Sobrevida em 5 anos sem metástase: 94,7%

Diferença absoluta de 1,5% (favorável ao grupo com Qt)

Table 1. Characteristics of the Patients and Tumors at Baseline, According to Risk Group.*

Characteristic	Low Clinical Risk		High Clinical Risk		All Patients (N=6693)
	Low Genomic Risk (N=2745)	High Genomic Risk (N=592)	Low Genomic Risk (N=1550)	High Genomic Risk (N=1806)	
			number (percent)		
Age — yr					
<35	24 (0.9)	13 (2.2)	20 (1.3)	65 (3.6)	122 (1.8)
35 to <50	774 (28.2)	165 (27.9)	514 (33.2)	651 (36.0)	2104 (31.4)
50 to 70	1928 (70.2)	403 (68.1)	1006 (64.9)	1080 (59.8)	4411 (65.9)
>70	19 (0.7)	11 (1.9)	16 (1.0)	10 (0.6)	56 (0.8)
Tumor size — cm†					
<1	655 (23.9)	198 (33.4)	38 (2.5)	29 (1.6)	920 (13.7)
1 to 2	1968 (71.7)	383 (64.7)	[illegible]	914 (50.6)	3875 (57.9)
>2 to 5	122 (4.4)	11 (1.9)	843 (54.4)	843 (46.7)	1819 (27.2)
>5	0	0	58 (3.7)	20 (1.1)	78 (1.2)
Tumor grade‡					
1	1242 (45.2)	92 (15.5)	[illegible]	15 (0.8)	1447 (21.6)
2	1457 (53.1)	414 (69.9)	995 (64.2)	421 (23.3)	3287 (49.1)
3	36 (1.3)	83 (14.0)	443 (28.6)	1365 (75.6)	1927 (28.8)
Missing data	10 (0.4)	3 (0.5)	14 (0.9)	5 (0.3)	32 (0.5)
Lymph-node status§					
Negative	2570 (93.6)	577 (97.5)	812 (52.4)	1329 (73.6)	5288 (79.0)
Positive					
1 node	131 (4.8)	10 (1.7)	505 (32.6)	296 (16.4)	942 (14.1)
2 nodes	26 (0.9)	3 (0.5)	157 (10.1)	114 (6.3)	300 (4.5)
3 nodes	18 (0.7)	2 (0.3)	69 (4.5)	65 (3.6)	154 (2.3)
≥4 nodes	0	0	6 (0.4)	2 (0.1)	8 (0.1)
Hormone-receptor status¶					
ER-positive, PR-positive, or both	2741 (99.9)	535 (90.4)	1520 (98.1)	1118 (61.9)	5914 (88.4)
ER-negative and PR-negative	4 (0.1)	57 (9.6)	29 (1.9)	688 (38.1)	778 (11.6)
HER2 status‖					
Negative	2641 (96.2)	518 (87.5)	[illegible]	1461 (80.9)	6043 (90.3)
Positive	97 (3.5)	73 (12.3)	124 (8.0)	344 (19.0)	638 (9.5)
Missing data	7 (0.3)	1 (0.2)	3 (0.2)	1 (0.1)	12 (0.2)
Clinical–pathological subtype**					
Luminal HER2-negative: ER-positive, PR-positive, or both	2638 (96.1)	467 (78.9)	1402 (90.5)	895 (49.6)	5402 (80.7)
Luminal HER2-positive: ER-positive, PR-positive, or both	96 (3.5)	68 (11.5)	115 (7.4)	222 (12.3)	501 (7.5)
Nonluminal HER2-positive: ER-negative, PR-negative	1 (<0.1)	5 (0.8)	9 (0.6)	122 (6.8)	137 (2.0)
Triple negative: ER-negative, PR-negative, HER2-negative	3 (0.1)	51 (8.6)	20 (1.3)	566 (31.3)	640 (9.6)
Missing data	7 (0.3)	1 (0.2)	4 (0.3)	1 (0.1)	13 (0.2)

33,5% < 50 ANOS

58,1% > 2cm

92,8% G2/3

47,6% N+

98,1% ER+

8% Her2

TENDÊNCIA

Biomarcadores únicos

Assinaturas multigênicas prognósticos

Tempo ideal

Time to Surgery and Breast Cancer Survival in the United States

Bleicher RJ, Ruth K, Sigurdson ER et al:
JAMA Oncol 2(3):330-339, 2016

Methods

- Population-based investigation
- Data from SEER-Medicare and NCDB databases
- SEER: n=94,544; 1992-2009
- NCDB n=115,790; 2003-2005
- TTS was defined as number of days from diagnosis to surgery

Tempo ideal

Results

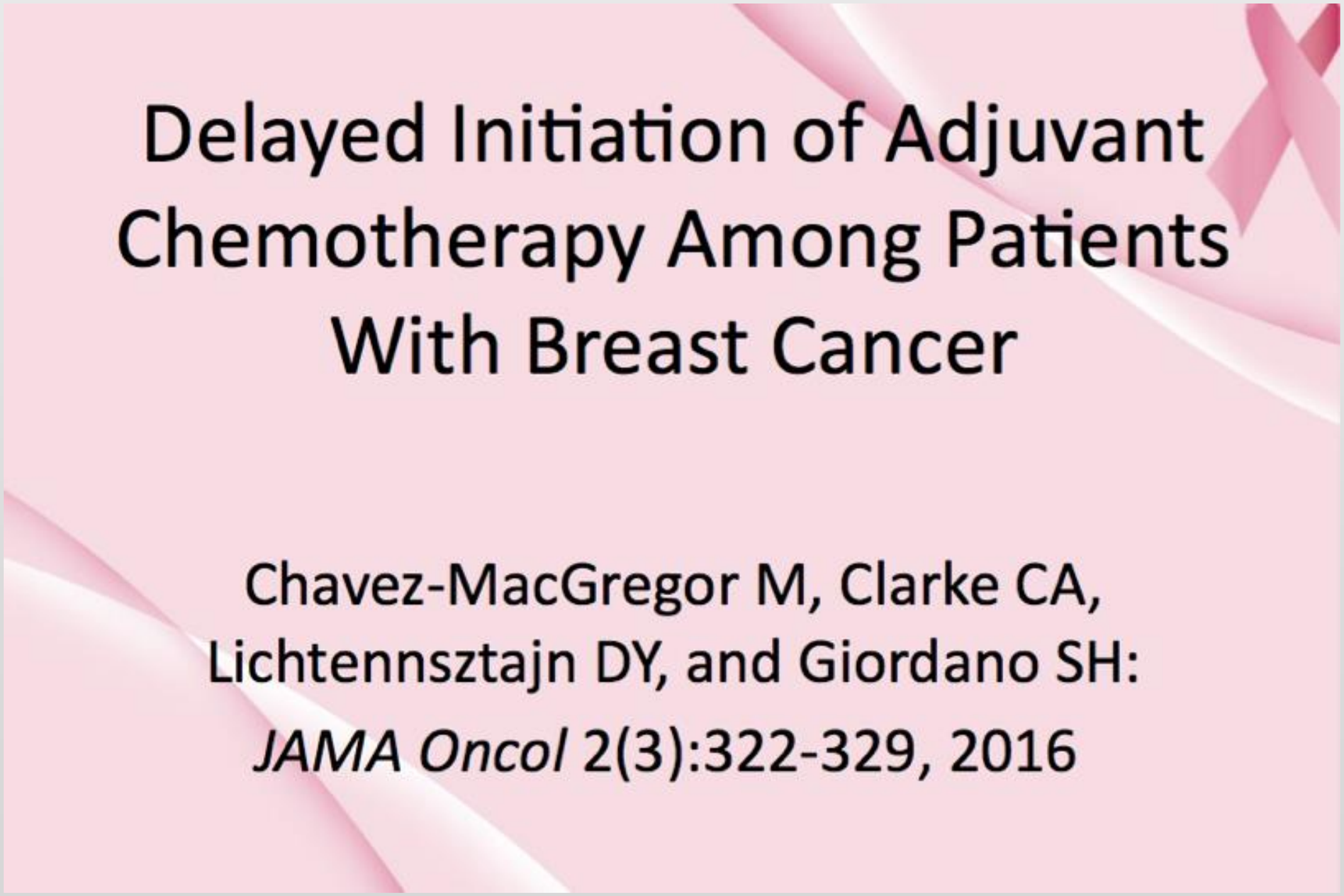
- Each 30 day increase in the interval of delay, decreased OS and increased BCSM
  - ≤ 30, 31-60, 61-90, 91-120, and 121-180 days
- SEER-Medicare:
  - OS: HR 1.09: 95%CI 1.06-1.13; p<0.001
  - BCSM: HR 1.26: 95% CI1.06-1.54; p=0.03
- NCDB:
  - OS: HR 1.10: 95%CI 1.07-1.13; p<0.001

Tempo ideal

Conclusions

- Greater TTS is associated with lower overall and disease-specific survival
- The begins with delays ≥ 30 days
  - NB: SEER 77.7% and NCDB 69.5% of patients underwent surgery by 30 days

Tempo ideal


Delayed Initiation of Adjuvant Chemotherapy Among Patients With Breast Cancer
Chavez-MacGregor M, Clarke CA, Lichtennsztajn DY, and Giordano SH:
JAMA Oncol 2(3):322-329, 2016

Tempo ideal

Methods

- Observational, population-based investigation
- Data from the California Cancer Registry
- Jan. 1, 2005 – Dec. 31,2010
- N=24,843
- Stage I-III
- TTC was defined as number of days from surgery to first dose of adjuvant chemotherapy
- Delayed TTC was defined as $\geq$ 91 days

Tempo ideal

Results

- Median TTC = 46 days
- No difference in adverse outcomes for
  - TTC <31 days vs 31-60 days vs 61-90 days
- TTC > 90 days was associated with poorer OS
  - HR 1.34; 95%CI 1.15-1.57
- TTC > 90 days was associated with poorer breast cancer specific survival
  - HR 1.27; 95%CI 1.05-1.53
- Difference most pronounced in patients with TNBC
  - OS: HR 1.53; 95%CI 1.17-2.00
  - BCSS: HR 1.53; 95%CI 1.17-2.07

Tempo ideal

Logística

Material em PARAFINA
20 dias corridos (máximo)

Tempo ideal

Pós BIÓPSIA X Pós CIRURGIA

2 cenários → **ER/PR + / Her2 -**

→ **Her2 + / Triplo -**

Ann Surg Oncol
DOI 10.1245/s10434-017-6016-y

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

The Optimal Treatment Plan to Avoid Axillary Lymph Node Dissection in Early-Stage Breast Cancer Patients Differs by Surgical Strategy and Tumor Subtype

Melissa Pilewskie, MD[1], Emily C. Zabor, MS[2], Anita Mamtani, MD[1], Andrea V. Barrio, MD[1], Michelle Stempel, MPH[1], and Monica Morrow, MD[1]

[1]Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Subtype	Upfront BCS *n* (%)	NAC *n* (%)	*p* value	Upfront mastectomy *n* (%)	NAC *n* (%)	*p* value
ER/PR$^+$, HER2$^-$	85/564 (15.1)	25/73 (34.2)	<0.001	268/724 (37)	25/73 (34.2)	0.62
HER2$^+$	9/68 (13.2)	9/112 (8)	0.26	53/146 (36.3)	9/112 (8)	<0.001
ER$^-$, PR$^-$, HER2$^-$	5/37 (13.5)	6/86 (7)	0.26	32/126 (25.4)	6/86 (7)	0.001

BCS breast-conserving surgery, *NAC* neoadjuvant chemotherapy, *ER* estrogen receptor, *PR* progesterone receptor, *HER* human epidermal growth factor

Qt Neo: Menor ALND em Triplo - e Her2 + x Mastectomia
ER/PR + e Her2 -: Menor ALD em BCS inicial

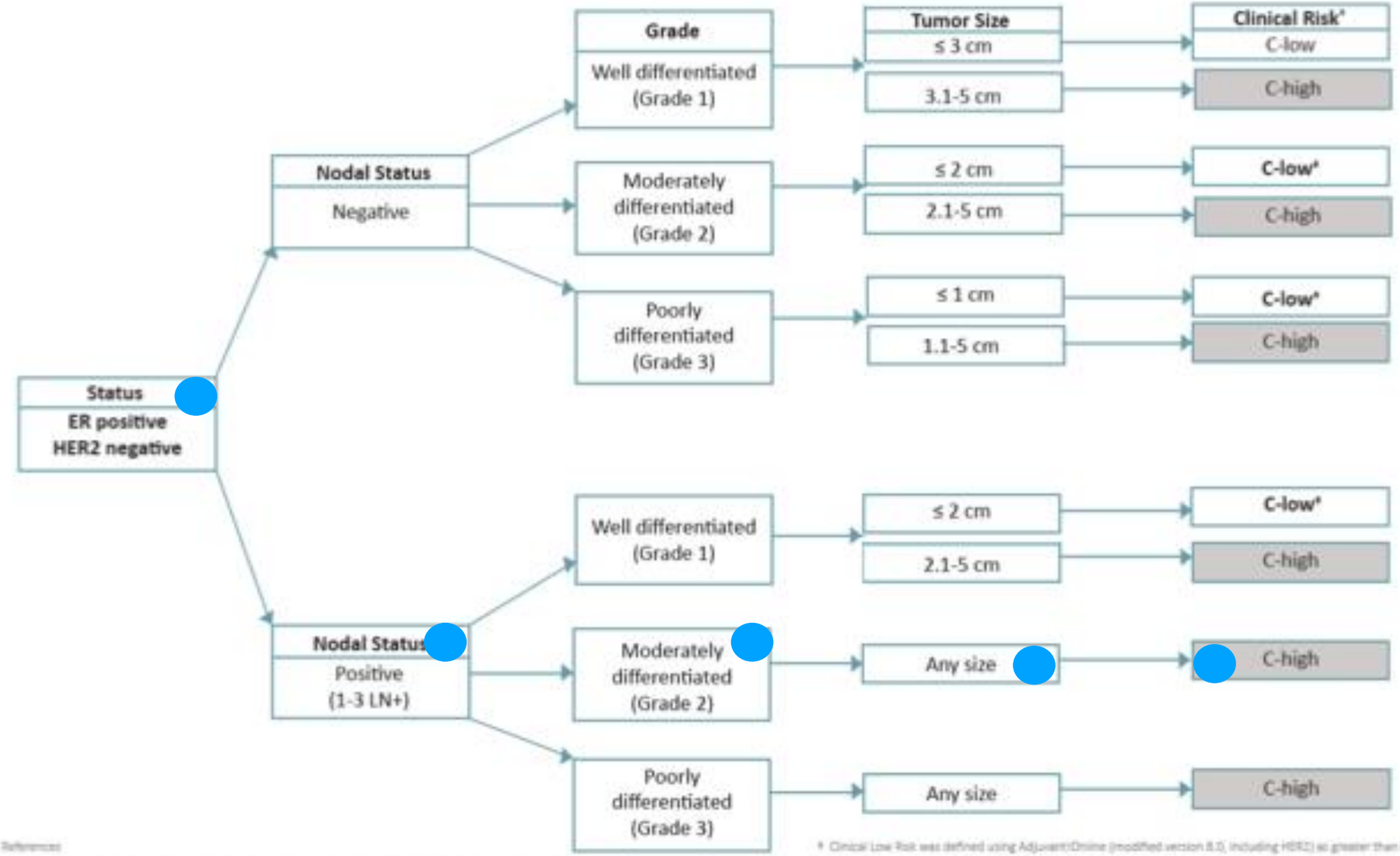
Caso clínico 1:

70 year old woman
Microcalcs on mammo, 2.5cm
Bx: IDC, ER+, HER2 -
Resection:
T1c: 2cm
ER+, PR+, HER2-, Ki67 “low”
Grade 2
LVI present
1/7 LN+
Stage IIA

Clinical Risk Assessment in the MINDACT Trial

agendia® mammaprint®

HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE, INVASIVE BREAST CANCER (HR+ / HER2-)



References

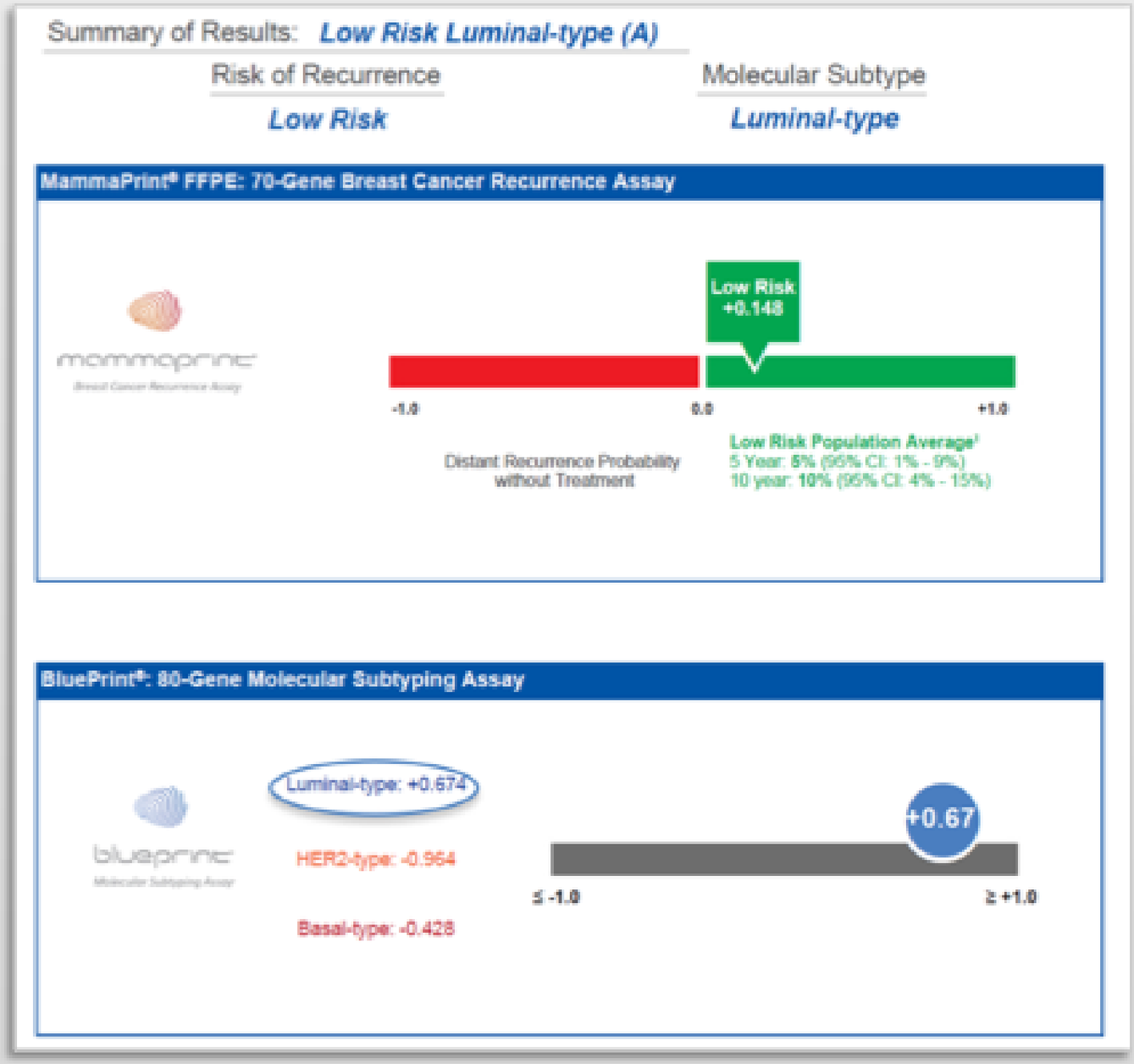
1. Cardoso, Fatima et al. "70-Gene Signature as an Aid to Treatment Decisions in Early Breast Cancer" *N Engl J Med* Supplemental. Published Online: Aug 2016.

* Clinical Low Risk was defined using AdjuvantOnline (modified version 8.0, including HER2) as greater than 88% breast cancer specific survival capability at 10-years, without systemic therapy to account for the average absolute benefit of adjuvant endocrine therapy for ER+ patients.

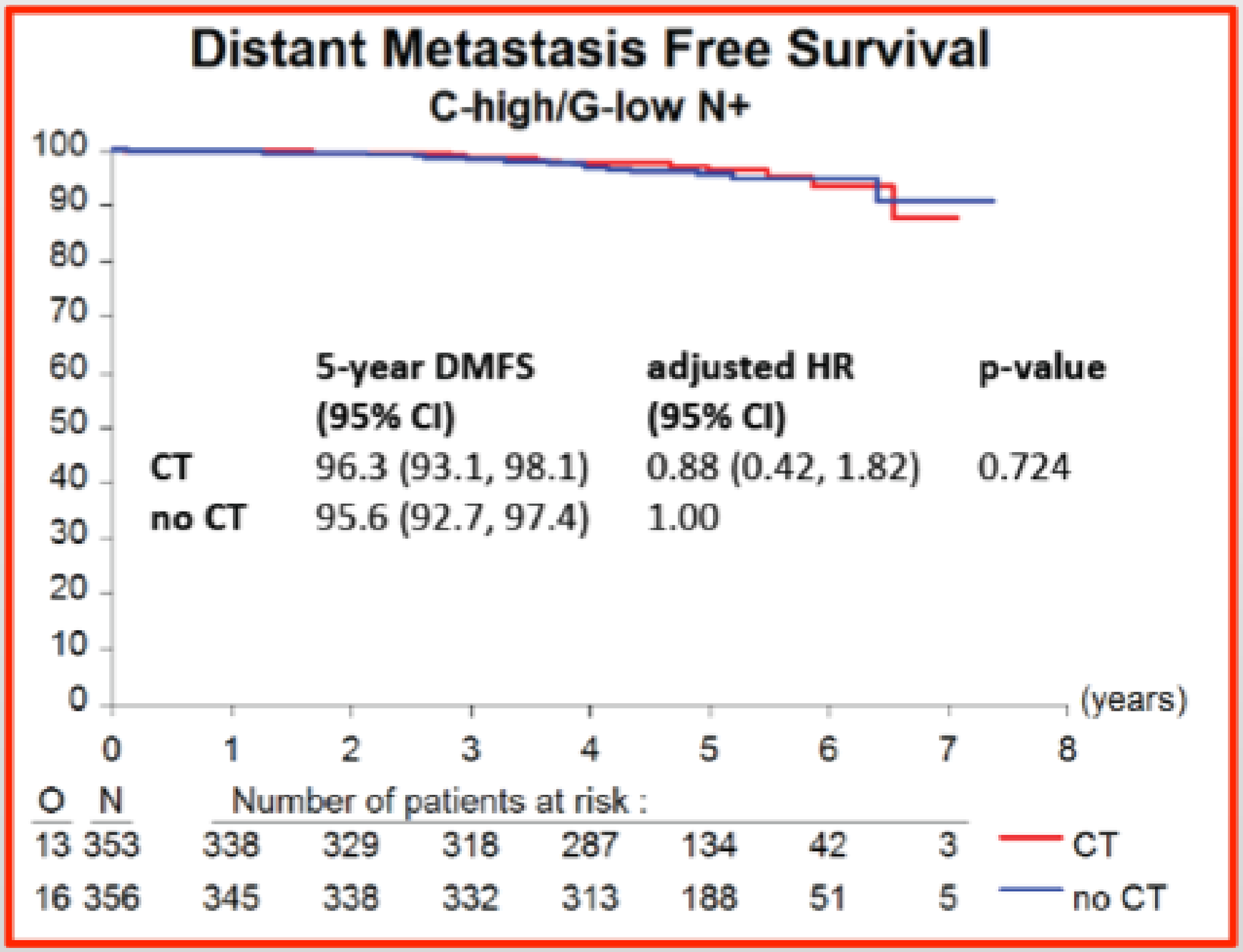
† Comprehensive Consensus Guidelines may differ and categorize a patient with these clinical factors as high risk.

Case 1: Clin High

- 70 year old woman
- Microcalcs on mammo, 2.5cm
- Bx: IDC, ER+, HER2 -
- Resection:
  - T1c: 2cm
- ER+, PR+, HER2-, Ki67 “low”
- Grade 2
- LVI present
- 1/7 LN+
- Stage IIA



Sub-group: LN Positive,
CT vs no CT in Clin-High / MP Low group



95.6% DMFS without chemo

Cardoso, F., et al. N Engl J Med. Supplemental. 2016 Aug 25;375(8):717-29

Caso clínico 2:

65 year old woman

Two Primary Tumors bx

4.5cm apart on mammo

1: ER+,HER2-, Grade 1

2: ER+, HER2 2+, Grade 2

Resection: (2^{nd} tumor)

T1b, ER+, PR –

HER2 2+, FISH equiv ratio 1.8

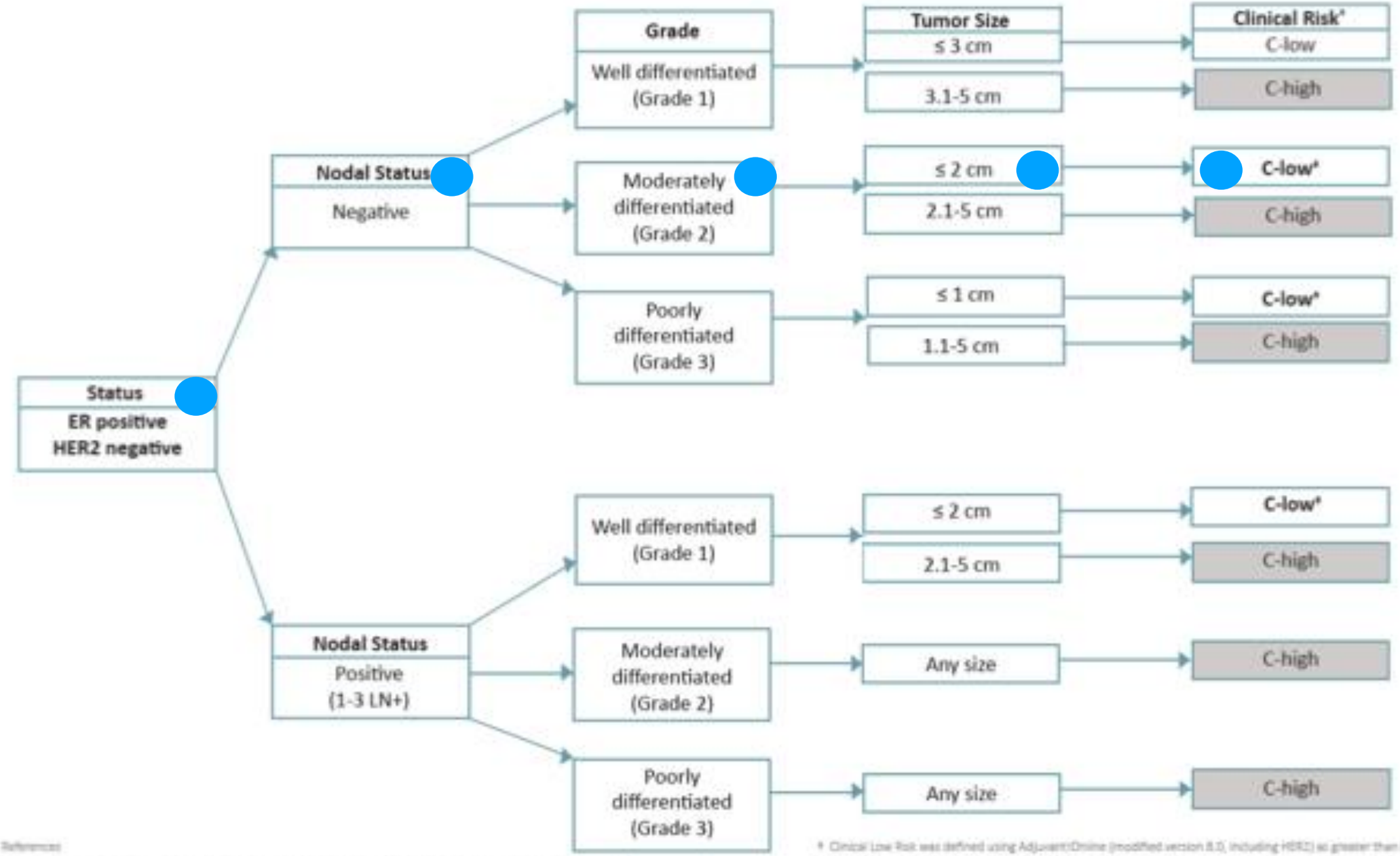
Ki67 >20%

Stage I

Clinical Risk Assessment in the MINDACT Trial

agendia® mammaprint®

HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE, INVASIVE BREAST CANCER (HR+ / HER2-)



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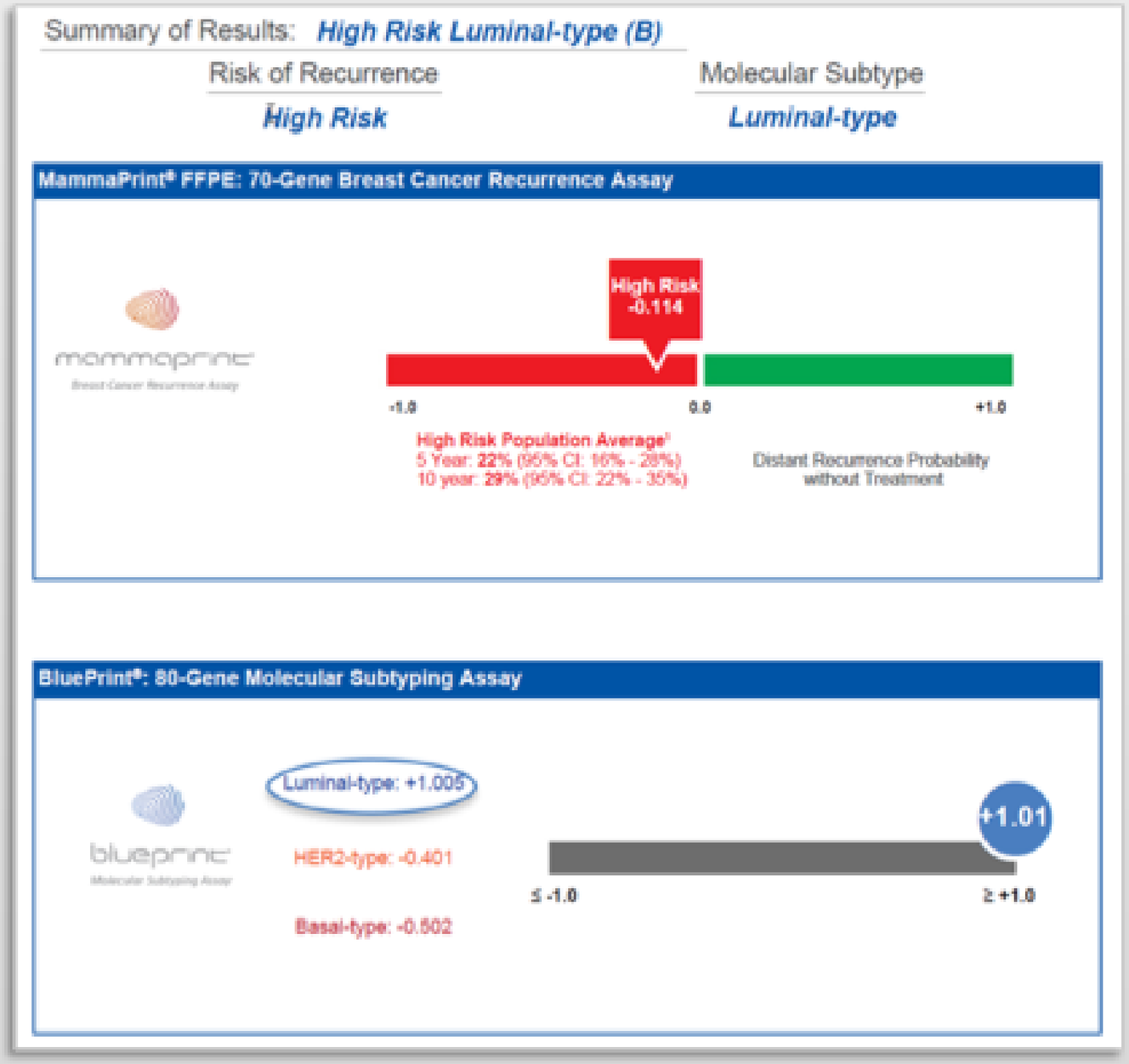
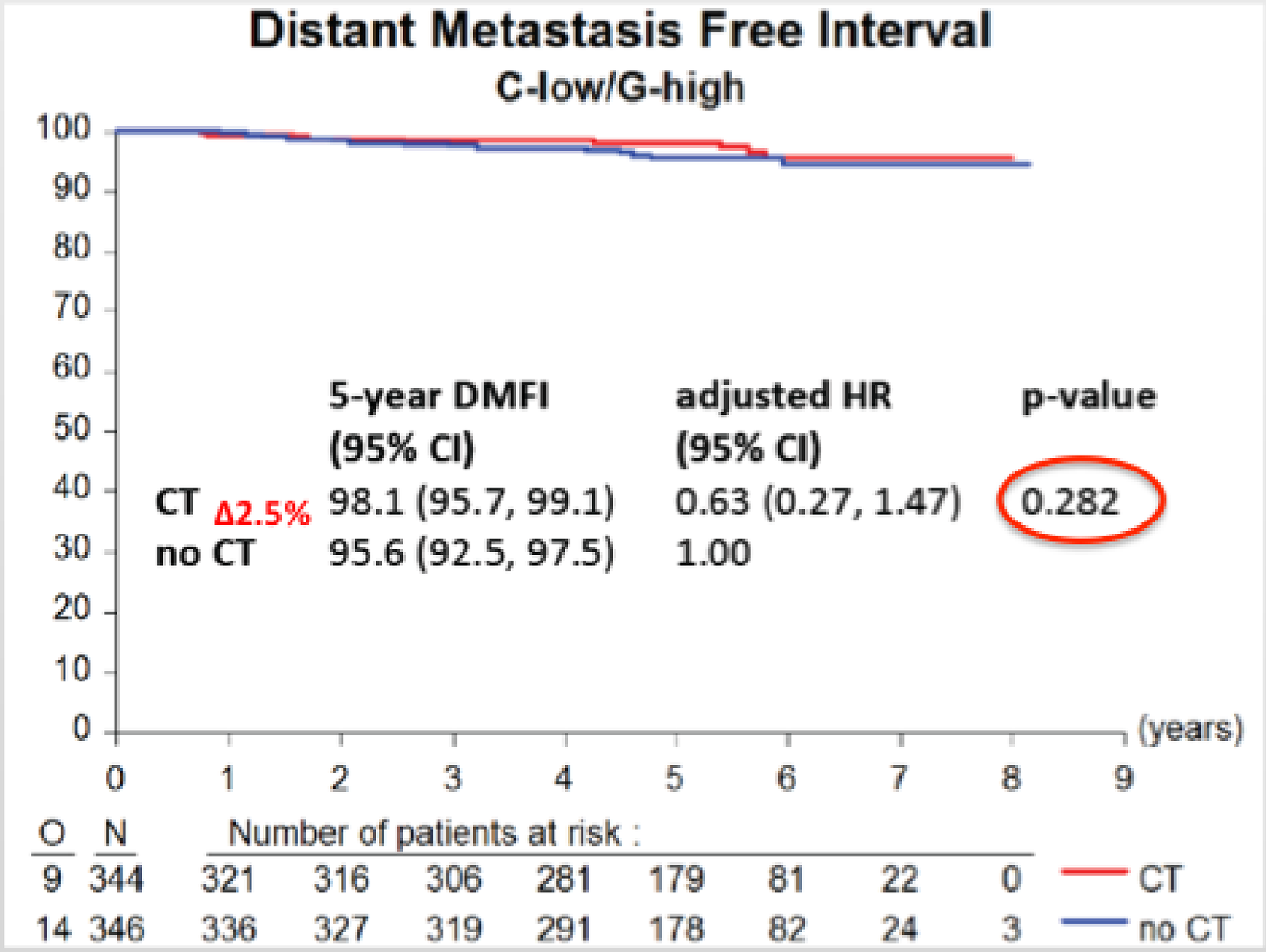
† Comprehensive Consensus Guidelines may differ and categorize a patient with these clinical factors as high risk.

Case 2: Clin Low

- 65 year old woman
- Two Primary Tumors bx
  - 4.5cm apart on mammo
- 1: ER+,HER2-, Grade 1
- 2: ER+, HER2 2+, Grade 2
- Resection: (2nd tumor)
- T1b, ER+, PR –
- HER2 2+, FISH equiv ratio 1.8
- Ki67 >20%
- Stage I



Chemo efficacy in Clin-Low / MP High (DMFI)



Potential Risk Reduction from Chemo?

Amount of benefit with clin low: ~2.5%

Cardoso, F., et al. N Engl J Med. Supplemental. 2016 Aug 25;375(8):717-29

Caso clínico 3:

41 year old woman

Palpable mass R breast, 3cm

Bx: IDC, ER+, HER2-

Resection:

T2: 3 cm

Grade II

LVI present

DCIS present

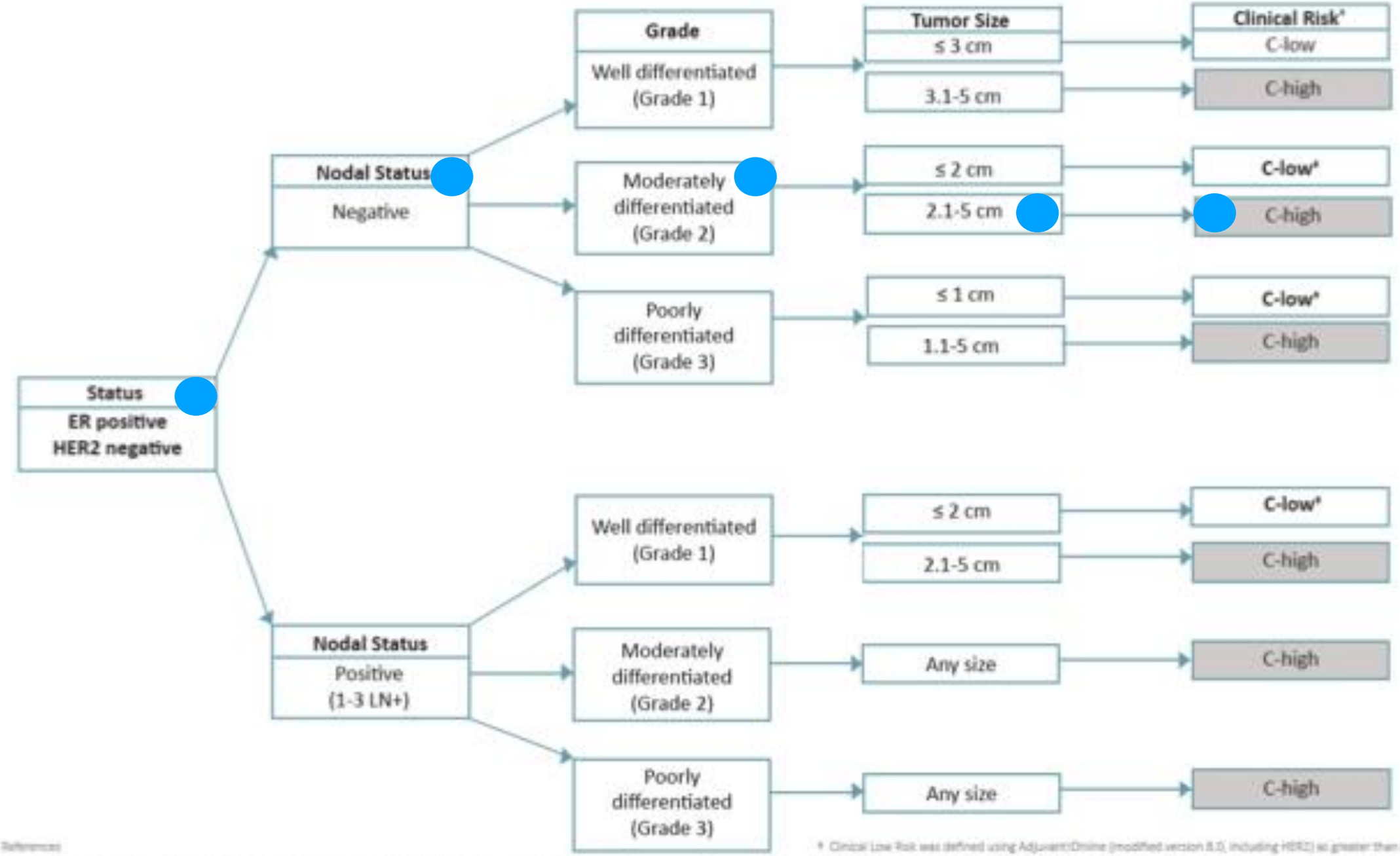
0/4 LN +

Stage IIA

Clinical Risk Assessment in the MINDACT Trial

agendia® mammaprint®

HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE, INVASIVE BREAST CANCER (HR+ / HER2-)



References

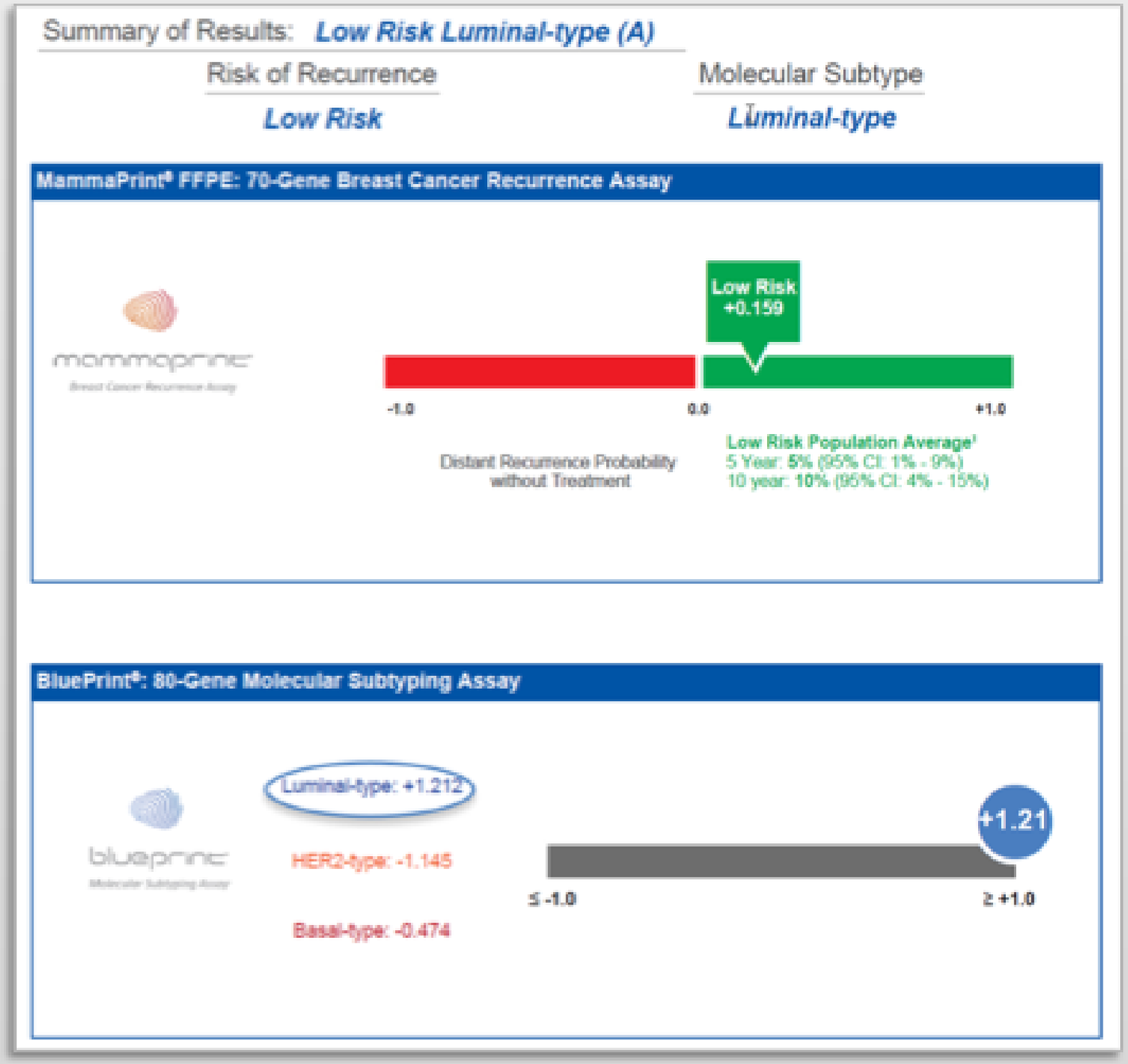
1. Cardoso, Fatima et al. "70-Gene Signature as an Aid to Treatment Decisions in Early Breast Cancer" *N Engl J Med* Supplemental. Published Online: Aug 2016.

* Clinical Low Risk was defined using AdjuvantOnline (modified version 8.0, including HER2) as greater than 88% breast cancer specific survival capability at 10-years, without systemic therapy to account for the average absolute benefit of adjuvant endocrine therapy for ER+ patients.

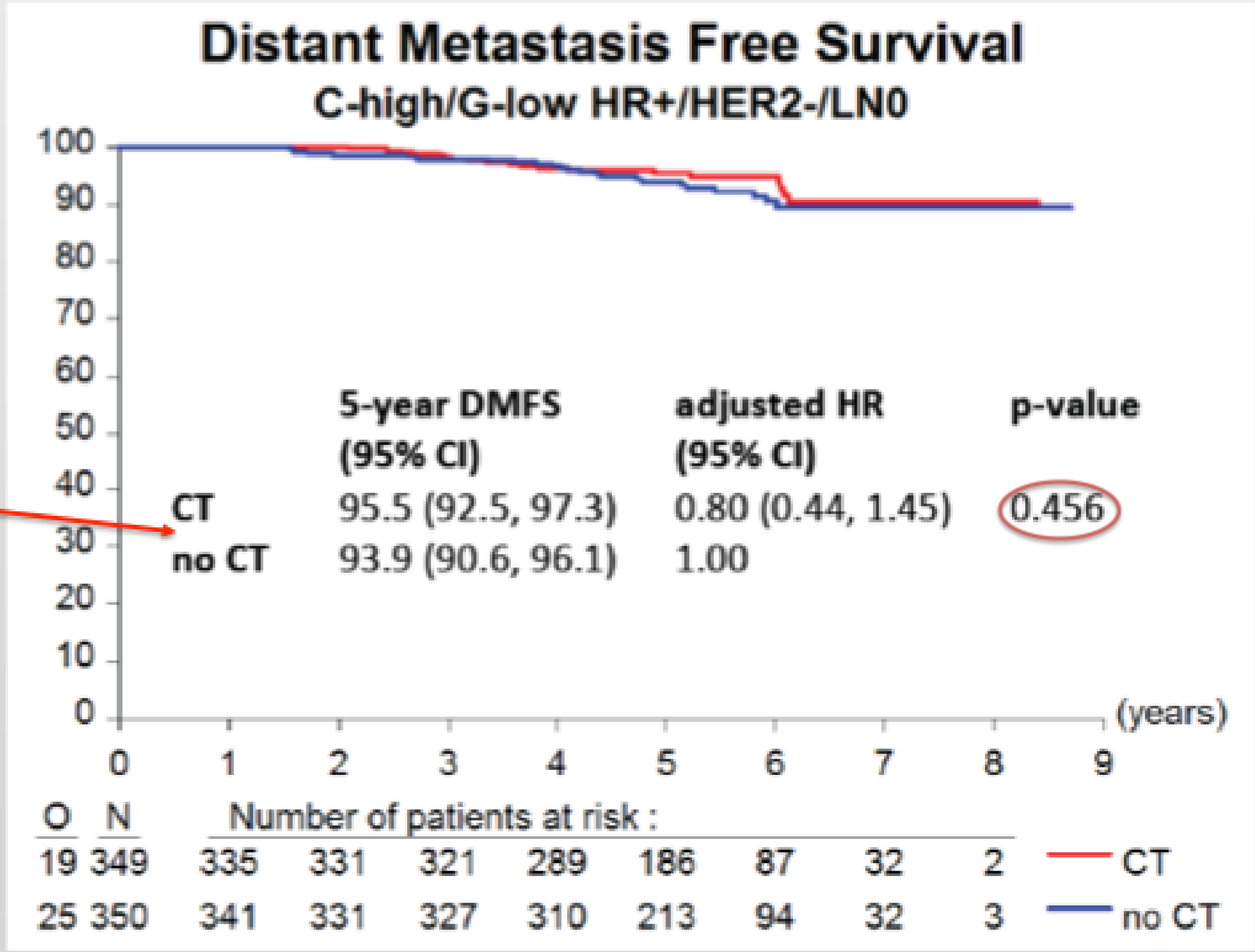
† Comprehensive Consensus Guidelines may differ and categorize a patient with these clinical factors as high risk.

Case 3: Clin-High

- 41 year old woman
- Palpable mass R breast, 3cm
- Bx: IDC, ER+, HER2-
- Resection:
- T2: 3 cm
- Grade II
- LVI present
- DCIS present
- 0/4 LN +
- Stage IIA



Sub-group: ER+ / HER2- / LN0,
CT vs no CT in Clin-High / MP Low group



Adjuvância em pacientes com tumores luminais

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