San Antonio Breast Cancer Symposium – December 5-9, 2017

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A randomized phase III study of adjuvant trastuzumab for a duration of 9 weeks versus 1 year, combined with adjuvant taxane-anthracycline chemotherapy, for early HER2-positive breast cancer

The Synergism Or Long Duration (SOLD) trial

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Antecedentes

- Duración óptima de Trastuzumab (Tz) en adyuvancia en cáncer de mama temprano HER2+ es desconocida.

[1]Pinto AC et al. Breast 2013; 22(Suppl) 2:S:152-5
[2]Mathew A et al. Curr Probl Cancer 2016; 40:106-11
[3]Pivot X et al. Lancet Oncol 2013; 14:741-48
[4]Mavroudis D et al. Ann Oncol 2015; 26:1333-40
[5]Cameron D et al. Lancet 2017; 389:1195-1205

- Estándar: 12 meses, sustento en pocos estudios.

- Tz concomitante con taxanos mejora la eficacia del Tz y puede tener efecto sinérgico.

- Hipótesis: Tz luego de (Tz – taxanos) concomitante pudiese no agregar un beneficio significativo y ser más tóxico.

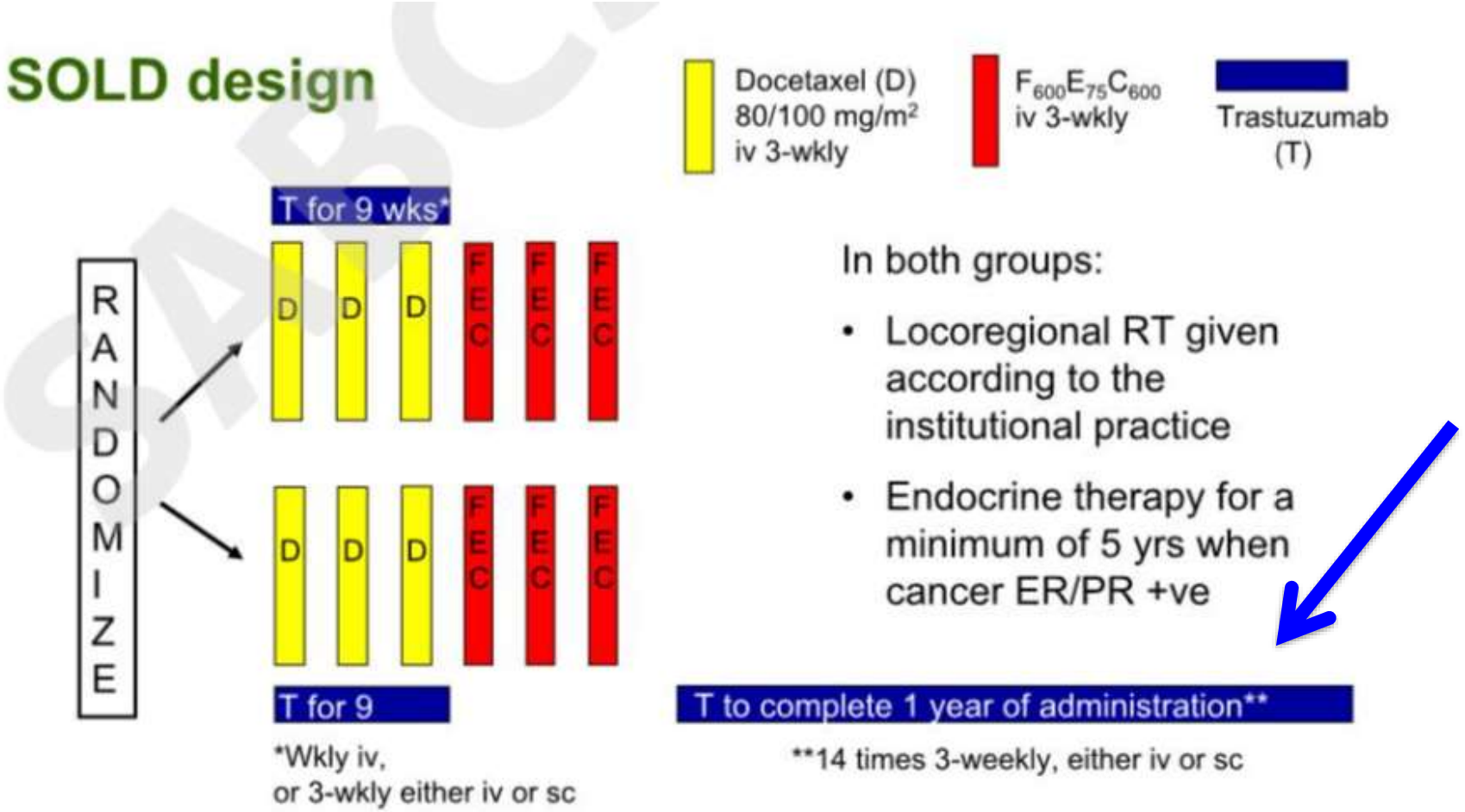
[1]Pegram MD et al. Semin Oncol 2000; 27 (6 Suppl 11):21-5; [2]Pegram MD et al. JNCI 2004; 96:739-49; [3]Inoue K et al. Breast Cancer Res Treat 2010; 119:127-36; [4]Hamberg P et al. Clin Breast Cancer 2011; 11:103-13; [5]Perez EA et al. JCO 2011; 29:4491-7; [6]Schneider BP et al. Br J Cancer 2015; 113:1651-7; [7]Conte PF et al. JCO 2017; 35 (Suppl): abstr 501

Metodología

- Objetivos
  - **Principal: sobrevida libre de enfermedad (SLE)**
  - Secundarios: sobrevida libre de enfermedad a (SLEM) distancia, sobrevida global (SG), seguridad (S), sobrevida libre de eventos cardíacos, calidad de vida, FEVI

- Cálculo de tamaño muestral
  - **No inferioridad**
  - SLE a 5 años en grupo control 85%
  - Diferencia clínicamente significante >5%
  - Margen de no inferioridad relativa de 1,3
  - Tamaño muestral 2168 pacientes
  - 366 eventos, usando nivel de significancia de 0,05 con “una cola”

Diseño


SOLD design
Docetaxel (D)
80/100 mg/m²
iv 3-wkly
F600E75C600
iv 3-wkly
Trastuzumab
(T)
T for 9 wks*
RANDOMIZE
D D D F E C F E C F E C
D D D F E C F E C F E C
T for 9
*Wkly iv,
or 3-wkly either iv or sc
In both groups:
• Locoregional RT given according to the institutional practice
• Endocrine therapy for a minimum of 5 yrs when cancer ER/PR +ve
T to complete 1 year of administration**
**14 times 3-weekly, either iv or sc

Criterios

- Inclusión
  - WHO performance status 0 o 1
  - Cáncer de mama HER2+ confirmado con FISH o IHQ+++
  - N1-3, T1bN0 G2-3 o T1cN0
- Exclusión
  - Enfermedad a distancia
  - Tratamiento neoadyuvante
  - Cardiopatía clínica relevante
  - Cáncer de mama inflamatorio
  - FEVI <50%

Pacientes

Key baseline characteristics

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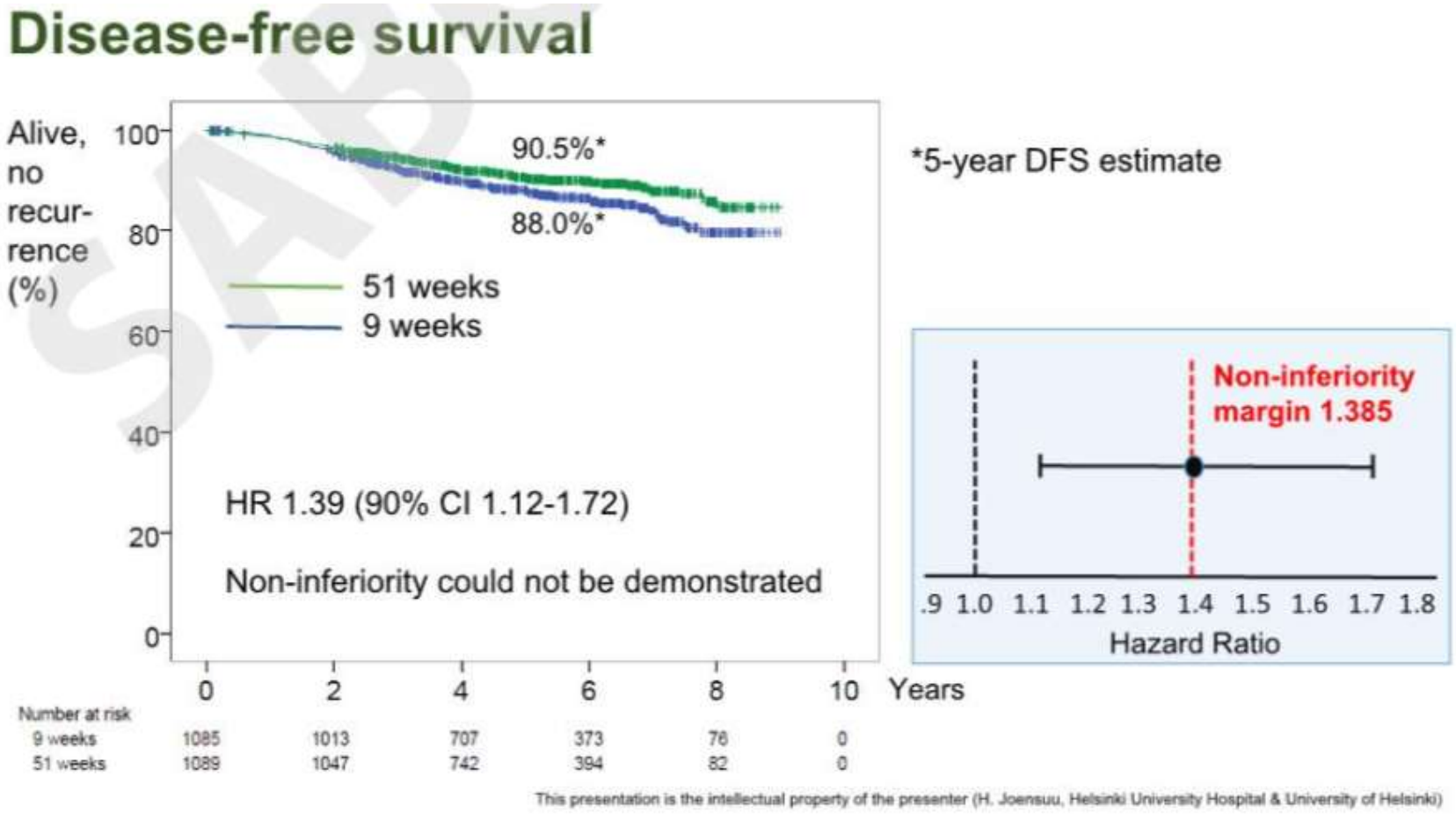
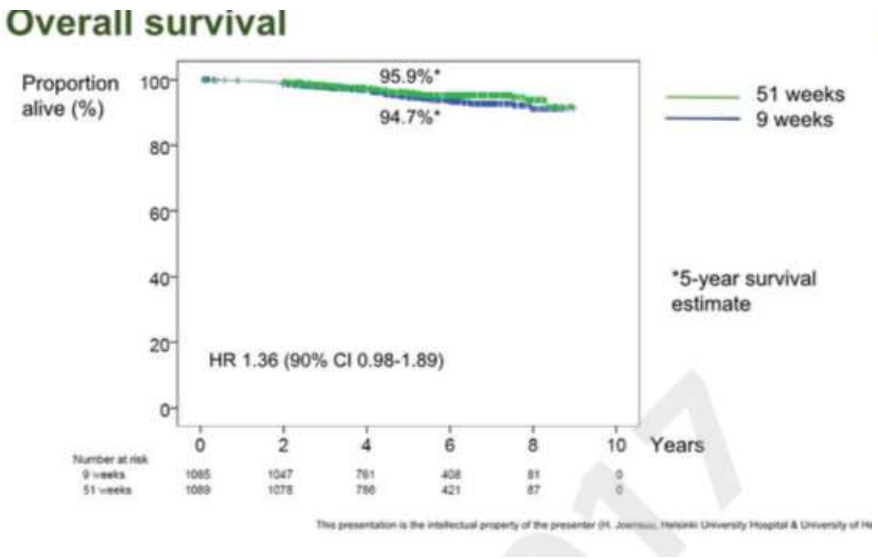
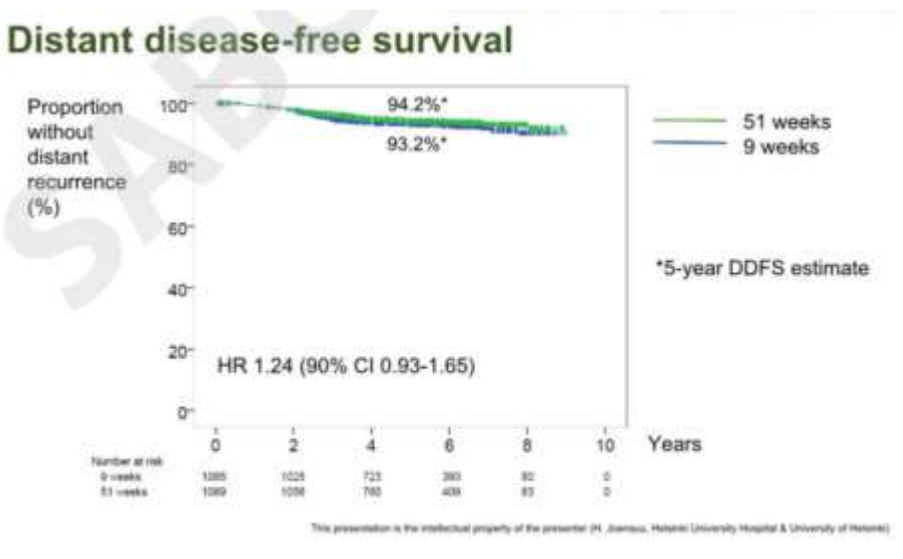
Characteristic	9-week group (n=1,085)	1-year group (n=1,089)
Median age (range) – years (range)	56 (23-82)	56 (27-79)
Premenopausal	33 %	33 %
Breast tumor diameter		
≤10 mm	12 %	14 %
11-21 mm	44 %	42 %
21-50 mm	41 %	42 %
>50 mm	3 %	3 %
Axillary lymph nodes with cancer		
0	60 %	60 %
1-3	30 %	29 %
>3	11 %	11 %
Ductal histological type	92 %	92 %
Estrogen receptor-positive	66 %	66 %
Progesterone receptor-positive	46 %	47 %

Mayoría T1, T2, N0



Resultado principal: 9 semanas con menor SLE que 51 semanas (88 vs 90,5% a 5 años)





Sobrevida global y sobrevida libre de recaída a distancia: sin diferencias

DFS events (ITT)

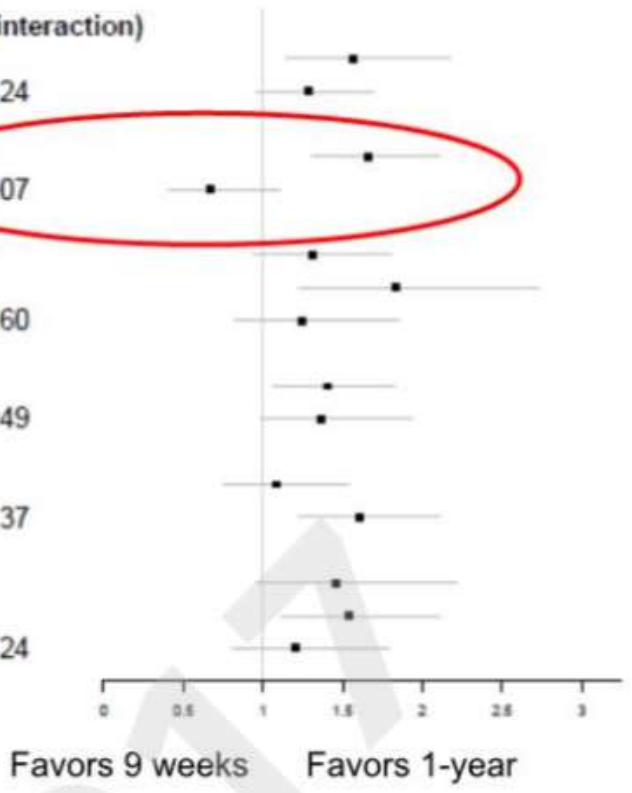
Event	9-wk group (n=1,085) n (%)	1-yr group (n=1,089) n (%)
Any recurrence or death	140 (13)	105 (10)
Distant recurrence	73 (7)	61 (6)
Locoregional recurrence	17 (2)	13 (1)
Contralateral BC	15 (1)	7 (1)
Second cancer	27 (3)	24 (2)
Death without cancer	14 (1)	5 (0)
Death from any cause	58 (5)	44 (4)
Death from BC	34 (3)	33 (3)
Death from another cause	24 (2)	11 (1)

Diferencias: SLE, pequeña en Nº absoluto

Sin diferencias: mortalidad causa específica, sobrevida global

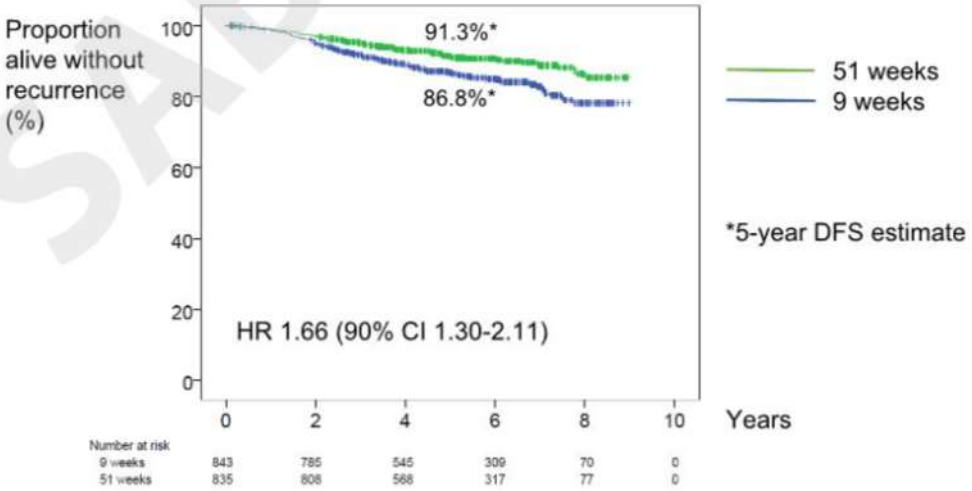
Predefined subgroup analyses for DFS

Subgroup		Hazard Ratio (90–% CI)	p (interaction)
ER status	Negative	1.57 (1.14–2.17)	
	Positive	1.28 (0.96–1.69)	0.424
Docetaxel dose	80 mg/m2	1.66 (1.30–2.11)	
	100 mg/m2	0.67 (0.41–1.10)	0.007
Nodes with cancer	0	1.31 (0.95–1.80)	
	1–3	1.83 (1.22–2.74)	
	3+	1.24 (0.82–1.85)	0.460
Centre accrual	< 100 patients	1.40 (1.06–1.83)	
	=> 100 patients	1.37 (0.98–1.93)	0.949
Age	< 50 yrs	1.08 (0.76–1.53)	
	>= 50 yrs	1.61 (1.23–2.11)	0.137
Stage	I	1.46 (0.96–2.22)	
	II	1.54 (1.12–2.11)	
	III	1.21 (0.81–1.79)	0.724

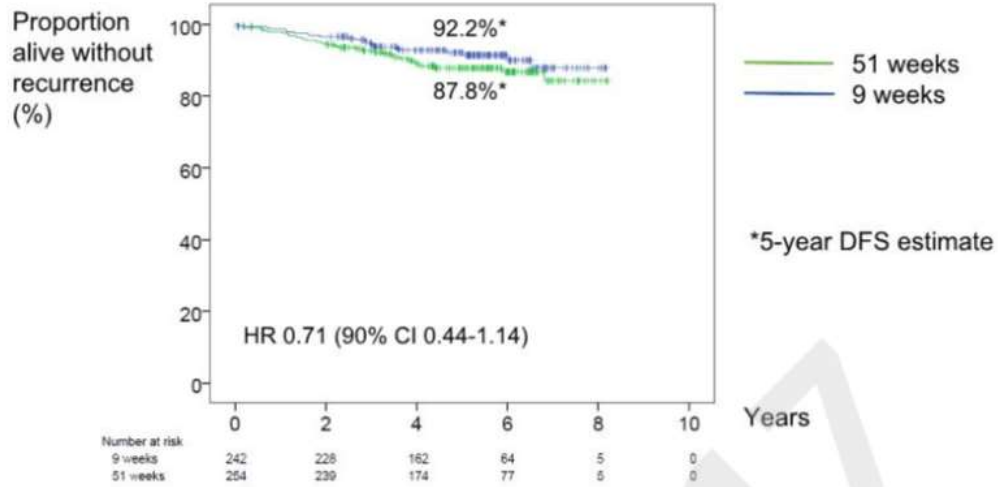


Análisis de subgrupo pre-definido:
Docetaxel 80 mg/m2: mejor SLE para 51 semanas de Tz
Docetaxel 100 mg/m2: sin diferencias en SLE

DFS: Docetaxel dose 80 mg/m²



DFS: Docetaxel dose 100 mg/m²



Toxicidad

Treatment safety

- Chemotherapy-related toxicity generally similar and expected in the 2 groups

	9-week group n (%)	1-year group n (%)
Discontinued chemotherapy	44 (4.1)	51 (4.7)
Discontinued trastuzumab	96 (8.9) -53% for toxicity	217 (19.9) -66% for toxicity
Died from a treatment-related cause	2 (0.2)	2 (0.2)

Cardiac safety

- Less cardiac toxicity was observed in the 9-week group

Event	9-week group n (%)	1-year group n (%)	
Any protocol-defined cardiac adverse event*	22 (2.0)	42 (3.9)*	*P = 0.012
Congestive heart failure	21 (1.9)	36 (3.3)**	**P = 0.046

*Any Gr. 3 or 4 cardiac event; symptomatic cardiac failure; cardiac failure requiring medical management; LVEF decrease >10 percentage points and to a value <50%; LVEF decrease to <45% from any baseline value

Rama con Tz por 51 semanas

- Mayor suspensión de Tz
- Mayor incidencia de eventos cardíacos adversos
- Mayor incidencia de falla cardíaca (clínica)

Conclusiones

- Tz 9 semanas es inferior a Tz por 51 semanas en SLE
- Menor duración de Tz, menos eventos cardíacos
- La dosificación de docetaxel con tratuzumab requiere de mayores estudios.
- Trastuzumab por un año: terapia estándar

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Gracias