

Point-Counter-Point
 Treatment of Stage IV Disease-
 Patient with BRAF Mutant Melanoma

BRAF targeted therapy is the first line treatment of choice for patients with advanced melanoma

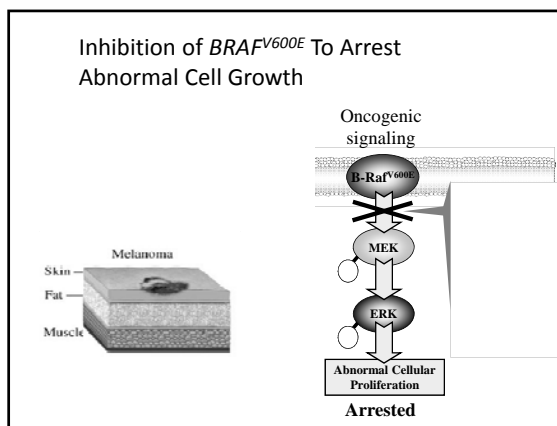
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Treatment Options for *BRAF*^{V600} mutant metastatic melanoma patients

- High Dose Interleukin-2
- Ipilimumab (3mg/kg) q 3 weeks x 4
- BRAF inhibitor, Vemurafenib
- Chemotherapy- Dacarbazine, Temozolomide, Carboplatin+Paclitaxel



What are the goals and what is the reality ?

- Vemurafenib-
 - Induces tumor regression in over 80% of patients and few patients progress in the initial 4-8 weeks
 - Median progression-free survival is 6-7 months, but there are patients with much longer remissions
 - At a f/u of between 24-32 months, 3/44 (7%) patients remain progression free on vemurafenib and 7/44 remain on vemurafenib with disease control (16%)
 - In those patients without bulky disease, normal LDH and PS=0, outcome is much better and median survival is well over 2 years
 - Of the 48 patients enrolled on phase I trial who received effective doses of vemurafenib, the median overall survival is close to 50% at 2 years

BRIM 2 trial objective

- To confirm the ORR and anti-tumor activity of vemurafenib in previously treated patients with *BRAF*^{V600}-mutated melanoma

Metastatic melanoma
 Prior treatment
 BRAFV600E-positive
 [cobas® 4800 BRAF V600
 Mutation Test]

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**Vemurafenib
 (960 mg BID)**

Primary endpoints:
 ORR (IRC)

Secondary endpoints: duration
 of response, PFS, OS, and safety

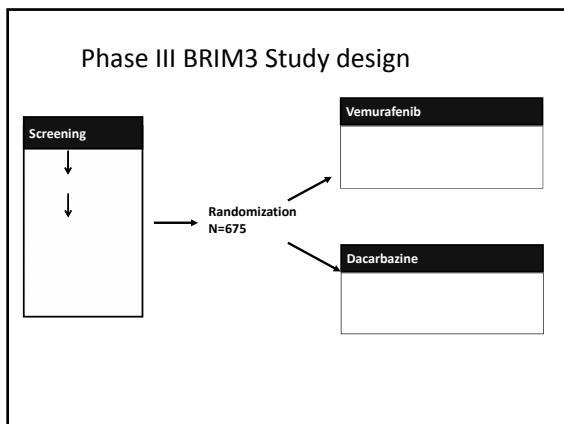
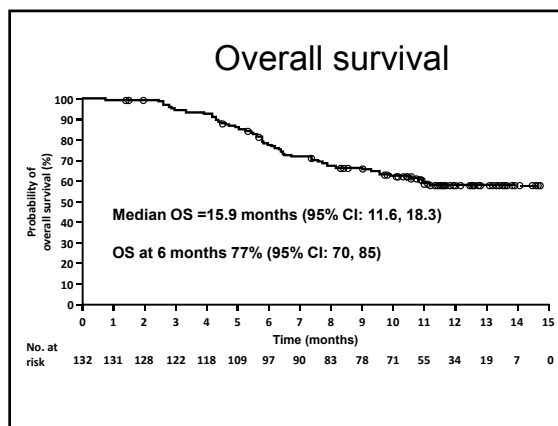
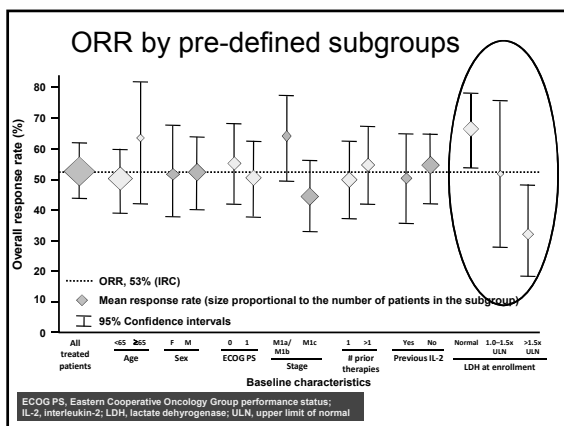
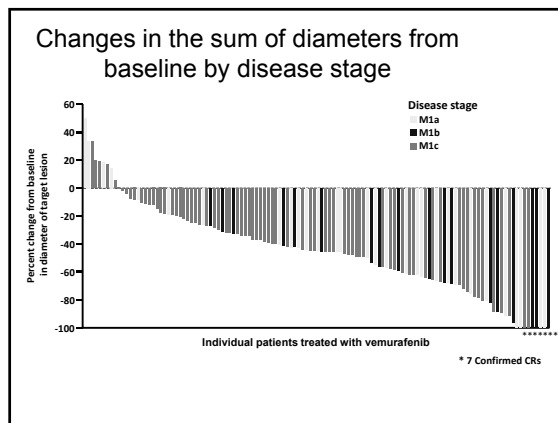
IRC: independent review committee
 BID, twice daily; IRC, independent review committee; ORR, overall response rate;
 OS, overall survival; PFS, progression-free survival

Patient demographics and baseline disease characteristics

n=332

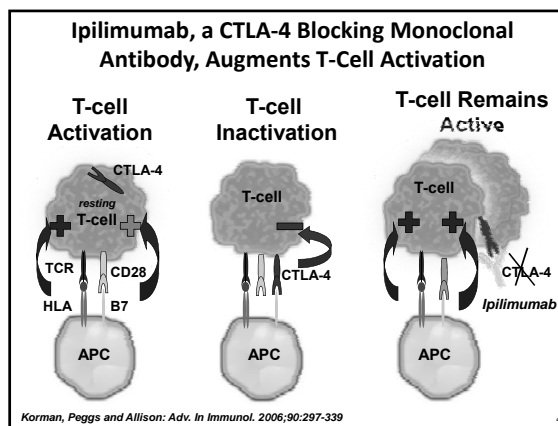
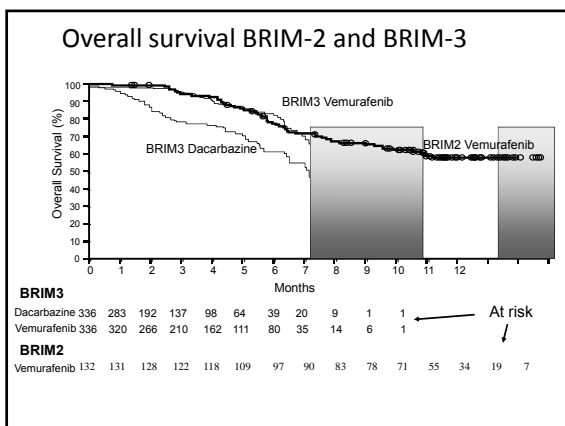
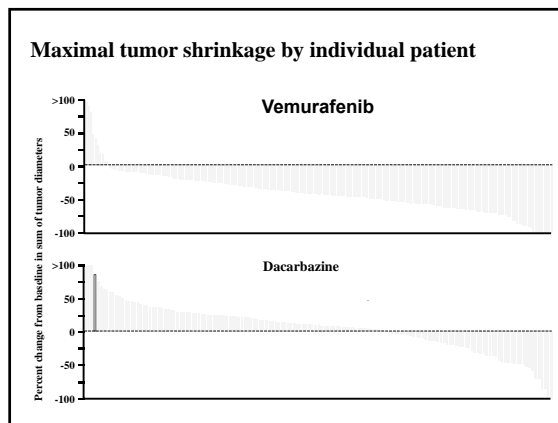
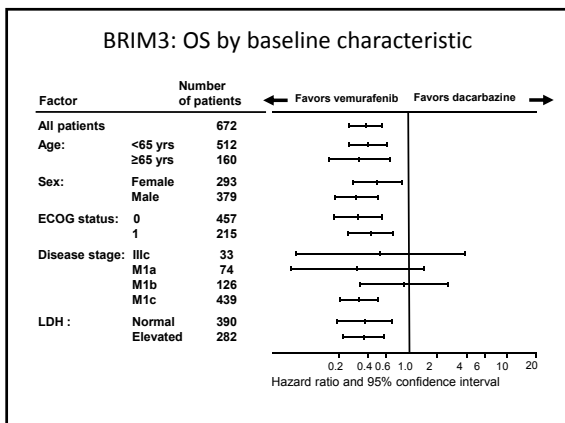
| Characteristic | n (%) | Characteristic | n (%) |
|-------------------------------|----------|-------------------------------------|----------|
| Sex | | | |
| Female | 51 (39) | Stage at diagnosis | |
| Male | 81 (61) | M1a | 33 (25) |
| Race | | | |
| Caucasian | 130 (98) | M1b | 28 (14) |
| Hispanic | 2 (2) | M1c | 81 (61) |
| Age (yr) (median 51.5) | | | |
| <65 | 107 (81) | Serum LDH | |
| ≥65 | 25 (19) | Normal | 67 (51) |
| ECOG | | | |
| 0 | 61 (46) | Elevated | 65 (49) |
| 1 | 71 (54) | No. prior therapies | |
| Previous IL-2 | | | |
| No | 81 (61) | 1 | 67 (51) |
| Yes | 51 (39) | 2 | 36 (27) |
| | | ≥3 | 29 (22) |
| | | Previous ipilimumab or tremelimumab | |
| | | No | 125 (95) |
| | | Yes | 7 (5) |

IL-2, interleukin-2; LDH, lactate dehydrogenase



Patient characteristics

| | Dacarbazine (N=338) | Vemurafenib (N=337) |
|-------------------|---------------------|---------------------|
| Median age, yr | 52.5 | 56.0 |
| Male, no. (%) | 181 (54) | 200 (59) |
| ECOG PS, no. (%): | | |
| 0 | 230 (68) | 229 (68) |
| 1 | 108 (32) | 108 (32) |
| Stage, no. (%) | | |
| Unresectable IIIc | 13 (4) | 20 (6) |
| M1a | 40 (12) | 34 (10) |
| M1b | 65 (19) | 62 (18) |
| M1c | 220 (65) | 221 (66) |
| LDH >ULN | 142 (42) | 142 (42) |



What are the goals and what is the reality ?

- Ipilimumab-
 - Induces few objective RECIST responses, but can be associated with delayed response, stable disease, growth of isolated lesion only
 - Greatest problem is quantitating clinical responses and benefit, since RECIST 1.1 does not work
 - Median progression-free survival is on 2.6 months and disease control on phase III upfront was 44%
 - At 2 years in the second line trial, overall survival is at 24% while 3 year overall survival appears to be 20%
 - Generally, offers minimal to no likelihood of a response in rapidly progressing symptomatic disease
 - Are there really cures? maybe

Ipilimumab +/- gp100 vs gp100 Baseline Characteristics

| | Ipi + gp100 N=403 | Ipi + pbo N=137 | gp100 + pbo N=136 |
|--------------------|----------------------|--------------------|----------------------|
| Age (years) | | | |
| Mean | 55.6 | 56.8 | 57.4 |
| Gender (%) | | | |
| Male | 61 | 59 | 54 |
| Female | 39 | 41 | 46 |
| M Stage (%) | | | |
| M0 | 1 | 0.7 | 3 |
| M1a | 9 | 10 | 8 |
| M1b | 19 | 16 | 17 |
| M1c | 71 | 73 | 72 |

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Ipilimumab +/- gp100 vs gp100 Baseline Characteristics

| | ipi + gp100 N=403 | ipi + pbo N=137 | gp100 + pbo N=136 |
|-----------------------|----------------------|--------------------|----------------------|
| ECOG PS (%) | | | |
| 0 | 58 | 53 | 52 |
| 1 | 41 | 47 | 45 |
| 2 | 1 | 0.7 | 3 |
| 3 | 0.2 | 0 | 0 |
| LDH (%) | | | |
| ≤ ULN | 63 | 61 | 60 |
| > ULN | 37 | 39 | 38 |
| CNS metastases | 11 | 11 | 15 |

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Ipilimumab Improves Best Overall Response Rate (BORR)

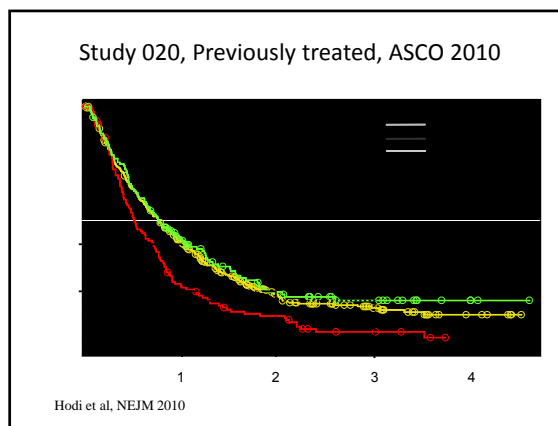
| | ipi + gp100 N=403 | ipi + pbo N=137 | gp100 + pbo N=136 |
|-----------------------------|----------------------|---------------------|----------------------|
| BORR, % (95% CI) | 5.7 (3.7–8.4) | 10.9 (6.3–17.4) | 1.5 (0.2–5.2) |
| P-value: A vs C | 0.0433 | | |
| P-value: B vs C | 0.0012 | | |
| DCR‡, % (95% CI) | 20.1 (16.3–24.3) | 28.5 (21.1–36.8) | 11.0 (6.3–17.5) |
| P-value: A vs C | 0.0179 | | |
| P-value: B vs C | 0.0002 | | |

‡: Disease control rate: percentage of patients with CR, PR, or SD 20

Ipilimumab alone Improves Overall Survival Compared to gp100

| | ipi + pbo | gp100 + pbo | P-value |
|--------------------------------------|--------------------|-------------------|---------|
| Secondary Comparison | | | |
| N | 137 | 136 | 0.0026 |
| Number of deaths | 100 | 119 | |
| Hazard ratio (95% CI) | 0.66 (0.51,0.87) | | |
| Median OS, Month (95% CI) | 10.1 (8.0,13.8) | 6.4 (5.5, 8.7) | |

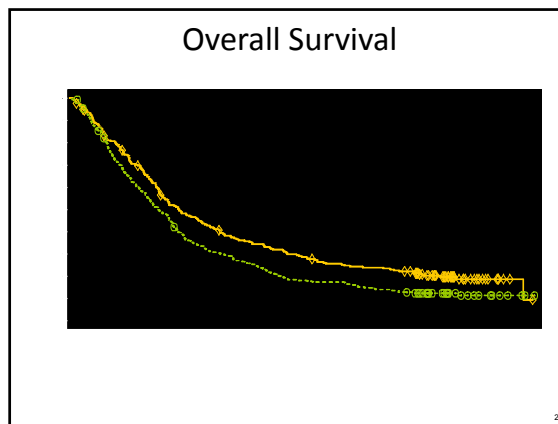
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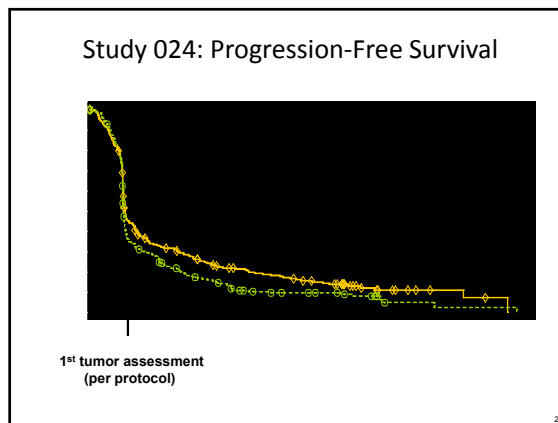
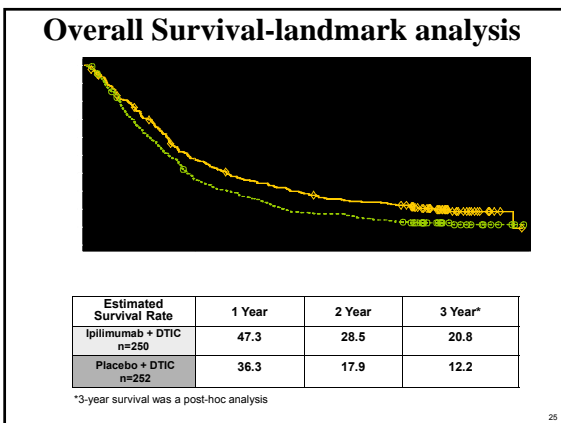


Ipi+ DTIC vs DTIC: Baseline Characteristics

| | Ipilimumab + DTIC n=250 | Placebo + DTIC n=252 |
|--------------------|----------------------------|-------------------------|
| Age (years) | | |
| Mean | 57.5 | 56.4 |
| Gender (%) | | |
| Male | 60.8 | 59.1 |
| Female | 39.2 | 40.9 |
| M Stage (%) | | |
| M1a | 14.8 | 17.1 |
| M1b | 25.6 | 24.6 |
| M1c | 57.2 | 55.2 |
| ECOG PS (%) | | |
| 0 | 70.8 | 71.0 |
| 1 | 29.2 | 29.0 |
| LDH (%) | | |
| ≤ ULN | 62.8 | 55.6 |
| > ULN | 37.2 | 43.7 |

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Study 024: Tumor Response

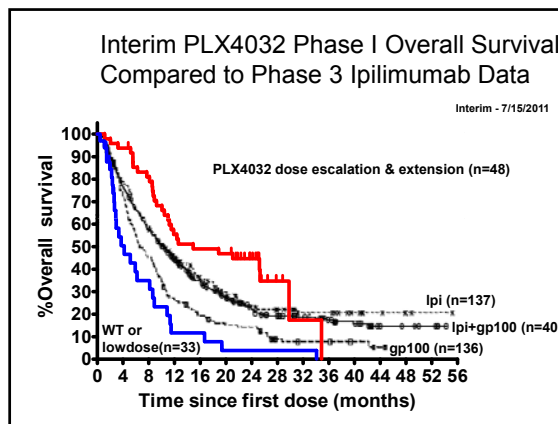
| | Ipiilimumab + DTIC n=250 | Placebo + DTIC n=252 |
|------------------------------|-----------------------------|-------------------------|
| Disease Control Rate, n (%) | 83 (33.2) | 76 (30.2) |
| BORR (CR + PR), n (%) | 38 (15.2) | 26 (10.3) |
| Complete response | 4 (1.6) | 2 (0.8) |
| Partial response | 34 (13.6) | 24 (9.5) |
| Stable disease | 45 (18.0) | 50 (19.8) |
| Progressive disease | 111 (44.4) | 131 (52.0) |
| Duration of response, months | 19.3 | 8.1 |

BORR=Best Overall Response Rate
 Patients (%) not evaluable for response (no follow-up scans): 56 (22.4) vs 45 (17.9)
 Where are all the patients only 77.6% of patients accounted for with CR, PR, SD, PD

Most Common Immune-Related Adverse Events (irAEs; All Grades)

| irAE | % of Patients | | |
|--------------|----------------------|--------------------|----------------------|
| | Ipi + gp100 N=380 | Ipi + pbo N=131 | gp100 + pbo N=132 |
| All grades | | | |
| Any | 57 | 60 | 32 |
| Dermatologic | 39 | 42 | 17 |
| GI | 31 | 28 | 14 |
| Endocrine | 3 | 8 | 2 |
| Hepatic | 2 | 3 | 4 |

- ### Prolonged responses or disease control on vemurafenib
- Phase I trial 48 BRAF V600 mutant melanoma patients on extension and escalating phase received 720-960mg BID
 - At 2-3 years f/u 7 still on treatment and 3 without any signs of progression.
 - Median overall survival was 14.5 months for 48 pts with 54% one-year and 33% two-year survival rates
 - Again, the PS, cumulative tumor bulk by RECIST elevated LDH, and M1c associated with poor outcome and those without had excellent outcome
 - The BRIM2 phase II had a 15.9 month median overall survival



Vemurafenib vs Ipilimumab: Long-term outcome

| | Presented at | N of pts | PS=1 | M1c | 1 yr survival | 2 yr survival |
|------------------------------|--------------|----------|------|-----|---------------|-----------------|
| Vemurafenib phase I | SMR 2011 | 48 | 56% | 71% | 54% | 33% |
| Vemurafenib Phase II | ASCO 2011 | 132 | 54% | 61% | 58% | Median 15.9 mos |
| Ipilimumab phase III | NEJM 2010 | 137 | 47% | 71% | 46% | 24% |
| Ipilimumab + gp100 phase III | NEJM 2010 | 403 | 42% | 71% | 43% | 21% |

Take Home Message

- Disease control rate- 86% for vemurafenib vs 44% for Ipilimumab
- Vemurafenib is only effective therapy for symptomatic patients, with bulky disease, and/or high LDH- allow rapid improved in QOL
- While median PFS is less than 7 months overall, there are multiple patients who remain on treatment beyond 2 years (7/48)
- Median overall survival in phase II and phase I (15.9 and 14.5 months, respectively).
- It is a misnomer that everyone progressing on vemurafenib has rapidly progressing disease and will die quickly
- No evidence that you can not get durable remission in BRAF mutant patients to Ipilimumab after BRAF inhibitor failure

Melanoma therapy standards 2011

| Setting | | Phase III |
|---|--------------|--|
| First line- Genotype for at least BRAF (Cobas™ or Sanger sequencing) and c-kit mutations Also NRAS, GNA11, GNAQ-uveal | BRAF mutated | Patient with sx, bulky disease, or increased LDH Vemurafenib |
| | | Indolent disease-asx, M1a /M1b, asx Vemurafenib or Ipilimumab HD IL-2 first line |
| | | Trial options: BRAFi+MEKi BRAFi + Ipilimumab |

*Phase III data available